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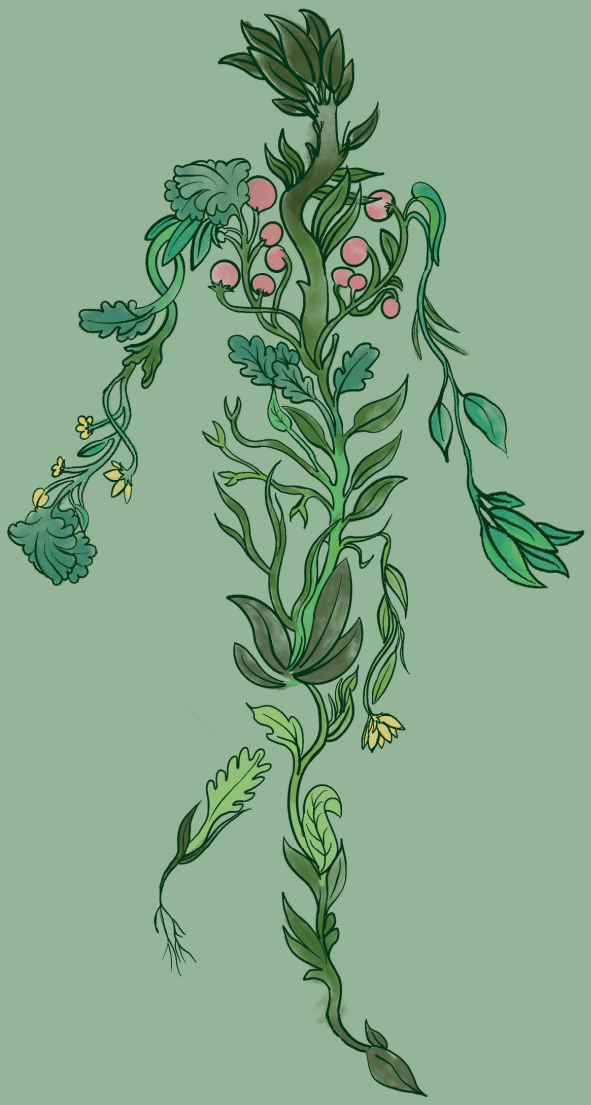

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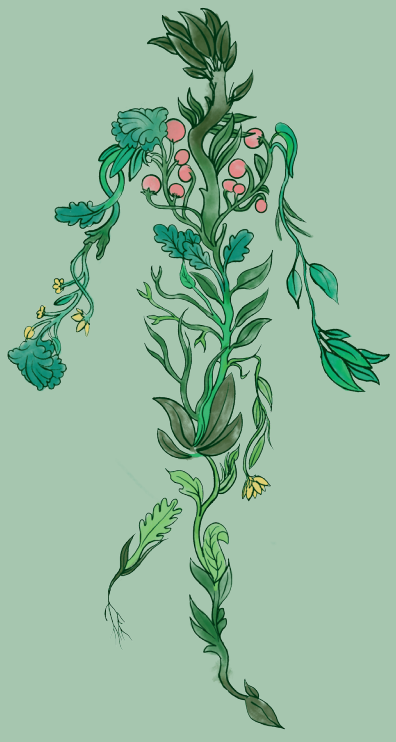


Chapter 1

General introduction

In 1985, a cow died in the UK from a then mysterious new disease. The cow first displayed erratic behaviour and then progressive motor coordination problems and convulsions before collapsing. Worryingly, this new animal disease appeared to be spreading, prompting the UK government to order the slaughter of cattle showing any signs of "mad cow disease". Scientists identified the animal disease as bovine spongiform encephalopathy (BSE): a transmissible, neurodegenerative, and fatal disease (1). To further halt the spread of BSE, the UK government banned cattle feed containing meat or bone meal. Initially, the BSE crisis was thought to be an animal health crisis only, but that changed when in the 1990s cases of a new variant of Creutzfeld-Jakob disease (vCJD) were diagnosed – a rare human spongiform encephalopathy that mainly affects young adults (2). Cases were largely concentrated in the UK, and it was established that vCJD is the human equivalent of BSE and that it is likely contracted from consuming contaminated beef (2). Consequently, the European Commission (Commission) imposed an export ban on UK cattle (its meat and products; Commission Decision 96/239/EC) in 1996 (3). Consumer trust and beef consumption in the European Union (EU) plummeted (4).

The number of new cases of BSE in the EU peaked in the 1990s and currently any new cases are incidental (5). The UK beef ban was lifted by the Commission in 2006. However, in the aftermath of the BSE crisis, as well as other food scares, food law in the EU was extensively revised (6). Risk analysis was one of the tools developed to foster consumer protection and optimise functioning of the internal market, the two main objectives of EU food law (Art. 1.1) (6,7). Risk analysis has consequently been implemented in the EU (GFL, Art. 6) for the assessments of risks of, for example, new food ingredients (Art. 10-12), but also for the assessment of benefits of products such as for nutrition and health claims (7–9). In the EU's General Food Law (Regulation EC (No) 178/2002, GFL), risk analysis is described as an approach in which risk assessment, risk management and risk communication are separated (Art. 6) (7). Risk management is mostly conducted by the Commission or individual Member States, acting as decision-makers (Art. 6.3) (7). In their decision-making, risk managers should take into consideration the results from risk assessment. This risk assessment is conducted by the European Food Safety Authority (EFSA), the independent scientific agency supporting policy related to food and food safety (Art. 22) (7). In article 6.2 of the GFL, it is specified that this risk assessment should take into account all available scientific evidence. The third and final element in the risk analysis cycle, risk communication, is a process that should result in clear and transparent communication of food and nutritional issues to other stakeholders including food business

operators and consumers (Art. 6.4) (7). It is a collaborative effort of EFSA, the Commission and EU Member States (Art. 8a & 8b) (7,10).

1.1 EU food law and risk analysis in practice

The GFL lays the foundation for all secondary food legislation (7), that is, legislative acts that deal with specific aspects of food production (11) or food information (12). The GFL also sets the standard for food safety (Art. 14): food should not be placed on the market if it is unsafe, given (that?) the conditions of use (e.g. preparation methods) are met (13). Regulation (EU) 2019/1381 on the transparency and sustainability of EU risk assessment, known as the Transparency regulation, amends the GFL and eight sectoral legislative acts in an attempt to improve openness and communication within EU food law. The Transparency regulation also sets clear objectives for risk communication, of which one is to provide consumers with information on risk prevention strategies (Art. 1) (10). Hence, information to guide consumption behaviour should be provided, which can help them to avoid adverse effects caused by food products (GFL, Art. 8a) (7,10).

Mandatory requirements for food information provision to consumers are further specified in Regulation (EC) No 1169/2011 on food information to consumers (12). In this Regulation, it is, for example, specified that details on the preparation of a specific food product must be provided to the consumer (Art. 9.1.c) (12). When it comes to voluntary information provision about health effects ascribed to food (ingredients) by food business operators, the conditions are described in the nutrition and health claims regulation (NHCR; Regulation EC (No) 1924/2006) (9).

The NHCR is one of many regulations in which risk analysis is an important procedure: the authorisation of health claims, statements that describe the relationship between a food (constituent) and a health benefit (Art. 2.2.5), follows the risk analysis principles (9). Upon request of the Commission, EFSA evaluates the evidence that is collected by food business operators and issues a scientific opinion on this evidence, after which the Commission eventually decides upon the authorisation of the health claim (Art. 17) (9). The evaluation of EFSA is based upon findings from different research projects: Functional Food Science Europe (FUFOSE) (14) and Process for the Assessment of Scientific Support (PASSCLAIM) (15). In these projects, the scientific requirements for showing beneficial effects of food products were studied, taking into consideration the views of key

stakeholders such as leading scientists in the field of nutrition research. The findings of these research projects were translated into the NHCR, *Commission Regulation 353/2008 on implementing rules for the application for authorisation of health claims* and various guidance documents on the development of the scientific dossier issued by EFSA (15–17). Amongst other recommendations, these projects have led to the necessity of conducting studies and measuring the beneficial health outcome in humans, but also the requirement to include the total body of evidence in the scientific dossier (15). The Commission can take other relevant provisions of EU law and other legitimate factors, such as societal aspects, into consideration that may influence the authorisation of the proposed health claim (Art. 17.1) (9). Following authorisation by the Commission, the health claim is added to the Annex of the positive list described in *Commission Regulation 432/2012* (Art. 1.1) (18). Competent authorities in individual EU member states are responsible for the enforcement and sometimes provide additional assistance to interpret legislation, e.g. the translation of claims (9,19).

Even though theoretically, risk analysis can support meeting the objectives of EU food law (6), when applied in practice, problems have emerged which to date have not been solved. The 2019 Commission's review of the effectiveness (REFIT) of EU food law in general showed various points in risk analysis that could be optimised further (20), but problems have also been shown in specific regulatory procedures. One particular regulatory issue concerns the authorisation of health claims used on botanicals and botanical preparations (21).

1.2 The issue with botanical health claims

Botanicals are products derived from plants, algae, fungi and lichens (22). Botanicals can be sold as food, food ingredients, herbal dietary supplements, or as herbal medicinal products (e.g., Ginkgo biloba tablets, garlic oil capsules, ginseng tea, or St. John's wort drops). Marketing of botanicals often appeals to the product's 'naturalness' alluding to potential benefits for health and wellness (23,24). But evil abounds in nature and thus the appeal to nature can obfuscate the safety risks associated with the use of various botanicals as is briefly illustrated below in Box 1.

Approximately 20% of the European population reported to have consumed at least one herbal dietary supplement per year in 2012 (34). The majority of botanical supplement users in both Europe and the United States are highly educated white women (35,36). Consumers use botanicals because of their alleged health benefits (37). For example, the most commonly used herbal dietary supplements

Box 1. Safety considerations for botanicals

The use of botanicals is growing and so is the number of adverse events reports after consuming herbal dietary supplements (25,26). The consumption of certain botanical supplements can create a health risk for specific consumers. One example comprises the case of supplements containing Ginkgo biloba. A Dutch report indicated that toxic levels are not yet determined but consumers occasionally experienced bleeding after ingesting products that contain Ginkgo biloba (27). Another example concerns the possibility of dangerous drug interactions. As described in article 14 of the GFL, when determining whether a dietary supplements is not unsafe, one must consider 'normal conditions of use' (7,28). The average consumer – the consumer who according to EU case law is reasonably well-informed, reasonably observant and circumspect (29) – is assumed to be aware of how to safely use dietary supplements. One aspect of such normal consumption behaviour is knowing not to combine herbal dietary supplements with prescription medicinal products (23,30). For example, St. John's wort, a dietary supplement that may be used against mild depressive feelings (31) can impact drug metabolism via its potently inducing effects on cytochrome P450 3A4 and P-glycoprotein activity (32,33). Such impact on drug metabolism may alter the effects of a prescription drug taken alongside St. John's wort and result in severe adverse effects, even death.

are preparations or extracts of Echinacea (for its suggested positive effect on the immune system), cranberry (for the prevention of urinary tract infections), and garlic (for its beneficial effect on the blood vessels) (30,31).

Botanicals can be used in medicines or foods. In the EU, medicinal products are regulated by Directive 2001/83/EC on medicinal products for human use and the amendment, Directive 2004/24/EC on traditional herbal medicinal products (Art. 16a) (38,39). When used in food products, including dietary supplements, botanicals are regulated by the legislative framework for foods. Upon the entry into force of the NHCR, food business operators could file an application for the authorisation of, amongst others, a botanical health claim based on article 13.1 of the NHCR before January 2008. These claims were to be based on generally accepted scientific evidence (9). The first scientific opinions that were issued by

EFSA on botanical health claims stated that based on the scientific evidence in the underlying scientific dossier, a cause-and-effect relationship could not be established. After the publication of these first scientific opinions, the assessment these botanical claims was put on-hold in 2010 (40).

In 2012, the Commission published a discussion paper in which two options to move forward were presented: (i) resume the evaluation with the existing requirements (including two randomized controlled trials) or (ii) give recognition to evidence based on traditional use data for supporting botanical health claims (40). Subsequently, various formal consultation procedures were issued by the Commission with the most recent one being the Commission's REFIT programme in which the on-hold status of botanicals was part of the review (21). With the REFIT programme, the Commission aims to assess whether the current European legislation is fit for purpose, with the eventual objective of making EU law simpler and more cost-effective (41). As part of this REFIT programme, together with a review of the General Food Law, the NHCR was evaluated with a specific focus on nutrient profiles and claims on plants and their preparations, botanical claims (42). The results of the REFIT evaluation were published in 2020 and revealed amongst other issues, that the objectives of the NHCR and therefore EU food law in general may not be achieved due to current on-hold status of the botanical health claims (21). The protection of consumers from unsafe products and misleading information may therefore not be achieved as consumers may still be exposed to false and/or misleading information.

1.3 Traditional use evidence and risk assessment

Should risk assessment in EU food law consider historical evidence, documentation that is also referred to as 'evidence on traditional use' or 'traditional use evidence' (40)? This question was raised by various stakeholders who compared the assessment of botanical claims to the adjusted registration procedure for herbal medicinal products. In this adjusted registration procedure, laid down in Directive 2004/24/EC, the long history of use of a herbal medicine is recognised as evidence that can support that consumption does not cause adverse effects, but also can support the efficacy of such products (Art. 16) (39). These products are therefore known as traditional herbal medicinal products in the Directive on medicinal products (39). Data on the long history of safe use should show that the product has been used safely in the treatment for a specific disease for already 30 years, of which at least 15 years within the EU (Art. 16c) (39). Even though medicinal products are considered to be a different category of products, 'history

of safe use' is also allowed to support safety in the notification of novel foods, as laid down in Regulation (EU) No 2015/2283 (Art. 14-19) (8). But can traditional use evidence also be used in evaluating support for botanical health claims? If so, what would that imply for risk management and risk communication? And what would that mean for the consumer?

So far, scientific research into health claims on botanicals focused mainly on studying strategies and requirements for the substantiation of health claims with traditional use evidence (40,43,44). These studies highlight what data requirements should be fulfilled when invoking 'traditional use evidence' as support for a health claim on botanicals, together with other important considerations such as the quality of the product, which can influence the safety of these products (40,43,44). These are valuable studies, but the authorisation of botanical health claims involves all three components of the risk analysis cycle, not just risk assessment. Even when traditional use evidence can be adopted as criterium in a new risk assessment procedure, that does not automatically indicate its feasibility in the overall risk analysis cycle. Any change in the risk assessment procedure likely warrants new ways of risk communication. Effective risk communication is already challenging as it is. Studies examining consumer perception of benefit or risk information of food products show that consumer understanding of benefit information in the form of health claims is generally low. Consumers believe that products bearing claims offer health benefits beyond those claimed on the product (45,46). Further, risk perception studies show that – for example – reporting familiar and well-known risks has little influence on a consumer's behaviour (21,22). A new risk assessment procedure would also warrant a careful evaluation of whether it still allows risk managers to evaluate a health claim in concordance with the GFL. Therefore, in the current thesis, the central question is whether traditional use evidence should be considered in the risk analysis of botanical health claims.

1.4 Aim and overview of studies

Since 2010, the authorisation of botanical health claims is on hold in the EU, pending a decision on whether traditional use evidence should be taken into consideration when assessing these claims. Clearly, there is a pressing need for the EU to take a stand on this issue as the enduring stalemate impedes effective consumer protection. In light of this issue, the aim of the current thesis is to answer the following question: *Is there a potential role for traditional use*

evidence in the risk analysis of botanicals? To answer this question, the present thesis comprises a set of studies described in detail in the subsequent chapters.

'Traditional use evidence' is a fuzzy term as it is neither a legal nor a scientific concept. Before one can evaluate its potential role in risk analysis, it should be clear what exactly 'traditional use evidence' means. **Chapter 2** describes a study in which legislative acts, institutional guidance documents, and scientific research into substantiation criteria were analysed to more narrowly and clearly define the concept of traditional use evidence.

Risk communication is an important component of risk analysis. One risk communication objective defined in the GFL is that information must be provided to consumers concerning risk prevention behaviours. Information provision can serve as a tool to protect consumers from being misled, allowing consumers to freely choose. It is essential to know how product information is used by consumers when determining whether and how to consume a product such as a botanical. This allows for estimating the impact of the substantiation of botanical health claims with traditional use evidence on consumer behaviour. **Chapter 3** describes exploratory research into whether provided benefit and/or risk information influences the intention to use a botanical dietary supplement. A case study presented in **chapter 4** aims to provide insights into how risk and benefit related information is provided to consumers at point-of-purchase of a botanical dietary supplement.

Chapters 5 through 8 address the ongoing debate on 'traditional use evidence' for botanical health claims in more detail. In c**hapter 5** the debate is scrutinized by identifying the involved stakeholders and the arguments they put forward. This critical analysis makes use of information that became available from the consultation procedures of the Commission and is focussed on issues related to risk management, risk assessment and risk communication. **Chapter 6** provides a critical reflection on existing regulation of botanicals, including the substantiation requirements for health benefits and safety of food and medicinal products across various international jurisdictions. In **chapter 7,** the evaluation of the Article 13.1 health claims on antioxidants is studied by analysing scientific opinions and several scientific dossiers submitted by food business operators. In **chapter 8**, allowing traditional use evidence to substantiate botanical health claims is critically reviewed in light of the current legal framework. Integrating insights from nutritional sciences, pharmaceutical sciences, regulatory analyses, consumer use and food information, this critical review brings into focus the relevant arguments for and against using traditional use evidence and discusses

circumstances in which traditional use evidence can and cannot play a role in the assessment of botanical health claims.

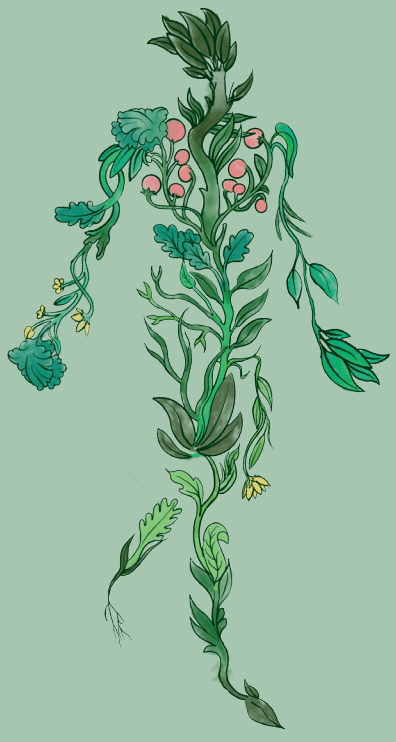
Finally, in **chapter 9**, the main results from all studies in this thesis are briefly summarized and its findings are discussed considering the question whether there is a potential role for traditional use evidence in the risk analysis of botanical health claims.

1.5 References

1. Cleeland B. The bovine spongiform encephalopathy (BSE) epidemic in the United Kingdom. Int Risk Gov Counc. 2009;1–11.
2. Will PG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Smith PG, Poser S, Pocchiari M, Hofman A. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet. 1996;347:921–5.
3. European Commission. Commission decision of 27 March 1996 on emergency measures to protect against bovine spongiform encephalopathy. Off J Eur Communities. 1996;78:47–8.
4. Oosterveer P. Reinventing risk politics: reflexive modernity and the European BSE crisis. J Environ Policy Plan. 2002;4(3):215–29.
5. Watson N, Brandel J-P, Green A, Hermann P, Ladogana A, Lindsay T, Mackenzie J, Pocchiari M, Smith C, Zerr I, Pal S. The importance of ongoing international surveillance for Creutzfeldt-Jakob disease. Nat Rev Neurol. 2021;17(6):362–79.
6. Vos E. EU food safety regulation in the aftermath of the BSE crisis. J Consum Policy. 2000;23(3);227-255.
7. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Off J Eur Union. 2002;31:1–44; 1-7-2022.
8. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel food, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Off J Eur Union. 2015;327:1–22; 27-03-2021.
9. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
10. The European Parliament and the Council of the European Union. Consolidated version of regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC. Off J Eur Union. 2019;L231:1–28; 6-9-2019.
11. The European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 852/2004 of the European Parliament and the Council of 29 April 2004 on the hygiene of foodstuffs. Off J Eur Union. 2004;139:1–54; 24-03-2021.
12. European Parliament and the Council of the European Union. Consolidated version of regulation ((EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Off J Eur Union. 2011;304:1–60; 01-01-2018.

13. Huizing Edinger W. Food, safety and the behavioural factor of risk. Eur J Risk Regul. 2014;5(4):491–504.
14. Binns N, Howlett J. Functional foods in Europe: international developments in science and health claims. Eur J Nutr. 2007;48(1):3–13.
15. Aggett P, Antoine J, Asp N, Bellisle F, Contor L, Cummings J, Howlett J. PASSCLAIM, process for the assessment of scientific support for claims on foods. Eur J Nutr. 2005;44:i1–2.
16. European Commission. Consolidated version of commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. Off J Eur Union. 2008;109:11–6; 21-12-2009.
17. Diplock A, Aggett PJ, Ashwell M, Bornet F, Fern EB, Roberfroid MBl. Scientific concepts in functional foods in Europe: consensus document. Br J Nutr. 1999;81:S1–27.
18. European Commission. Consolidated version of commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. Off J Eur Union L. 2012; 17-05-2021.
19. de Boer A, Urlings M, Vos E, Bast A. Enforcement of the Nutrition and Health Claim Regulation. Eur Food Feed Law Rev. 2015;10;334.
20. European Commission. Commission Staff Working Document: the Refit Evaluation of the General Food Law (Regulation (EC) No 178/2002)(SWD(2018) 37 Final). 2019.
21. European Commission. Commission staff working document - evaluation of the Regulation (EC) No 1924/2006 on nutrition and health claims made on foods with regard to nutrient profiles and health claims made on plants and their preparations and of the general regulatory framework for their use in foods. Brussels;SWD(2020) 95 final; 2020.
22. EFSA. Botanicals [Internet]. 2018 [cited 2018 Apr 3]. Available from: https://www.efsa.europa.eu/en/topics/topic/botanicals
23. Lynch N, Berry D. Differences in perceived risks and benefits of herbal, over-the-counter conventional, and prescribed conventional, medicines, and the implications of this for the safe and effective use of herbal products. Complement Ther Med. 2007;15:84–91.
24. Samojlik I, Mijatovic V, Gavaric N, Krstin S, Bozin B. Consumers' attitude towards the use and safety of herbal medicines and herbal dietary supplements in Serbia. Int J Clin Pharmacol. 2013;35:835–40.
25. Bijwerkingcentrum Lareb. Overview of reports on St. John's wort (Hypericum perforatum). 2018.
26. Netherlands Pharmcovigilance Centre Lareb. Valeriaan [Internet]. 2019. Available from: https://www.lareb.nl/nl/databank/Result?formGroup=&atc=N05CM09&drug=VALERIAAN
27. Pelgrom SMGJ, Fransen HP, Rompelberg CJM, de Rooij EK, Pronk MEJ, Baars AJ, de Kaste H, Verhagen H. Gezondheidsclaims voor kruidenpreparaten op basis van Ginkgo biloba. Rijksinst voor Volksgezond en Milieu. 2007;320106001:1–93.
28. Purnhagen K. More Reality in the CJEU's Interpretation of the Average Consumer Benchmark–Also More Behavioural Science in Unfair Commercial Practices? Eur J Risk Regul. 2017;8(2):437–40.
29. Huizing Edinger W. Promoting educated consumer choice. Has EU food information legislation finally matured? J Consum Policy. 2016;39(1):9–22.
30. Egan B, Bruno F, Badea M, Peacock M, Laccisaglia M, Dima L, Raats MM. Consumers' understanding of plant food supplements: benefits, risks and sources of influence. In: Food supple-

ments containing botanicals: benefits, side effects and regulatory aspects. Springer, Cham; 2018. p. 437–58.
31. Müller WE. Current St. John's wort research from mode of action to clinical efficacy. Pharmacol Res. 2003;47:101–9.
32. Mannel M. Drug interactions with St John's Wort. Mechanisms and clinical implications. Drug Saf. 2004;27(11):773–97.
33. Markowitz JS, Donovan JL, DeVane CL, Taylor RM, Ruan Y, Wang J-S, Chavin KD. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. J Am Med Assoc. 2003;290(11):1500–4.
34. Garcia-Alvarez A, Egan B, Klein de S, Dima L, Maggi F, Isoniemi M, Ribas-Barba L, Raats MM, Meissner EM, Badea M, Bruno F, Salmenhaara M, Milà-Villarroel R, Knaze V, Hodgkins C, Marculescu A, Uusitalo L, Restani P, Serra-Majem L. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One. 2014;9(3):1–18.
35. Block G, Jensen CD, Norkus EP, Dalvi TB, Wong LG, McManus JF, Hudes ML. Usage patterns, health, and nutritional status of long-term multiple dietary supplement users: a cross-sectional study. Nutr J. 2007;6(30):1–11.
36. de Jong N, Ocké MC, Branderhorst HAC, Friele R. Demographic and lifestyle characteristics of functional food consumers and dietary supplement users. Br J Nutr. 2003;89(2):273–81.
37. Jeurissen SMF, Buurma-Rethands EJM, Beukers MH, Jansen-Vliet van der M, Rossum van CTM, Sprong RC. Consumption of plant food supplements in the Netherlands. Food Funct. 2018;9:179–90.
38. European Parliament and the Council of the European Union. Consolidated version of directive 2001/83/EC of the European Parliament on of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J Eur Union. 2001;311:1–188; 01-01-2022.
39. European Parliament and the Council of the European Union. Consolidated version of directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;136:85–90; 30-04-2004.
40. Anton R, Serafini M, Delmulle L. The substantiation of claims for botanical food supplements in relation to traditional use. Eur Food Feed Law Rev. 2013;8(5):321–8.
41. European Commission. REFIT - making EU law simpler and less costly [Internet]. 2019. Available from: https://ec.europa.eu/info/law/law-making-process/evaluating-and-improving-existing-laws/refit-making-eu-law-simpler-and-less-costly_en#main-achievements
42. European Commission. REFIT- Evaluation of the Regulation on nutrition and health claims [Internet]. 2019. Available from: https://ec.europa.eu/food/safety/labelling_nutrition/claims/refit_en
43. Geurts S. Health claims and botanicals: how to proceed with European harmonisation. Eur Food Feed Law Rev. 2018;13(1):29–33.
44. Anton R, Serafini M, Delmulle L. Traditional botanical preparations and health benefits: the key concept of history of use. Eur Food Feed Law Rev. 2014;6:391–8.
45. Grunert KG, Scholderer J, Rogeaux M. Determinants of consumer understanding of health claims. Appetite. 2011;56:269–77.
46. Orquin JL, Scholderer J. Consumer judgements of explicit and implied health claims on foods: misguided by not misled. Food Policy. 2015;51:144–57.
47. Fischer ARH, Frewer LJ. Consumer familiarity with foods and the perception of risks and benefits. Food Qual Prefer. 2009;20(8):576–85.



Chapter 2

Data supporting ‘traditional use’ for safety and health effects: information in risk assessment of food and medicinal products

2.1 Introduction

Risk assessment is an important part of the risk analysis, a procedure to assess risk and benefits of products. In the European Union (EU) risk analyses are conducted before the authorisation of both food and pharmaceutical products. In the EU, risk assessments of foods are conducted by the European Food Safety Authority (EFSA) (GFL, Art. 22), whereas the European Medicines Agency (EMA) is involved in risk assessments for medicinal products (1,2). The main aim of risk assessment is to establish the potential risks or adverse effects of products, or to establish the beneficial effects of such products. The assessment is based on scientific studies that support these effects (GFL, Art. 6.2) (2,3). The outcomes of the risk assessment should be used by the risk manager in, amongst others, the decision making upon authorisation of market entry of products, or authorisation of health claims (1,2).

When discussing the substantiation requirements of safety and efficacy of foods and pharmaceutical products, reference is often made to 'evidence on traditional use' or 'traditional use evidence'. Traditional use evidence is believed to show, in general, a history of use of a product for a specific purpose which serves as an indication for the product's lack of adverse effects and the efficacy (4,5). The long history of use is often expressed in generations, either one or two, and a generation is considered to be 25 to 30 years (6).

In the EU, traditional use evidence can be used as support for traditional herbal medicinal products, showing that a product is not unsafe and for establishing the product's efficacy in the treatment of a disease. This is dealt with in the traditional herbal medicinal product Directive, Directive 2004/24/EC which amends the medicinal products Directive, Directive 2001/83/EC (Art. 16a) (1,5). For food products, traditional use evidence can be used in a simplified registration procedure, currently in place for products with a known history of use in a third country (Art. 14-19) (7). For both application procedures, the risk assessor provides guidance on the data that is required for a successful application (8,9). In these guidance documents, it is also indicated which sources can be used to show a product has been used traditionally (8,9).

In this short, in-depth review, the definition of 'traditional use evidence' in the registration procedures for traditional herbal medicinal products and traditional foods from a third country will be clarified, and the required data for substantiation based on the traditional use of a product will be discussed. These requirements are described in EU legislation and the associated guidance documents

issued by the risk assessor. In addition, a review of the literature is conducted to identify the current suggestions made for utilising traditional use evidence for the substantiation of botanical health claims.

2.2 Traditional use evidence for herbal medicinal products

For traditional herbal medicinal products, a simplified procedure is instated in the EU (Art. 16) (1,5). An application for authorisation of a medicinal product must include the results of pharmaceutical tests, pre-clinical tests and clinical trials (Art. 8.3) (1). Together with other relevant data, these studies must show potential risks of a product and show the efficacy of the product in the treatment of disease (1). Based on a risk-benefit analysis of the product, in Directive 2001/83/EC referred to as 'risk-benefit balance', a product can obtain marketing authorisation if the benefits significantly outweigh the risks of a product. A simplified registration procedure is currently in place for herbal medicinal products for which it can be showed that the product is used for over 30 years of which 15 years within the EU (Art. 16c) (1,5). The long history of use is then considered to be an indication of the safety and efficacy of a product and replaces the pharmaceutical tests, pre-clinical tests and clinical trials (Art. 16c) (1). The efficacy must however be plausible on the basis of the long history of use, and authorities are allowed to ask for additional information on the safety of the product (Art. 16e) (1,10). Further requirements are that the products must be suitable for use without medical supervision and the mode of administration must be orally, externally or via inhalation (Art. 16a) (1,10). The strength and posology must furthermore be specified (Art. 16a) (1).

Directive 2001/83/EC describes the necessary information required in the application procedure of medicinal product in the EU (1). An application for the authorisation of traditional herbal medicinal products must contain similar information as compared to other medicinal products when it comes to, for example, description of applicant and product, description of use of the product and potential adverse effects, and information on product storage conditions (Art. 8) (1). Additionally, the results of the physico-chemical, biological and microbiological tests must be provided in the application to provide details on quality assurance (Art. 8) (1). The composition of herbal medicinal products is considered to be complicated, and the test results of the aforementioned analyses can standardise the product which is necessary to maintain the quality of the herbal medicinal product (9). The application must furthermore provide details on the manufacturing process including the effect of temperature and the potential of

resolvents that remain in the product (9). Next to the mandatory shelf-life and storage information, additional information must be provided on the profile and the stability of the herbal medicinal product (9). When the traditional herbal medicinal product was used in safety and/or efficacy tests, it must be determined from which batch the products under assessment were.

The efficacy in the treatment or prevention of diseases, as well as the lack of adverse effects, of traditional herbal medicinal products is based on a long history of safe use: the use of a product for 30 years, of which 15 years within the EU, for a specific purpose (Art. 16c) (5,10). In Directive 2004/24/EC, it is indicated that the application for authorisation of a traditional herbal medicinal products must contain bibliographical and expert evidence that shows the product's efficacy and proves the product is not unsafe (Art. 16c) (5). In their guidance documents, EMA provides insights into which documents and sources can be used to substantiate the safety and efficacy of traditional herbal medicinal products (table 1) (10).

Table 1. sources to establish traditional use for traditional herbal medicinal products (10)

Excerpt from archives of national competent authorities	Documentation that shows that a product has been authorized for medical use. This can be under different legislation and under different names including, but not limited to, herbal medicinal product, natural remedy, traditional herbal drug.
Comprehensive literature search	Literature review of publications in medical and toxicological databases. The main focus of the publications must be safety.
Handbooks of medicine, phytotherapy, herbal medicine etc.	The handbooks can provide information on the therapeutic indication, strength of the product, the posology and details on the safe use of a product.
Official expert committee reports	The committee reports can be published by different parties including, but not limited to, the World Health Organization, the European Commission or national compendia. These committee reports can provide information on the therapeutic indication, strength of the product, posology and details on the safe use of a product.
Monograph of a pharmacopoeia	This includes both the European pharmacopoeia as well as official national pharmacopoeias. These monographs show medicinal use during the years the monograph has been valid as well as information on the strength and type of extract of a product.
Product related documentation	This information can come from, but not limited to, sales reports, product leaflets and post marketing studies.

From the submitted documentation, it must become evident how long a product has been used as medicinal product and for which purpose, the dose or strength of the product as well as the route of administration (10). The applicant must furthermore provide evidence that the product is not unsafe as well as provide a clear indication of how the product can be used safely (10). Another important aspect mentioned in the guidance document by EMA, is the condition that a product may not prevent individuals from going to a medical professional if this can lead to a physical condition to worsen and result in a risk for that individual (10).

The different guidance documents on the application for authorisation of a traditional herbal medicinal product clearly stipulate which sources can be used in the application. It is furthermore emphasised which analyses and sources can prove that a product is not safe, and is efficient in the treatment, prevention, or cure of a disease.

2.3 Evidence for proving the safety of traditional foods from a third country

In the EU, the regulation of food products and medicinal products is strictly separated. Whereas medicinal products will only be authorised following a risk-benefit analysis that shows the benefits of a product outweigh the risks (1), for food products the authorisation for market entry is merely based on their safety (Art. 7) (7). The communication of the potential health benefits of a product is voluntary and is not a condition for market authorisation.

Proving the safety of new food products with traditional use is possible under EU legislation. The Novel Food Regulation, Regulation (EU) No 2015/2283, allows for a simplified registration of foods that are traditionally used in countries outside of the EU (Art. 14-19) (7). The application procedure should be accompanied with details on the production process, the compositional data including information on the stability (Art. 14) (7,8). Additionally, data must be provided on the experience of continued use (Art. 14) (7,8). The sources include, but are not limited to, scientific publications, monographs, documentation on cultivation, sale and trade, cookbooks and anecdotal data (8). Altogether, these sources must show that the product can be used safely within the EU. In order to determine the safety, the evidence must provide information on various aspects. It must become evident to what extent the product is used in the third country, including the quantity and duration of use, which groups use the product and what the

role of the product is in the diet, any details on preparations methods of the product and the restriction of use (8). In addition, human data must be show the product's kinetics, toxicology, nutritional, microbiology, allergenicity, tolerability, and potential interaction with (prescription) medicines. (8)

Besides the data from the third country, the information on the conditions of use must also be known for consumption in the EU (Art. 14) (7,8). Hence, if the consumption pattern differ between the third country and the EU, exposure to the different compounds in the product will also differ which may potentially lead to risk.

2.4 Traditional use evidence as support for botanical health claims

In the Nutrition and Health Claims Regulation, Regulation (EC) No 1924/2006, traditional use evidence is not specified as being sufficient substantiation for health claims (11). Health claims must be substantiated with human intervention trials (Art. 5) (12,13). The difference in the recognition of different types of evidence as substantiation in food and medicinal law has been the subject of an ongoing debate (14,15). This debate mainly addresses whether traditional use evidence must be considered as sufficient support for health claims on botanicals. There is, to date, no decision made on using traditional use evidence as substantiation. That consequently means it is not determined what the data requirements are on which the risk assessor will base its risk assessment. There is, however, research conducted into potential data requirements for traditional use evidence as substantiation for health claims (6,16,17). These studies mainly determine what should be known about a specific product, such as the preparation methods and the conditions of use (6), and refer to some sources based on the risk assessment procedures of medicinal products based on traditional use in the EU (18). Additionally, the option of a weighted evidence approach suggested in which the level of evidence will determine the strength of the wording of a claim (16). In the following sections, the proposed criteria for health claim substantiation with traditional use evidence will be discussed.

2.4.1 Weighted evidence

It has previously been suggested in scientific literature as well as by the European industry association on health products, the European Federation of Associations of Health Product Manufacturers (EHPM), that the evidence provided in the scientific dosser should be weighted, and graded based on the methodology

of the evidence (4,16,19). In general, three levels of evidence are defined: the highest level with blinded randomised controlled trials that scientifically establish a cause-and-effect relationship between a food product and health effect, the medium level or tier containing epidemiological and observational studies as well as non-randomised intervention trials which shows that the relationship between a food product and health benefits has scientific support, and a third layer for evidence on traditional use (16,19). The wording of the claim would then be adjusted in accordance with the evidence in the scientific dossier. For the first level, conclusive wording is allowed: 'product x contributes to y' or 'product x maintains y' in which 'y' is the beneficial physiological effect (16,19). For the second level, the wording will be less conclusive: 'product x can contribute to y' or 'product x may maintain y' (16,19). For the third tier, reference is made to the traditional use origin of the provided evidence: 'product x is traditionally used to contribute to y' or 'product x is traditionally used for the maintenance of y' (16,19).

The assessment of the evidence would require a thorough review of both the methodology and the results of a study, as well as the conclusions that can be drawn from this information (16).

2.4.2 Preparation methods of the botanical product

In addition to establishing a cause-and-effect relationship by traditional use evidence, it is suggested in the literature that the preparation or manufacturing method of the botanical product should be documented and assessed (4,6,14,18,20). The preparation method should be in line with the gathered information on the botanical product in both the part of the botanical that is used to make the product and the way the botanical product is manufactured (4,6,14,18,20).

Different parts of plants can be used to make a botanical product such as roots, leaves or flowers (21). For some product, the part of the plant used can determine the amount of the bioactive substance in the eventual product (14,18,21). When the source of information specifies which part of the plant must be used to make the botanical product according to its tradition, this should not be changed when manufacturing the products that are consumed in today's society.

The preparation method refers to how the specific botanical or part of the botanical are handled. Examples of preparation methods are fresh, dried, infusions or extractions (14,18). This preparation method will partially determine how much of the bioactive substance is in the product and changing the method may lead

to different concentrations of the different bioactive substances in the product (14). It is important to note that the concentrations may differ for the beneficial substance, but also for potential toxic substances (21). Hence, details on the preparation methods are also important for the safety of a botanical product.

When a food business operator changes the preparation method, additional analysis, such as a chemical analysis, must be conducted to determine that the composition of a product did not significantly change(14). These analyses are also necessary for combination products that were not traditionally used together (14,18). With the analyses, it must be determined that the combination of product and substances within the product, do not lead to strong beneficial and toxic effects, as this would potentially require a different categorisation of the product (to a herbal medicinal product) or to adverse effects.

2.4.3 Conditions of use

Similar to the application to the traditional food from a third country are the conditions of use specifically mentioned in the literature on substantiating botanical health claims with evidence on traditional use (4,6,14,18,20). It is described in the literature that the traditional consumption patterns of the botanical must be compared to consumption patterns of the botanical product in today's society (14,18,20). Details on the desired consumption pattern should be known, including the amount of the product that is ingested daily and the duration of intake.

The Food Supplements Directive, Directive 2002/46/EC, already establishes that the consumption pattern and the amount of bioactive substance ingested in a daily dose must be on the package (Art. 6) (22). In addition, the authorisation of a health claim is accompanied by setting the conditions of use (NHCR, Art. 17.2) (Art. 1.2) (11,23). These conditions of use are often referring to the amount of bioactive substance that must be in one portion of the product, which can exemplified by the authorised health claim on the antioxidant effects of olive oil polyphenols (23). In order to use that claim, there must be 5 mg of hydroxytyrosol in 20 g of the product and there must be a statement that the beneficial effect will only be obtained when one consumes at least those 20 g. The literature suggests that setting these conditions of use in order to ensure a sufficient amount of the bioactive substance is consumed, should also be done for botanical products with a health claim substantiated with evidence on traditional use.

2.4.4 Sources of traditional use data

There is limited scientific research available in which the actual sources that could constitute the efficacy of a botanical product for a health benefit based

on traditional use are discussed. When reference is made to specific sources, this is often made to the procedures and suggested sources used for showing traditional use of medicinal products (18). Table 2 lists the different sources that were mentioned in the literature (15,18,24).

Table 2. Suggested traditional use sources for the support health claims (18,24)

Documentation showing history of use	The information should cover the use of the product in at least one generation. Sources can be, but are not limited to, old books on the product.
Document use in different regions	The documented use must be under similar conditions of use. The strength of the evidence increases when information is available for multiple different regions.
Documented information on the botanical preparation	Information must be provided on the type of plant and the part of the plant used to make the botanical product. Additional information on the chemical composition of the product is required.
Evidence from experience gathered from unrecorded observations	
Monographs	The monographs can be composed by different authorities, including but not limited to, the European Medicines Agency Herbal Medicinal Product Committee, leading experts in the field and the European Scientific Cooperative on Phytotherapy.
Scientific data	Information can be related to chemistry, pharmacology, toxicology, clinical studies and other experimental data.

2.5 Conclusion

Traditional use evidence is not a concept that is defined in EU food law, even though it is often referred to in scientific research when discussing the on-hold status of botanical health claims. In general, traditional use evidence can be defined as textual sources showing that a product has been used without safety concerns for a specific purpose over one or two generations. More detailed criteria on the type of source and the content that needs to be described in such sources differ among product categories. Previous research provides suggestions that could be considered when health claims were to be substantiated with traditional use evidence. This includes i.a. the standardisation of manufacturing practices and defining the conditions of use for a product. These suggestions

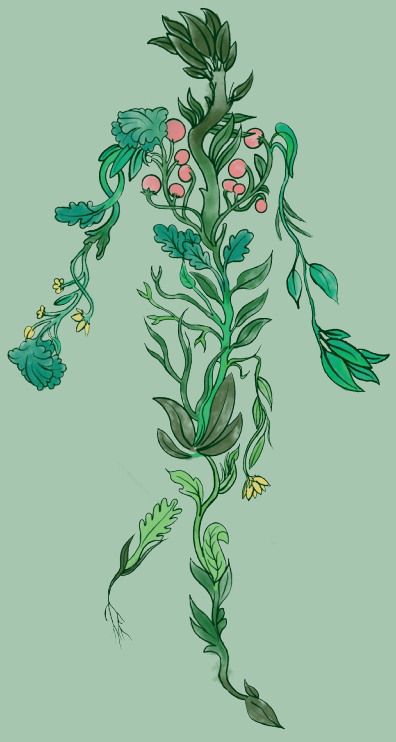
stem from substantiation requirements that exist for other authorisation procedures (e.g., novel foods) or other product categories (e.g., medicinal products).

Traditional use evidence can be used as a source of information in the risk analysis procedures of various European regulations. Its use in the risk assessment of health benefits for the authorisation of health claims requires two things: firstly, it must be determined that consumers are not being misled by health claims substantiated with traditional use evidence and secondly, the final assessment criteria must be clear and defined in such a way that the objectives of the NHCR can be met.

2.6 References

1. European Parliament and the Council of the European Union. Consolidated version of directive 2001/83/EC of the European Parliament on of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J Eur Union. 2001;311:1–188; 01-01-2022
2. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Off J Eur Union. 2002;31:1–44; 1-7-2022.
3. Zio E. The future of risk assessment. Reliab Eng Syst Saf. 2018;177:176–90.
4. van den Berg S, Serra-Maje L, Coppens P, Rietjens IMCM. Safety assessment of plant food supplements (PFS). Food Funct. 2011;2(12):760–8.
5. European Parliament and the Council of the European Union. Consolidated version of directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;136:85–90; 30-04-2004.
6. Geurts S. Health claims and botanicals: how to proceed with European harmonisation. Eur Food Feed Law Rev. 2018;13(1):29–33.
7. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel food, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Off J Eur Union. 2015;327:1–22; 27-03-2021.
8. EFSA NDA Panel. Guidance on the preparation and submission of the notification and application for authorisation of traditional foods from third countries in the context of Regulation (EU) 2015/2283 (Revision 1). EFSA J. 2021;19(3):6557–78.
9. European Medicines Agency. Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products. 2011.
10. Committee on Herbal Medicinal Products. Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products - Final. 2017. Report No.: EMA/HMPC/104613/2005 – Rev. 1.
11. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
12. European Commission. Consolidated version of commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. Off J Eur Union. 2008;109:11–6; 21-12-2009.
13. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of a health claim application (revision 2). EFSA J. 2017;15(1):4680.
14. Anton R, Serafini M, Delmulle L. Traditional botanical preparations and health benefits: the key concept of history of use. Eur Food Feed Law Rev. 2014;6:391–8.

15. Schwitters B. Want to harmonize botanicals: take the broader perspectives of traditional health claims and other substances. Eur Food Feed Law Rev. 2012;7:328–40.
16. Chevallier H, Herpin F, Kergosien H, Ventura G, Allaert F-A. A graded approach for evaluating health claims about plant-based food supplements: application of a case study methodology. Nutrients. 2021;13(8):2684.
17. Hoogenraad E, Duivenvoorde B. Health claims for botanicals: "on hold", yet forbidden? Eur Food Feed Law Rev. 2016;1:58–9.
18. Anton R, Serafini M, Delmulle L. Traditional knowledge for the assessment of health effect for botanicals - a framework for data collection. Eur Food Feed Law Rev. 2012;74–80.
19. European Federation of Associations of Health Product Manufacturers. Botanical health claims on foods and food supplements in the EU - EHPM proposal. 2021.
20. Anton R, Serafini M, Delmulle L. The substantiation of claims for botanical food supplements in relation to traditional use. Eur Food Feed Law Rev. 2013;8(5):321–8.
21. Schilter B, Andersson C, Anton R, Constable A, Kleiner J, O'Brien J, et al. Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements. Food Chem Toxicol. 2003;41(12):1625–49.
22. European Parliament and the Council of the European Union. Consolidated version of directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Off J Eur Union. 2002;183:1–14; 30-03-2012.
23. European Commission. Consolidated version of commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. Off J Eur Union L. 2012; 17-05-2021.
24. Coppens P, Delmulle L, Gulati O, Richardson D, Ruthsatz M, Sievers H, et al. Use of botanicals in food supplements - Regulatory scope, scientific risk assessment and claim substantiation. Ann Nutr Metab. 2006;50(6):538–54.



Chapter 3

Assessing the influence of information on dietary supplement use: an online questionnaire study

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Abstract

Since it is observed that the consumption of herbal dietary supplements is increasing, we aimed to research whether front-of-pack risk and benefit information influences a consumer's intention to use (ITU) a dietary supplement.

A total of 268 subjects participated in an online questionnaire, in which they were exposed to one of four different labels with risk and/or benefit information about the product, and were provided with additional risk-benefit information. Their ITU was measured at three time points: after exposure to the label, after reading the additional information and after a wash-out period.

The results from our study showed that information on the label did not significantly impact the ITU. In all groups, ITU significantly increased after exposure to detailed information, and again after the wash-out period.

We therefore conclude that front-of-pack information did not influence a consumer's intention to use dietary supplements, but additional information may have influenced their intentions.

3.1 Introduction

An increasing number of people in Europe consume dietary supplements, leading to rising demand for such products in the past 10 years (1–3). Dietary supplements are often consumed because of the health benefits that these products are believed to provide (4) and are products in dosed form used to supplement the diet (Art. 2.a) (5). Supplements can contain botanicals which are, in the EU (European Union), defined as substances derived from plants, algae, fungi and lichens (6). When a dietary supplement contains a botanical, it is often referred to as a herbal dietary supplement (in this study abbreviated as HDS). A 2014 survey on herbal dietary supplement consumption found that, among six European countries, on average 18.8% of consumers report taking HDS in the past year (4). In the Netherlands, 11% of men aged 19-50 years, and 18% of women aged 19-50 report to use plant food supplements (7).

Dietary supplements available on the EU market should be compliant with EU legislation for foods. EU legislation requires foods to be safe (Art. 14), as described in the framework regulation for foods, the General Food Law, Regulation (EC) No 178/2002 (8). Voluntary communication of health benefits on food products in Europe is regulated by Regulation (EC) No 1924/2006 on nutrition and health claims (NHCR) (Art. 1.2) (9). This Regulation requires health claims to be supported by scientific evidence (Art. 6.1) (9), which in practice includes at least two independent human intervention trials (10).

At the same time however, various dietary supplements are known to pose risks upon consumption, by i.e. interacting with medicinal products (11,12). Well-known examples of such interactions are the adverse effects caused by the interaction of St. John's wort with specific prescription medicinal products such as contraceptives or anti-depressants (13,14). Reported adverse effects are in such cases the result of specific consumption behaviour, e.g. combining the consumption of dietary supplements with specific (prescription) medication (15). Following EU food law, it is the responsibility of a food producer to place only safe products on the market, and when necessary, inform a consumer about its conditions of safe use (Art. 4.1.b) (16). Even though the label can highlight potential benefits of the product through health claims (Art. 1.2) (9), there is, besides the declaration of allergens (Art. 9.1.c) (16), no legal obligation to provide insights into potential risks of (combined) intake of HDSs (Art. 6) (5). This exploratory study aims to investigate whether front-of-pack risk and benefit information influences the intention to use (ITU) HDSs of consumers, as intention is the main predictor for behaviour according to the reasoned action approach (17). In this study, the ITU

of four groups are compared: a group that is provided with a label displaying (1) only the benefit of the product, (2) only the risk of the product, (3) both the risk and the benefit of the product and finally, (4) with no risk and benefit information, the control group.

3.1.1 Background and hypothesis

Empowering consumers by means of providing information to enable well-informed decision making about the products they consume, is one of the aims of the EU's food policy and legislation, as put forward in the Commission's Farm to Fork Strategy (18). To determine strategies to provide the information, further understanding of the effectiveness of different information channels is required.

The label can serve as an information source, as all consumers are confronted with the label and are consequently exposed to similar information (19). This information currently consists of the mandatory particulars described in Regulation (EU) No 1169/2011, e.g., including an ingredient list and nutritional information, and voluntary information such as a health claim. Risk statements – of which some are required for food supplements – are currently not displayed front-of-pack. It has been established that the intention to use a dietary supplement is influenced by knowledge on the risks and benefits of a dietary supplement (21,22). It however remains to be determined whether communicating these risks and benefits on the front-of-pack of an HDS influences a consumer's intention to use such supplements. Previous research is inconclusive on whether benefit information (health claims) and risk information (warnings or disclaimers) on labels are noticed or understood by consumers (22,23), and whether it is subsequently processed (24). Other research has determined that processing of information is influenced by many different factors, including gender, ethnicity, age and geographical region (25), perceived source credibility (26) and previous knowledge about the provided information (27). Consumers are furthermore unaware of underlying rules and regulations for food label information (28) and health claims (29) which may influence the perceived source credibility. The first hypothesis (H1) tested in this study therefore is that front-of-pack benefit information leads to a higher ITU compared to control (H1a); whereas presenting front-of-pack risk information leads to a low ITU compared to control (H1b). Showing both front-of-pack risk and benefit information is expected to result in a ITU similar to the control label (H1c), as study participants may determine their ITU on personal experience resulting in a confirmatory bias (30).

As knowledge on risks and benefits of a product are known to influence the intention to use (20,21), we also study the influence of a more extensive description

of the risks and benefits of the product on the ITU. Based on previous research into guarana (the supplement studied), summaries of risks and benefits of the product were created. We hypothesise (H2) that this more detailed information given in addition to the front-of-pack information, will nullify the effect of the one-sided front-of-pack information (31).

We thirdly aimed to determine whether front-of-pack information provided influences the time that participants have spent on reading the different types of (risk and benefit) information. Confirmatory bias was expected to result in participants looking for the information in line with the front-of-pack information they were exposed to (30). It was hypothesised (H3) that participants who were exposed to front-of-pack risk information would spend more time on the extensive description of the risk information (H3a), whereas the participants exposed to front-of-pack benefit information would spend more time on the benefit information (H3b). Participants exposed to front-of-pack risk-benefit information or the control label were expected to spend an equal amount of time on the risk and the benefit information (H3c).

Finally, we aimed to determine the influence of time following single exposure to information. Previous research found that one time exposure does not lead to long-term changes in knowledge (32,33). We therefore hypothesise (H4) that consumers recall the information which they already had prior to participating in the study, and therefore that ITU after one month would not significantly differ from ITU on t0.

3.2 Methods

To analyse whether front-of-pack information provision influences the ITU a dietary supplement, an online questionnaire study was conducted (Qualtrics). In this questionnaire, participants were exposed to a label with specific front-of-pack information, that differed between four groups (one control group and three intervention groups). Between the four groups, the information varied from mentioning merely a health benefit (group 1), merely a risk (group 2), both the benefit and the risk (group 3), or providing no information on benefits or risks (control group).

3.2.1 Study sample

Data was collected between December 2018 and December 2019. Respondents were aged 18 to 65 and could only participate when they were fluent in Dutch and

had access to a computer or laptop with internet and a mouse, as for part of the questionnaire, a mouse tracking software was used (MouselabWEB v1.00beta), which required the use of a cursor on the screen.

An *a priori* power calculation was conducted with G*power (34). As no previous studies on this subject with a similar research design were conducted, the effect size was presumed to be small and set at 0.2 with a $p<0.05$ and 0.8 power. In determining the sample size, an important consideration was that ITU was measured at three timepoints (t0, t1 and t2), participants were divided in four experimental conditions (four groups), and two additional variables (health regulatory focus and risk perception) were measured. This resulted in a sample size of 280 participants.

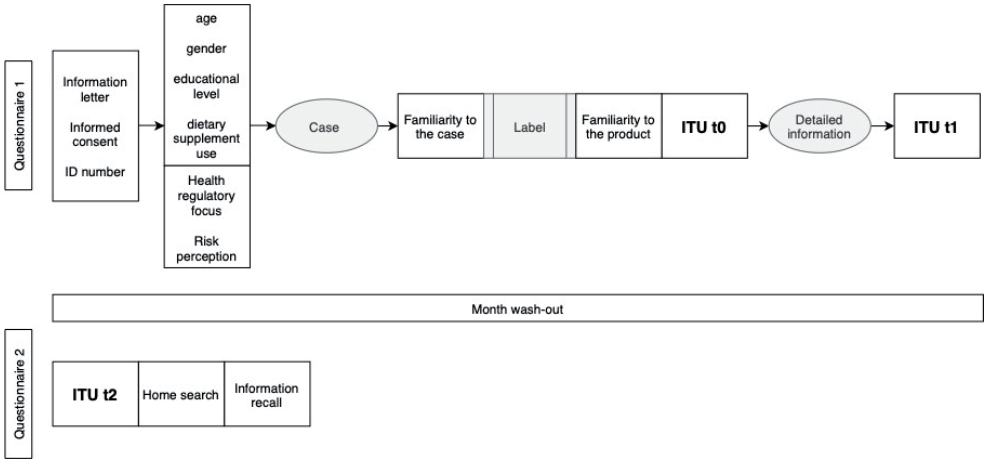
A total of 343 participants applied to participate in the study, of which 282 completed the first questionnaire (82%). The second questionnaire was completed by 268 participants (95%). The loss to follow-up between the first and second questionnaire was 5% (n=14).

3.2.2 Procedure and questionnaire design

Study participants were recruited through flyers and social media (Facebook, Twitter, Instagram & LinkedIn). After expressing their interest, study participants received an e-mail with their ID number and a personal link to the questionnaire. The participant gave consent to participate by ticking a designated box in the questionnaire. Contact details were saved securely to link the first and second questionnaire to the experimental category of participants. No personal data was collected via the questionnaire software.

The study was designed to measure ITU three times (flowchart presented in figure 1): two times in questionnaire 1 (before (t0) and after being presented detailed information (t1)), and once after a wash-out period of one month (t2).
After giving consent, the questionnaire started with questions regarding the demographics of the participant: age, gender, highest completed education and dietary supplement use. Subsequently, the health regulatory focus and the risk perception were measured using two standardised questionnaires (35). The health regulatory focus and risk perception have been reported to influence the intention to consume dietary supplements (35). One study indicated that health behaviour of consumers, measured by the health regulatory focus, is either based on a prevention focus (they conduct behaviour to prevent falling ill), or on a promotion focus (promoting to stay healthy) (36). Individuals with a high promotion focus were shown to be more likely to use dietary supplements (35), but

Figure 1. Flowchart of the conducted study



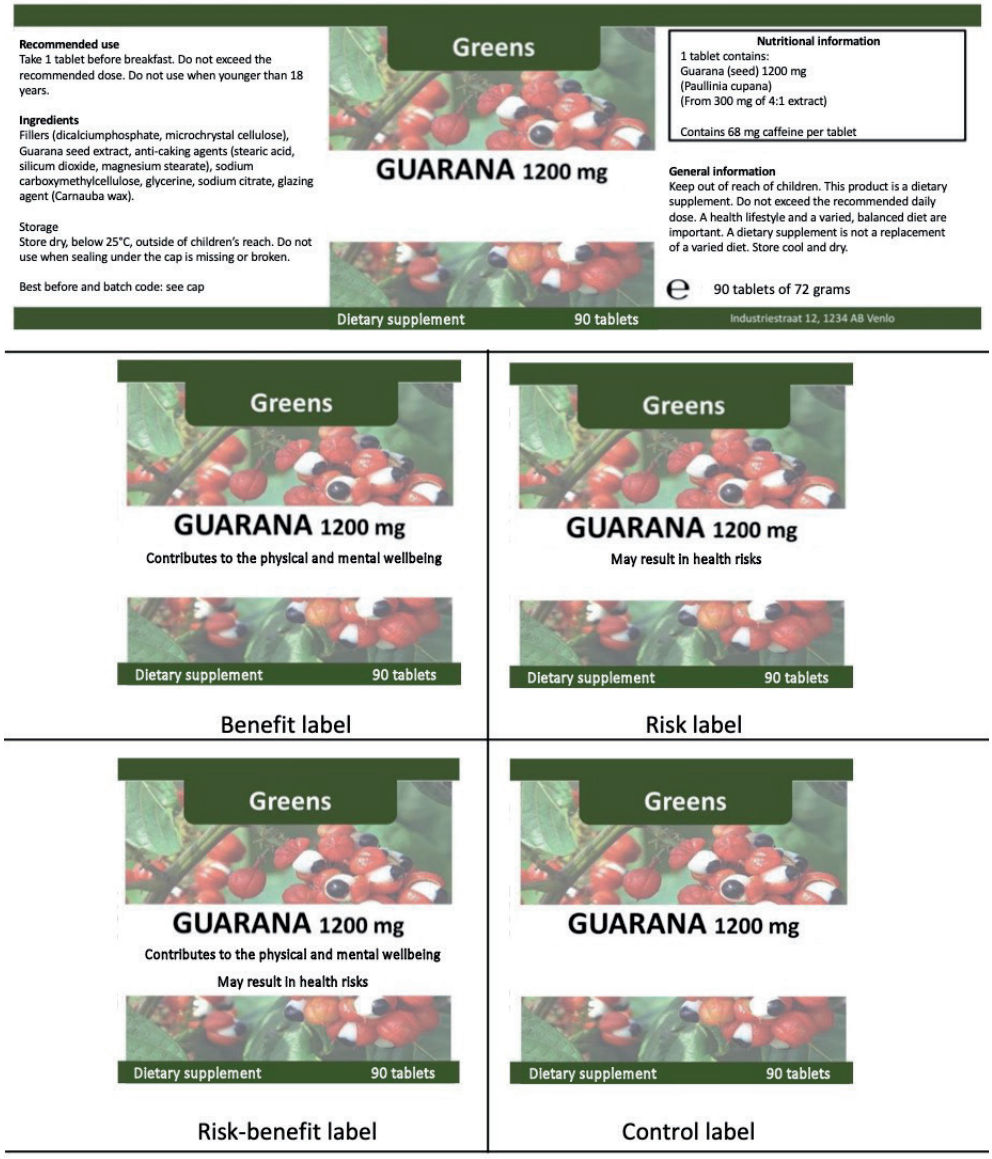
The flow chart shows which measurements are taken at what moment in the study. Everything in grey is provided to the participants and does not constitute a measurement. The outcome measurement (ITU) is presented in bold. The information recall was an open question.

were also more interested in product design characteristics (37,38). This healthy regulatory focus may therefore affect the relationship between information read on a label and intention to consume a product. Risk perception, how individuals judge the severity of a risk and the likelihood that risks may occur, may affect the intention to consume a product: consumers with a low risk perception reported a higher intention to consume dietary supplements in previous research (39). Risk perception can however also be influenced by a positive message displayed on the product.

In the second part of the questionnaire, participants were asked to imagine the situation that they felt fatigue during the day and were looking for a product to energise them. Following exposure to this case, the familiarity to this imaginary problem was measured. Participants were instructed to answer the remainder of the questionnaire as if they were experiencing the case in real life. Next, participants were randomly exposed to one of the four labels of the dietary supplement with guarana: a label (1) presenting only the main benefit of the product, (2) presenting only the main risk, (3) presenting both the benefit and the risk, or (4) the control condition, a label without any risk or benefit (Figure 2). After the exposure to the label, the familiarity to the product was measured ('Do you know this product?'). Familiarity was found to influence understanding of the health claim and subsequently the ITU (22,23). Previous research furthermore indicated

that familiarity to a product, influences the risk and benefit perception (40). The attitude towards a familiar food product is the predominant determinant of the risk and benefit perception (40). The risk perception, health regulatory focus and

Figure 2.



The figure displays the four different labels, presented to the four experimental groups in the study. All information on the label is in line with European legislation and, except for the front-of-pack communication of risks and benefits, similar for all labels.

familiarity to the problem and to the product were measured to assess whether randomization was successful for these personal attributes.

After exposure to the label, ITU was measured (t0) using a visual analogue scale ranging from 0 'definitely not' to 10 'definitely yes' (H1). Then, participants were exposed to further, more detailed information on Guarana. This information was based on previous research into guarana or one of its bioactive components and was presented in digital cards in MouselabWEB v1.00beta, where it was divided into general information, information on the benefits and information on the risks. When placing their cursor on the card, participants could reveal the information. MouselabWEB measured the time that a specific card was opened, allowing for determining how long the participant accessed which type of information. In the next step, participants were again asked about their ITU (t1) with the visual analogue scale (H2). This completed the first questionnaire.

After a one-month wash-out period, the follow-up questionnaire was sent to the participants. The one-month wash-out was selected to determine whether participants could memorise the information long-term. The second questionnaire started by asking participants to describe the ITU (t2) on the visual analogue scale (H3). Participants were then asked to indicate whether they collected additional information on the product after they had completed the first questionnaire. It was expected that being exposed to the information multiple times could influence a participant's ITU at t2. Finally, participants were asked to write down any of the information on guarana they could recall. After completion of data collection, all study participants received an e-mail with the debriefing letter which revealed the true study objective.

3.2.3 Data analysis

In order to establish the effect of risk and benefit information on the participants' interest in consuming the product, the main outcome measurement was the ITU, measured at t0, t1 and t2 (figure 1). Answers provided by participants to the open question in questionnaire 2, asking what information they recalled, were analysed qualitatively to gain deeper understanding of the findings from the quantitative analysis of the ITU measurements.

3.2.3.1 Quantitative analysis

Collected data was first analysed to detect outliers because of incorrect data entry (such as an age of 611). Demographics of the study sample were compared to ensure the analysis was not confounded by differing demographics of the four experimental groups. Additionally, the four experimental groups were compared

for the potential confounding variables: familiarity, health regulatory focus, risk perception and home search.

To assess the influence of the labels on the ITU (H1), a one-way ANOVA was conducted. The ITU before exposure to the information (t0) was compared within the four experimental categories: benefit, risk, risk and benefit and control. A post-hoc analysis was performed to determine the difference between the intervention categories.

To determine the influence of the balanced information and time on the ITU (H2 and H3), a one-way repeated measures ANCOVA was conducted with the three measurements of the ITU at t0, t1 and t2 as dependent variable. A contrast analysis was done to gain insight in the differences between each of the measurements, in which the Bonferroni correction was used to reduce the probability of finding significant differences due to multiple comparisons (Type I error) (41). Differences between time spent on risk information and time spent on benefit information were assessed with two independent one-way ANOVAs, comparing the four experimental categories.

All analyses were conducted with IBM SPSS version 26. The effects were considered significant when $p<0.05$. Plots were designed in SPSS.

3.2.3.2 Qualitative analysis

A thematic analysis based upon open coding was performed on the answers provided in the recall-question of the second questionnaire (42). Coding was based on the three types of information that was provided to the participant: general information, risk information and benefit information. Subcodes were used to further code recalled risk information and benefit information, to explore whether participants could merely recall the fact that there were risks and benefits (level 1), whether they could name specific risks or benefits (level 2) and whether they mentioned any detailed information regarding the risks and benefits (level 3) (table 1).

Additional codes were applied to information that was not provided to study participants in the first questionnaire, but that was reported as answer in the second questionnaire.

To determine whether specific information was recalled more readily, the results from the analysis on the open question were quantified. This was done by calculating how often a specific code or subcode was applied to the data. An ex-

Table 1. Layers in provided information

	Label information	General (level 1)	Specific (level 2)	Detailed (level 3)
Risks	May result in health risks	There are risks when using the product	Heart palpitations Addiction Medicine interaction	It can increase the amount of cAMP which can result in an increased heart rate. It increases the number of adenosine receptors leading to tired feeling when one stops using it. It influences cytochrome P450 which results in an altered functioning of medicines
Benefits	Contributes to the physical and mental wellbeing	There are benefits when using the product	The product provides energy The product is an antioxidant The product can aid in weight loss	Caffeine is an antagonist of adenosine which results in the signalling of fatigue not occurring in the brain when caffeine binds to the adenosine receptor. The product contains catechines which can act as antioxidant and prevent free radical damage. The product contains caffeine and catechines which can suppress catechol O-methyltransferase and phosphodiesterase.
General		Contains caffeine		

The table shows the different layers of information that was provided to the study participants.

ploratory chi-square analysis was conducted to determine whether the different levels and recurring codes were present more often in one of the experimental groups.

3.2.4 Ethical approval

This study was reviewed and approved by the Ethical Review Committee Inner City Faculties of Maastricht University (ERCIC_099_03_10_2018).

3.3 Results

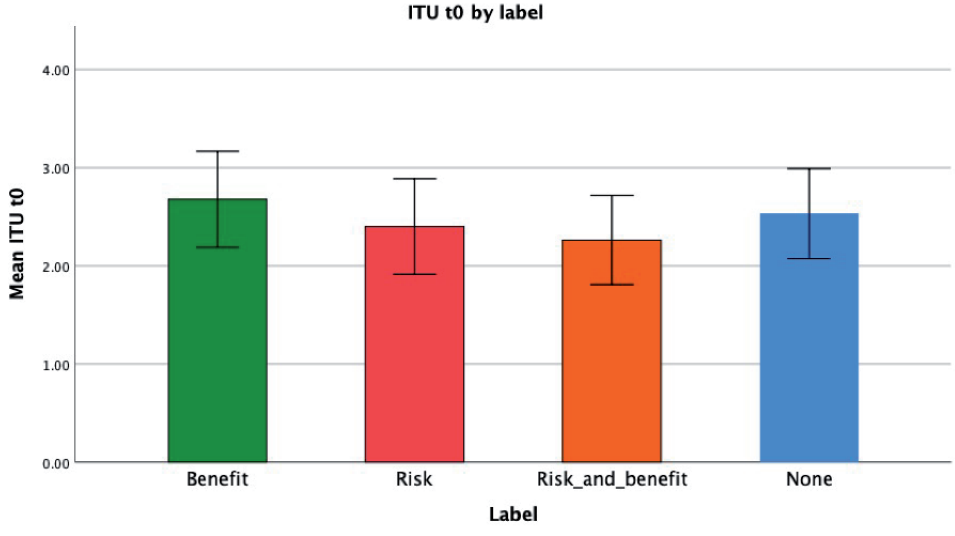
The mean age of the total sample (n=282) was 33.3 years old, ranging from 31.5 to 34.0 in the four label conditions (table 2). One participant in the risk-benefit group reported an age of 611 and this participant's age was therefore labelled as a missing value.

The majority of participants was female in the total sample (69.5%) and in the four experimental groups. A large majority (>90% in the total sample and all experimental groups) completed tertiary education, which includes both vocational education and university education. A small majority in the total sample (55.0%), and in the risk (58.0%), risk-benefit (54.2%) and control groups (58.0%) reported not to use any dietary supplements. This was exactly 50% in the benefit group. As expected after randomization, no relevant differences were observed between the four groups in health regulatory focus and risk perception. The risk label group reported a relatively higher familiarity to the product (17.4% vs 9.6% in the total sample). The risk-benefit group reported a relatively low familiarity to the problem (56.9%). The control group had a low rate of home search, but it was not possible to conduct any quantitative analysis because of the small numbers of the group that reported to have conducted a home search.

3.3.1 Front-of-pack information on ITU

The one-way ANCOVA analysing whether front-of-pack risk and benefit information influences the ITU (H1), did not unveil a significant difference between the four groups ($F(3, 274)=0.508$, $p=0.677$) after controlling for the covariates gender, dietary supplement use, familiarity to the product and familiarity to the problem. This indicates that ITU this product in these circumstances is not influenced by different types of front-of-pack information, varying from no to complete risk-benefit information (H1).

Figure 3.



The figure displays the different in ITU at t0 between the four experimental conditions. The error bars represent 95% confidence intervals.

Table 2. Demographics of the total sample and per experimental group (label condition).

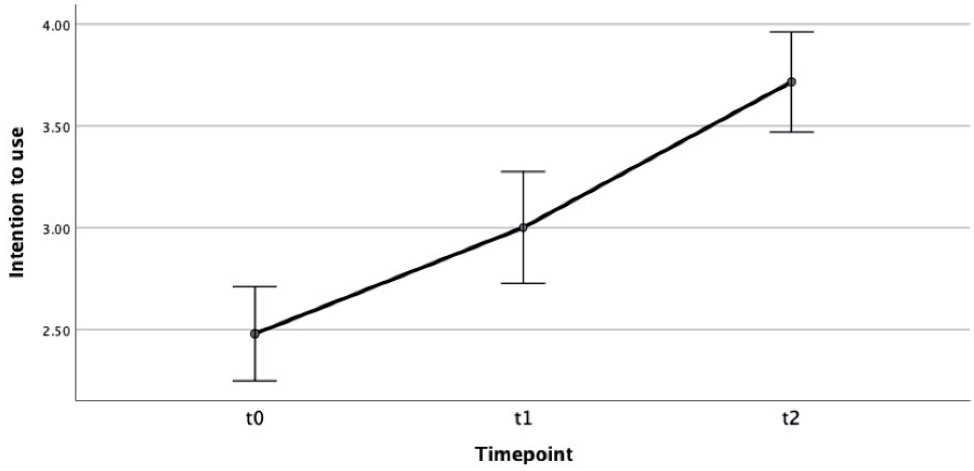
	Total n=282	**Benefit n=72 (25,5%)**	**Risk n=69 (24,5%)**	**Risk-Benefit n=72 (25,5%)**	**Control n=69 (24,5%)**
Age					
Mean (SD)	33.3 (13.13)	33.9 (14.05)	31.52 (12.62)	34.0 (13.22)	33.71 (12.67)
Gender					
Male (n, %)	86 (30.5%)	27 (37.5%)	20 (29.0%)	24 (33.3%)	15 (21.7%)
Female (n, %)	196 (69.5%)	45 (62.5%)	49 (71.0%)	48 (66.7%)	54 (78.3%)
Education					
Secondary (n, %)	19 (6.7%)	5 (6.9%)	5 (7.2%)	6 (8.3%)	3 (4.3%)
Tertiary (n, %)	262 (92.9%)	67 (93.1%)	64 (92.8%)	66 (91.7%)	65 (94.3%)
Undisclosed (n, %)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Supplement use					
Yes (n, %)	127 (45.0%)	36 (50.0%)	29 (42.0%)	33 (45.8%)	29 (42.0%)
No (n,%)	155 (55.0%)	36 (50.0%)	40 (58.0%)	39 (54.2%)	40 (58.0%)
Health regulatory focus					
Promotion focus (mean, SD)	3.5 (0.60)	3.5 (0.65)	3.6 (0.56)	3.6 (0.68)	3.5 (0.50)
Prevention focus (mean, SD)	2.8 (0.74)	2.7 (0.71)	2.9 (0,78)	2.7 (0.77)	2.9 (0.69)
Risk perception (mean, SD)	3.0 (0.54)	3.0 (0.52)	3.0 (0.50)	3.0 (0.48)	3.1 (0.65)
Familiarity to problem					
Yes (n, %)	185 (65.6%)	52 (72.2%)	49 (71.0%)	41 (56.9%)	43 (62.3%)
No (n, %)	97 (34.4%)	20 (27.8%)	20 (29.0%)	31 (43.1%)	26 (37.7%)
Familiarity to product					
Yes (n, %)	27 (9.6%)	6 (8.3%)	12 (17.4%)	5 (6.9%)	4 (5.8%)
No (n,%)	255 (90.4%)	66 (91.7%)	57 (82.6%)	67 (93.1%)	65 (94.2%)
Home search					
Yes (n, %)	22 (8.2%)	8 (11.3%)	6 (9.0%)	7 (10.4%)	1 (1.6%)
No (n, %)	246 (91.8%)	63 (88.7%)	61 (91.0%	60 (89.6%)	62 (89.4%)

Additional analysis showed that only familiarity to the problem was significantly related to the ITU at t0 ($p<0.05$).

3.3.2 Effects of detailed information and reading time

The one-way repeated measures ANOVA to test for the influence of detailed information and wash-out showed a significant increase over the three measurement points (t0, t1, t2) [$F(2, 526)=3.52$, $p<0.05$] (H2). The model was corrected for the covariates gender, dietary supplement use, familiarity to the problem and familiarity to the product. The analyses did not show any significant influences of these covariates on the different measurements of the ITU.

Figure 4.

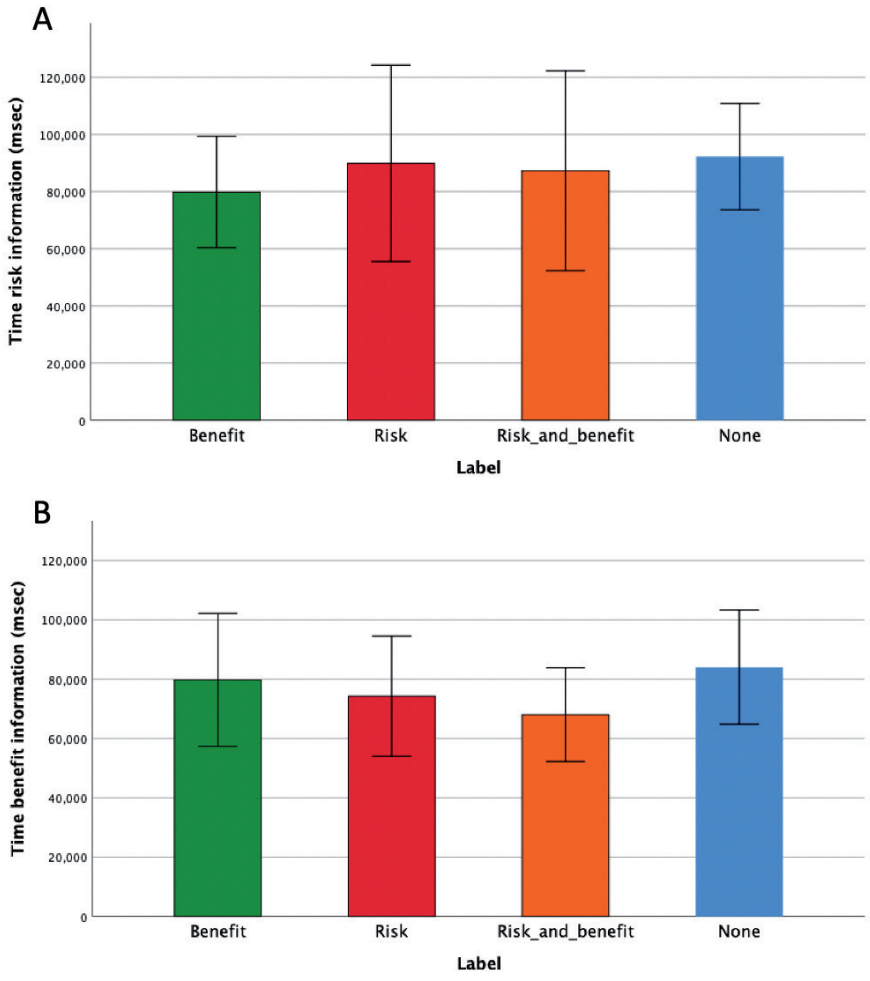


The figure shows the mean ITU measured at timepoint t0, t1 and t2.

The contrasts show that the ITU increased after exposure to the information from 2.47 to 3.00, but this was not significant. A significant increase in ITU from 3.00 to 3.72 was observed after the one-month wash-out period.

How being exposed to risk and/or benefit information would affect the time that participants took to read additionally provided information, was measured in MouselabWEB and analysed with two one-way ANOVAs (H3): to analyse (1) the time exposed to risk information and (2) the time exposed to benefit information. Both analyses unveiled no relevant differences between the labels regarding the time the participants exposed themselves to the information provided in MouselabWEB (benefit information [$F(3,239)=0.481$, $p>0.05$] and risk information [$F(3.235)=1.36$, $p>0.05$]).

Figure 5.



The figure shows the time spent on accessing information in the four experimental conditions. Figure A shows the average time spent on reading the risk information, figure B shows the average time spent on the benefit information.

This indicates that the type of front-of-pack information to which consumers are exposed does not influence the time consumers spend on informing themselves further on the risks and benefits.

3.3.3 Information recall

To gain insights into whether (and which) information was recalled by the participants, to explore whether this could have influenced the ITU, participants were asked to report their recalled information. Categorisation and subsequent

quantification indicated that benefit information is more often recalled compared to risk information (table 3). Recalled information showed to be mostly concerning 'level 2' information, where participants recalled benefit or risk but not the specific details of the products leading to these. Participants also mentioned benefits and risks which were not provided to them in this study. This information either entailed 'new' risk or benefits that were not named in the information, or information related to a mentioned risk or benefit but that was wrongfully remembered. This new or incorrect information seemed to be related to risks more often than benefits.

Table 3. Quantitative analysis on recall of risk and benefit information.

	Total	Benefit	Risk	Risk-benefit	Control
Benefit information	150	36	37	38	39
Detailed	10	2	3	2	3
Specific	120	29	32	30	29
General mention	20	5	2	6	7
Risk information	128	29	28	33	38
Detailed	9	4	2	2	1
Specific	53	12	12	13	16
General mention	66	13	14	18	21
General information	98	24	23	22	29
New/incorrect	46	5	14	13	14
Risk	31	4	9	8	10
Benefit	15	1	5	5	4
No recall	38	10	11	9	8

The table shows the number of recalls of risk and benefit information and the type of recall: detailed information, specific risk or benefit or general mentioning of the existence of risk and benefits. The table furthermore specifies the number of recalls of general information and the mentioning of new or incorrect information which was not provided in the first questionnaire. It lastly gives the number of people that did not recall any information.

The analysis furthermore unveiled that participants often recalled the bioactive substance 'caffeine' and the benefit 'increased energy' (table 4): 119 study participants recalled caffeine as being a bioactive substance (44.4%); increased energy was a benefit recalled by 31.7% of the total sample. A combination of increased energy and caffeine was mentioned by 14.9% of all study participants.

Participants in the control group, exposed to the label without any front-of-pack information, recalled caffeine more often (4.8%).

An exploratory analysis using a chi-square test to compare the recall between the four experimental groups did not show any significant differences (p>0.0) in the different levels of information or the recall of caffeine or the health benefit energy.

Table 4. Recall of caffeine and increased energy.

	Total N=268	Benefit N=71	Risk N=68	Risk-benefit N=67	Control N=62
Caffeine (%)	119 (44.4%)	31 (43.7%)	29 (42.6%)	2 (37.3%)	34 (4.8%)
Energy (%)	8 (31.7%)	21 (29.6%)	24 (3.3%)	23 (34.3%)	17 (27.4%)

In this table, the number (and percentage) of participants is displayed who recalled that the product contained the bioactive substance caffeine (row 2), and that the described benefit was related to increased energy (row 3).

3.4 Discussion

Providing consumers with information can support them in determining whether or not to take a dietary supplement (20,21). One way to inform consumers is via the label of the dietary supplement. This study aimed to determine whether front-of-pack risk and benefit information on the HDS guarana influenced the intention to use this product. To this end, an online questionnaire was designed where 282 participants were exposed to labels containing different types of front-of-pack information. The influence of three elements on the ITU was measured: (a) front-of-pack information provision, (b) the exposure to extensive risk and benefit information as well as (c) time following exposure to information.

3.4.1 Intention to use

Although it was expected that differences would be shown in the ITU between the four experimental groups because of their exposure to one of the four labels (H1), this was not observed in the analysis, possibly because the ITU was already low in all participants. Hypothesis 1a and 1b predicting a difference between one-sided information and control were therefore rejected. Hypothesis 1c was maintained as there was not significant difference between the label with risk and benefit information and the control label.

Prior studies into the effect of warning labels and disclaimers described on packaging on consumer perceptions of products have shown diverging results. When researchers made consumers aware of the warning on the product, their product perception was influenced: the product was perceived less safe but more effective (43). Other studies however found that warnings and disclaimers on food product labels were not noticed by consumers (44–46). The lack of difference in ITU between the four experimental groups might henceforth result from participants not noticing front-of-pack risk and benefit statements.

The mean ITU was low in all experimental groups for all measurements (t0=2., t1=3.0 and t2=3.72). The ITU increased from 2.47 to 3.00 after being exposed to the additional, more detailed information on general aspects, risks, and benefits of the product. After the one-month wash-out period, this ITU significantly increased again from 3.00 to 3.72.

The increase in the ITU between t0 and t1 is expected to be attributable to the participants recognising the active substance caffeine in guarana. Participants were informed about this bioactive substance in the detailed information provided to them between t0 and t1. Previous research into the effect of information of dietary supplements found that disclosing potential risks of a dietary supplement decreases the intention to consume that product (21). The bioactive substance caffeine is however a so-called 'familiar risk': in the analysis of the recalled information in the second questionnaire, it was observed that 44.4% of the participants recalled the bioactive substance of the dietary supplement to be caffeine. The high recall of caffeine as bioactive substance is attributed to the recognition of this well-known substance. As familiarity to the product is known to decrease risk perception, this familiarity with caffeine can explain the increased ITU (40,47). Although the questionnaire did address familiarity to guarana, familiarity to caffeine was not measured. Consumers perceive familiar risks, such as caffeine, as less risky compared to unknown risks (40,48). Participants' familiarity to caffeine may therefore have biased the result.

In their Farm to Fork Strategy, published in 2020, the European Commission emphasised that increasing efforts should be put in providing information to consumers on the food they consume (18). The provision of information is however influenced by many other attributes then just the message itself (20,35). Hence, exposure to information on the label did not show any significant differences between the four experimental groups, whereas exposure to more elaborate information did result in an increase in the ITU. This indicates that communicating risks and benefits of dietary supplements on the standardised and regulated

label of this dietary supplement did not significantly impact the ITU of this product. As elaborate information was found to influence ITU the product, further research is required to determine how to provide consumers with standardised information beyond the label.

3.4.2 Strengths and limitations

This is the first study in which the effect of different types of front-of-pack communication on the ITU dietary supplements has been explored. Exposing participants to one of four types of front-of-pack risk-benefit information without disclosing the purpose, allowed for studying the effect of providing a specific type of information on a participant's intention to consume a product. Although information provision on the label has been subject of previous research before, this is the first study that specifically explores the influences of particularly risk and benefit information both alone and combined on the ITU dietary supplements.

One of the main limitations results from the study sample not being representative of the general population with relatively low age, a large majority was female and had completed tertiary education (table 1). The sample does however resemble the characteristics of dietary supplement users defined in previous research: being predominantly higher educated women (49–51). The similarities of the study sample and dietary supplement users in general might be caused by the convenience sampling applied in this study (1), as dietary supplement users might have been more interested in participating. Approximately half of the participants indicated being a dietary supplement user, whereas previous research reported 10% of men and 17% of women to be supplement users (7).

Another limitation results from the loss to follow-up. Although the loss to follow-up was only %, this influences measurements of ITU at t2. This part of the analysis is henceforth underpowered. Reasons for dropping out were unknown.

Other limitations follow from our online study design. Participants indicated their ITU in an online environment based on a fictional case, without them needing to purchase or consume the dietary supplement. It remains to be determined whether the findings from this study can be translated fully to real-life situations. Also, participants might not have been fully focused on answering the questionnaire. The data from the MouselabWEB software unveiled that participants had spent a maximum of several minutes reading the information on guarana. It was not assessed whether participants had actually read and understood the information. On the one hand, this may have resulted in answers deviating from

participants' behaviour in real-life: when an individual intends to consume the product, they might put more effort in studying risk-benefit information. On the other hand, consumers are also responsible themselves for informing oneself on risk and benefits of products they aim to consume. By allowing participants themselves to determine how much time they would spend on reviewing the information, this research design allowed for resembling a real-life decision-making process.

3.5 Conclusion

Whilst information is deemed important in decision-making when it comes to buying and consuming food products (18,20), it is not always clear how benefit and/or risk information influences the decision-making process of consumers. This study aimed to identify whether disclosing risk and benefit information on the front-of-pack label would influence a consumer's intention to use a dietary supplement. The four experimental groups, groups which were exposed to different types of information on the label, were not shown to have a different ITU, indicating that risk-benefit information provided on the label did not affect the ITU. In all four experimental categories, the ITU increased after people were exposed to more detailed information on the risks and benefits of guarana, and again increased after a wash-out period of a least one month. This suggests that providing consumers with any type of information on a dietary supplement influences a consumer's ITU. It is expected that the ITU mainly increased because the participant became aware of the – already familiar – bioactive substance in the dietary supplement (caffeine), and not necessarily due the balanced, more complete information made available to them. Additional studies on front-of-pack information provision with the use of other dietary supplements are needed to verify the results found in this study. The bias caused by familiarity to the bioactive substance (caffeine) suggests that future research and policy into the provision of information to consumers should go beyond merely the content of the information and also take into account personal and external factors that influence the use of the provided information.

Informing consumers about risks and benefits of a dietary supplement is important: only when all information is provided, are consumers enabled to make a well-informed decision. In Europe, voluntarily informing consumers about health benefits of foods is regulated. But even though the *use* of a product may negatively affect its safety, it is currently not required to disclose risk information about food to consumers, as all food products are assumed to be safe. This means

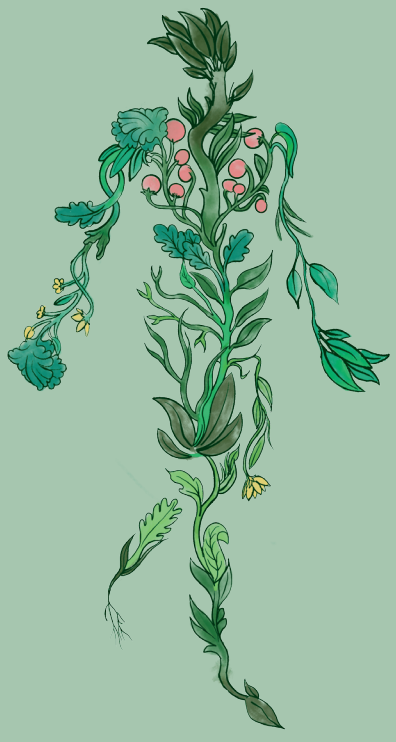
there is currently no requirement to provide information related to such risks on the product. The results of this study indicate that consumers use both risk and benefit information in their decision-making process upon using a dietary supplement, but also shows that the label may not be the primary source for determining their intention to consume that specific dietary supplement.

3.6 References

1. Euromonitor International. Vitamins and Dietary Supplements. Market Sizes | Historical. 2018.
2. Euromonitor International. Herbal/Traditional Products. Market Sizes | Historical. 2018.
3. Skeie G, Braaten T, Hjartaker A, Lentjens M, Amiano P, Jakszyn P, et al. Use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition calibration study. Eur J Clin Nutr. 2009;63(4):S226–38.
4. Garcia-Alvarez A, Egan B, Klein de S, Dima L, Maggi F, Isoniemi M, Ribas-Barba L, Raats MM, Meissner EM, Badea M, Bruno F, Salmenhaara M, Milà-Villarroel R, Knaze V, Hodgkins C, Marculescu A, Uusitalo L, Restani P, Serra-Majem L. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One. 2014;9(3):1–18.
5. European Parliament and the Council of the European Union. Consolidated version of directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Off J Eur Union. 2002;183:1–14; 30-03-2021.
6. EFSA. Botanicals [Internet]. 2018 [cited 2018 Apr 3]. Available from: https://www.efsa.europa.eu/en/topics/topic/botanicals
7. Jeurissen SMF, Buurma-Rethands EJM, Beukers MH, Jansen-Vliet van der M, Rossum van CTM, Sprong RC. Consumption of plant food supplements in the Netherlands. Food Funct. 2018;9:179–90.
8. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food saf. Off J Eur Union. 2002;31:1–44; 26-05-2021.
9. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2004.
10. Lenssen KGM, Bast A, de Boer A. Clarifying the health claim assessment procedure of EFSA will benefit functional food innovation. J Funct Foods. 2018;47:386–96.
11. Smet PAGM. Clinical risk management of herb-drug interactions. Br J Clin Pharmacol. 2006;63(3):259–67.
12. de Boer A, van Hunsel F, Bast A. Adverse food-drug interactions. Regul Toxicol Pharmacol. 2015;73:859–65.
13. Hall SD, Wang Z, Huang S-M, Hamman MA, Vasavada N, Adigun AQ, Hilligoss JK, Miller M, Gorski JC. The interaction between St John's wort and an oral contraceptive. Clin Pharmacol Ther. 2003;74(6):525–35.
14. Mannel M. Drug interactions with St John's Wort. Mechanisms and clinical implications. Drug Saf. 2004;27(11):773–97.
15. Huizing Edinger W. Food, safety and the behavioural factor of risk. Eur J Risk Regul. 2014;5(4):491–504.
16. European Parliament and the Council of the European Union. Consolidated version of regulation ((EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives

2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Off J Eur Union. 2011;304:1–60; 01-01-2018.
17 Fishbein M. Theory of reasoned approach to health promotion. Medical Decision Making. 2008;28(6);834-844.
18. European Commission. Farm to fork strategy. For a fair, healthy and environmentally-friendly food system. 2020.
19. Schifferstein HNJ, de Boer A, Lemke M. Conveying information through food packaging: a literature review comparing legislation with consumer perception. J Funct Foods. 2021;86:104734.
20. Dodge T, Jaccard JJ. Negative beliefs as a moderator of the intention-behavior relationship: Decisions to use performance-enhancing substances. J Appl Soc Psychol. 2007;37(1):43–59.
21. McDonald DD, Nicholson NR. Dietary supplement information and intention to continue and recommend supplements. Int J Nurs Stud. 2006;43(1):51–7.
22. Wills JM, Storcksdieck gerannt Bonsmann S, Kolka M, Grunert KG. Nutrition and health claims: help or hindrance European consumers and health claims: attitudes, understanding and purchasing behaviour. Proc Nutr Soc. 2012;71:229–36.
23. Lahteenmaki L. Claiming health in food products. Food Qual Prefer. 2013;27:196–201.
24. Cowburn G, Stockley L. Consumer understanding and use of nutrition labelling: a systematic review. Public Health Nutr. 2005;8(1):21 28.
25. Rembischevski P, Dutra Caldas E. Risk perception related to food. Food Sci Technol. 2020;40:779–85.
26. Hernandez-Fernandez A, Kuster-Boluda I, Vila-Lopez N. Nutritional information labels and health claims to promote healthy consumption. J Bus Ind Mark. 2021;1–12.
27. Meerza SIA, Yiannaka A, Gustafson C, Brooks K. Information avoidance behavior: does ignorance keep us informed about antimicrobial resistance? Food Policy. 2021;102:102067.
28. Krnàçovà P. Consumer awareness of food labelling. In: Proceedings of 16th international joint conferences: Central and Eastern Europe in the changing business environment. 2016. p. 258–69.
29. Di Fonzo A, Liberati C. Consumers are unaware about European legislation on communication of the health benefits conveyed by claims. An empirical survey. Ital Rev Agric Econ. 2020;75(1):51–9.
30. Walker Naylor R, Droms CM, Haws KL. Eating with a purpose: consumer response to functional food health claims in conflicting versus complementary information environments. J Public Policy Mark. 2009;28(2):221–33.
31. Keller SB, Landry M, Olson J, Velliquette AM, Burton S, Andrews JC. The effects of nutrition package claims, nutrition facts panels, and motivation to process nutrition information on consumer product evaluations. J Public Policy Mark. 1997;16(2):256–69.
32. Scammon DL. "Information load" and consumers. J Consum Res. 1977;4(3):148–55.
33. Clark KL, AbuSbha R, von Eye A, Achterberg C. Text and graphics: manipulating nutrition brochures to maximize recall. Health Educ Res. 1999;14(4):555–64.
34. Faul F, Erdfelder E, Lang AG, Buchner A. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175–91.
35. Pajor EM, Eggers SM, Curfs KCJ, Oenema A, de Vries H. Why do Dutch people use dietary supplements? Exploring the role of socio-cognitive and psychosocial determinants. Appetite. 2017;114:161–8.

36. Gomez P, Borges A, Pechmann C. Avoiding poor health or approaching good health: does it matter? The conceptualization, measurement, and consequences of health regulatory focus. J Consum Psychol. 2013;23(4):451–63.
37. Karnal N, Machiels CJA, Orth UR, May R. Healthy by design, but only when in focus: Communicating non-verbal health cues through symbolic meaning in packaging. Food Qual Prefer. 2016;52:106–19.
38. Pham MT, Avnet T. Contingent reliance on the affect heuristic as a function of regulatory focus. Organ Behav Hum Decis. 2009;108(2):267–78.
39. Braun LA. Risky business - or is it? Risk perception and integrative medicine. Adv Integr Med. 2014;1:48–51.
40. Fischer ARH, Frewer LJ. Consumer familiarity with foods and the perception of risks and benefits. Food Qual Prefer. 2009;20(8):576–85.
41. Napierala MA. What is the Bonferroni correction. AAOS Now. 2012;6(4):40.
42. Polit DF, Beck CT. Qualitative data analysis. In: Nursing Research Generating and assessing for nursing practice. 9th Editio. Wolters Kluwer Health I Lippincott Williams & Williams; 2012. p. 556–81.
43. Mason MJ, Scammon DL, Fang X. The impact of warning, disclaimers, and product experience on consumers' perception of dietary supplements. J Consum Aff. 2007;41(1):74–99.
44. Spink J, Singh J, Singh SP. Review of package warning labels and their effect on consumer behaviour with insights to future anticounterfeit strategy of label and communication systems. Packag Technol Sci. 2011;24:469–84.
45. Kesselheim AS, Connolly J, Rogers J, Avorn J. Mandatory disclaimers on dietary supplements do not reliably communicate the intended issues. Health Aff. 2015;34(3):438–46.
46. Mason MJ, Scammon DL. Health claims and disclaimers: extended boundaries and research opportunities in consumer interpretation. J Public Policy Mark. 2000;19(1):144–50.
47. Song H, Schwarz N. If it's difficult to pronounce, it must be risky. Fluency, familiarity, and risk perception. Psychol Sci. 2009;20(2):135–8.
48. Siegrist M, Keller C, Kiers HAL. Lay people's perception of food hazards: comparing aggregated data and individual data. Appetite. 2006;47:324–32.
49. Block G, Jensen CD, Norkus EP, Dalvi TB, Wong LG, McManus JF, Hudes ML. Usage patterns, health, and nutritional status of long-term multiple dietary supplement users: a cross-sectional study. Nutr J. 2007;6(30):1–11.
50. de Jong N, Ocké MC, Branderhorst HAC, Friele R. Demographic and lifestyle characteristics of functional food consumers and dietary supplement users. Br J Nutr. 2003;89(2):273--81.
51. Dickinson A, MacKay D. Health habits and other characteristics of dietary supplement users: a review. Nutr J. 2014;13(14):1–8.
52. Polit DF, Beck CT. Sampling in quantitative research. In: Nursing Research Generating and assessing for nursing practice. 2012. p. 273–92.



Chapter 4

How does scientific information reach the consumer: a case study among students into providing verbal information on dietary supplements at point of purchase

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Abstract

Consumers of dietary supplements should be made aware of the benefits and risks of the products. This case study therefore aimed to identify the content of the risk-benefit information provided during the purchase of St. John's wort supplements and how consumers perceive this information. Fifteen participants visited a shop to purchase a St. John's wort supplements after which they were interviewed on the provided information during the visit.

This case study shows that the spontaneous information provision is not consistent in Dutch drugstores and health food shops. The provided information was either very detailed, or no information was provided at all. The perceived reliability of information was mainly determined by the authority of the employee and the type of shop where the product was purchased.

Information consistency at the moment of purchase is of influence in the perceive value of it.

4.1 Introduction

In the past years, dietary supplement usage has been increasing globally (1–3). A study in six European countries found that 18.8% of consumers reported to use specifically herbal dietary supplements (4). In the Netherlands, it is estimated that 10% of men and 17% of women use herbal dietary supplements (5). In the European Union (EU) dietary supplements are regulated as food products in concentrated, dosage-like form, that have the purpose to supplement the diet (Art. 2.a) (6). Besides vitamins and minerals, these dietary supplements can also contain other substances (Art. 2.a) (6), including botanicals: substances from plants, algae, fungi, or lichens (7). These so-called herbal dietary supplements are used by consumers because of their alleged health benefits (4,8).

In the Netherlands, St. John's wort (*Hypericum perforatum*) is sold as dietary supplement to improve mood. This health claim has not yet been evaluated by the European Food Safety Authority, as the evaluation of all botanical health claims has been put on hold by the European Commission. The active substances causing the beneficial effect are considered to be hyperforin and hypericin. Hyperforin has been shown to inhibit the re-uptake of the neurotransmitters serotonin, noradrenaline, dopamine, gamma-aminobutyric and L-glutamate (9). An increased availability of these neurotransmitters positively influence mood and is described to improve mild symptoms of depression (9). Hypericin has been suggested to be responsible for inhibiting mono-amine oxidases, a group of enzymes responsible for the breakdown of monoamines including adrenaline, serotonin and dopamine, but was later found to be of little effect (10,11). Various mild side effects have been reported for St. John's wort usage, such as dizziness, nausea, diarrhoea and skin irritations (12–14). Additionally, St. John's wort is known for its potential to interact with conventional medicine. Examples of medicines that are affected when taken concurrently with St. John's wort are anti-HIV drugs and oral contraceptives (15–17). St. John's wort is proven to influence the cytochrome P450 3A4 and P-glycoprotein activity (15,18). Medicines that are metabolised through these pathways are consequently affected when taken together with St. John's wort (15).

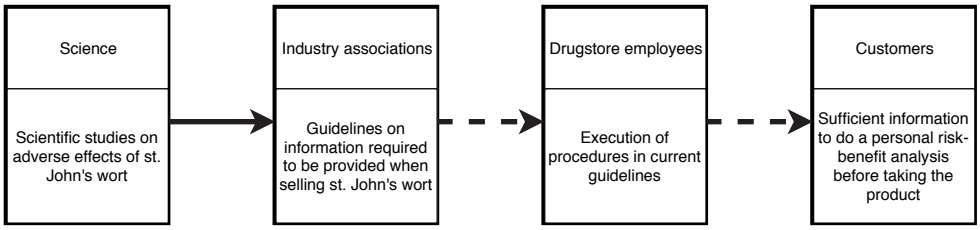
In the EU, all food products on the market should be safe for consumers, as regulated by the General Food Law and subsequent secondary legislation (19). These laws aim to ensure that consumers are offered the highest level of protection from firstly unsafe substances and secondly misleading statements (20). Still, it is known that some herbal dietary supplements, including St. John's wort containing supplements, can elicit adverse effects (14,17,21). Voluntary, commercial

marketing statements made about the efficacy of dietary supplements, whether the product has a beneficial effect on health, are separately regulated by the Nutrition and Health Claims Regulation (Art. 1.1) (22). General requirements for what information is provided on the label are regulated by the Regulation on Food Information to Consumers (Art. 1.2) (23). Additional requirements for labelling dietary supplements are laid down in Directive 2002/46/EC on food supplements, which defines i.a. that the label must include statements to not exceed the recommended dose, and that the product is not to be used as a substitute for a varied diet (Art. 6.3) (6).

The most important aim of EU food law is to protect consumers from unsafe substances and from being misled, with the second aim being the harmonisation of European legislation throughout member states, to facilitate the development of one internal market (20). When it comes to the protection of consumers, European food legislation often refers to 'the average consumer', that is protected by these laws and regulation. This 'average consumer' is assumed to be reasonably well-informed, reasonably observant and circumspect (24). This average consumer would take into consideration the provided information and make a personal risk-benefit analysis before consuming a food product (25). In order to do this, consumers must first become well-informed and then use this information to make a sound decision upon the consumption of a dietary supplement. Consumers should therefore be made aware of both the benefits and risks of the product (25). This requires the transfer of scientific findings to the consumer (26).

One moment where this scientific information can be provided is during the purchase of a dietary supplement in a drugstore, which in the Netherlands mostly taking place over the counter in a drugstore or health food shop. In the case of St. John's wort containing food supplements, scientific information is, as described above, available on potential adverse effects when using product concomitantly with prescription drugs for example. This information is known to be made available to relevant shops, via the Dutch industry association for drugstores and health food shops (CBD), who publish the Dutch drugstore guidelines. These include guidelines related to *i.a.* information provision on over-the-counter medicines and dietary supplements. Specifically, for St. John's wort containing products, the guidelines state that customers purchasing St. John's wort should be made aware of its potential to interact with conventional medicine (27). The guidelines are an important source of information on known herb-drug interactions for staff employed in these stores, to allow them to inform consumers who purchase the product. Figure 1 shows the potential stages in information

Figure 1. information transfer from science to the consumer



A schematic representation of the suggested information transfer from science to consumers through industry associations and drugstore employees. The figure additionally shows required actions for the information transfer to take place on a product containing St. John's wort. The information transfer from drugstore employees to customers is the subject of this research.

transfer from scientific literature to the consumer during the purchase of St. John's wort based on current guidelines. When information is provided through all these stages, consumers can be made aware of the risks and benefits of a product, and consequently should be enabled to conduct a personal risk-benefit analysis as a well-informed, reasonably observant and circumspect consumer.

Previous research into in-store information have predominantly focussed on the role and viewpoint of pharmacists in providing this information to consumers (28,29). As dietary supplements are readily available in drugstores and health food shops in which no pharmacist is present, it is important to gain understanding in the in-store information provision in these types of shops as well. It is currently unknown to what extent the information that is available in the drugstore guidelines is actually transferred to employees working in drugstores, and whether these employees subsequently inform the consumer who is purchasing such products. As the perspective of customers, who are supposed to become reasonably well-informed, has not yet been investigated, this case study focusses on the perception of consumers on this information provision, who purchase dietary supplements as over the counter products in health food shops or drugstores.

To asses this information transfer from science towards consumers, the research questions of this exploratory case study was: how do consumers perceive the in-store provided verbal information on benefits and risks? This study therefore aimed to identify whether consumers are provided spontaneously with verbal information on the benefits and potential risks (for adverse effects) during the purchase of St. John's wort in Dutch drugstores and health food shops, as

prescribed in the stores' guidelines and how consumers perceive this information. Participants were therefore sent to a shop to purchase a St. John's wort containing food supplement and were interviewed afterwards upon this visit and the information they had received in the store during purchase and how they perceived this information.

4.2 Methods

To assess the consumer perception of the provided in-store information on benefits and risks of St. John's wort supplements, an exploratory case study was conducted in which 15 participants were sent to stores to experience this situation, who were subsequently interview upon their experience. These 15 participants were recruited through convenience sampling (30), by which students from the university were included in the sample. These participants were sent to a preselected drugstore or health food shop, which was determined beforehand by the research team based on ensuring different types and brands were included, to purchase a product containing St. John's wort. Prior to the store visits, participants were informed about the research aim and received instructions for the shop visit (section 2.2). Participants were instructed not to ask questions actively to store employees, but when asked about the purchase, would engage in the conversation. Subsequent to purchasing the product, the participant to the university to engage in a one-on-one semi-structured interview to address the information provision and the perception of the participant. This case study with a phenomenological research set-up allows for data collection from participants who all experienced the same phenomenon: visiting a shop to purchase a product containing St. John's wort and receiving information in the store about this product (31). This phenomenological case study thereby provides a deeper understanding of how a specific group of consumers experience the process of purchasing a product with St. John's wort and specifically the information that is provided to them (32). The collected data provides both textural descriptions of what the participants have experienced as well as structural descriptions of their experience (31). The structural descriptions give understanding as to how consumers perceived the provided information and consequently which factors influenced this perception.

4.2.1 Theoretical framework

By reviewing the available scientific literature, previous research was identified in which the purchase of dietary supplements in pharmacies, drugstores and health food shops was studied. Additionally, and related consumer research into

over-the-counter product purchases identified two themes that seem to influence this purchase decision: (i) the information provision and (ii) the reliability of information provided during purchase.

Consumers of dietary supplements and over-the-counter medicines were shown to not consider retail clerks as an information source, but rather use pharmacists, physicians, natural medicine practitioners and nurses to obtain information (33). Research into information provision upon health affecting products is predominantly conducted in pharmacies, analysing information for over-the-counter products. The type of information that consumers are interested in when purchasing such over-the-counter products varies greatly: some consumers only want to know the location of the product in the store, whereas others seek a diagnosis (34). In a survey, pharmacists indicated that they answered multiple questions on complementary and alternative medicines on a daily basis, most often related to efficacy of the product, adverse effects and potential interactions with other medicines (28). This was also found in an observational study in community pharmacies, where employees often were described to aim for managing risks related to over-the-counter products (29). These risks may result from inadequate use, or drug interactions, and providing information on such products is thought to decrease such risks for consumers. Whereas information is often welcomed by consumers, they are also shown to occasionally ignore the information that is provided to them, when they for example are already familiar with the product (29).

Besides providing information verbally, written information, in the form of product labels, may be also available during the purchase. Warnings on labels are mainly effective when they are shown on the front of the package (35). However, for a warning to be effective, consumers must notice the warning, encode it, comprehend it and comply with it (35). Any error in one of the stages has been shown to result in the warning being ineffective (35). Additionally, characteristics of the consumer themselves can impact the effectiveness of the warning (36).

The above-mentioned studies on the provision of information to consumers were either online consumer questionnaires or were focused on the employee's perspective. No previous research has been conducted into the actual content of the provided information. Based on the Dutch Drugstore Guidelines, costumers that are purchasing a product containing St. John's wort should, at minimum, be made aware if its potential interaction with other medicines (27). One of the themes in the interviews with participants will therefore address the content of the information that is provided to the customer when the product is purchased.

A second theme identified in literature and therefore addressed in the interviews is the perceived reliability of information provided during the purchase of an over-the-counter product. The perceived reliability of information from retail clerks is lower compared to information from pharmacists, physicians, natural medicine practitioners and nurses (33). This finding is supported by another study that showed that information in health food shops is more often not based on scientific facts compared to information provided in pharmacies (37). Although it is not the main purpose of a pharmacist to promote or advice complementary and alternative medicines to customers, previous research has shown that some pharmacists receive questions about dietary supplements from customers who are interested in purchasing such products, that sometime are sold on the same site where the pharmacist operates (38). Such questions can for example relate to side effects, herb-drug interactions or the conditions of use of supplements. Merely 15% of the pharmacists participating in the study by Semple et all (2006) who studied the barriers to provide information about complementary and alternative medicines, however indicated to be very confident in having sufficient knowledge to provide this information when answering questions on complementary and alternative medicine however (39).

Although training can improve this confidence, whether employees get training on over-the-counter products, and the amount of training they get, depends on the type of store (34). In the 2006 survey among pharmacists, 80% indicated to have received some training on the effects of herbal products (39). The varying amount of training in the different types of stores is also estimated by the consumer, and used in the decision where to purchase a product (34).

Since in EU food law the concept of the 'average consumer' is used to determine what is needed for the protection of consumers (24), describing that this consumer is expected to be reasonably well-informed, a third theme that was included in the semi-structured interview is the responsibility to inform consumers. Various legislative acts describe that certain information must be provided to a consumer through, for example, the label. Examples of such legislative acts are the Regulation (EU) No 1169/2011 on food information to consumers and Directive 2002/46/EC on food supplements (6,23). Regulation (EC) No 1924/2006 on nutrition and health claims is completely dedicated to the voluntary communication of the health benefits of consuming a product (Art. 1.1) (22). The communication of risks such as adverse effects or herb-drug interactions is however not included in any legislative act, which might be caused by the overarching requirement that food should be safe (Art. 14.1) (19). Since some dietary supplements are however shown to pose risks to a specific consumer (group) (40), it

is important these consumer (groups) are informed these risks. It is however unknown whose responsibility that is.

4.2.2 Study population

This case study was conducted in May and June 2019. Participants were recruited through advertisements or personal contact at the university campus. Subjects (18 years of age and older) were required to be enrolled in a bachelor or master's programme and needed to be fluent in both Dutch and English. Participants were recruited with convenience sampling and recruitment was terminated upon theoretical saturation: the inclusion of more participants would not result in any new findings. A total of 15 students (13 females and 2 males), ranging from 19 – 26 years old, participated in the study. Seven of the 15 participants reported to currently use dietary supplements, with none reporting current use of a dietary supplement containing St. John's wort. The potential bias introduced by including only young adults in this study population who were involved in food related education was taken into consideration in the data analysis (section 2.4).

4.2.3 Study design

After being fully informed about the study and the study procedure by a member of the research team participants signed informed consent to participate to the study. Firstly, a questionnaire consisting of questions related to age, gender, dietary supplement use and usual place of purchasing over-the-counter medicines and dietary supplements was completed to obtain a general overview of the study populations' characteristics. Participants were subsequently asked to visit one of the 12 preselected shops (in the south of the Netherlands) to purchase a product containing St. John's wort. In the Netherlands, a distinction is made between drugstores and pharmacies: prescription drugs can only be provided by pharmacies, and drugstores and health food shops sell over-the-counter medicines and dietary supplements. The participants only visited drugstores or health food shops; pharmacies were excluded from this case study. Preselection of these shops was required to ensure that a representative sample of drugstores and health food shops of various chains were visited. Of the 12 pre-selected shops, three were visited twice to assess whether experiences would differ between participants visiting a similar store. Participants were instructed to not ask questions, to guarantee the information was provided spontaneously. Upon their return, participants were interviewed by the research team.

The 15 conducted interviews with participants who visited a shop and purchased a supplement containing St. John's wort served as data for this case study. All interviews were conducted in person. During the interview, participants were

asked comparable questions based on the themes identified in the theoretical framework (section 2.1). Participants were firstly asked to elaborate on the shop visit in general, and to disclose any unexpected events, after which questions were asked about the content of the provided information and the perceived reliability. Participants were additionally asked about their previous knowledge of St. John's wort, as this may influence their perception of the product and consequently the information they had received. To ensure participants disclosed all relevant information related to this visit, the interview was concluded by asking the participant whether they had any additional remarks.

The interview, conducted in English as members of the research team were not fluent in Dutch, was audio recorded and transcribed verbatim. All participants were asked to review the transcripts for potential inaccuracies and could indicate by e-mail whether they would be interested in receiving a summary of the study findings.

4.2.4 Data analysis

All transcripts were analysed systematically by means of directed content analysis, to identify key concepts from the interviews using the existing theoretical framework (41). Based on the phenomenological research approach (31), it was first determined what the participants experienced (textural description), in this study related to *what* information was provided. Secondly, data related to *how* participants had experienced the shop visit (structural description) was analysed. In the process of reading and re-reading the transcripts, the previously developed category scheme based on the theoretical framework (section 2.1) was adjusted by the additionally identified themes and subthemes. Finally, all transcripts were coded based on the final category scheme to ensure consistency in data analysis. The category scheme was transformed into a code book, describing the categories, the explanation of the category and an example from the transcripts. By providing insight into the content of the information that was provided to the participants, and their perceptions of this information, this codebook gives some understanding of the final step of information transfer which contributes to understanding the full information transfer from science to the consumer (figure 1). In the data analysis, the potential bias resulting from only including young (age 19-25) students involved in food related education was taken into account. This inclusion criterion might have influenced the participants' perception of the information as well as the way these people were approached by employees in the stores, which was taken into consideration in the coding.

To reduce the possibility of confirmation bias all interviews were analysed by two members of the research team.

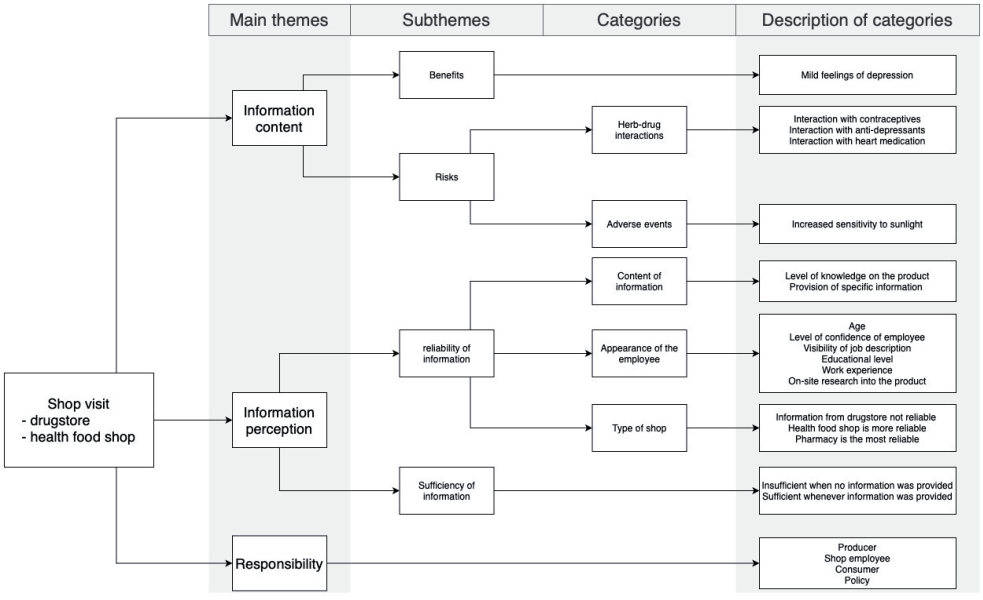
4.2.5 Ethical approval

The study protocol (ERCIC_137_07_05_2019) was reviewed and approved by the ethical review committee of Maastricht University.

4.3 Results

The qualitative interviews, based on the theoretical framework (section 2.1), resulted in the identification of three main themes on the perception of information provision in shops: (1) the content of information provided during purchase, (2) the perceived reliability of this information and (3) the responsibility of informing the consumer about risks and benefits of herbal dietary supplements (figure 2).

Figure 2. Interview themes



The coding tree displaying the results from the semi-structured interviews. The first column displays the three main themes related to the information content, the participants' perception of the information and the responsible actors for warning consumers. The second and third column display the subthemes related to the three main themes, and the identified categories within these subthemes. In the final column, detailed descriptions of the main- or sub themes are provided.

4.3.1 Information provided in the shop

The first theme relates the content of information provided spontaneously to consumers when purchasing St. John's wort. The information provision could be either verbally or in writing on for example the package or the shelf. The content of the information provided, can be divided in two subthemes: information on the benefits and information on the risks.

4.3.1.1 Information provided to the consumer during the shop visit

In general, during the visits either no information was provided at all, or the information was highly specific and detailed.

The information on the benefits was related to the scientifically established information on the positive aspects of using St. John's wort: the product is to be used when a person feels slightly depressed. One participant stated: *'She mentioned, I remember, that it was beneficial for depression, feelings of depression.'*

Information that was provided on the risks of the product can be divided in general risks and potential herb-drug interactions.

Regarding the general risks, participants were merely informed about the increased sensitivity to sunlight, whereas various potential herb-drug interactions were mentioned by the shop employees. Participants were most often informed about the potential of St. John's wort to interact with contraceptives. Other mentioned herb-drug interactions were the interaction of St. John's wort with anti-depressants and heart medication:

> *Participant: 'The lady was nice, and she asked questions. So yeah, she was really sweet.'*
>
> *Interviewer: 'Which questions did she ask?'*
>
> *Participant: 'Whether I'm on contraceptives, whether I take something for my heart.'*

No specific brands or substances of the contraceptives, anti-depressants and heart medication were mentioned when the herb-drug interactions were explained to the participants.

4.3.1.2 Written information

Besides verbal communication, participants were made aware of the benefits of the product by means of health claims on the label: *'I only just looked at the product itself, just the front thing. Like this,* (points towards the label) *for relaxation.'*

Additionally, also the thematic shelf where the product is placed on in the store was described as an indication of the benefit of the product. In some shops, the product was placed on a shelf with a theme related to relaxation, calmness or sleeping. The theme of the shelf was by participants considered to be communicating the benefit of the product: *'No, we were standing in front of the shelf that said calmness and sleeping or something, it was like a thematic shelf'*

4.3.2 Perception of information provision

The next section unveils the participants' perception of the information. Insights were provided into the perceived reliability of the information, originating from the theoretical framework, and an additional emerging subtheme from the data: the perceived sufficiency of information (figure 2).

4.3.2.1 Perceived reliability of information

Participants were asked whether they considered the information that was provided to be reliable, and what to them influences the perceived reliability. Three subthemes for the perceived reliability were identified through the interviews: the content of information, the appearance of the shop employee and the type of shop (figure 2)

The authority of the employee was referred to as the main contributor to the reliability. This authority should be visible in both their appearance and the content of the information.

Shop employees that provide specific and detailed information were perceived to be reliable, also because of the time dedicated to informing the consumer: *'if she did give me all the benefits and the side effects and everything, if she is very informative about the information, then I would see that as reliable, or more reliable.'*

The tone of voice of the conversation was also described to affect the perceived reliability. Participants stated that whenever the information was provided with confidence, the information was perceived to be reliable: *'I think if they're really confident then you can maybe, I think, trust that a little bit.'*

The second contributor to the authority of the employee was their appearance. Younger age and apparent little work experience decrease the reliability of the employee.

A visible job description, by means of a name tag, and a professional appearance by wearing, for example, a white lab coat was also suggested to increase the perceived reliability of the information provided.

Finally, the type of shop that the participant visited was indicated to influence the perceived reliability. Information from employees working in health food shops were by the participant perceived as more reliable, mainly because the employee's educational level was regarded to be higher. Additionally, participants mentioned that they considered pharmacists to be even more reliable. This is also related to the level of education employees were perceived to have: whenever a participant considered the employee to be educated, the perceived reliability increased; a lower level of education was consequently related to decreased perceived reliability.

In-store research by the employee, either via computer or paper sources, was perceived differently among participants. Whereas for some this decreased the reliability (since the employee does not know the information by heart), some considered it to be positive when the information that is provided is "double-checked": *'When I was paying, he looked it up in his computer as well and he said something. So that is reliable. I think he wanted to confirm it for himself'*

4.3.2.2 Perceived sufficiency of information

The perceived sufficiency of information, whether they had received a sufficient amount of information, varied between participants. The participants that did not receive any information, did not consider the in-store information provision to be sufficient. All participants that did receive information, perceived this to be sufficient, independent of the amount or details provided.

For some participants, the first response was indicating that the received information was sufficient. However, when asked to further elaborate on this, they indicated that some essential information was still missing: more information about the benefits, risks and potential drug interactions would have been useful. Also, participants critically described that the information was not personalized or that they were not provided with additional sources to further research the product.

Another identified subtheme related to perceived sufficiency, was the expectations participants had of shops and their employees. Various participants stated that although they would have liked to receive more information, it is questionable whether this can be expected from these stores: *'I think they provide an extra service with giving the information. And it's also, to me it's normal that in shops as *drugstore* they sell a lot of more stuff and it's busier, that it's difficult to give that information as well.'*

4.3.3 Responsibility for communicating risks and benefits of dietary supplements

Upon the question whose responsibility it is to inform consumers about effects of dietary supplements, participants provided different insights (figure 2).

4.3.3.1 Producer

Participants indicated that the producer is responsible for informing consumers about risks and benefits of product they intend to purchase, and communication should be done via the packaging of the product: *'Well on the packaging; the producer in the end, of course'*

Some participants expressed however uncertainty as to whether this is possible, or that this way of communicating may result in consumers not willing to use the product anymore because of the risks associated with the product, whilst the product may provide many benefits for them.

4.3.3.2 Shop employee

The subjects participating in this study believed that information on the benefits and risks of products should be provided upon purchase, also because of the trust consumers may have in their local shop employees: *'I think, the seller would have to tell something more about the product.'*

Participants did however also express, as observed for the perceived sufficiency of information provision, that providing all available information might cause an information overload for the consumer, and that providing information is an extra service these shops provide.

Information provision may be difficult for the employees in these stores because of a lack of knowledge. This can however, according to one of the participants, be resolved by creating a database with all information, that shop employees can use to research potential risks associated with these products: *'Of course, she*

cannot know of all products, but at least have a database, so when somebody buys a product, look it up and find them.'

4.3.3.3 Consumer

The consumer also was considered to have some responsibility, since they are the user of the product. Their responsibility was mainly described as needing to read the provided information and asking additional information about the product: *'If I were to consume the product myself, yes, I would ask the employee, what are the benefits, and what are the risks.'*

The consumer is, however, not considered to be fully responsible by various participants: participants recognize the different educational levels of consumers which was considered to be influencing the level of knowledge on dietary supplements as well: *'I mean there is responsibility, but it's so difficult, because it relies so much on education and a lot of factors that a consumer can't control for. There is a lot of information that is unknown, and then it's really understandable that's unknown to a lot of consumers.'*

4.3.3.4 Regulating communication

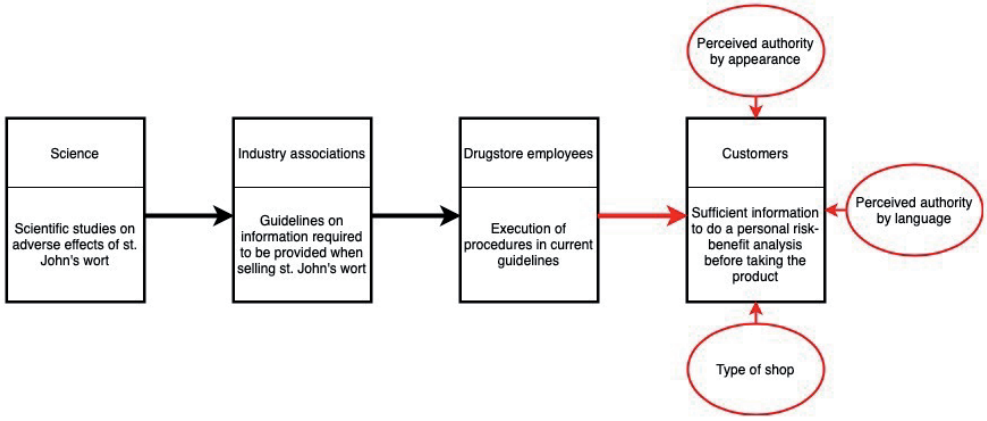
Various participants suggested to adjust policy related to the availability of dietary supplements. They believed that it should be reconsidered that such products are currently so widely available whilst they are not without risks: *'I think it's maybe unwanted that these kinds of things can just be bought by anyone in any amount. For me, I don't feel like it is regulated that well.'*

4.4 Discussion

As highlighted in this case study into the perception of risk and benefit information provision on supplements containing St. John's wort, the provision of science-based information in drugstores and health food shops is inconsistent. Whereas some participants were provided with highly detailed information, other participants were not given any information (figure 3). The participants perceived the information differently and various external factors are shown to influence this perception.

The aim of this study was to identify how consumers perceive the verbal information provision on both risks and benefits on St. John's wort containing products when purchasing such supplements in a Dutch drugstore or health food shop. The findings indicate that the risk and benefit information transfer from science to consumers via retail employees is influenced both by the content of the informa-

Figure 3. Influences on information transfer from science to consumer



The information transfer from science to consumers and the found influence that impact on the information transfer. Firstly, the transfer of information from employee to consumers is shown to not be consistent in this case study. Most importantly however, the results from this study show that the way a consumer perceives this information is influenced by three main factors: the type of shop in which the information is provided, the perceived authority of an employee due to the language used, and the perceived authority of an employee due to their appearance.

tion that was provided and how this information is perceived by the consumer. There were no major differences observed between the answers provided by participants visiting a drugstore and those visiting a health food shop.

4.4.1 Information content

According to the Dutch Drugstore Guidelines, a verbal warning on the potential of St. John's wort containing products to interact with certain medicinal products should be provided to customers when they purchase such products in a drugstore or health food shop (27). Findings from this study indicate that the verbal in-shop information provision does not always follow these guidelines: the information provision was either very elaborate and detailed, or no information was provided at all.

Previous research conducted with pharmacists indicate that they regularly answer questions about *i.a.* herbal products (28,39). Although pharmacies are different from drugstores and health food shops, it indicates that professionals provide information during the purchase of a product. These studies however focussed on questions asked by consumers, whereas the participants in this study were instructed not to ask any questions, to analyse spontaneous information provision. The study set-up therefore provides no insight as to whether the

knowledge is available in the shop, as the participants, upon asking questions, could have been provided with more insights into risks and benefits. Employees henceforth might have knowledge on St. John's wort, but this information is not transferred spontaneously. Additionally, regardless of this knowledge, the warning regarding the potential of St. John's wort to interact with conventional medicines was not consistently provided, consequently leading to inconsistency in the information provision.

Whenever information was provided, this was in line with adverse effects and potential herb-drug interactions as described in scientific literature (12,15–17). This finding differs from previous research in which information provided during the purchase of a wide variety of products was classified as being unscientific (37). Participants in this study only purchased St. John's wort, a dietary supplement of which the risks and benefits are thoroughly studied. Information on other dietary supplements of which the body of evidence is limited, may subsequently be of varying quality.

Secondly, besides the verbal information, participants also reported to have observed written information. These written statements predominantly seemed to describe benefits of products. Participants indicated that they learned about the benefits of St. John's wort through the shelf or the packaging of the purchased product. Previous research indicates that consumers are known to focus mainly on the front of the package when aiming to rapidly inform themselves (35). Only when specifically asked to determine the risks of a dietary supplement, 98% of participants in a study among female dietary supplement users was able to correctly name them (42). Hence, the health benefit is immediately visible for the consumer, whereas they are required to put additional effort in determining potential risks. Although it seems that a warning statement should be provided on the front of the package, previous research showed that consumers do not read warning labels, or that it does not impact on the safety evaluations of such products (35,36). Communication by means of the label is therefore effective for benefits, but might not be sufficient for communicating the risks.

Besides the information on the product, participants became aware of product health benefits due to the thematic shelf where the product was placed upon in the shop. All voluntary statements about the nutritional content or health benefits of products are in the EU considered to be nutrition and health claims (Art. 2.2) (22,43). Although such health claims are often used in advertisements and on labels, this observation indicates that health benefits are also communicated by the placement of the product in the shop. Henceforth, by placing the product on

a thematic shelf, there might be unintentional information transfer by implicitly attributing health benefits to the product on that specific shelf.

It is known that consumers also use other sources to inform themselves about dietary supplements they intend to use (33,44). An example of such an additional source is the information available on the internet, of which research has shown that it is used for information on dietary supplements by 45.1% of males and 26.1% females who are interested to buy such supplements. However, information provided online is not necessarily complete, as a study into the Wikipedia pages of commonly used botanicals showed (45). Although these pages are reported to mostly contain information on the health benefits and potential adverse effects is often provided, information regarding herb-drug interactions, use of the product during pregnancy and contraindications for usage is often lacking (45). The use of other information sources by consumers indicates that information provision does not only occur in drugstores and health food shops. The poor quality of the information available on the internet does however show that this information is often incomplete. Drugstore and health food shop employees might be capable of providing more complete and balanced information.

4.4.2 Perception

The perceived sufficiency of the provided information was directly related to whether participants received any information at the moment of purchase, or not. Whenever information was provided, the participants' initial responses were positive towards this information being sufficient. Only when no information was provided at all, participants considered the information provision to be insufficient. Some participants however, changed their initial response from stating the information was sufficient to it being insufficient during the interview. This can be attributed to study sample characteristics: the sample only included students who are enrolled in a food related university programme. The recall of their background knowledge and previous awareness of potential adverse effects from St. John's wort may have influenced this shift towards perceived insufficiency.

The main contributor to the perceived reliability of information provided to participants, is the authority of the shop employee who provides the information. This authority could, according to the participants, be visible in both language and appearance.

One of the contributors to authority and consequently the perceived reliability is the level of confidence by which the employee provided the information.

Previous research found that only 15% of pharmacists was very confident when informing consumers about complementary and alternative medicines (39). The interviewees in this study indicated that this level of confidence appears to be visible to the consumer as well, and that it thus has an impact on the perceived reliability.

The appearance of the employee, specified in the interview as the age, the assumed level of work experience and educational level, and the visibility of a job description, also influenced the perceived reliability of the information provided. Previous research indicates that information was also provided to consumers by non-licensed employees who may be have little understanding of scientific information and are less experienced (28). This can influence the reliability of provided information. The Dutch Drugstore Guideline does however state that a general warning about potential herb-drug interactions should be provided (27). Such a basic warning can be provided regardless of the level of knowledge of the employee and ensures that consumers are at least made aware of potential negative effects of the product. Additionally, even when the employee providing the warning is not considered to be reliable by the consumer, the warning itself might result in additional research by the consumer. This consequently leads to a more informed decision and potentially less adverse effects due to dietary supplements among users.

Various participants indicated that the employee they were in contact with researched the product during the purchase process which was valued differently among participants. On site research into herbal products is not uncommon, as 43.8% of pharmacists indicated they do use resources when providing advice to consumers (28). Whether this increases reliability depends on the type of source where scientific sources may increase reliability, whereas information from manufacturers may be more subjective (39).

Finally, the type of shop seems to influence the reliability of the provided information. Participants in this study visited drugstores and health food shops, pharmacies were excluded. Information provided by employees from health food shops was perceived to be more reliable. Some participants also indicated that pharmacists would be even a better source of information, which is in line with previous findings where pharmacists were seen as most trustworthy, whilst retail clerks were rated lowest (33). This study, in line with previous findings, shows that employees in drugstores and health food shops are not always perceived as reliable information sources in selling herbal dietary supplements. Since pharmacists, but also natural practitioners and nurses are seen as more reliable

information sources by consumers (33), these findings give rise to the question whether dietary supplements should be sold without the interferences of any health professional. When consumers could only purchase a dietary supplement after consulting with such a professional, they would be able to obtain information from a source they consider to be reliable. In the Netherlands, dietary supplements are however widely available over the counter in drugstores and health food shops and also in supermarkets. Employees particularly in health food shops and drugstores have to adhere to the code of conduct on selling herbal dietary supplements, which dictates that information should be provided during the purchase of such supplements. The employees in these shops could therefore serve as a source of information when products are purchased, to create awareness on potential adverse effects of dietary supplements. What has however not been studied in this case study, is whether the employees themselves are aware of the potential health benefits or risks. Before employees in these stores can be considered credible sources of information by consumers, it should be ensured the employees have the knowledge on the risks and benefits. If consumers then research the dietary supplement by means of other sources such as the internet, newspapers or magazines, the information provided in the shop can serve as a confirmation of the information for the consumer.

The consumer's perceived reliability of the information influences the information transfer since consumers disregard the information when they do not consider it to be trustworthy. Previous research found that consumers are occasionally not receptive for the information provided at the counter (29). Henceforth, besides incomplete or unreliable information provision, the consumer's attitude towards the provided information can stagnate the information transfer. An increased perception of reliability may positively influence the receptiveness.

Many aspects influence the perceived reliability of the in-shop information provision. This perceived reliability is expected to impact the information transfer, since interviewees indicated they would not use the information when it is not considered to be reliable.

4.4.3 Responsibility

The third theme that resulted from the theoretical framework and was consequently addressed in the interviews was the responsibility for informing consumer about the potential risks of a dietary supplement. The interviewees identified three potential responsible actors to provide or find this information: the consumer, the manufacturer and the shop employee, and that this responsibility should be regulated in policy.

Previous research into functional foods found that the industry, governmental parties and health professional should cooperate in order to improve education which can lead to more informed choices of consumers (46). This is in line with the participants' comments in this study as they explained consumers to be, at most, partial responsible as although they should attempt to inform themselves by asking questions to, for example, their physician. However, knowing everything about dietary supplements requires in-depth knowledge, which most of the consumer do not have. This was also found in previous research: general understanding of health benefits and risks of a food product is influenced by the educational level of the consumer (47,48). And even highly educated consumers are not fully informed on nutrition, as it was observed that the participants that visited the shops in this study, students enrolled in higher nutrition-related education, were unaware of the distinction between food and medicinal products since they referred to the dietary supplement as being a medicinal product. This is in line with previous research that also found that consumers link medicinal attributes to dietary supplements (49). It is therefore unlikely that consumers know detailed information on risks and benefits of specific herbal dietary supplements. This makes determining the level of responsibility difficult, as the general understanding of consumers varies and depends on various other attributes.

Various participants stated that policies regulating sales of dietary supplements should not allow for dietary supplements with adverse effects to be sold in drugstores, and that policy should lay down requirements for a mandatory warning for consumers. Information communication by the label is regulated by the Regulation on food information to consumers and the food supplements Directive, and these do not require warning statements (6,23). One of the objectives of EU food legislation is to protect human health, which would make warning statements on products unnecessary (Art. 1.1) (19). It is however questionable if it can be guaranteed that food products never pose a risk to human (50). This is exemplified by scientific literature that revealed that dietary supplements can have negative health consequences when taken concurrently with a medicinal product such as anti-depressants (9). Hence, written warning statements for such products might reduce the number of people suffering from adverse effects. It must however be taken into account that warning statements and disclaimers have been proven to be unsuccessful in informing consumers in previous research (35,36). Solely requiring warning statements by law might henceforth not result in full consumer awareness of risks and benefits of herbal dietary supplement.

Another possibility for addressing the communication of potential risks of dietary supplement in policy are the conditions of use of authorised health claims.

Health claims on botanicals are currently on hold pending a decision upon the required evidence to substantiate these health claims (51,52). The debate mainly revolves around the question whether evidence on traditional use is sufficient to substantiate health claims on botanicals (52). Authorised health claims and their conditions of use are published in the Commission Regulation establishing a list of permitted health claims made on foods (Art. 1) (53). Since the evaluation of health claims on botanicals are on hold, these claims may be used pending the decision of the European Commission on the required evidence, but they are not published in this list, and there are no conditions of use. When the evaluation is however resumed and the health claims would be authorised, using such conditions of use may provide an opportunity for warning statements for consumers about potential herb-drug interactions.

Finally, national food and pharmaceutical legislation may provide rules on the communication of risks and benefits of dietary supplements. For pharmaceuticals, the Dutch national law distinguishes between prescription products, products that can only be sold in pharmacies, and the over the counter products that can be sold in both pharmacies and drugstores (54). This is however not instated for dietary supplements, and it is unclear whether this is legally possible as dietary supplements are food products and the General Food Law states that food products can be sold in retail including i.a. supermarkets, shops and other food service operations (Art. 1.3) (19).

The interviewees pointed towards policies for ensuring that consumers are warned about potential adverse effects of dietary supplements. Various relevant European regulations dealing with information (Regulation on Food Information to Consumers), food supplements (Food Supplements Directive) or claims (Nutrition and Health Claim Regulation) provide opportunities for changes by means of, for example, mandatory warning statements. It must however be recognized that, although this are guidelines established by an industry association and it is not laid down in public law, there are currently already guidelines on the verbal communication of risks and benefits of over-the-counter products (27). Based on these shop visits, it can be established that these guidelines are not successfully implemented in all Dutch drugstores and health food shops. Hence, before changing policy, improved implementation of current guidelines is necessary to improve the scientific benefit-risk communication towards consumers in shops.

4.4.4 Strengths and limitations

This case study was the first study that analysed the actual information transfer on risks and benefits of herbal dietary supplements to consumers in drugstores

and health food shops and how this is perceived by these consumers. Whereas previous research has studied information provision in pharmacies, no research had yet focused on other retail facilities selling herbal dietary supplements, and limited findings from the consumer's perspective had been reported in literature. As the published research so far only used a quantitative methodology (by conducting surveys into the number of people who were asked to provide information for example on risks and benefits), this case study allowed for gaining a detailed understanding of this consumer perception towards the provided information, following a phenomenological research approach. As the interviews immediately followed the moment of purchase, participants could more easily recall the provided information.

The main limitation of this study results from the study sample: all participants were students. Even though participants were instructed not to ask any question to trigger the information transfer but to allow for a spontaneous information provision in the store by the employee, the selection of young adults may have triggered a specific response from the shop employee. Therefore, the experience of these participants is not necessarily the experience of all members of the population, as for example frail or elderly persons may be treated differently by such employees (55). Additionally, the selection of students studying food-related subjects may have resulted in a highly critical study sample, as shown in the results on perceived sufficiency of information where interviewees later started to question the amount of information provided during the moment of purchase. Specifically, various participants were already aware of potential adverse effects of St. John's wort because of studying this in university courses. They therefore may have expected to hear all this information from a shop employee, whereas some of this information is advanced scientific knowledge. The obtained results do indicate that participants were aware of their knowledge status, exemplified by statements on the feasibility of information provision in the shops, and references to educational levels when discussing the consumer responsibility for becoming aware of potential side effects. Even though this might have influenced the perception of the participants and may be even the way these participants were approached by the employees, the findings do show an inconsistency in information provision within a group of customers with similar characteristics.

The study sample was furthermore composed of predominantly women, who seem to judge the received information more on their perceived reliability compared to men (56). These aspects, however, mainly influence the study results regarding the participants' perceptions, and do not influence the actual informa-

tion provision nor the content of this information. The content of information provided to the interviewees was irrespective of educational level, since this information was provided spontaneously and is therefore assumed to be common practice in these shops. This case study furthermore shows the complexity of communicating risk and benefit information to consumers because of the external influences determining a consumers' perception. It can therefore serve a base for future qualitative and quantitative studies into risk and benefit communication to consumers.

4.5 Conclusion

The disclosure of potential risks and benefits of herbal dietary supplements can aid the consumer in making an informed decision whether to take the product. One channel to gain such information is the retail shop, where herbal dietary supplements can be purchased over the counter. It is however unknown whether the information available from scientific studies is sufficiently transferred to the consumer. This case study was the first to determine how the provision of verbal information on risks and benefits of a dietary supplement containing St. John's wort is perceived by consumers. These insights provide a deeper understanding in the information transfer from science to consumers, which is important in order to ensure consumers can make a well-informed decision on the purchase of dietary supplements.

The findings of this study indicate that verbally, there is either no information provision at all in these stores, or the provided information is very detailed. Whenever no information was provided, participants seemed to inform themselves about the benefits only through the packaging of the product or the thematic shelf upon which the product was placed. The perceived reliability of information was predominantly determined by the perceived authority, in appearance, such as age, the confidence in the conversation and the specificity and amount of details in the provided information. Conducting on-site research, in a textbook or the computer, was valued differently among participants. Finally, the type of shop was also found be influence the perceived reliability: although excluded in this study, pharmacies were perceived to be most reliable, and drugstore the least reliable source of information. These aspects, contributing to the perceived reliability, eventually have an impact on information transfer as consumers appear to not use the information when they do not consider it to be reliable. Concerning the final theme on the responsibility for warning the consumer on potential adverse effects of dietary supplements, the interviewees

mentioned for actors: the manufacturer, the shop employee, the consumer or policymakers. This study does however show that the current guidelines are not fully implemented. Henceforth, including consumer warnings in the policies for the various actors would at first require full implementation for any change in policy to become successful.

4.5.1 Implications for research and practice

The information provision to consumers in drugstores and health food shops varies between shops. Since some of the 15 participants received detailed and scientifically proven information, it can be said that information transfer from science to consumer through retail is possible. It remains unknown whether the knowledge is present in the shops where no information was provided. Potentially, employees are not even informed about the adverse effects of a product, or the necessity to inform consumers about these adverse effects. This case study is limited in terms of study sample and design, as the purchase of a single product was studied. It does however show that communicating risk and benefit information from science to consumers is rather complex and influenced by many factors. Further research is required to analyse the information transfer from science to employees working in shops selling products that contain botanicals with potential adverse effects and the factors influencing the perception of consumers regarding risk and benefit information of dietary supplement. As the average consumer in the EU is expected to be reasonably well-informed, it is essential that consumers can make well-informed decisions about consuming such products, but this can only be guaranteed when this information is also made available at the point of purchase.

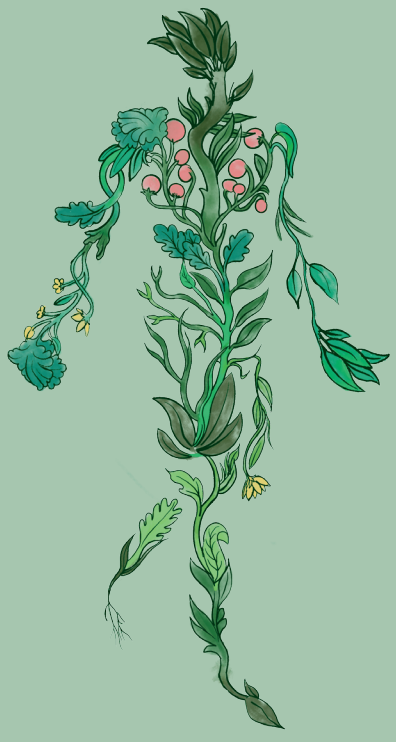
4.6 References

1. Euromonitor International. Vitamins and Dietary Supplements. Market Sizes | Historical. 2018.
2. de Boer A, Bast A, Godschalk R. Dietary supplement intake during pregnancy; better safe than sorry? Regul Toxicol Pharmacol. 2018;95:442–7.
3. Menrad K. Market and marketing of functional food in Europe. J Food Eng. 2003;56(2–3):181–8.
4. Garcia-Alvarez A, Egan B, Klein de S, Dima L, Maggi F, Isoniemi M, Ribas-Barba L, Raats MM, Meissner EM, Badea M, Bruno F, Salmenhaara M, Milà-Villarroel R, Knaze V, Hodgkins C, Marculescu A, Uusitalo L, Restani P, Serra-Majem L. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One. 2014;9(3):1–18.
5. Jeurissen SMF, Buurma-Rethands EJM, Beukers MH, Jansen-Vliet van der M, Rossum van CTM, Sprong RC. Consumption of plant food supplements in the Netherlands. Food Funct. 2018;9:179–90.
6. European Parliament and the Council of the European Union. Consolidated version of directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Off J Eur Union. 2002;183:1–14; 26-07-2017.
7. EFSA. Botanicals [Internet]. 2018 [cited 2018 Apr 3]. Available from: https://www.efsa.europa.eu/en/topics/topic/botanicals
8. Knudsen VK, Rasmussen LB, Haraldsdottir J, Ovesen L, Bulow I, Knudsen N, Jørgensen T, Laurberg P, Perrild H. Use of dietary supplements in Denmark is associated with health and former smoking. Public Health Nutr. 2001;5(3):463–8.
9. Müller WE. Current St. John's wort research from mode of action to clinical efficacy. Pharmacol Res. 2003;47:101–9.
10. Greeson JM, Sanford B, Monti DA. St. John's wort (Hypericum perforatum): a review of the current pharmacological, toxicological, and clinical literature. Psychopharmacology (Berl). 2001;153(402–414).
11. Butterweck V, Schmidt M. St. John's wort: Role of active compounds for its mechanism of action and efficacy. Wiener Medizinische Wochenschrift. 2007;157(13–14):356–61.
12. Ernst E, Rand JI, Barnes J, Stevinson C. Adverse effects profile of the herbal antidepressant of St. John's wort (Hypericum perforatum L.). Eur J Clin Pharmacol. 1998;54:589–94.
13. Knüppel L, Linde K. Adverse effects of St. John's wort: a systematic review. J Clin Psychiatry. 2004;65(11):1470–9.
14. Bijwerkingcentrum Lareb. Overview of reports on St. John's wort (Hypericum perforatum). 2018.
15. Mannel M. Drug interactions with St John's Wort. Mechanisms and clinical implications. Drug Saf. 2004;27(11):773–97.
16. Hall SD, Wang Z, Huang S-M, Hamman MA, Vasavada N, Adigun AQ, Hilligoss JK, Miller M, Gorski JC. The interaction between St John's wort and an oral contraceptive. Clin Pharmacol Ther. 2003;74(6):525–35.
17. de Boer A, van Hunsel F, Bast A. Adverse food-drug interactions. Regul Toxicol Pharmacol. 2015;73:859–65.
18. Markowitz JS, Donovan JL, DeVane CL, Taylor RM, Ruan Y, Wang J-S, Chavin KD. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. J Am Med Assoc. 2003;290(11):1500–4.
19. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European

Food Safety Authority and laying down procedures in matters of food safety. Off J Eur Union. 2002;31:1–44; 26-07-2019.
20. de Boer A. Scientific assessments in European food law: making it future-proof. Regul Toxicol Pharmacol. 2019;108:1–6.
21. Lieberman HR, Austin KG, Farina EK. Surveillance of the armed forces as a sentinel system for detecting adverse effects of dietary supplements in the general population. Public Health Nutr. 2017;21(5):882–7.
22. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
23. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Off J Eur Union. 2011;304:1–60; 01-01-2018.
24. Schebesta H, Purnhagen K. The behaviour of the average consumer: A little less normativity and a little more reality in CJEU's case law? Reflections on Teekanne. Wageningen Work Pap Law Gov. 2016;03:1–23.
25. van Dijk H, Fisher ARH, Frewer LJ. Consumer responses to integrated risk-benefit information associated with the consumption of food. Risk Anal. 2011;31(3):429–39.
26. Rowe SB. Communicating science-based food and nutrition information. J Nutr. 2002;132(8):2481S-2482S.
27. Centraal Bureau Drogisterijbedrijven. Nederlandse Drogistennorm. Bij terhandstelling van UAD-geneesmiddelen onder toezicht en verantwoordelijkheid van drogisten. 2017.
28. Nathan JP, Cicero LA, Koumis T, Rosenberg JM, Feifer S, Maltz F. Availability of and attitudes toward resources on alternative medicine products in the community pharmacy setting. J Am Pharm Assoc. 2005;45(6):734–9.
29. Banks J, Shaw A, Weiss MC. The community pharmacy and discursive complexity: a qualitative study of interaction between counter assistants and customers. Heal Soc Care Community. 2007;15(4):313–21.
30. Polit DF, Beck CT. Sampling in quantitative research. In: Nursing Research Generating and assessing for nursing practice. 2012. p. 273–92.
31. Creswell JW, Poth CN. Five qualitative approaches to inquiry. In: Qualitative inquiry & research design. 2018. p. 65–110.
32. Neubauer BE, Witkop CT, Varpio L. How phenomenology can help us learn from the experiences of others. Perspect Med Educ. 2019;8:90–7.
33. Bouldin AS, Smith MC, Banahan BF, McCaffrey DJ, Croom EM. Herbal supplement information and the consumer. Drug Inf J. 2000;34:1339–53.
34. Cramer H, Shaw A, Wye L, Weiss M. Over-the-counter advice seeking about complementary and alternative medicines (CAM) in community pharmacies and health shops: an ethnographic study. Heal Soc Care Community. 2010;18(1):41–50.
35. Spink J, Singh J, Singh P. Review of package warning labels and their effect on consumer behaviour with insights to future anticounterfeit strategy of label and communication systems. Packag Technol Sci. 2011;24:469–84.

36. Mason MJ, Scammon DL, Fang X. The impact of warning, disclaimers, and product experience on consumers' perception of dietary supplements. J Consum Aff. 2007;41(1):74–99.
37. Temple NJ. The marketing of dietary supplements: a Canadian perspective. Curr Nutr Rep. 2013;2(4):167–73.
38. Howard M, DiDonato K, Janovick D, Schroeder M, Powers M, Azzi A, Lengel AJ. Perspectives of athletes and pharmacists on pharmacist-provided sports supplement counseling: an exploratory study. J Am Pharm Assoc. 2003;58(4S):S30–6.
39. Semple SJ, Hotham E, Rao D, Martin K, Smith CA, Bloustien GF. Community pharmacists in Australia: barriers to information provision on complementary and alternative medicines. Pharm World Sci. 2006;28:366–73.
40. Péter S, Navis G, de Borst MH, von Schaky C, van Orten-Luiten ACB, Zhernakova A, Witkamp RF, Janse A, Weber P, Bakker SJL, Eggersdorfer M. Public health relevance of drug-nutrition interactions. Eur J Nutr. 2017;56:23–36.
41. Polit DF, Beck CT. Qualitative data analysis. In: Nursing Research Generating and assessing for nursing practice. 9th Editio. Wolters Kluwer Health I Lippincott Williams & Williams; 2012. p. 556–81.
42. Miller CK, Russell T. Knowledge of dietary supplement label information among female supplement users. Patient Educ Couns. 2004;52:291–6.
43. de Boer A, Vos E, Bast A. Implementation of the nutrition and health claim regulation–The case of antioxidants. Regul Toxicol Pharmacol. 2014;68(3):475–87.
44. Lieberman HR, Marriott BP, Williams C, Judelson DA, Glickman EL, Geiselman PJ, Dotson L, Mahoney CR. Patterns of dietary supplement use among college students. Clin Nutr. 2015;34(5):976–85.
45. Philips J, Lam C. Analysis of the accuracy and readability of herbal supplement information on Wikipedia. J Am Pharm Assoc. 2014;54(4):406–14.
46. McCannon A, Cade J, Pearman A. Stakeholder interactions and the development of functional foods. Public Health Nutr. 2001;5(3):469–77.
47. Mogendi JB, de Steur H, Gellynck X, Makokha A. Consumer evaluation of food with nutritional benefits: a systematic review and narrative synthesis. Int J Food Sci Nutr. 2016;67(4):355–71.
48. Nocella G, Kennedy O. Food health claims - what consumers understand. Food Policy. 2012;37:571–80.
49. Khedkar S, Carreresi L, Bröring S. Food or pharmaceuticals? Consumers' perception of health-related borderline products. PharmaNutrition. 2017;5:133–40.
50. de Boer A, Bast A. Demanding safe foods - safety testing under the novel food regulation (2015/2283). Trends Food Sci Technol. 2018;72:125–33.
51. Hoogenraad E, Duivenvoorde B. Health claims for botanicals: "on hold", yet forbidden? Eur Food Feed Law Rev. 2016;1:58–9.
52. Lenssen KGM, Bast A, de Boer A. International perspectives on substantiating the efficacy of herbal dietary supplements and herbal medicines through evidence on traditional use. Compr Rev Food Sci Food Saf. 2019;18(4):910–22.
53. European Commission. Consolidated version of commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring reduction of disease risk and to children's development and health. Off J Eur Union L. 2012; 22-08-2017.
54. Hoogervorst JF, Hirsch Ballin EMH. Geneesmiddelenwet [Internet]. 2007. Available from: https://wetten.overheid.nl/BWBR0021505/2019-04-02

55. Koster ES, Philbert D, Blom L, Bouvy ML. “These patients look lost” - Community pharmacy staff’s identification and support of patients with limited health literacy. Int J Pharm Pract. 2016;24(6):403–10.
56. Zheng T, Yao D, Chen W, Hu H, Ung COL, Harnett J. Healthcare providers’ role regarding the safe and appropriate use of herbal products by breastfeeding mother: a systematic literature review. Complement Ther Clin Pract. 2019;35:131–47.



Chapter 5

Should botanical health claims be substantiated with evidence on traditional use? Reviewing the stakeholders' arguments

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Abstract

Background

The evaluation of botanical health claims was put on hold to determine whether traditional use evidence is sufficient to substantiate these health claims. To gain a deeper understanding of the discussion on the substantiation of botanical health claims, a critical review of the stakeholders' arguments was conducted.

Methods

The relationships of stakeholders were analysed with a social network analysis and the stakeholders' arguments were critically reviewed with scientific literature.

Results

The social network analysis showed that the majority of the stakeholders were in favour of using evidence on traditional use for botanical health claim substantiation. These stakeholders were however highly interrelated which may explain their similar viewpoints on botanical health claims.

The arguments that were put forward by the stakeholders cover a wide array of subjects indicating the discussion's complexity. Various arguments could furthermore not be assessed with scientific literature as these were focused on the unpredictable impact of a decision on the substantiation of botanical health claims. The review also shows that stakeholders interpret various underlying concepts such as consumer misleading differently.

Conclusions

This study shows that the discussion is scattered. A political decision on various unclear concepts is required to eventually make a decision upon using traditional use evidence to substantiate botanical health claims.

5.1 Introduction

Herbal dietary supplements on the European market can currently carry health claims that are not scientifically evaluated nor authorised, even though voluntary communication of health benefits is strictly regulated in Europe (Art. 1) (1). Communicating and advertising benefits of foods, including dietary supplements, is regulated under the Nutrition and Health Claims Regulation (NHCR), Regulation (EC) No 1924/2006) (1). Since its entry into force in 2006, the NHCR requires that claims cannot be false and misleading, and only scientifically substantiated claims are authorised by the European Commission (EC). The scientific assessment of the 44,000 proposed claims in 2008 is however not yet complete: the assessment of health claims on botanical substances has been put on hold (2).

Botanicals are in the European Union (EU) referred to as products from plants, algae, fungi or lichens (3). Botanicals are not regulated as such but are dealt with under the legal frameworks of foods and pharmaceuticals, depending on the dose and consequently the health effect of the specific botanical (4,5). When used as medicinal product, botanicals can be centrally registered as traditional herbal medicinal products (Art. 16a.1) (6). This simplified registration procedure allows for the substantiation of both safety and efficacy by 'evidence on traditional use', defined as evidence proving the product has had medicinal use for 30 years of which 15 years within the EU (Art. 16c.1.c) (6). When used in a food product however, the health benefit (efficacy) of the product needs to be substantiated with evidence that the food is effective in reaching this health benefit, based on data from two independent human intervention trials showing the effect of the food in humans (7). This indicates that evidence on traditional use is not sufficient to substantiate a food's efficacy.

The EC's decision to put the assessment on hold was the result of a long-lasting debate on whether or not to allow the use of traditional evidence to substantiate efficacy claims on foods, similar to the evidence requirements for traditional herbal medicinal products (4). Because of the debate on this differing approach, the EC asked the European Food Safety Authority (EFSA) to temporarily stop the evaluation of health claims on botanicals in 2010 (8). Before continuing the assessment of health claims, it should be determined whether evidence on traditional use can be of significance in the body of evidence on botanical health claims. To date, the evaluation of claims on botanical foods and food ingredients has not yet been resumed.

In order to resolve the impasse created by putting the evaluation of botanical health claims on hold, the substantiation of botanical health claims has been the subject of a 2012 discussion paper published by the EC, but was also considered in reviewing the effectiveness of EU food legislation, and specifically the effectiveness of the NHCR (8,9).

The EC's discussion paper proposes two possibilities for resolving the impasse: (1) resume the evaluation as was conducted before, with the requirement of human intervention trials to substantiate a putative health effect, or (2) give recognition to evidence on traditional use as basis for food health claims (8). To date, no decision has been made on either of the two proposed suggestions. When EU food legislation was analysed under the regulatory fitness and performance (REFIT) programme, in which the EC reviews whether legislation meets its objectives, is efficient and not unnecessarily costly (10,11), the NHCR was specifically looked into. The REFIT evaluation of the NHCR focused on two elements: the necessity of nutrient profiles and the on-hold status of health claims on plants and their preparations, the botanicals (12). This REFIT evaluation commenced with publishing the roadmap in October 2015, in which the aim and questions of the evaluation are disclosed (12). Stakeholders were invited to provide feedback on this roadmap by October 2015, to ensure that the actual evaluation would address all questions deemed relevant (9). The provided feedback was published on the EC's webpage on the REFIT evaluation of health claims on botanicals (13). The results from REFIT suggest that the NHCR is currently not meeting its objectives of protecting consumers from false and misleading claims and harmonising legislation, due to the on-hold status of botanical health claims (14). It however does not give any insight into the way to move forward with the evaluation of botanical health claims. Previous research mainly studied the required data for substantiation with traditional use evidence (15,16). These studies consider traditional use evidence to be sufficient to substantiate botanical health claims (4,15–17). One study stated that the current situation prevents European harmonisation in food law, and that allowing traditional use evidence would equalise European food legislation as this evidence is allowed for traditional herbal medicinal products (17).

Scientific studies seem to already focus on the required data that should be presented when a health claim is substantiated with traditional use evidence for health claim substantiation. A decision regarding the substantiation of botanical health claims is however still pending as it remains to be determined whether health claim substantiation traditional use evidence is sufficient to reach the objectives of the NHCR. A critical review of the stakeholders' viewpoints regard-

ing the substantiation of botanical health claims with evidence on traditional use is currently unavailable. Analysing these viewpoints may provide insight into the underlying issues related that complicate a decision on the substantiation of botanical health claims. This study therefore aims to clarify the discussion on the substantiation of botanical health claims by reviewing the stakeholder arguments by determining which stakeholders were involved in the feedback procedure and critically reviewing all arguments put forward by these stakeholders.

5.2 Methods

To gain understanding of the viewpoints of stakeholders involved with botanical health claims, firstly a social network analysis was conducted to understand shared opinions, and secondly, a critical review of arguments was conducted to assess the scientific grounds for the presented viewpoints. As any self-identified stakeholder could provide feedback within the EC's REFIT feedback procedure in 2015, the inclusion of stakeholders for this analysis was based on their participation to the feedback procedure. This ensured the inclusion of self-declared stakeholders and provided a demarcated group of stakeholders and arguments which led to a focused and detailed review (13).

5.2.1 Identification of stakeholders and arguments

All feedback forms submitted in the EC's REFIT feedback procedure, which were published on the EC's webpage, were reviewed to identify relevant stakeholders. Only feedback forms written in English were included, excluding 1 feedback form submitted in French. A subsequent thorough search was conducted to retrieve all publications from the identified stakeholders on botanical health claims, including previous published reports or opinion papers. The search strategy included the stakeholder's name (in full and abbreviated), combined with the keywords 'botanical' and 'health claim' in both scientific and regular databases, including Google, Google Scholar and PubMed. Retrieved relevant publications were reviewed to identify additional relevant stakeholders, as a form of snowball sampling (18). All identified stakeholders were included in the social network analysis.

All publications were reviewed to identify arguments that were put forward about the substantiation of botanical health claims. Arguments were included for the scientific review when an argument was related to one of the two objectives of the NHCR: (i) protecting consumers from misleading and (ii) stimulating the harmonisation of the European internal market (Art. 1.1) (1), or when they were

described by multiple stakeholders. Arguments mentioned by multiple stakeholders were included in the critical scientific review as recurrent addressing of these topics by stakeholders was considered demonstrating the importance of that topic.

5.2.2 Social network analysis

To understand the relationships between stakeholders and the influence this might have on their viewpoint, a social network analysis was conducted (19). The official status (to typify the organisation) of all identified stakeholders (hereafter referred to as 'actors'), was reviewed in the EU's transparency register. This transparency register serves as a database in which all parties that are involved in policy making are registered (20). It discloses the activities of an organisation, such as memberships of EU working groups, that may influence policy making at the European level, but also their field of interest, such as consumer protection, animal health or human health, as well as their budget. It was furthermore reviewed whether an identified stakeholder serves interests on a national or international level.

Relationships between actors in the network were identified by analysing partnerships and memberships as disclosed on public webpages, as well as collaborative publications on the scientific substantiation of health claims on botanicals. Stakeholders which were not involved in the feedback procedure, but who were disclosed as affiliated with an actor that was involved in the feedback procedure, were added to this network as having a one-way relationship (displayed in figure 1). Actors representing multiple industries or Member States, such as European industry organisations, were marked as such; the members (national associations or industry associations) were not disclosed separately.

Following the identification of all relevant actors in the network, their described position of either being in favour or against accepting evidence on traditional use to substantiate botanical health claims, was visualised (figure 1).

5.2.3 Scientific review of arguments from stakeholders

To clarify the ongoing discussion on the substantiation of botanical health claims, the scientific grounds of the identified arguments was reviewed in two databases. This review aimed to identify academic literature related to the specific arguments and to the botanical-issue on health claims in Europe in general. The topics of the arguments covered multiple scientific disciplines, leading to the use of two general scientific databases: Google Scholar and ScienceDirect. Studies published since the publication of the NHCR (2006) could be included in the

study. A separate literature search was conducted for every provided argument with the keywords 'traditional', 'botanical', 'European Union' and/or 'dietary supplement'. In order to prevent biased results from the literature search, all identified arguments from the stakeholders' publications were generalised: no 'positive' or 'negative' words were used as keywords. Results from the database search were screened by title and abstract and included for the review when the subject of the article related to the argument. If any new terms or definitions appeared in literature, additional searches were conducted with these terms. Whenever the initial search strategy did not result in any publication, the argument was reviewed in relation to nutrition in general instead of focused on dietary supplements and botanicals. This allowed for a broader search, resulting in more identified publications which again were screened on title and abstract before being included in the review.

Following this literature search, all included studies were critically reviewed to provide insights into the underlying reasoning for each argument given by the stakeholders.

5.3 Results

5.3.1 Social network analysis

A total of 21 feedback forms were submitted in the feedback procedure. Of these 21 feedback forms, 18 addressed botanicals health claims. The three other feedback forms that solely commented on nutrient profiles were excluded from this network analysis. The 18 stakeholders either individually submitted a feedback form or did so in collaboration with other stakeholders.

Four of the stakeholders that submitted feedback are also member of working groups of the EU. These working groups deal with specific issues in European food policy such as animal products, or animal and plant health in the food chain. They provide the risk manager (the EC) with information regarding stakeholder viewpoints. As such, various stakeholders are represented in these working groups.

Figure 1 presents the network of stakeholders who have responded to the request to provide feedback on the presented roadmap, regarding the NHCR's REFIT evaluation.

Table 1. Stakeholders that responded to feedback request.

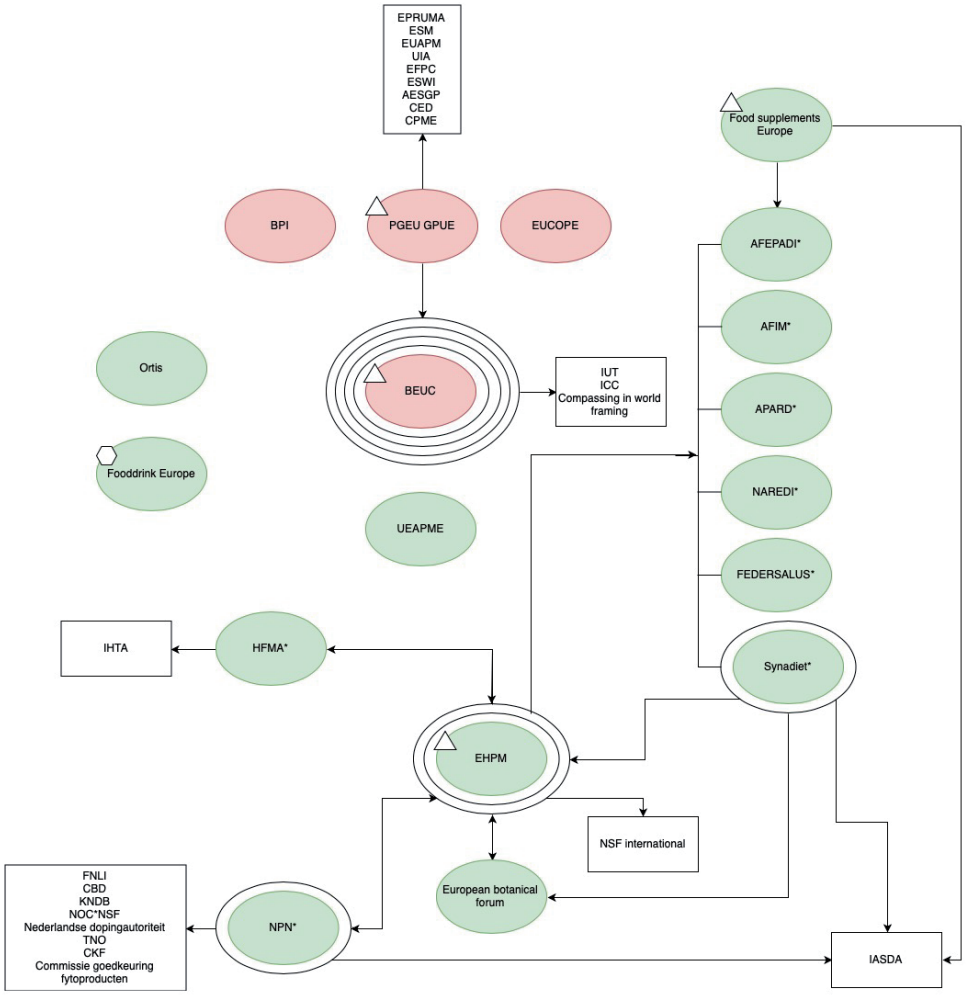
	Organisation type		Transparency register	Member of working group
PGEU GPEU	Non-profit organisation representing community pharmacists	International	Yes	Yes
BEUC	Non-profit organisation representing European consumers	International	Yes	Yes
BPI	Non-profit Industry association	National	Yes	No
EUCOPE	Non-profit Industry association	International	Yes	No
EHPM	Non-profit trade organisation	International	Yes	Yes
European botanical forum			No	No
Fooddrink Europe	Non-profit Industry association	International	No	No
Food supplements Europe	Non-profit Industry association	International	Yes	Yes
HFMA*	Industry association	National	Yes	No
Ortis	Company		Yes	No
UEAPME (now: SMEunited)		International	Yes	No
NPN*	Industry association	National	Yes	No
Synadiet*	Industry association	National	Yes	No
AFEPADI*	Industry association	National	No	No
AFIM*	Industry association	National	No	No
APARD*	Industry association	National	No	No
NAREDI*	Industry association	National	No	No
FEDERSALUS*	Industry association	National	No	No

The table displays the stakeholders that submitted a feedback form, its organisation type and whether operate at a national or international level. It furthermore show whether the stakeholder is registered in the EU's transparency register and whether it is active in European working groups.

The provided feedback forms disclosed, besides views on the questions that would be asked in REFIT, the position of the stakeholder regarding the acceptance of evidence on traditional use for the substantiation of botanicals health claims. These positions, together with the arguments stated to support this position, were used for the analyses conducted in this study.

Of the 18 stakeholders providing feedback on the roadmap, four describe to oppose the use of evidence on traditional use to substantiate health claims on botanicals. These stakeholders, three operating at an international level and one

Figure 1. network of respondents to feedback request.



Network of the responders in the feedback request. Red ovals present stakeholders that are against evidence on traditional use for the substantiation of health claims on botanicals. Green ovals present stakeholder that are in favour.

 # ⬭ = the numbers of documents published regarding the on-hold status of botanical health claims.

▭ = affiliated organisations that were not part of the feedback procedure.

⬡ = actor has industry associations as members.

△ = actor has national associations as members.

at the national level (Germany), are all registered in the Transparency register as a non-profit association (table 1).

The other 14 stakeholders disclosed in their provided feedback to be in favour of using evidence on traditional use for the substantiation of health claims on botanicals. Six stakeholders operate on an international level representing specific industries or consumers. The additional eight stakeholders are national industry associations, representing companies in the health products industry who are all member of EHPM, the European industry association for health products. Henceforth, although the majority of stakeholders seems to be supporting the use of evidence on traditional use, this majority consist of organisations that represent the same industry. This is exemplified by the joint position paper published by six out of eight industry associations.

5.3.2 Argumentation

Seven arguments of the stakeholders provided in the submitted scientific and technical viewpoints met the inclusion criteria for this study: these were arguments directly related to the NHCR's objectives or put forward by multiple stakeholders. Three topics were used for arguments that were used to support both the views of being in favour and those opposing traditional use evidence for substantiation of health claims, relate to three topics: (1) the impact on the market of dietary supplements and traditional herbal medicinal products; (2) the influence on the single European market; and (3) consumer misleading. Additionally, three arguments put forward to support the use of traditional use evidence are included: (4) the financial burden of human intervention research which small and medium enterprises (SMEs) are said to not be able to carry; (5) the similarity of the assessment for pharmaceutical products and food products; and (6) the increased sales from third countries. Lastly, the argument put forward against using this type of evidence, argument 7, is focused on the absence of manufacturing standards for dietary supplements compared to traditional herbal medicinal products.

5.3.2.1 Argument 1: Impact on the market

Both stakeholders for and against using evidence on traditional use to substantiate botanical health claims, expect that any decision on how to substantiate botanical health claims will negatively influence the market of botanical products (either sold as supplement or medicinal product). Stakeholders against using traditional use evidence on the one hand indicate that allowing such evidence will negatively affect the market for traditional herbal medicinal products: they expect this to lead to more authorised health claims, which will result in herbal

medicinal product manufacturers shifting to producing and selling herbal dietary supplements. On the other hand, stakeholders in favour of allowing traditional use evidence state that resuming the evaluation of submitted health claims with its current standards for scientific evidence, is expected to result in mainly negative opinions for health claims on botanicals. These stakeholders believe that not authorising such botanical health claims and not being able to communicate the health benefits of a product, will substantially decrease sales of dietary supplements.

Currently, it is impossible to estimate the market effects of any decision regarding traditional use evidence: the consequences of a decision on the substantiation requirements are unknown which means the following effects on the production and sales of traditional herbal medicinal products and herbal dietary supplements cannot be determined. Previous research does indicate that the wording of health claims on herbal dietary supplements and the wording of claims on traditional herbal medicinal products are very similar in the EU (8). This suggests that only minor adjustments to the claim's wording would enable changing the classification of a product from medicine to food. Traditional herbal medicinal products are so-called medicinal products by presentation(21): the claim indicates that the product has the property of preventing, treating or curing disease (Art. 1.2.a) (22). Differences between a traditional herbal medicinal product and an herbal dietary supplement may however also arise from the dosing of the active ingredient. Herbal monographs of the European Medicines Agency describe dosage requirements for traditional herbal medicinal products (Art. 16c.4) (6), and specific conditions of use for health claims describe the minimum quantity of a food (ingredient) when it is allowed to use a claim (Art. 13.2) (1), (Art. 1.2) (23). So even though the wording of claims on traditional herbal medicinal products and herbal dietary supplements might be similar, the dosage (and subsequent effectiveness) requires a distinction between these products. Shifting from producing traditional herbal medicinal products to herbal dietary supplements might thus only require minor adjustments to a communicated claim, it can still require adjustments to the dosage of the active substance and thereby the production process of the product.

5.3.2.2 Argument 2: Internal market effects

Stakeholders expect that the EU's internal market will be influenced by the eventual decision whether or not traditional use evidence can be used to substantiate botanical health claims. The main supporting argument of the stakeholders follows the mutual recognition principle: a product lawfully marketed as a food product should also be allowed as such on another Member State's market (24).

Some products are currently marketed as a food product in one Member State, whereas the same botanical (in the same dose) is regulated as pharmaceutical product in another Member State. The stakeholders in favour of using traditional use evidence argue that recognising traditions of Member States, by allowing traditional use evidence, provides a more harmonised legal framework for the application of the mutual recognition principle.

The argument opposing this traditional use evidence argues in exactly the opposite direction: as traditions differ from Member State to Member State, evidence on traditional use cannot be used for substantiating botanical health claims across Member States. Henceforth, what is considered to be a traditional product for a specific health benefit in one Member State, may not be traditionally used for this health benefit in another Member State.

The stakeholders describe two issues related to the current impasse on traditional health claims: classification differences (food vs medicine) in Member States, and the different traditions in Member States. In the EU, a botanical is through mutual exclusive legal frameworks classified as being either a food product, or a medicinal product and can never be both (21). Member States may classify a product as food product or medicinal product themselves and may take cultures and beliefs into account when deciding upon this classification (25). This can create differences in product status between Member States. Legally defining traditional use, as instated for traditional herbal medicinal products, may resolve some of the classification issues, as traditional use would then be similar for all Member States. Defining traditional use does however not clarify the difference between an herbal dietary supplement versus an herbal medicinal product and will henceforth not completely resolve those classification issues which will remain difficult to harmonise between member states.

The second issue described by stakeholders who oppose to using traditional use evidence for the substantiation of botanical health claims, are the differences in traditions between Member States. Within other jurisdictions, such as China and India, traditional medicinal systems, for which simplified registration procedures are instated, are officially recognised by governments, and it is clarified when a botanical product falls within this medicinal system (4). Such a traditional medicinal system does not exist in the EU. Although the EU does not recognise any specific traditional medicinal system, currently there is a centralised procedure for medicinal products that have a long tradition of use: traditional herbal medicinal products (Art. 16a.1) (6). To get a registration for a traditional herbal medicinal product, evidence is required to show the product has been used as a medicine

to treat a certain disease for 30 years, of which 15 within the EU (Art. 16c.1.c) (6). Even when traditions may differ among Member States, a centralised procedure is currently installed with requirements that are depending on showing a long tradition of use. Apparently substantiating safety and efficacy of medicinal products with evidence on traditional use is possible, which raises the question as to why this should not be possible for health claims on food products.

5.3.2.3 Argument 3: Consumer misleading

Consumer misleading is the third topic that is mentioned by stakeholders as an argument to both support and oppose the use of traditional use evidence for botanical health claim substantiation. The protection of consumers from misleading, false, unsubstantiated or medicinal claims is one of the main objectives of the NHCR (Art. 1.1) (1). Stakeholders opposing the use of traditional evidence believe that health claims which are based on such evidence are misleading, because their efficacy is not proven by well-controlled human intervention studies. Stakeholders supporting traditional use evidence however state that not communicating the health benefits of botanicals prevents the full disclosure of information to consumers, which they consider to be misleading. Even though both arguments deal with misleading, both issues arise from different concepts. The first argument highlights substantiation requirements: when should an effect be considered substantiated. In EFSA's guidance document for health claim applications, evidence from human intervention studies is described as requirement (7). Currently, an effect is thus only considered proven when two independent human intervention studies support the relationship between the food (constituent) and health. The second argument, that is used to support traditional use evidence, is based on information provision to consumers. Full information provision has been reported to be important for, amongst others, businesses involved in the food chain as they consider it important for consumer self-protection (26). However, this full information provision appears not to contribute to consumer understanding: when a consumer cannot interpret and process the provided information, it will not contribute to the decision to purchase and consume the product (27). Additionally, previous research has shown varying results into whether health claims can be considered misleading: whereas some approved health claims are reported as vague by consumers and increased the overall perceived healthiness of the product (26,28), other research indicates that such vague claims are not necessarily misleading but may be misguiding consumers (29). Whether a consumer comprehends the meaning of 'traditional' in a health claim, or when mentioned on traditional herbal medicinal products, remains to be determined.

5.3.2.4 Argument 4: Resources for research

Stakeholders in favour of allowing evidence on traditional use for the substantiation of health claims on botanicals argue that conducting human intervention studies, that are required for efficacy substantiation, is too expensive for SMEs. Due to their limited resources, SMEs would be unable to get their health claims studied and subsequently authorised, and these health claims can thus not be communicated to the consumer. These stakeholders expect that consumers will consequently not purchase these products without such claims, which is again thought to result in decreased sales of botanical containing dietary supplements.

Previous research has indicated that new legislation has a bigger impact on small companies compared to big industrials, which is mainly attributed to the lack of regulatory knowledge available in these smaller companies (30). The participating stakeholders in favour of traditional use evidence estimate that 80% of the companies selling herbal products can be considered an SME. A study analysing the impact of the introduction of the Canadian natural health product regulation showed that SMEs, predominantly those producing products for a niche market, faced the disappearance of their products from the market because of a lack of resources to adjust to new legislation (30). These smaller companies might henceforth be negatively influenced by increasing regulatory measures.

The impact of the NHCR on food businesses has already been the subject of different studies. With relatively small research and development budgets in the food industry, little money is available for research into health benefits of products (31). The limited financial resources have been reported as one of the main challenges for food business when reviewing the NHCR's impact (32,33). Although the majority of companies (66.7%) did increase their research and development expenditure, this has not resulted in radical innovations (32).

Although herbal dietary supplements are not radical innovations, but products that are already on the market, previous research does indicate that SMEs may not have the resources to gather the required data from human intervention studies.

5.3.2.5 Argument 5: Methodological requirements

To support allowing evidence on traditional use, an argument relating to the research methodology for substantiating health claims has been put forward. Various stakeholders argue that foods are not drugs, and therefore should not be assessed as such. The current requirements for health claim substantiation describe that the scientific dossier of a putative health claim should include two

independent human intervention studies (Art. 5) (34), preferably randomized controlled trials, where one group receives the product or substance and the other group is provided with a placebo (7). The stakeholders criticise this methodology as this may be relevant for assessing safety and efficacy of pharmaceuticals, studying a single effect of one active ingredient, but that the method disregards the minor and pleiotropic health effects elicited by food products.

The randomized controlled trail is currently seen as the golden standard in nutritional science to establish health effects of foods (35). This methodology allows for the definition of a clear cause and effect relationship between consuming a food and measuring a beneficial health effect (36).

Recent scientific advances highlight that many effects of foods are multi-target and are mostly subtle (35,37). This indicates that, even though current guidelines are based on establishing the effect of one substance on one target, food products might have beneficial effects on multiple targets. As these effects may additionally be subtle, the conducted studies may not show the positive research outcomes that are experienced in real-life settings following consumption (37). Another recognised issue with the use of placebo-controlled trials in nutrition research, is the impossibility of creating a nutrient free state (38). Whereas in drug research it is possible to create two groups of which one receives the drug and the other receives a placebo, it is not possible to provide one group with a nutrient and the other group without that nutrient. The true effect on health can therefore not be established.

5.3.2.6 Argument 6: Increased consumer purchases from third countries

Stakeholders who support allowing botanical health claim substantiation with traditional use evidence believe that not allowing traditional evidence will result in negative opinions and consequently no authorisation of botanical health claims. According to these stakeholders, this would drive consumers to purchase dietary supplements from other jurisdictions, where less strict rules apply to claims on products. These products are expected to pose an increased risk for consumers because of their lower quality, potential contaminations or adulterations. According to the stakeholders, these safety issues are already visible in the European Rapid Alert System for Food and Feed (RASFF). The RASFF system monitors food and feed safety issues in the EU, to ensure these issues are dealt with effectively (Art. 50) (39). The majority of alerts report issues on food products sold within the EU (40), whereas the majority of dietary supplement related notifications address products that do not originate from Europe but from other jurisdictions such as the United States, China and India (49% of all notifications)

(41,42). Products from the United States, China and India accounted for 49% of all notifications on dietary supplements (42).

It cannot be determined whether the consumer purchases of products outside the EU jurisdiction will increase when botanical health claims are not authorised, and whether this will increase food safety risks. Previous research does indicate that the main safety risk for dietary supplements is adulteration of these supplements with (illegal) pharmaceutical substances (43). Previous research furthermore showed that 58% of online purchased supplements were contaminated (42).

A large proportion of consumers in the EU purchase their supplements online, after which they are delivered without any direct contact with a seller or a professional (42). Products purchased from businesses in countries outside the EU, are not always produced and labelled in accordance with European standards (44). Health claims on these products have been found to be unscientific and even medicinal, which is not allowed for products on the EU market (1,44). Consumers might therefore misinterpret the health benefits of these products, next to being exposed to potentially unsafe substances due to contamination or adulteration.

5.3.2.7 Argument 7: Lower manufacturing standards for dietary supplements

Manufacturing standards of dietary supplements and herbal medicinal products differ from each other, which is for stakeholders who oppose the use of traditional evidence for botanical health claims another reason to question traditional use as substantiating evidence. Whereas registered herbal medicines need to comply with good manufacturing standards for pharmaceuticals, dietary supplements are subject to general requirements laid down in European food legislation which do not describe specific good manufacturing standards. According to these stakeholders, this may result in differences between batches of dietary supplements, where products can contain higher or lower amounts of the active substance, which is expected to result in risks for consumers. Increased sales resulting from authorised botanical health claims based on traditional use evidence would increase consumption. If dietary supplements are then unsafe because of poor production, an increase in consumption would lead to an increase in risk for consumers.

Previous studies into manufacturing requirements of botanicals in food and pharmaceutical products predominantly focused on safety aspects resulting from both batch-to-batch differences and adulteration (45,46). Registered traditional

herbal medicinal products, after receiving marketing authorisation, can have limited batch-to-batch differences (46). Additionally, although traditional herbal medicinal products are exempted from clinical trials establishing the efficacy of such product, safety data and production according to good manufacturing practices are required (47).

Although there are no good manufacturing practice guidelines instated for herbal dietary supplements, these products are subject to the extensive legislative framework for food products. Besides the requirement that food products should be safe (Art. 14.1) (39), additional legislation for example puts limits to residue levels, or deals with labelling requirements (47,48). Labelling requirements for herbal dietary supplements furthermore require to disclose the active substance of the dietary supplement on the label (Art. 8.1) (49). The label of a dietary supplement should furthermore disclose how much of this active substance is consumed in the daily portion (Art. 8.2) (49). The absence of good manufacturing practice guidelines does henceforth not mean that the production of dietary supplements is without any rules. Previous research does however indicate that botanical products not produced with Good Manufacturing Practice guidelines show more contaminations and adulteration and production is less standardised (46).

Instating good manufacturing guidelines could improve the standardisation of the production of dietary supplements and subsequently, decrease potential risks from batch differences. If sales would increase because more health claims are authorised due to the acceptance of traditional use as evidence for botanical health claim substantiation, this should not lead to an increased risk for consumers due to the consumption of adulterated or otherwise unsafe dietary supplements.

5.4 Discussion

Various arguments on using traditional use evidence to substantiate botanical health claims are published by stakeholders both in favour and against using this type of evidence. The conducted social network analysis shows that the stakeholders responding to the EC's call for feedback were highly connected, explaining shared opinions among stakeholders. Secondly, the critical review of the provided arguments provided deeper understanding of the discussion regarding the substantiation of botanical health claims: the presented arguments cover a

wide array of topics of which several were predictions that can only be verified after an eventual decision on botanical health claim substantiation is made.

5.4.1 Social network analysis

The network of the stakeholders (figure 1) shows that even though the majority of identified stakeholders appears to support using 'traditional use evidence' for the substantiation of botanical health claims, these stakeholders are highly inter-related. This is different from the stakeholders opposing this type of substantiation.

The involved stakeholders in this feedback procedure are predominantly industry associations. This is not surprising, as it has been previously shown that European legislation on food products, including the NHCR, has significant impact on the industry as companies might need to adjust their business operations (31,32). When the NHCR entered into force, the substantiation requirements were unclear to many food businesses. It is expected that this unclarity led to uncertainty, which negatively influenced functional food innovation (50). The stakeholders involved in the industry of herbal dietary supplements might have responded to the feedback procedure to provide the EC with their viewpoints to ensure any future decision would not lead to further uncertainty.

A second observation from the network is that several stakeholders are also involved in EU working groups (table 1). These working groups are involved in policy developments, which is an important aspect in the EU (51). This involvement is two-sided: stakeholders involvement creates legislative control, but they also serve as a source of expertise for the authorities (51,52). It is however also known that stakeholders with greater resources have more influence compared to stakeholders with smaller resources, which can lead to the stakeholders with more resources having more influence (53). In the current debate regarding botanical health claims, stakeholder also serve as a source of information, as they were asked to provide feedback on the EC's discussion paper in 2012 and again on the REFIT procedure (8,9). It may henceforth be that various stakeholders are involved in multiple consultations and can consequently express their view more often compared to others. This should be taken into account as overly expressing one viewpoint my skew the eventual decision regarding the substantiation of botanical health claims.

5.4.2 Arguments from stakeholders in the network

Different concerns and concepts of the arguments put forward by the stakeholders were reviewed to assess whether they could be validated with scientific

literature. This was done to clarify the topics related to botanical health claim substantiation in order to gain a deeper understanding of the discussion. For various arguments, including the potential influence on the internal market, the impact on the market of botanical products and the potential increased sales from third countries, little scientific literature was available and the impact from a decision regarding traditional use evidence cannot yet be estimated.

Consumer misleading was put forward by stakeholders both in favour and opposing to traditional use evidence, as a reason underlying their position to support or be against using this type of evidence. Stakeholders in favour of evidence on traditional use to substantiate botanical health claims argue that withholding information is consumer misleading, whereas stakeholders opposing traditional use evidence argue that communicating claims of which the effects have not been researched with human intervention studies is misleading. This raises the question as to what consumer misleading is. The subject of consumer misleading has been subject of various European Court of Justice (CJEU) cases and in these rulings, it becomes apparent that it is the opinion of the CJEU that consumers can be protected from misleading by appropriate labelling, including health claims (54). Communicating false or unsubstantiated health effects is known to be considered misleading (55). It should however be clarified whether withholding information can also be considered misleading. If this is not defined beforehand, the discussion whether substantiating botanical health claims with traditional use evidence will lead to consumer misleading remains. If consumer misleading is defined more clearly, this definition can be applied to the current debate.

Whereas consumer research has mainly focused on consumer understanding of health claims, little research is available on misleading. Consumers are shown to have little understanding of health claims, with the level of understanding depending on specific characteristics such as familiarity, age and country of origin (28,56,57). Product characteristics such as the form of the product (58) and aspects of the claim itself such as the terminology and the amount of information provided (28,59) also influence a consumer's understanding. It should henceforth be determined whether consumer misleading is predominantly initiated because of the claim itself or because of a consumer's lack of understanding of the health claim.

Even though the technical feedback analysed in this study may have been provided at a point in the REFIT process where this would not yet have been expected, the feedback in itself is shown to mainly address risk assessment issues, by discussing: what type of (scientific) evidence is considered to support

a certain claim. In the fifth argument, the methodological requirement for substantiating health claims: conducting two independent placebo-controlled intervention trials, is criticised. According to the stakeholders, the current substantiation requirements resemble the methodology for pharmaceutical testing, even though food products are different products. In the EU, risk management and risk assessment are strictly separated: the EC and Member States are risk managers, EFSA is the risk assessor for scientific and technical questions related to food and nutrition (Art. 6 & 22.2) (39). Any risk assessment for food safety and food policy, conducted by independent scientific assessors, should be based on studies from the highest scientific standards (Art. 6) (39). As risk assessor, EFSA is responsible for ensuring the highest scientific standard in risk assessment (Art. 22.2) (39). At this point, placebo-controlled randomised control trials are considered to be the highest scientific standard.

The REFIT evaluation on botanical health claims addresses the substantiation requirements for such claims. Whereas this substantiation in itself is a risk assessment matter, the REFIT evaluation is a risk management procedure. Even though the EC is expected to provide clear terms of reference, the reviewed arguments seem to imply that stakeholders expect more involvement of the risk manager into how the risk assessment is conducted. As this is a scientific issue, it can be questioned whether this REFIT evaluation is the correct procedure to discuss and determine whether evidence on traditional use can be considered the highest scientific standard to support any health claim on botanical food products.

5.4.3 Implications for future research

The arguments put forward by the stakeholders cover a wide array of subjects related to botanical health claims ranging from market impact to methodologies used in nutritional sciences. This shows that it is unclear which questions require answering in order to decide upon the substantiation of botanical health claims. Even though the REFIT evaluation shows that the NHCR is currently not completely meeting its objectives (9), meaning consumers might still be misled by claims on food products, the critical review of the arguments shows that the concept of consumer misleading in itself requires further clarification. As the decision on how to proceed with botanical claims is still pending, there is currently an opportunity to further clarify these concepts, which will also benefit other EU nutritional policies. In the EC's new from farm to fork strategy, specific emphasis is given to the provision of information on food to consumers (60). In light of this aim, clarifying concepts such as consumer misleading is even more important. Hence, it should be ensured that the food information provision intensifies, and that such information is true, clear and understandable for consumers.

Previous studies have focussed on the provision of information on botanical products sold as dietary supplements or alternative medicines. In the US, 90% of pharmacists reported to answers questions related to botanical products daily (61). And even though pharmacists may be considered a valuable source of information by consumers, another study identified that merely 15% of pharmacists felt comfortable answering such questions (62). Information was furthermore often provided by employees that were unlicensed and therefore not sufficiently educated (61). A case study conducted in the Netherlands into over-the-counter sales of dietary supplements also highlight that besides the content of information provided, the consumer's perception of both the employee and the message influences whether the information is effectively used when it is provided (63). Whenever consumers describe the authority of the employee is to be too low (for example because of the young age of the employee), the information is not trusted and cannot be expected to be acted upon (63). These studies show that providing information to consumers, even by professionals such as pharmacists, is complicated and that the effectiveness of the provision of information is influenced by many different factors. This should be taken into consideration when determining the strategies for empowering consumers with information.

By showing how specific concepts are explained differently by stakeholders, such as consumer misleading, this study can serve as a basis for clarifying various concepts related to European food law and more specifically, the substantiation of botanical health claims.

5.5 Conclusion

This study aimed to unravel the viewpoints of stakeholders regarding the substantiation of botanical health claims with evidence on traditional use to further understand the discussion on botanical health claim substantiation.

The conducted social network analysis showed that of the respondents to the feedback procedure, the majority is in favour of allowing traditional use evidence for the substantiation of botanical health claims, but that various respondents are interrelated sharing the same interest. The identified relationships between the responding stakeholders indicate that focusing on numbers of stakeholders would skew the discussion on botanical health claims. Not taking the relationships into consideration may result in the overemphasis of one viewpoint or argument, without reflecting the actual interest of such stakeholders.

The critical review of the arguments provided by the stakeholders shows that a wide array of topics is considered when discussing the needs and wishes related to traditional use evidence. Some of these arguments cannot be assessed before a decision is made, and the botanical health claim evaluation is resumed. Other concepts which are instated as objective of European food law, such as consumer misleading, can be explained differently from different perspectives. In order to move towards a solution regarding the evaluation of botanical health claims, these concepts should be clarified and a political decision needs to be made regarding the role of food law in achieving these objectives. Only then can a discussion lead towards a decision upon the use of traditional use evidence for health claim substantiation.

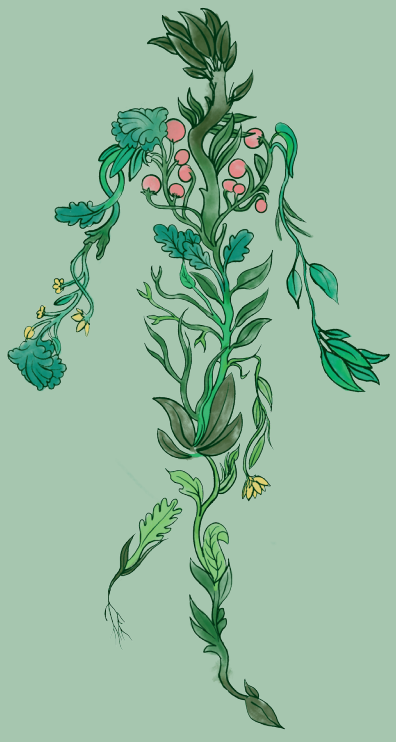
5.6 References

1. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
2. Hoogenraad E, Duivenvoorde B. Health claims for botanicals: "on hold", yet forbidden? Eur Food Feed Law Rev. 2016;1:58–9.
3. EFSA. Botanicals. 2018. Available from: https://www.efsa.europa.eu/en/topics/topic/botanicals [Accessed 15 May 2020]
4. Lenssen KGM, Bast A, de Boer A. International perspectives on substantiating the efficacy of herbal dietary supplements and herbal medicines through evidence on traditional use. Compr Rev Food Sci Food Saf. 2019;18(4):910–22.
5. Garcia-Alvarez A, Egan B, Klein de S, Dima L, Maggi F, Isoniemi M, Ribas-Barba L, Raats MM, Meissner EM, Badea M, Bruno F, Salmenhaara M, Milà-Villarroel R, Knaze V, Hodgkins C, Marculescu A, Uusitalo L, Restani P, Serra-Majem L. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One. 2014;9(3):1–18.
6. European Parliament and the Council of the European Union. Consolidated version of directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;136:85–90.
7. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of a health claim application (revision 2). EFSA J. 2017;15(1):4680.
8. Anton R, Serafini M, Delmulle L. The substantiation of claims for botanical food supplements in relation to traditional use. Eur Food Feed Law Rev. 2013;5:321–8.
9. European Commission. REFIT- Evaluation of the Regulation on nutrition and health claims [Internet]. 2019. Available from: https://ec.europa.eu/food/safety/labelling_nutrition/claims/refit_en [Accessed 15 May 2020]
10. European Commission. REFIT - making EU law simpler and less costly. 2019. Available from: https://ec.europa.eu/info/law/law-making-process/evaluating-and-improving-existing-laws/refit-making-eu-law-simpler-and-less-costly_en#main-achievements [Accessed 15 May 2020]
11. de Boer A. Scientific assessments in European food law: making it future-proof. Regul Toxicol Pharmacol. 2019;108:1–6.
12. European Commission. Evaluation and Fitness Check (FC) Roadmap. DG Sante. 2015;1–8. Available from: http://ec.europa.eu/smart-regulation/roadmaps/docs/2015_sante_595_evaluation_health_claims_en.pdf
13. European Commission. Consultations and feedback. Food Safety. 2019. Available from: https://ec.europa.eu/food/consultations-and-feedback_en#fbk [Accessed 15 May 2020]
14. European Commission, 2020. Commission staff working document - evaluation of the Regulation (EC) No 1924/2006 on nutrition and health claims made on foods with regard to nutrient profiles and health claims made on plants and their preparations and of the general regulatory framewor. Brussels.
15. Anton R, Serafini M, Delmulle L. Traditional knowledge for the assessment of health effect for botanicals - a framework for data collection. Eur Food Feed Law Rev. 2012;74–80.
16. Schwitters B. Want to harmonise botanicals: take the broader perspectives of traditional health claims and other substances. Eur Food Feed Law Rev. 2012;6:328–40.
17. Geurts S. Health claims and botanicals: how to proceed with European harmonisation. Eur Food Feed Law Rev. 2018;13(29).

18. Polit DF, Beck CT. Sampling in Qualitative Research. In: Nursing Research Generating and assessing for nursing practice. 2012. p. 515–31.
19. Cullerton K, Donnet T, Lee A, Gallegos D. Exploring power and influence in nutrition policy in Australia. Obes Rev. 2016;17(1218–1225).
20. The European Parliament and the European Commission. Agreement between the European Parliament and the European Commission on the transparency register for organisation and self-employed individuals engaged in the EU policy-making and policy implementation. Off J Eur Union2. 2014;277:11–24.
21. Quintus C, Schweim H. European regulation of herbal medicinal products on the border area to the food sector. Phytomedicine. 2012;19:378–81.
22. European Parliament and the Council of the European Union. Consolidated version of directive 2001/83/EC of the European Parliament on of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J Eur Union. 2001;311:1–188; 26-07-2019.
23. European Commission. Consolidated version of commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. Off J Eur Union L. 2012; 22-08-2017.
24. European Parliament and the Council of the European Union. Consolidated version of egulation (EC) No 764/2008 of the European Parliament and of the Council of 9 July 2008 laying down procedures relating to the application of certain national technical rules to product lawfully marketed in another Member State and repealing Decision No 3052/95/EC. Off J Eur Union. 2008;219:21–9; 02-09-2008.
25. Silano V, Coppens P, Larrañaga-Guetaria A, Minghetti P, Roth-Ehrang R. Regulations applicable to plant food supplements and related products in the European Union. Food Funct. 2011;2:710–9.
26. Mason MJ, Scammon DL. Unintended consequences of health supplement information regulations: the importance of recognizing consumer motivations. J Consum Aff. 2011;45(2):201–23.
27. Nocella G, Kennedy O. Food health claims - what consumers understand. Food Policy. 2012;37:571–80.
28. Lahteenmaki L. Claiming health in food products. Food Qual Prefer. 2013;27:196–201.
29. Orquin JL, Scholderer J. Consumer judgements of explicit and implied health claims on foods: misguided by not misled. Food Policy. 2015;51:144–57.
30. Laeeque H, Boon H, Kachan N, Cohen JC, D'Cruz J. The Canadian Natural Health Products regulation: industry perceptions and compliance factors. BMC Health Serv Res. 2006;6(63):1–11.
31. Bröring S, Khedkar S, Ciliberti S. Reviewing the Nutrition and Health Claims Regulation (EC) No. 1924/2006: What do we know about its challenges and potential impact on innovation? Int J Food Sci Nutr. 2017;68:1–9.
32. Khedkar S, Bröring S, Ciliberti S. Exploring the Nutrition and Health Claims Regulation (EC) No. 1924/2006: What is the impact on innovation in the EU food sector? Int J Food Sci Nutr. 2017;68(1):10–7.
33. de Boer A, Bast A. Stakeholders' perception of the nutrition and health claim regulation. Int J Food Sci Nutr. 2015;66(3):321–8.
34. European Commission. Consolidated version of commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. Off J Eur Union. 2008;109:11–6; 21-12-2009.

35. de Boer A, Vos E, Bast A. Implementation of the nutrition and health claim regulation–The case of antioxidants. Regul Toxicol Pharmacol. 2014;68(3):475–87.
36. Todt O, Luján J. The role of epistemic policies in regulatory science: scientific substantiation of health claims in the European Union. J Risk Res. 2017;20(4):551–65.
37. Bast A, Briggs W, Calabrese E. Scientism, legalism and precaution-contending with regulating nutrition and health claims in Europe. Eur Food Feed Law Rev. 2013;6:401–9.
38. Heaney R. Nutrition, chronic disease, and the problem of proof. Am J Clin Nutr. 2006:471-472.
39. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Off J Eur Union. 2002;31:1–44; 26-07-2019.
40. Pigłowski M. The correlation analysis of alert notifications in the RASFF to food from the non-EEA countries and from the EEA countries. Logforum. 2015;11.
41. Koncic MZ. Getting more than you paid for: unautorized "natural" substances in herbal food supplement on EU market. Planta Medica2. 2018;84:394–406.
42. Petroczi A, Taylor G, Naughton DP. Mission impossible? Regulatory and enforcement issues to ensure safety of dietary supplements. Food Chem Toxicol. 2011;49:393–402.
43. Walker MJ, Naughton DP, Deshmukh N, Burns DT. A review of methods for the simultaneous detection of illegal ingredients in food supplements. J Assoc Public Anal. 2016;44:51–66.
44. Lachenmeier DW, Löbell-Behrends S, Böse W, Marx G. Does European Union food policy privilege the internet market? Suggestions for a specialized regulatory framework. Food Control. 2013;30:705–13.
45. Rocha T, Amaral JS, Oliveira MBPP. Adulteration of dietary supplements by the illegal addition of synthetic drugs: a review. Compr Rev Food Sci Food Saf. 2016;15:43–62.
46. Ruparel P, Lockwood B. The quality of commercially available herbal products. Nat Prod Commun. 2011;6(5):733–44.
47. Kusar A, Pravst I. Quality and safety of botanical food products and their labelling. Agro Food Ind Hi Tech. 2014;25:33–5.
48. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the Eruopean Parliament and of the Council, Commission Directive 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Off J Eur Union. 2011;304:1–60; 01-01-2018.
49. European Parliament and the Council of the European Union. Consolidated version of directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Off J Eur Union. 2002;183:1–14; 26-07-2017.
50. Lenssen KGM, Bast A, de Boer A. Clarifying the health claim assessment procedure of EFSA will benefit functional food innovation. J Funct Foods. 2018;47:386–96.
51. Arras S, Braun C. Stakeholders wanted! Why and how European Union agencies involve non-state stakeholders. J Eur Public Policy. 2018;25(9):1257–75.
52. Jackson L, Jensen M. Based on science: stakeholder influence on risk assessment in the context of international food standards. Int Agric Trade Res Consort. 2006;Bonn.

53. Timotijevic L, Raats MM, Barnett J, Brown K, Shepherd R, Fernandez L, Dömölki L, Ruprich J, Sonne A-M, Hermoso M, Koletzko B, Frost-Andersen L, Timmer A. From micronutrient recommendations to policy: consumer and stakeholder involvement. Eur J Clin Nutr. 2010;64:S31–7.
54. Purnhagen K. More Reality in the CJEU's Interpretation of the Average Consumer Benchmark–Also More Behavioural Science in Unfair Commercial Practices? Eur J Risk Regul. 2017;8(2):437–40.
55. Leible S. Consumer information beyond food law. Eur Food Feed Law Rev. 2010;5(6):316–24.
56. Wills JM, Storcksdieck gerannt Bonsmann S, Kolka M, Grunert KG. Nutrition and health claims: help or hindrance European consumers and health claims: attitudes, understanding and purchasing behaviour. Proc Nutr Soc. 2012;71:229–36.
57. Grunert KG, Scholderer J, Rogeaux M. Determinants of consumer understanding of health claims. Appetite. 2011;56:269–77.
58. Khedkar S, Carreresi L, Bröring S. Food or pharmaceuticals? Consumers' perception of health-related borderline products. PharmaNutrition. 2017;5:133–40.
59. Williams PG. Can health claims for foods help consumers choose better diets. 2006;
60. European Commission. Farm to fork strategy. For a fair, healthy and environmentally-friendly food system. 2020.
61. Nathan JP, Cicero LA, Koumis T, Rosenberg JM, Feifer S, Maltz F. Availability of and attitudes toward resources on alternative medicine products in the community pharmacy setting. J. Am. Pharm. Assoc. 2005;45(6):734–739.
62. SSemple SJ, Hotham E, Rao D, Martin K, Smith CA, Bloustien GF. Community pharmacists in Australia: barriers to information provision on complementary and alternative medicines. Pharm. World Sci. 2006;28:366–373.
63. Lenssen KGM, Bast A, de Boer A. How does scientific information reach the consumer? A case study among students into providing verbal information on dietary supplements at point of purchase. Int. J. Food Sci. Nutr. 2021:72(3):402-417.



Chapter 6

International perspectives on substantiating the efficacy of herbal dietary supplements and herbal medicines through evidence on traditional use

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Abstract

The efficacy of botanicals in medicines can be substantiated with evidence on traditional use, whereas in foodstuffs this is often not possible. In Europe for example, the evaluation and subsequent authorisation of health claims on herbal dietary supplements has been put on hold by the European Commission. This study aims to analyse the role of evidence on traditional use in international legal frameworks of foods and pharmaceuticals.

Both legal sources as well as scientific studies offering insights into these regulatory frameworks were included into the analysis. The international approach towards evidence on traditional use for substantiating efficacy of botanicals vary highly. For herbal medicines, substantiating efficacy with evidence on traditional use is possible in all studied jurisdictions, except for Japan and the United States. Herbal dietary supplement efficacy can only be substantiated with evidence on traditional use in India and New Zealand, although the enforcing authorities do not describe which data is required. Australia and Canada regulate botanicals in a separate 'borderline' category from foods and pharmaceuticals. Both jurisdictions allow for substantiating efficacy with evidence on traditional use.

This study's second objective was to assess the applicability of the international approaches in the European legal framework, in light of the ongoing political debate regarding the use of traditional evidence. Implementation of the analysed international approaches would require major revisions of the current European legal framework. This review of international approaches might, however, aid in deciding upon future approaches for substantiating health claims with evidence on traditional use.

6.1 Introduction

Botanicals are substances that are derived from plants, algae, fungi or lichens (1,2). Historically, these products have been part of medicinal systems, like Traditional Chinese Medicine and Ayurveda (3). In many countries however, botanicals can be sold in both pharmaceutical products and in food products, as well as in a concentrated form as dietary supplements (sold in dose form e.g. pills, capsules or droplets). Dietary supplements containing botanicals are here referred to as herbal dietary supplements (HDSs), medicinal products with botanicals are described as herbal medicinal products (HMPs). Products containing botanicals are also often referred to as nutraceuticals, products in between the categories of food and medicinal products (4,5). Whether a botanical is considered to be a food or pharmaceutical product, depends on a jurisdiction's legal framework. This classification has been the subject of an ongoing debate in many countries (6,7). Depending on how a product is classified, different requirements are set within these jurisdictions regarding the evidence to substantiate safety and efficacy. In the United States of America (USA) for example, manufacturers should merely notify the FDA when marketing a HDS, whereas a new drug application including the evaluation of the evidence is required before the marketing of a HMP (8,9). Since it is increasingly recognised that botanicals, including those in HDSs, may pose risks to consumers, the regulation of these product has also been highly debated in the scientific community (7,10).

Globally, the sales of both dietary supplements and herbal or traditional products increased in the past years (11–14). Research showed that 35% of adults in the United States use herbal products (15). A study in six European countries found that the use of HDSs among their citizens varies between 9.6% in Finland and 22.7% in Italy (16). The USA's Food and Drug Administration estimated that herbal dietary supplement use results in 5000 adverse events per year (17). The consumer perception that botanical products are safer compared to conventional medicines might contribute to this (18).

6.1.1 Regulation of botanicals in the European Union

In the European Union (EU), botanicals are sold as both foodstuffs and pharmaceuticals (19). The classification of a botanical as either food or as medicinal product depends on the function the product has, or how it is presented to a consumer (5,20–22). The legal frameworks of foods and pharmaceuticals are mutually exclusive: a product is either a food or a medicine, and pharmaceutical law prevails when there is doubt about the status of a product (22). Hence, when the product c*ontains a dose* that will give rise to a pharmacological effect in the

human body, it is always considered a pharmaceutical ('medicine by function'), as well as when a product *is claimed* to have a pharmacological (versus a physiological) effect ('medicine by presentation') (5).

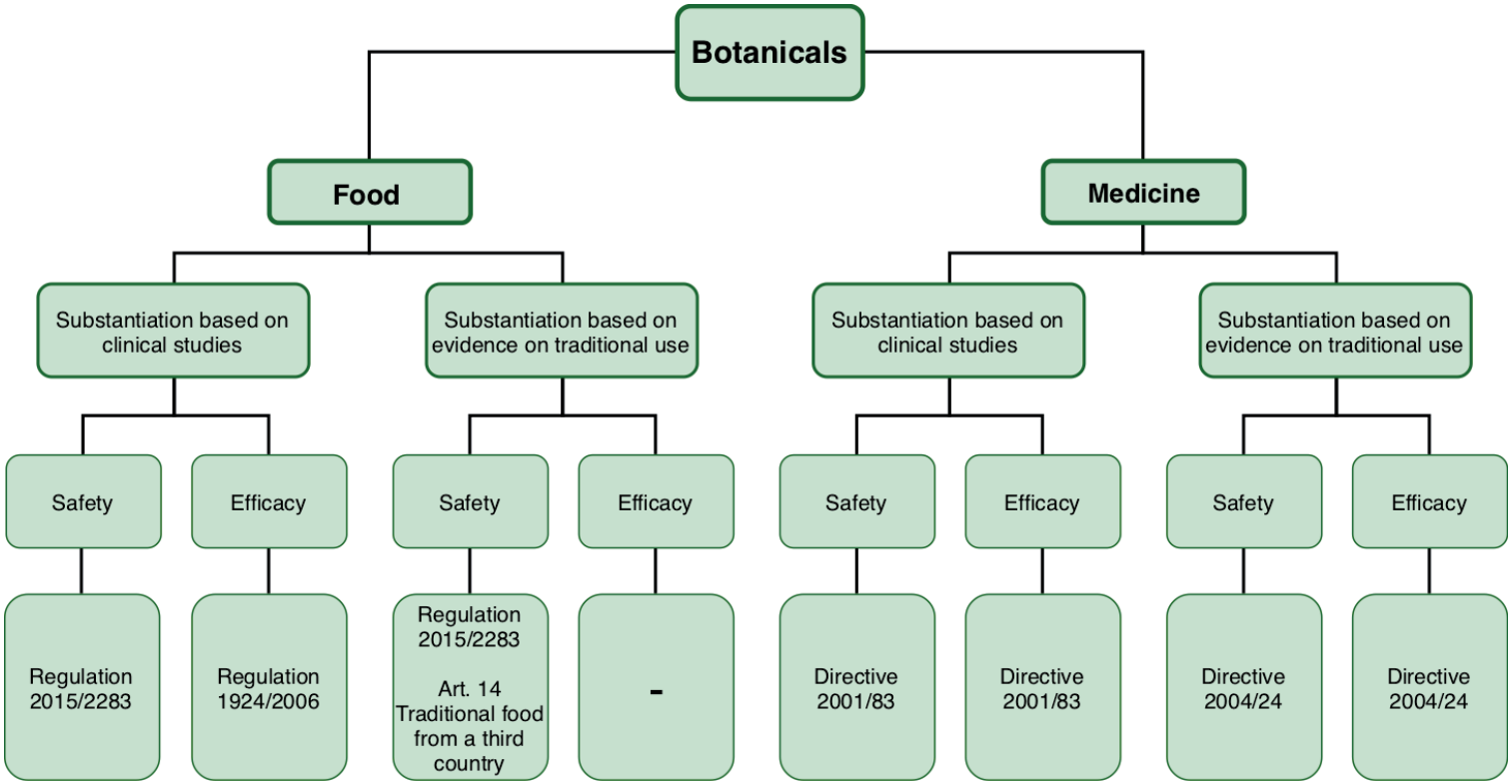
For medicines, safety and efficacy are evaluated simultaneously, after which a risk-benefit analysis will be conducted by the scientific assessors (Art. 19) (23). When HMPs are used to treat a specific disease for more than one generation, Directive 2004/24, allows for the use of this evidence on traditional use as substantiation of efficacy and safety for this product (Art. 16.a.1) (24*).* According to this Directive, safety and efficacy are substantiated when it can be demonstrated that the pharmaceutical has been used in the treatment of a specific disease for 30 years of which 15 years within the EU (Art. 16c.1.c) (24). HMPs are then, in accordance to this Directive authorised as traditional herbal medicinal products (THMPs).

Botanicals in food cannot have medicinal effects but foodstuffs may have properties for the maintenance or promotion of health (20). Food supplements are in the EU regulated under Directive 2002/46/EC, the Food Supplements Directive (25). The general requirement for food products is that they should always be safe for human consumption (Art. 14.1) (26). Hence, the basic assumption is that also botanicals sold as dietary supplements are safe. Marketing a new food product, including a new HDS, requires a safety evaluation under the Novel Food Regulation (Art. 10) (27). In the Novel Food Regulation, special consideration is given to products that can prove safe use in a country outside the EU, a so-called traditional food from a third country (Art 14) (27). For these products, historical data on the use should be provided indicating the product posed no safety issues in this country (28).

Voluntary displaying the health benefit of a product on the label or in other commercial outings, in the EU referred to as a health claim, is regulated under the Nutrition and Health Claims Regulation (NHCR) (Art. 2.2.5) (29). Health claims can currently only be substantiated with scientific data from human clinical intervention studies (30,31). There is no possibility to make use of evidence on traditional use to substantiate such health effects (30).

As summarised in Figure 1, historical data, the evidence on traditional use can be used to substantiate the efficacy and safety of HMPs and the safety of novel food products including novel dietary supplements.

Figure 1.



The figure displays the legal framework of botanicals in the European Union.

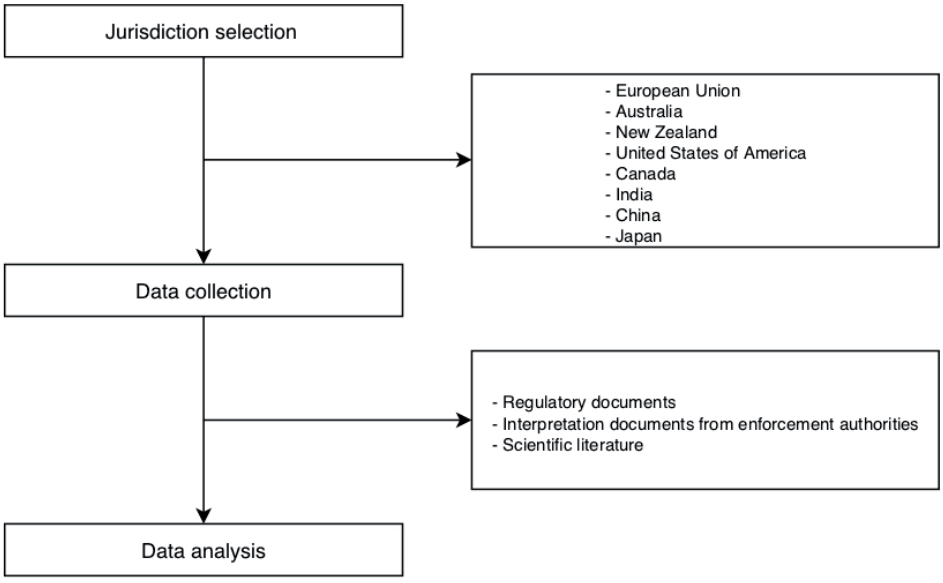
The evaluation of botanical health claims has been put on hold by the European Commission (EC) (32). Botanical substances for which a health claim application has been submitted to the EC, but which have not yet been scientifically reviewed by the risk assessor the European Food Safety Authority (EFSA), may carry the health claim until a formal decision upon the evaluation approach is made. Since no decision has been made upon the evaluation approach for all botanicals, the EC decided that the current impasse on botanical health claims should be reviewed in the Regulatory Fitness and Performance Programme (REFIT) (33). The programme aims to assess whether European laws are able to achieve their objectives and whether they are still 'fit for purpose'. For food law, the main objectives are the stimulation of the European internal market and the protection of consumers from unsafe products and misleading information on food products. REFIT reviews, in relation to food law, specifically the issue of botanical health claims. To date, no results of REFIT on the specific issue of botanicals have been published, consequently meaning no decision upon the evaluation approach has been made.

Previous exploratory research has identified discrepancies in either the legal frameworks of HDSs or HMPs, or was focussed on the international legal frameworks of HMPs (8,9,34–37). The current impasse regarding botanical health claims has only been addressed shortly in previous studies, that mainly dealt with explaining the EU regulatory status and providing potential future approaches to solve the issue without including the international perspective of dealing with botanicals in foods (19,21,32,38,39). This paper analyses these international approaches, and aims to determine the role of evidence on traditional use in international legal frameworks dealing with supplements and medicines. The second objective is to uncover the potential role of evidence on traditional use in the substantiation of botanical health claims in the EU.

6.2 Review process

In order to obtain a comprehensive review of relevant jurisdictions, to ensure a valid global comparison regarding the use of botanicals in food and medicines, firstly appropriate jurisdictions were selected. Subsequently, specifications regarding definitions and evidence requirements from the legal frameworks were collected and subsequently analysed.

Figure 2.



The figure displays the process of reviewing the legal frameworks of the international jurisdictions.

6.2.1 Jurisdiction selection

The jurisdictions selected for this analysis are included based on one of the following inclusion criteria: (i) the percentage of the jurisdiction's population using botanical products is similar to the percentage of the EU population using botanicals products; or (ii) the countries' medicinal system is partly based on a traditional medicinal system (systems founded before modern medicine and based on ancient theories in a culture); or (iii) the legal jurisdiction constitutes a supranational system, including various sovereign countries. Data was collected from scientific studies and legislative and constitutional documents and were only included in this study when they were available in English.

Based on the first inclusion criterion the United States of America (USA) and Canada were included in the analysis. 19% of the USA's population and 13-16% of the Canadian population have been shown to use botanical products, which is similar to the percentage of the population using botanical products in EU Member States (ranging from 9,6-22,7%) (16,40,41).

China, India and Japan were included in the analysis based on the second criterion. In China, India and Japan, traditional medicine is an intrinsic part of the countries' medicinal systems (42–44).

Australia and New Zealand established a supranational system for their food legislation, being the Food Standards Australia and New Zealand (45). These jurisdictions were therefore included in the analysis based on the third inclusion criterion.

Relevant legislative documents were also available for Australia, New Zealand, Canada, India, the USA and the EU. Chinese and Japanese constitutional documents that were published in English were used as information source, although these documents are not legally binding (46–48)

Based on these selection criteria, the included countries and jurisdiction for this comparative analysis are the USA, Canada, China, India, Japan, Australia and New Zealand.

6.2.2 Data collection

All information upon the legislative framework of botanicals used in pharmaceuticals or food product was obtained from three types of documents: legislation, interpretation documents and scientific literature:

(1) Regulatory documents obtained through governmental websites.

(2) Interpretation documents issued by enforcement authorities. These documents are not legally binding, but provide an interpretation of the law by the enforcement authority. Additionally, documents from self-regulatory authorities, such as those regulating good advertising practices or representing the industry were included as sources of information.

(3) Scientific literature related to legal frameworks on botanicals of the selected jurisdictions. A combination of the following terms formed the search strategy in the databases Google Scholar and Hein Online: for HDSs: 'dietary supplement', 'food supplement', 'herb', 'botanical', 'health claim' and one of the selected jurisdictions; for HMPs: 'herbal drug', 'herbal medicine', 'regulation', 'legislation', 'legal', and one of the selected jurisdictions. Only articles available in English were included in the analysis.

Due to the variety in terminology used to refer to the HDSs and HMPs in the selected jurisdictions, newly identified terms to refer to such substances and products were subsequently added to the search strategy for that specific jurisdictions.

6.2.3 Data analysis

As one of the objectives of the study was to compare international legal frameworks to the EU's legal frameworks for botanicals, first the definitions of HMPs and HDSs in the studied jurisdictions were analysed. Subsequently, for HMPs, the potential to use evidence on traditional use to establish efficacy of such medicinal products was analysed. This was followed by a comparison of the procedure for conventional medicinal products. Finally, the laws and regulations of health claims (as defined in the EU) on HDSs was reviewed and the potential to use of evidence on traditional use to substantiate such claims was studied. This study is focussed on the substantiation of efficacy, and not safety, of HDSs and HMPs with evidence on traditional use. The analyses are therefore solely aimed upon substantiating efficacy and disregard the safety aspect of the laws.

6.3 Results

6.3.1 Herbal medicines

In the EU botanicals can be used in THMPs and therefore, international legal frameworks on HMPs are analysed. This analysis aimed to identify whether HMPs are separately regulated, if efficacy of HMPs can be substantiated with evidence of traditional use and what the authorisation procedures are for HMPs when sold as conventional medicines.

6.3.1.1 Herbal medicines as separate category in medicinal legislation

In the EU, when safety and efficacy of HMPs can be proven with evidence on traditional use they are considered a separate category in medicinal legislation: THMPs (Art. 16a.1) (24). In order to compare the European legal framework to the legal frameworks of the included jurisdictions, it was analysed first whether HMPs are also described as a separate category in medicinal legislation in the other jurisdictions (Table 1).

In Australia and Canada, all herbal products are considered to be one category of products positioned between foods and pharmaceuticals. In Australia, these products are indicated as 'complementary and alternative medicines', in Canada, such products are defined as 'natural and non-prescription health products'

Table 1. Legal definition of herbal medicines.

	Special category for herbal medicines	Terminology used
EU	✓	Traditional herbal medicine
Australia	✓	Complementary medicine
New Zealand	✓	Herbal remedy
USA	✓	Special category of dietary supplements
Canada	✓	Natural and non-prescription health product used as traditional medicine
India	✓[a]	Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy drugs
China	✓[a]	Traditional Chinese Medicine
Japan	✓[a]	Kampo formulas

The table indicates whether the country legislation specifies a special category for herbal medicines and how this category is defined.
a Traditional medicinal system.

(49,50). Within the natural and non-prescription health products, a distinction is made between products with modern health claims and products used as traditional medicines (51,52). Since this study analyses evidence on traditional use, only the latter category was reviewed.

India, China and Japan have a traditional medicinal system that includes HMPs (36,43,44).

In the USA, HMPs are not defined as a separate category in medicinal law, but they are considered a special category of dietary supplements by the Food and Drug Administration (8,37). A botanical product is regarded a medicine when the product constitutes a medicinal effect, such as treating, curing or preventing a disease, rather than an effect related to general health or reduction of a risk factor related to a disease (2,36).

In the medicinal legislation of New Zealand, a separate section defines HMPs as ‘herbal remedies’ (53).

6.3.1.2 Scientific substantiation of herbal medicines with evidence on traditional use

Table 2 displays the results of the analysis to assess whether the legal frameworks of the studied jurisdictions allow for substantiation of efficacy with evidence on traditional use, and which data is described to be required for authorisation of such an HMP.

The Australian authority responsible for the evaluation of medicines, the Therapeutic Goods Administration, describes, in its guidance document, the requirements for efficacy substantiation of complementary medicines with evidence on traditional use, in Australian regulation referred to as listed medicines (54). This guidance document indicates that substantiation with traditional evidence requires three independent written histories.

The Canadian authority responsible for the evaluation of 'natural and non-prescription health products' also published requirements for the substantiation of traditional medicines (51). These requirements include establishing a long history of use with evidence on the use of the product over two generations, which should be available in written documentation, so-called references. This documentation should also indicate for which health conditions the product is used. Efficacy can additionally be substantiated through the pharmacopoeia or by two independent references establishing the conditions of use of the product (51).

In India, China and Japan, traditional medicinal systems are commonly used alongside conventional medicinal practice (43,44,55). Traditional medicinal systems are based on ancient theories and are used for centuries in a culture. Indian and Chinese legal frameworks define that HMPs which are part of a traditional medicinal system (being Traditional Chinese Medicine in China and Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy drugs in India) are exempted from the marketing authorisation procedures of conventional medicines (43,55).

In Japan, traditional medicines are referred to as Kampo medicines (44). Simplified requirements are instated for only one category of Kampo medicines, those falling under the Approval Standards (44). These are products that have been used over centuries and therefore no substantiation of safety and efficacy, either human clinical evidence or evidence on traditional use, is required. In all three jurisdictions, HMPs not included in the traditional systems have to obtain marketing authorisation similar to conventional medicines (8,36,44).

Table 2. Substantiation for the efficacy of herbal medicines with traditional evidence.

Country	Herbal medicine market authorisation based on traditional evidence	Required evidence
EU	✓	"Bibliographical or expert evidence that the medicinal product has been in medicinal use throughout a period of 30 years, including at least 15 years within the community. General information and quality studies required"
Australia	✓	"Therapeutic Goods Administration approved pharmacopoeia" "Therapeutic Goods Administration approved monograph" "Three independent written histories of use in the classical or traditional medical literature"
New Zealand	N/A	Herbal remedies do not require marketing authorisation if they are not stating a therapeutic purpose on the package and if they are sold to one person on request of that person
USA	✗[a]	N/A
Canada	✓[b]	"Two references of traditional preparation or use of international pharmacopoeias" "Two generations of traditional use of a medicinal ingredient within a cultural belief system or healing paradigm"
India	✓[c]	When part of traditional system
China	✓[c]	"The Chinese Food and Drug Administration will separately provide the rules governing the registration of Chinese herbal medicines" "Medicines that can prove a long tradition of use may be exempted from the strict approval standards of conventional medicines"
Japan	✗[c]	Over The Counter Kampo products under the Approval Standards have simplified procedure but not based on traditional use.

The table displays whether efficacy of herbal medicines can be substantiated solely by traditional evidence, and, if allowed, the required traditional evidence.
a Herbal medicines are a special category of dietary supplements.
b Natural and non-prescription health products as traditional medicines.
c Traditional medicinal system.

In the USA, where HMPs are considered a special category of dietary supplements, health claim substantiation cannot be solely based on evidence on traditional use (Table 6). Whenever the herbal ingredient is shown or presented to cure, prevent or treat a disease, it is considered a conventional medicine (8). Hence, based on the intention to use the product, it falls within one of the various legal frameworks of the USA, such as those of food and medicine but also others like regulatory framework dealing with cosmetics could be relevant (56).

In New Zealand, herbal remedies are exempted from the regulation on medicinal products when the product does not state a recommendation upon its use for a certain condition (53,57). The product label may only state the herb that is included, and the way in which the product is manufactured. Upon request of a customer, products can be recommended for treating a specific complaint. Hence, a practitioner may sell such products to prevent, treat or cure a certain disease whenever they are consulted by patients, however no pre-market approval and thus no evaluation of efficacy is required.

6.3.1.3 Herbal medicines outside the scope of separate category

In the EU, HMPs not meeting the criteria of a THMP, are required to follow the procedure of conventional medicines. Four general aspects of the authorisation procedure for conventional medicines were analysed (Table 3): (i) application submission in the Common Technical Document (CTD) format, which is an international developed format that allows for a more structured submission leading to a more efficient evaluation; (ii) classification of prescription or non-prescription medicine before requesting the marketing authorisation procedure; (iii) the possibility for a pre-submission meeting with the competent authority; and (iv) the need to approve clinical trials to establish the efficacy of a new medicine (58).

All studied jurisdictions require, either by law or according to the assessment authorities' guidance documents, the application to be submitted in the CTD format (23, Annex I)(59–65).

It is also in all jurisdictions possible for an applicant, or sometimes referred to as 'sponsor', to have a pre-submission meeting with the assessment authority (59,66–72).

The classification of the prescription status of a product may determine which evidence is considered sufficient to determine the safety, quality and efficacy required for marketing authorisation. In all jurisdictions, except for India and the EU, the decision upon the prescription status is made before the marketing authorisation application is submitted (59,66,71,73–77). In the EU, Member States decide upon the prescription status of a pharmaceutical, in India over-the-counter drugs have no legal status and procedures for determining the prescription status are unclear (75,77).

Conducting a clinical trial requires pre-notification to the national assessment authority in Australia and Japan, and approval in New Zealand, the USA, Canada, India, China (63,67,71,76,78–80). In the EU, Member States are responsible for

Table 3. Required aspects for the conventional medicine marketing authorisation procedure.

Country	CTD	Determining prescription status	Pre-submission meeting	Clinical trial approval
EU	✓	✗	✓	✗[b]
Australia	✓	✓	✓	NOT
New Zealand	✓	✓	✓[a]	✓
USA	✓	✓	✓	✓
Canada	✓	✓	✓	✓
India	✓	✗	✓	✓
China	✓	✓	✓	✓
Japan	✓	✓	✓	NOT

The table shows the analysis of four aspects of the conventional medicine marketing authorisation procedure. CTD: application must be submitted in Common Technical Document format. Classification: classification of the prescription status is determined before start of the application procedure. Pre-submission meeting: meeting during the application procedure with evaluating authority is possible. Clinical trial approval: clinical trials need to be approved by the evaluating authority before the start of the trial.

[a] There is limited capacity of authority a pre-submission meeting is therefore not advised.

[b] Clinical trial approval by national competent authority.

NOT: notification before start of the trial.

the authorisation of clinical trials which is in the Netherlands, for example, done by medical ethical review committees (77,81). The new Regulation 536/2014 on clinical trials on medicinal product for human use aims to install a European database to make this process more centralised and therefore efficient (82).

6.3.2 Herbal dietary supplement

In order to compare the international legal frameworks of botanicals as dietary supplements, the definition, the use of health claims and the substantiation of health claims with traditional evidence was analysed.

6.3.2.1 Definition

Different jurisdictions are shown to employ different legal definitions for dietary supplements. To enable a comparative analysis of legal frameworks dealing with dietary supplements, these definitions are reviewed.

By the European definition, a dietary supplement should be sold in dose form, such as pills, capsules and sachets, and supplement the diet by being a concentrated source of nutrients or other substances which have a nutritional or physiological effect (Art. 2.a) (25). A health claim is defined as a statement on a

relationship between food and health, excluding claims referring to the property of preventing, treating or curing a human disease, which are known as medicinal claims (Art. 12) (29,31).

Three attributes of the European definitions of dietary supplements and health claims were selected to compare the definitions used internationally (Table 4), being: dietary supplements can contain *herbal ingredients*, the product should be sold in a *dose form* (Art. 2.a) (25), and an allowed *health claim* should address the relationship between food and health and cannot claim to prevent, treat or cure a disease (Art. 6.2) (25).

Both in Australia and Canada, a separate legal framework for products on the 'borderline' of food and medicines is developed as discussed in the previously described HMPs section (section 'herbal medicines').

In the USA, EU, New Zealand and India dietary supplements should be marketed in dose form (Art. 2.a) (25,83–85). In the Indian regulation, dietary supplements are referred to as nutraceuticals (84,86). These nutraceuticals can however not claim to treat, cure or prevent disease. Dietary supplements may be named nutraceuticals for marketing purposes in the USA, but are legally considered to be food products (85,86).

In China and Japan, there is no separate legislation dealing with dietary supplements and therefore no specificities on the dose form are given (87–89). Dietary supplements are considered food products that are beneficial to the human body, products which are all regulated as 'health foods'. In Japan, three categories of foods with health purposes are defined: (i) foods with specified health uses (FOSHU), (ii) foods with nutrient function claims and (iii) foods with function claims (87). Dietary supplements are categorised in either of these three categories, based on the beneficial effect described on the product. In China, 'health foods' are defined as products that claim to have a specific health purpose within nutrition legislation (87,88). In Japan and China, botanicals can be used in health foods and medicinal health claims on these products are not permitted.

6.3.2.2 Health claims on herbal dietary supplements

In the EU, health claims are defined as voluntary statements that suggest a relationship between the food or one of its constituents and health (Art. 2.2.5) (29). Previous research showed that international variations exist in both the definition of such claims as well as the requirements for substantiating these claims (9).

Table 4. Dietary supplement definition.

Country	Herbs in dietary supplements	Product is in a pharmaceutical formation	Health claims exclude medicinal claims
EU	✓	✓	✓
Australia	✓	×	×
New Zealand	✓	✓	✓
USA	✓	✓	✓
Canada	✓	×	×
India	✓	✓	✓
China	✓	×	✓
Japan	✓	×	✓

The table displays per country whether the legal definition includes specific aspects from the European Union's definition of dietary supplements and health claims. Herbs in dietary supplements: dietary supplements may contain herbs. Product is in dose form: the product is sold in dose form such as pills, capsules, powders and sachets. Health claims exclude medicinal claims: the allowed health claim on the product cannot be medicinal, as in referring to the treatment, prevention, cure or mitigation of a disease.
In all studied jurisdictions, herbal ingredients can be used in dietary supplements (49,50,83–85,87). Apart from Canada and Australia, legislation in all countries specifically excludes medicinal claims from the allowed claims for marketing purposes of the product (83–85,89,90).

In Australia and Canada, HDSs and their potential claims are regulated under the same legal framework as HMPs (section 'herbal medicines'). As depicted in Table 5, all other studied jurisdictions, allow the use of health claims on HDSs (83–85,90,91). In the EU, one of the main criteria for health claims is that such a claim cannot be a medicinal claim. As displayed in Table 4, in New Zealand, the USA, China, India and Japan, such claims are also not permitted.

Table 5. Health claims on dietary supplements.

Country	Health claim on dietary supplement
EU	✓
Australia	N/A
New Zealand	✓
USA	✓
Canada	N/A
India	✓
China	✓
Japan	✓

The table presents whether the legal framework allows for health claims to be used for labelling and/or marketing purposes.

6.3.2.3 Evidence on traditional use to substantiate health claims on herbal dietary supplements

Table 6 demonstrates the possibility for a health claim to be substantiated with evidence on traditional use and, if defined in the legislation, presents which data is required to substantiate the efficacy.

In New Zealand and Australia, health claims on food products are regulated by the Food Standards Australia New Zealand (92). Dietary supplements including HDSs are however exempted from this legislative agreement (87). It is not specified in the regulation on dietary supplements in New Zealand whether health claims are allowed on these products. Henceforth, it is not defined what evidence is required to substantiate health claims on HDSs (83). The competent authority responsible for the evaluation of these products did also not issue a guidance document on the subject. The therapeutic and health advertising code provides rules for advertising with health benefits (93). These guidelines do state that evidence on traditional use is recognised as supportive, but it does not define the type of evidence that should be considered in that respect. In Australia, HDSs are regulated by the Therapeutic Goods Regulation as 'complementary and alternative medicines' (section 'herbal medicines'). In India, the regulation dealing with dietary supplements specifies that the scientific literature available should be considered, and specifically described that this includes official traditional texts (84).

Table 6. Substantiation of health claims on herbal dietary supplements with traditional evidence.

Country	Health claim approval based solely on traditional use	Required evidence
EU	✗[b]	N/A
Australia	N/A	N/A
New Zealand	✓[a]	"Health benefits must be supported by scientific or traditional substantiation"
USA	✗	N/A
Canada	N/A	N/A
India	✓	"official traditional texts"
China	✗	N/A
Japan	✗	N/A

The table displays if the substantiation of a health claim can be based solely on traditional evidence and, if possible, what evidence is required.

[a] Based on the therapeutic and health advertising code.

[b] Not currently allowed, the evaluation of botanical health claims is on hold.

In the USA, China and Japan, evidence on traditional use is not considered sufficient to substantiate a health claim (90,91,94).

6.4 Discussion

This study aimed to determine the role of 'evidence on traditional use' in the substantiation of efficacy of HMPs and HDSs and its potential applicability in the EU. The analysis presented in the results section provides insights into detailed aspects of the international legal frameworks. Within this section, the assessment of the applicability of these international legal frameworks to the European situation is further discussed.

6.4.1 Comparison of international legal frameworks to the European situation

HMPs are regulated as a separate category in all analysed legal frameworks (Table 1). In the USA, HMPs are considered a special category of dietary supplements, and are therefore not, as in the EU, part of pharmaceutical legislation (8). In the USA, botanical products are regulated under various legal frameworks, however are not given any special status in these frameworks (56). In New Zealand, HMPs, referred to as herbal remedies, do not require pre-market approval when the intended use of the product is not stated on the product (53,57). The European legal framework on pharmaceuticals does not allow for medicines, including HMPs, to be placed on the market without pre-market authorisation (Art. 6.1) (23). It could jeopardise public health, when ineffective or dangerous substances are given to consumers, which would be a violation of Art. 168 on public health in the Treaty on the Functioning of the European Union[1]. Implementation of the New Zealand exceptions for herbal remedies would therefore conflict with the current European legal framework.

HMPs can be part of Indian, Chinese and Japanese traditional medicinal systems. These systems are based on ancient theories and so HMPs are considered effective and safe when described in the systems' medicinal books (8,43,44,55). In the EU, THMPs are not based on a traditional medicinal system, but rather have to proof efficacy by demonstrating a tradition of use over at least one generation, defined as 30 years of which 15 in the EU (Art. 16c.1.c) (24). Hence, historical medical books can be used as supportive evidence, but they are in the EU legally not considered sufficient to substantiate efficacy of THMPs. Implementation of

1 Consolidated version of the Treaty on the Functioning of the European Union. Part 3. Title 14 Public Health. Article 168.

the approach as applied in these countries would require the acknowledgement of ancient medical books as providing sufficient evidence for substantiating the efficacy. As cultures vary between Member States, acknowledging one ancient medical theory through supranational legislation might not be possible across all Member States.

Although efficacy of HMPs can be substantiated by a long history of use in different jurisdictions with traditional medicinal systems as well as the EU, evidence required to demonstrate the long history of use however differs substantially between these jurisdictions.

In India, the USA and New Zealand, the legal definition of dietary supplements is comparable to the definition used in the EU: dietary supplements may contain herbs, the product is sold in dose form, and no medicinal claims are allowed on these products (Table 4). There is no specific regulation dealing with nor defining dietary supplements in Japan and China. Dietary supplements are regulated as 'health foods' which include all food products that have beneficial effects on health (87,88).

All studied countries are shown to allow health claims on dietary supplements (Table 5). Only in New Zealand and India such claims can be substantiated with evidence on traditional use (Table 6). In India, the requirements for such evidence are defined in the regulation on dietary supplements. In New Zealand however, this is only specified in a guidance document published by a self-regulatory authority on good advertising practise (84,93). Both regulations do not define what evidence on traditional use entails. In 2017, the New Zealand Parliament was on the verge of enforcing a new law on dietary supplements: the Natural Health and Supplementary Products bill (95). This regulation aimed to regulate HDSs, dosed botanical products with health benefits and for which medicinal claims are specifically excluded. The bill however lapsed, and was not picked up by the newly instated government after elections (95). In the proposed regulation, the substantiation of health benefits of these 'natural health and supplementary products' was stated to be potentially based on empirical studies but also through evidence on traditional use (96). Similar to the Indian regulation, no further specificities were provided on the data that would constitute evidence on traditional use. Because the regulation lapsed and was not picked up by the new government, it never entered into force.

In the EU, Commission Regulation 353/2008 defines more detailed requirements regarding the substantiation of health claims (97). Art. 5 of this Commission

Regulation describes that the evidence should constitute human studies. Art. 15 of the NHCR describes the responsibility of EFSA to conduct the scientific assessment of the provided evidence on a putative health claim (26,29). EFSA should additionally, in accordance with Art. 15.5 of the NHCR, provide guidance for the applicant in order for them to prepare the application, and this guidance document was published in 2007 for the first time and specifically addressed the requirement of human data to support the putative health claim (29, 98). Hence, accepting evidence on traditional use would require a revision of the implementing rules in Commission Regulation 353/2008. EFSA would be requested to publish additional guidance documents describing the required data for substantiating a health claim with evidence of traditional use. Next to defining to accept evidence on traditional use, it should also be determined and communicated what type of data should be provided to substantiate a health claim with evidence on traditional use. Communicating the requirements for substantiating a health claim is important, as previous unclear communication of the requirements has been observed to have negatively impacted functional food innovation (99).

Whereas this study focusses on substantiating the efficacy of HDSs and HMPs, previous research showed that other aspects of health claim authorisation procedures also differ across international jurisdictions (9). Similar to the EU, the legal framework of the USA, for example, does not provide the possibility to substantiate efficacy of HDSs with evidence on traditional use (Table 6). Opposite to the EU, the USA's legal framework does not require pre-market approval procedure for health claims on dietary supplements (85,100). Whenever a company wants to display the health benefit of the product on its label, merely a notification needs to be made to the Food and Drug Administration. This differs from the EU, where only previously approved health claims can be used without notification, whilst all new claims need to be authorised by the EC based on a scientific assessment of EFSA.

In Australia and Canada, botanicals are regulated by a separate law that deals with products on the border of food and pharmaceuticals, which is in contrast with the EU where botanicals are regulated in two mutually exclusive legal frameworks (49,50,101). These products can be presented to have claimed functions comparable to EU health claims, as well as functions that are considered to be 'medicinal' in the EU. In the EU, the classification of botanicals as either food or medicinal product has been the subject of different European Court of Justice cases, of which one outcome is that whenever there is doubt, the product should be classified as a medicine (22). The classification in the EU is guided by the *inten-*

tion to use the product. Resolving these difficulties related to the classification of products as either food or medicine would be the main benefit of implementing the Australian and Canadian approach in the EU (22). The requirements for substantiating efficacy would then be similar for all products on the border of food and pharmaceuticals. Such products may be considered nutraceuticals and could henceforth be regulated as such (86). However, the clear legal separation of foods and medicine in the EU would need to be reconsidered before such a system could be implemented.

Because the legal frameworks of Australia and Canada do include products that are in the EU referred to as HDSs, the evidence requirements to substantiate efficacy might be applicable in the EU as well. In Australia, efficacy of complementary and alternative medicines can be substantiated by approved pharmacopoeias or monographs, or by independent references in medical literature (54). In Canada however, efficacy should be substantiated by proving the product has been used for a specific purpose for over two generations (51). This is an approach similar to the EU's procedure for THMPs, where in the EU the timespan is only one generation (30 years). Although differently defined, legal frameworks in both jurisdictions specifically describe what a 'long history of use' is.

Furthermore, both Canada and Australia refer to European documents on the substantiation of efficacy of medicinal products in their own guidance documents (51,54,102). International authorities seem to consider the European guidance documents and procedures substantiating efficacy to be of the highest scientific standard and consequently partially base their procedures on these. This may be an indication that the implemented procedures in the EU are considered to be of high quality.

6.4.2 Differences within the European Union

Whilst this study aims to identify potential solutions to the current impasse in assessing the efficacy of HDSs in the EU by reviewing international legal frameworks, the EU's legal framework on botanicals itself already allows for differences between the Member States. This is mainly due to the objective of the different legislative acts in the EU, and the apparent similarities between HDSs and THMPs.

The first difference arises from the different legislative acts that regulate botanicals. HDSs are regulated by the Food Supplement Directive and their claims are dealt with in the NHCR (25,29). Whereas a Regulation is legally binding in its entirety, a Directive determines the achievements that should be legally accom-

plished, whilst Member States are to decide upon the methods for achievement themselves[22]. As a result, the Food Supplement Directive specifies the achievements that should be accomplished by a Member State, including the information that should be displayed on the label of a dietary supplement. It however also allows for differences between Member States, exemplified by additional requirements for marketing food supplements that are demanded by German national law (103). Additionally, rulings of the European Court of Justice established that it is the responsibility of the Member State to determine whether the product is considered a food or a pharmaceutical within their Member State, by taking their cultures and beliefs into account (22). This allows for differing prescription states between Member States, whereas the mutual recognition principle should allow for a product marketed in one Member State to be also allowed on other Member States' markets[33]. The potential differences in Member States together with the current impasse surrounding botanical health claims has led to initiatives within Member States to further harmonise the regulation of botanicals (104). An example of such an initiative is BELFRIT: a collaboration between Belgium, France and Italy that aims to harmonise the regulation of botanicals as food, and is on the verge of establishing a list of botanicals which can be safely used (105). Within the BELFRIT project, the evaluation of a botanicals' health effect is however not discussed and, the list itself is not legally binding (105). It can nevertheless serve as a starting point for the harmonisation of regulating HDSs between Member States.

As medicinal products are regulated by a European Directive, several steps in the authorisation procedure of medicinal products remain the responsibility of the Member States (Art. 6) (23). In the EU, the prescription status of the new medicinal products is determined *after* the product is authorised for marketing, and is the responsibility of the Member States (77). As a result, the prescription status may differ between Member States, as they base this prescription status on, for example, the culture in that particular Member State. The authorisation of clinical trials for assessing the efficacy of new medicines is not part of the centralised procedure (77). It is the responsibility of the Member State to authorise a clinical trial that is conducted to study new medicines. Because of differences between Member States' procedures in this matter, a new Regulation was established and is expected to take effect from 2019 onwards (Art. 4) (82). This new Regulation, Regulation 536/2014, aims to increase centralisation of the authorisation of clinical trials for medicinal products, and therefore develops a portal in which au-

2 [2] Consolidated version of the Treaty on the Functioning of the European Union. Title 1. Chapter 2. Section 1 Legal acts of the Union. Article 288.

3 [3] Consolidated version of the Treaty on the Functioning of the European Union. Part 3. Title 2. Chapter 3 Prohibition of quantitative restrictions between Member States. Articles 34-36.

thorisation applications done in individuals Member States should be submitted (106). This new procedure aims to prevent unnecessary duplicate (Art. 78.5) (82). It should however be carefully considered that only clinical trials for medicinal products are subject to the new procedures, but not other clinical trials done conducted on for example, food products. These clinical trials are still subject to the rules and regulations of the individual Member States.

The second complicating aspect of the EU's legal framework on botanicals is that botanical products sold as dietary supplements and THMPs seem to be very similar. HMPs are considered to be comparable to HDSs as HMPs substantiated with evidence on traditional use should, like food products, not cause any harm (19). In the EU two types of medicinal product are identified (5,21). Products with observed pharmacological functions are considered 'medicinal product by function' (21). THMPs are included in the other category: products that present a pharmacological function on the label, and are therefore considered 'medicinal products by presentation' (21,22).

For HDSs, separate regulations account for the safety and the efficacy (26,27,29). This is different from the legal framework of pharmaceuticals, as for these products a risk-benefit analysis will be conducted (Art. 19), and marketing authorisation will be given when eventually the benefits outweigh the risks (23). The amending Directive of THMPs, Directive 2004/24, specifies however that these products allow for use without supervision of a medical specialist, which is argued to mean that THMPs are 'medicinal products by presentation' (Art. 16a.1.e) (19,24). Together with the requirement that THMPs should be safe, this aspect makes the author regard Directive 2004/24 to be similar to food law, and therefore THMPs comparable to HDSs (19).

Additionally, the conditions of use of THMPS have been argued to be more alike the health claims allowed on food products, rather than medicinal claims on the treating, curing or preventing a disease (39). Anton et al (2013) exemplify this with *Melissa officinalis L*. leaf: it is used as a THMP for "relief of mild symptom of mental stress and to aid sleep", and as a HDS for "alleviation of psychological stress and maintenance of normal sleep" which EFSA considers to be beneficial physiological effects (39).

Finally, not amending the NHCR is expected to lead to negative evaluations for the majority of the claims that are currently on hold. This is thought to negatively impact the market of dietary supplements (39). It should however be considered that one of the recitals of the NHCR indicates that the principles of that Regula-

tion should be equal for all submitted claims (19,29). When amending the Regulation, differences will occur between the substantiation of different products that are all regulated as foods.

The EC started with the evaluation of the European Regulations, under the REFIT programme, which includes an evaluation of European food law (33). The current impasse on health claims on HDSs is one of the focus points of this evaluation (33). During this evaluation, an opportunity will be given to involved stakeholders to give their insights on the issue. Former differences between Member States in the regulation of HMPs, led to the adoption of the simplified procedure for THMPs: allowing evidence on traditional use to substantiate traditionally recognised effects of THMPs (24,107). It has been argued that because of the different procedures for dietary supplements in Member States, the NHCR should be amended likewise (19).

6.4.3 Potential future European approaches

The EC has proposed two solutions for the current impasse on botanical health claims: (1) resume the evaluation, using the same requirements as used for the substantiation of all other health claims; or (2) recognise botanicals as a special category and subsequently adjust the requirements for the substantiation of botanical health claims (108). The second option would however require revision of the NHCR, as the Regulation is currently aimed to set similar requirements for all health claims (Art. 1) (19,29). The analysis of the international approaches as presented in this paper indicates that there are two other possibilities. Firstly, products on the 'borderline' of foods and pharmaceutical products can be regulated as being one category, as observed in Canada and Australia (49,50). Previous research has been suggesting this approach, referring to it as nutraceuticals (4,86). This approach would resolve the difficulties in categorisation of botanicals as foods or pharmaceutical products (22). It does however require major revision of the legal frameworks of both foods and pharmaceuticals, as these are currently mutually exclusive (5,22).

The second possibility is to 'split' the NHCR, and consequently having special consideration for botanicals and potentially other substances for which efficacy can be substantiated with evidence on traditional use, as observed in Canada and in Directive 2004/24 on THMPs. Although it would require an amendment of the NHCR, the THMP Directive has shown it is possible to differentiate between products in one legal framework (24,107).

6.4.4 Strengths and limitations

This study is the first to review efficacy substantiation with evidence on traditional use, a highly debated topic in both science as well as politics. By focussing solely on this specific part of the legal framework, the results are detailed and concise and provide a solid base for future research and policy on the use of evidence on traditional use in legal frameworks of food and pharmaceuticals. The substantiation of efficacy is however merely a part of the total legal frameworks of food and pharmaceuticals, and because of the specific focus on evidence on traditional use, the results do not stand alone. They should rather be considered in the context of the other aspects defined in the legal frameworks, such as the marketing authorisation procedure of HDSs and HMPs including the substantiation of safety.

Additionally, the study entails only seven jurisdictions, and is therefore not a global review. As one of the research objectives was to compare the international legal frameworks to the EU, the inclusion criteria were set to include jurisdictions relevant for the comparison, and so comparability of a jurisdiction to the EU's supranational system or consumption data of countries were decisive for inclusion in the study. The study on the consumption of botanical products in Europe only included six Member States, and it has shown that not all Member States have an equal percentage of the population consuming botanical products. The selected percentages might therefore not be reflective of all Member States.

6.5 Conclusion

This study aimed to determine the role of evidence on traditional use for the substantiation of efficacy of botanicals in dietary supplements (foods) and pharmaceutical products in international jurisdictions. Additionally, these international approaches were used to study the current European situation where an impasse has arised on substantiating health claims on botanical food products. In the EU, the legal frameworks of foods and pharmaceuticals are mutually exclusive; a product is either food or medicine where, when there is doubt on the status of a product, the medicine prevails (5,22).

Similar to the EU, evidence on traditional use is sufficient to substantiate the efficacy of HMPs in Australia, Canada, India and China (43,51,54,55). In New Zealand, the USA and Japan, substantiation of efficacy requires either clinical evidence or is not required for marketing authorisation at all (8,44,53).

For HDSs, substantiation their efficacy with evidence on traditional use is only sufficient in India and New Zealand (84,93). However, it is not conclusive which data is considered to be evidence on traditional use. In Canada and Australia, all products on the 'borderline' of foods and pharmaceutical products are regulated in one legal framework (49,50). In Canada, where there is one regulation which deals with all natural products on the 'borderline' of food and medicine, evidence on traditional use is sufficient for the substantiation of efficacy and entails data on the use of the product across two generations (51). Considering the regulation on natural health products includes products that in the EU would be considered food, this provides an indication that substantiation of health claims with evidence on traditional use is possible.

Based on the presented analysis and on the discussion paper, four potential future approaches have been identified: (i) continuing the evaluation of botanical health claims without changes; (ii) continuing the evaluation of botanical health claims but accepting evidence on traditional use; (iii) regulating all botanicals as one category of products on the 'borderline' of foods and pharmaceuticals and therefore regulate them under one separate legal framework; or (iv) splitting the NHCR as to identify two separate categories of food products. Except for the first option, all require major revisions of the legal framework of foods or even foods and pharmaceuticals.

The multiple European Court of Justice cases and the observed similarities between HDSs and THMPs indicate that the definition and classification of botanicals as foods or pharmaceutical products remains difficult. It can therefore be concluded that clarification whether botanicals should be regulated as food or pharmaceuticals is necessary. A complete reform of the legal framework for food and pharmaceuticals should be considered to either regulate all substance that are beneficial for health (being food and pharmaceuticals) as one comprehensive category, or to specify a third category for produce on the borderline of food and pharmaceuticals. This will aid in determining what the best future approach for botanicals may be.

6.6 References

1. EFSA. Botanicals. 2018. Available from: https://www.efsa.europa.eu/en/topics/topic/botanicals
2. U.S. Food & Drug Administration. Botanical Drug Development - Guidance for industry. US Department of Health and Human Services. 2016;1–30. Available from: https://www.fda.gov/downloads/Drugs/Guidances/UCM458484.pdf [Accessed 05 May 2019]
3. Jaiswal Y, Liang Z, Zhao Z. Botanical drugs in Ayurveda and Traditional Chinese Medicine. J Ethnopharmacol. 2016;194:245–59.
4. Daliu P, Santini A, Novellino E. From pharmaceuticals to nutraceuticals: bridging disease prevention and management. Expert Rev Clin Pharmacol. 2019;12(1):1–7.
5. de Boer A. Interactions between nutrition and medicine in effect and law. 2015.
6. Nicoletti M. Nutraceuticals and botanicals: overview and perspectives. Int J Food Sci Nutr. 2012;63(S1):2–6.
7. Marcus DM, Grollman AP. Botanical medicines - the need for new regulations. N Engl J Med. 2002;347(25):2073–6.
8. Verma N. Herbal medicines: regulation and practice in Europe, United States and India. Int J Herb Med. 2013;1(4):1–5.
9. de Boer A, Bast A. International nutrition and health claims regulation. Food Policy. 2015;55:61–70.
10. Mukherjee PK, Ponnusankar S, Pandit S, Hazam PK, Ahmmed M, Mukherjee K. Botanicals as medicinal food and their effects on drug metabolizing enzymes. Food Chem Toxicol. 2011;49:3142–53.
11. World Health Organization. National policy on traditional medicine and regulation of herbal medicines - Report of a WHO global survey. Geneva; 2005.
12. Euromonitor International. Vitamins and Dietary Supplements. Market Sizes | Historical. 2018.
13. Euromonitor International. Herbal/Traditional Products. Market Sizes | Historical. 2018.
14. Nirmal SA, Pal SC, Otimneyin SO, Aye T, Elachouri M, Kumar Kundu S, Thandavarayan RA, Mandal SC. Contribution of herbal products in global market. Pharma Rev. 2013;95–104.
15. Rashrash M, Schommer JC. Prevalence and predictors of herbal medicine use among adults in United States. J Patient Exp. 2017;4(3):108–13.
16. Garcia-Alvarez A, Egan B, Klein de S, Dima L, Maggi F, Isoniemi M, Ribas-Barba L, Raats MM, Meissner EM, Badea M, Bruno F, Salmenhaara M, Milà-Villarroel R, Knaze V, Hodgkins C, Marculescu A, Uusitalo L, Restani P, Serra-Majem L. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One. 2014;9(3):1–18.
17. Marcus DM. Dietary supplements: What's in the name? What's in the bottle? Drug Test Anal. 2015;8:410–2.
18. Lynch N, Berry D. Differences in perceived risks and benefits of herbal, over-the-counter conventional, and prescribed conventional, medicines, and the implications of this for the safe and effective use of herbal products. Complement Ther Med. 2007;15:84–91.
19. Schwitters B. Want to harmonise botanicals: take the broader perspectives of traditional health claims and other substances. Eur Food Feed Law Rev. 2012;6:328–40.
20. Bast A, Chandler RF, Choy PC, Delmulle L, Gruenwald J, Halkes SBA, Keller K, Koeman JH, Peters P, Przyrembel H, de Ree EM, Renwick AG, Vermeer ITM. Botanical health products, positioning and requirements for effective and safe use. Environ Toxicol Pharmacol. 2002;12:195–211.
21. Quintus C, Schweim H. European regulation of herbal medicinal products on the border area to the food sector. Phytomedicine. 2012;19:378–81.

22. Silano V, Coppens P, Larrañaga-Guetaria A, Minghetti P, Roth-Ehrang R. Regulations applicable to plant food supplements and related products in the European Union. Food Funct. 2011;2:710–9.
23. European Parliament and the Council of the European Union. Consolidated version of directive 2001/83/EC of the European Parliament on of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J Eur Union. 2001;311:1–188; 28-01-2019.
24. European Parliament and the Council of the European Union. Consolidated version of directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;136:85–90.
25. European Parliament and the Council of the European Union. Consolidated version of directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Off J Eur Union. 2002;183:1–14; 26-07-2017.
26. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Off J Eur Union. 2002;31:1–44; 01-07-2018.
27. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel food, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Off J Eur Union. 2015;327:1–22; 25-22-2015.
28. EFSA NDA Panel. Guidance on the preparation and presentation of the notification and application for authorisation of traditional foods from thrid countries in the context of Regulation (EU) 2015/2283. EFSA J. 2016;14(11):1–16.
29. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
30. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of a health claim application (revision 2). EFSA J. 2017;15(1):4680.
31. de Boer A, Vos E, Bast A. Implementation of the nutrition and health claim regulation–The case of antioxidants. Regul Toxicol Pharmacol. 2014;68(3):475–87.
32. Hoogenraad E, Duivenvoorde B. Health claims for botanicals: “on hold”, yet forbidden? Eur Food Feed Law Rev. 2016;1:58–9.
33. European Commission. Evaluation and Fitness Check (FC) Roadmap. DG Sante. 2015;1–8. Available from: http://ec.europa.eu/smart-regulation/roadmaps/docs/2015_sante_595_evaluation_health_claims_en.pdf [Accessed 05 May 2019]
34. Devla M, Acharya S, Acharya N, Kumar V. Dietary supplements: a legal status in India and in foreign countries. Int J Pharm Pharm Sci. 2011;3(3):7–12.
35. Bagchi D. Nutraceutical and functional food regulations in the United States and around the world. Second edi. Oxford: Elsevier; 2014. 1–591 p.

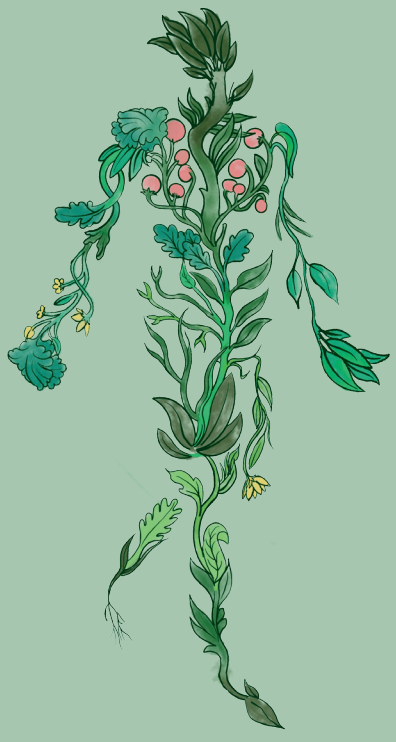
36. Fan T, Deal G, Koo H, Rees D, Sun H, Chen S, Dou JH, Makarov VG, Pozharitskaya ON, Shikov AN, Kim YS, Huang YT, Chang YS, Jia W, Dias A, Wong VC, Chan K. Future development of global regulations of Chinese herbal products. J Ethnopharmacol. 2012;140:568–86.
37. Liu F, Salmon J. Herbal medicine regulation in China, Germany, and the United States. Integr Med. 2010;9(5):54–61.
38. Korzycka-Iwanow M, Zboralska M. Never-ending debate on food supplements: harmonisation or disharmonisation of the law. Eur Food Feed Law Rev. 2010;3:124–35.
39. Anton R, Serafini M, Delmulle L. The substantiation of claims for botanical food supplements in relation to traditional use. Eur Food Feed Law Rev. 2013;5:321–8.
40. Troppmann L, Johns T, Gray-Donald K. Natural health product use in Canada. Can J Public Heal. 2002;93(6):426–30.
41. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Semin Integr Med. 2004;2(2):54–71.
42. Xu J, Yang Y. Traditional Chinese medicine in the Chinese health care system. Health Policy (New York). 2009;90:133–9.
43. Sahoo N, Manchikanti P, Dey S. Herbal drugs: standards and regulation. Fitoterapia. 2010;81:462–71.
44. Maegawa H, Nakamura T, Saito K. Regulation of traditional herbal medicinal products in Japan. J Ethnopharmacol. 2014;158:511–5.
45. Food Standards Australia New Zealand. Standard 1.1.1 Structure of the Code and general provisions. 2017;F2017C00712. Available from: http://www.foodstandards.gov.au/code/Documents/1.1.1 Structure and General Provs v159.pdf [Accessed 05 May 2019]
46. Library of Congress. Legal Research Guide: China. 2016. Available from: https://www.loc.gov/law/help/legal-research-guide/china.php [Accessed 05 May 2019]
47. Ministry of Justice. Japanese Law Translation. Japanese Law Translation Database System. 2018. Available from: http://www.japaneselawtranslation.go.jp [Accessed 05 May 2019]
48. Pan H. An overview of Chinese language law and regulation. Chinese Law Gov. 2016;48(4):271–4.
49. Australian Government. Therapeutic Goods Regulations 1990. 2018 p. 1–294.
50. Canada. Natural Health Products Regulation. http://laws-lois.justice.gc.ca. 2003;1–56.
51. Health Canada. Pathway for licensing natural health products used as traditional medicines. 2012;Version 1.:1–26. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodnatur/legislation/docs/tradit-eng.pdf [Accessed 05 May 2019]
52. Health Canada. Pathway for licensing natural health products making modern health claims. 2012;Version 1.:1–35. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodnatur/legislation/docs/modern-eng.pdf [Accessed 05 May 2019]
53. New Zealand Government. Medicines Act 1981. 28 Exemptions in respect of herbal remedies. Parliament Counsel Office. 1981; Available from: http://www.legislation.govt.nz/act/public/1981/0118/latest/DLM55427.html?search=ts_act%40bill%40regulation%40deemedreg_medicines+act_resel_25_a&p=1 [Accessed 05 May 2019]
54. Australian Government. Evidence guidelines. Guidelines on the evidence required to support indications for listed complementary medicines. Department of Health Therapeutic Goods Administration. 2014;Version 2.:1–72. Available from: https://www.tga.gov.au/sites/default/files/cm-evidence-listed-medicines-140724.pdf [Accessed 05 May 2019]

55. Wu W, Hou J, Long H, Yang W, Liang J, Guo D. TCM-based new drug discovery and development in China. Chin J Nat Med. 2014;12(4):241–50.
56. U.S. Food & Drug Administration. Guidance for Industry on Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration - Draft Guidance. US Department of Health and Human Services. 2006;1–14. Available from: https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm073200.htm [Accessed 05 May 2019]
57. Barnes J, McLachlan A, Sherwin C, Enioutina E. Herbal medicines: challenges in the modern world. Part 1. Australia and New Zealand. Expert Rev Clin Pharmacol. 2016;9(7):905–15.
58. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. M4: The Common Technical Document. 2018. p. 1.
59. Medsafe. Guideline on the regulation of therapeutic products in New Zealand. Part 2: obtaining approval for new and changed medicines and related products. Ministry of Health. 2016;(1):1–65. Available from: http://www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part2.pdf [Accessed 05 May 2019]
60. Australian Government. Mandatory requirements for an effective application. Applicable for application lodged from 1 July 2015. Department of Health. Therapeutic Goods Administration. 2015;(2):1–29. Available from: https://www.tga.gov.au/sites/default/files/mandatory-requirements-150701.pdf [Accessed 05 May 2019]
61. U.S. Food & Drug Administration. Providing regulatory submissions in electronic format - certain human pharmaceutical product applications and related submissions using the eCTD specifications. Guidance for industry. 2017;1–11. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf [Accessed 05 May 2019]
62. Government of Canada. Question and answer document. 1. must a sponsor provide an electronic regulatory activity in eCTD format? (Revised January 2018). 2018. Available from: https://www.nihcollaboratory.org/sites/CbyC/Document Library/QandA_CTD_submissions 2009.pdf [Accessed 05 May 2019]
63. Sutar M, Gawhane D, Tenpe C. Study of Drug Regulatory Approval Process an Comparative Requirement of Common Technical Documents (CTD) in Europe, USA and India in Coordination with Drug Development Process. Int J Pharm Sci Rev Res. 2013;20(2):68–79.
64. Pacific Bridge Medical. China regulatory and market access pharmaceutical report 2014. Bethesda; 2014. Available from: http://www.pacificbridgemedical.com/wp-content/uploads/2015/04/China-Regulatory-and-Market-Access-Pharmaceutical-Report-2014.pdf [Accessed 05 May 2019]
65. Garg V, Chopra S, Singh S, Gulati M, Kumar B, Mittal N. A comparative study of common technical document in different regulated market. J Pharm Res. 2017;11(8):1015–24.
66. Australian Government. Australian regulatory guidelines for prescription medicines. Department of Health. Therapeutic Goods Administration. 2004;1–64.
67. U.S. Food & Drug Administration. Investigational New Drug (IND) Application. U.S. Department of Health and Human Services. 2017. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm [Accessed 05 May 2019]
68. Health Canada. Guidance for the industry. Management of drug submissions. Minister of Public Work and Government Services Canada. 2013;1–38. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.pdf [Accessed 05 May 2019]

69. CDSCO. Notice. Pre-submission meetings - (regulatory pathways). 2015. p. 1–2. Available from: http://www.cdsco.nic.in/writereaddata/NOTICE15.pdf [Accessed 05 May 2019]
70. Wang B, Davidson A. An overview of major reforms in China's regulatory environment. Regul Rapp. 2017;14(7/8):5–9.
71. Japan Pharmaceutical Manufacturers Association. Pharmaceutical administration and regulations in Japan. Regul Inf Task Force. 2015;1–116.
72. European Medicines Agency. Procedural advice to CHMP Members. London; 2008. Available from: https://www.ema.europa.eu/documents/regulatory-procedural-guideline/procedural-advice-chmp-members_en.pdf [Accessed 05 May 2019]
73. U.S. Food & Drug Administration. Types of Applications]. U.S. Department of Health and Human Services. 2014. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/default.htm [Accessed 05 May 2019]
74. Health Canada. Guidance Document. Determining prescription status for human and veterinary drugs. Minist Public Work Gov Serv Canada. 2013;1–17. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/pdl-ord/pdl_gd_ord_ld-eng.pdf [Accessed 05 May 2019]
75. Mithun R, Raghavendra R. Regulatory and clinical requirements for prescription to OTC switches in USA and India. 2013. p. 1–18.
76. Mossialos E, Ge Y, Hu J, Wang L. Pharmaceutical policy in China. Challenges and opportunities for reform. Eur Obs Heal Syst Policies. 2016;1–212.
77. European Parliament. Medicinal products in the European Union. The legal framework for medicines for human use. Eur Parliam Res Serv. 2015;1–25.
78. Australian Government. Clinical trials. Department of Health. Therapeutic Goods Administration. 2018. Available from: https://www.tga.gov.au/clinical-trials [Accessed 05 May 2019]
79. Medsafe. Guideline on the regulation of therapeutic products in New Zealand. Part 11: Clinical trials - regulatory approval and good clinical practice requirements. Ministry of Health. 2015;(1.4):1–24. Available from: http://www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part11.pdf [Accessed 05 May 2019]
80. Health Canada. Guidance document. For clinical trial sponsors: clinical trial applications. Minister of Public Work and Government Services Canada. 2016;1–51. Available from: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.pdf [Accessed 05 May 2019]
81. Dutch Government. Wet medisch-wetenschapplijk onderzoek met mensen. 2018. Available from: https://wetten.overheid.nl/BWBR0009408/2018-08-01#SlotformulierEnOndertekening [Accessed 05 May 2019]
82. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Off J Eur Union. 2014;L158:1–76; 27-05-2014.
83. Ministry of Health. Dietary Supplements Regulations 1985. Gazette 1985 p. 1–17.
84. Ministry of Health and Family Welfare. Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulation, 2016. Gazette India. 2016;3(4):72–131.
85. United States. Dietary supplement health and education act of 1994. Public Law. 1994;108(4325).

86. Santini A, Cammarta SM, Capone G, Ianaro A, Tenore GC, Pani L, Novellino E. Nutraceuticals: opening the debate for a regulatory framework. Br J Clin Pharmacol. 2018;84:659–72.
87. Low TY, Wong KO, Yap ALL, De Haan LHJ, Rietjens IMCM. The Regulatory Framework Across International Jurisdictions for Risks Associated with Consumption of Botanical Food Supplements. Compr Rev Food Sci Food Saf. 2017;16(5):821–34.
88. O'Brien P. Regulation of functional foods in China: A framework in flux. Regul Rapp. 2015;12(7/8):1–5.
89. Tanaka H, Kaneda F, Suguro R, Baba H. Current system for regulation of health foods in Japan. J Japan Med Assoc. 2001;126(6):792–805.
90. Yang Y. Scientific substantiation of functional food health claims in China. J Nutr. 2008;138:1199S-1205S.
91. Shimizu T. Health claims and scientific substantiation of functional food - Japanese regulatory system and the international comparison. Eur Food Feed Law Rev. 2011;144:144–52.
92. Food Standards Australia New Zealand. Standard 1.2.7 Nutrition, Health and Related Claims. 2014;F2013L00054. Available from: http://www.foodstandards.govt.nz/code/Documents/1.2.7 Nutrition and health claims v159.pdf [Accessed 05 May 2019]
93. Advertising Standards Authority. Therapeutic and Health Advertising Code. 1990. Available from: http://www.asa.co.nz/codes/codes/therapeutic-health-advertising-code/ [Accessed 05 May 2019]
94. U.S. Food & Drug Administration. Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act. 2008.
95. New Zealand Parliament. Natural Health and Supplementary Products Bill. 2017. Available from: https://www.parliament.nz/en/pb/bills-and-laws/bills-proposed-laws/document/00DBHOH_BILL11034_1/natural-health-and-supplementary-products-bill [Accessed 05 May 2019]
96. Tokeley K. The natural health and supplementary products bill: homeopathy, the truth and the placebo effect. Victoria Univ Wellingt Fac Law Res Pap. 2016;6(4):421–40.
97. European Commission. Consolidated version of commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. Off J Eur Union. 2008;109:11–6; 21-12-2009.
98. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of the application for authorisation of a health claim. EFSA J. 2007;530:1–44.
99. Lenssen KGM, Bast A, de Boer A. Clarifying the health claim assessment procedure of EFSA will benefit functional food innovation. J Funct Foods. 2018;47:386–96.
100. Mason M. Drugs or dietary supplements: FDA's enforcement of DSHEA. J Public Policy Mark. 1998;17(2):296–302.
101. Lachenmeier D, Steffen C, El-Atma O, Maixner S, Löbell-Bahrends S, Kohl-Himmelseher M. What is a food and what is a medicinal product in the European Union? Use of the benchmark dose (BMD) methodology to define a threshold for pharmacological action. Regul Toxicol Pharmacol. 2012;64:286–95.
102. Australian Government. European Union guidelines used by the Office of Complementary Medicines. Department of Health. Therapeutic Goods Administration. 2006. Available from: https://www.tga.gov.au/european-union-guidelines-used-office-complementary-medicines [Accessed 05 May 2019]
103. Koch A, Brandenburger S, Turpe S, Birringer M. The need for a legal distinction of nutraceuticals. Food Nutr Sci. 2014;5:905–13.
104. Coppens P. The future of botanicals in the EU. Nutrafoods. 2011;10:2–3.

105. Cousyn G, Dalfra S, Scarpa B, Geelen J, Anton R, Serafini M, Delmulle L. Project BELFRIT. Harmonizing the use of plant food supplements in the European Union: Belgium, France and Italy - A first step. Eur Food Feed Law Rev. 2013;3:187–96.
106. Flear ML. The EU Clinical Trials Regulation: key priorities, purposes and aims and the implications for public health. J Med Ethics. 2016;42(3):192–8.
107. Silano M, Vincenza DM, Vincenzi DA, Silano V. The new European legislation on traditional herbal medicines: main features and perspectives. Fitoterapia. 2004;75:107–16.
108. EHPM & EBF. Discussion paper on health claims on botanicals used in foods EHPM - EBF joint position. 2012;1–4.



Chapter 7

Clarifying the health claim assessment procedure of EFSA will benefit functional food innovation

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Abstract

The rejection of many putative health claims in Europe is assumed to have negatively affected functional food innovation. This study analysed the influence of Article 13.1 health claims review procedure on the perception of functional food innovation.

The analysis of all scientific opinions related to antioxidants and a subsequent qualitative review of five scientific dossiers reveals that the evaluation by the European Food Safety Authority was not conducted consistently, as the Authority did not follow their own procedure. Several submitted scientific dossiers however also contain studies unrelated to the proposed health claim.

By not following their own procedure, the European Food Safety Authority has created uncertainty regarding health claim evaluations. This uncertainty presents a risk for food companies and impacts future investments for research and development of new functional food products. Although published guidance documents have partially clarified the evaluation process, further standardisation and clarification will benefit functional food innovation.

7.1 Introduction

Food innovation is important in small and medium enterprises (SMEs): a large part of the total profits of SMEs originates from strategically developed novel products (1). Food innovation gives rise to high industrial financial costs due to the required research and development (2). The majority of food businesses are SMEs and although innovation is of importance for all food companies, the high financial burden generally impacts SMEs as these companies do not have large research and development budgets. Food innovation is driven by food products contributing to improving health, also known as functional foods (1,3). Although functional foods are not defined legally, scientific literature regards these products to be providing additional benefits beyond the general benefits of nutrient intake and satisfaction of hunger (4,5).

In Europe, the use of statements on health benefits for marketing purposes is regulated under the Nutrition and Health Claim Regulation (NHCR), which requires that the suggested health benefits of foods are scientifically proven (Art. 6.1) (6). The NHCR aims to protect consumers from misleading, and to harmonise the internal market throughout the European Union. A secondary objective of the NHCR is to stimulate food innovation (7).

The NHCR defines a health claim as any voluntary statement that refers to the relationship between food and health (Art. 2.2.5) (6). Three categories are specified: the general function claims, which can be based on generally accepted (Art. 13.1) or newly developed scientific evidence (Art. 13.5); reduction of disease risk claims (Art. 14.1a); and claims referring to children's development and health (Art. 14.1b) (6). This paper focusses on the Art. 13.1 claims, which had to be submitted to the EC by January 2008 (6). These claims were subsequently sent to the European Food Safety Authority (EFSA), who performed a scientific evaluation of the evidence on the proposed claim (8). As described in previous analyses of the evaluation procedure by EFSA, this evaluation involves three criteria: (1) the bioactive substance is sufficiently characterised, (2) the proposed claim should comprise a beneficial physiological effect and (3) a cause and effect relationship between the bioactive substance and the beneficial physiological effect should be established (9,10). As the assessment procedure follows this specific order of evaluating these criteria, when a criterion is not evaluated with a positive outcome, the assessment is discontinued (11).

The outcome of this risk assessment is published in a scientific opinion. The assessment's results constitute the main element for the EC when deciding upon

the authorisation of the health claim (12). A total of 44,000 claims were submitted to the EC in January 2008. These were clustered by the EC to 4,637 claims, and after evaluation of 2,758 of these claims, only 222 were authorised for use in December 2012(9), by the entry into force of Regulation 432/2012, also known as the positive list (Art. 1) (13). Foods containing antioxidants were, at time of submission of the health claims, regarded as promising functional foods (14,15). In January 2008, 230 claims on antioxidants were proposed. After evaluation by EFSA, only eight claims received a positive opinion and were subsequently authorised (9).

Previous studies have investigated the influence of the NHCR on the food industry by determining the industry's perception. Interviews with industry stakeholders showed that industrials perceived the NHCR to have a negative influence on food innovation (12). Industrials expressed i.a. that investments are considered risky as the chance of getting a health claim authorised is small. Other research has identified that the required complex wording of claims, a lack of transparency of the evaluation process and limited financial resources of the company are the main challenges for the industry with regard to the NHCR and food innovation (16–18). Moreover, the NHCR is described to affect company strategies: companies more often use the product follower strategy, in which products that are already on the market are copied, or claims are used that were already authorised (7).

Whereas previous studies focussed on the stakeholder perceptions, the current study considers the influence of EFSA's Art. 13.1 health claim assessment procedure on the perception of future functional food innovation. To this end, the scientific opinions were analysed to determine the main determinants for a negative opinion by EFSA and analyse the consistency of the evaluation procedure. Subsequently, underlying scientific dossiers were reviewed to further explore the assessment procedure conducted by EFSA.

7.2 Methodology

To study the consistency of the evaluation procedure and to determine the most frequently used reasons for objection all scientific opinions were studied which present outcomes of submitted health claim evaluations on oxidative stress and related physiological conditions. Secondly, underlying submitted scientific dossiers of a selection of opinions were analysed in-depth by means of qualitative reviews, to further explore how dossier were evaluated exactly.

7.2.1 Scientific opinion collection

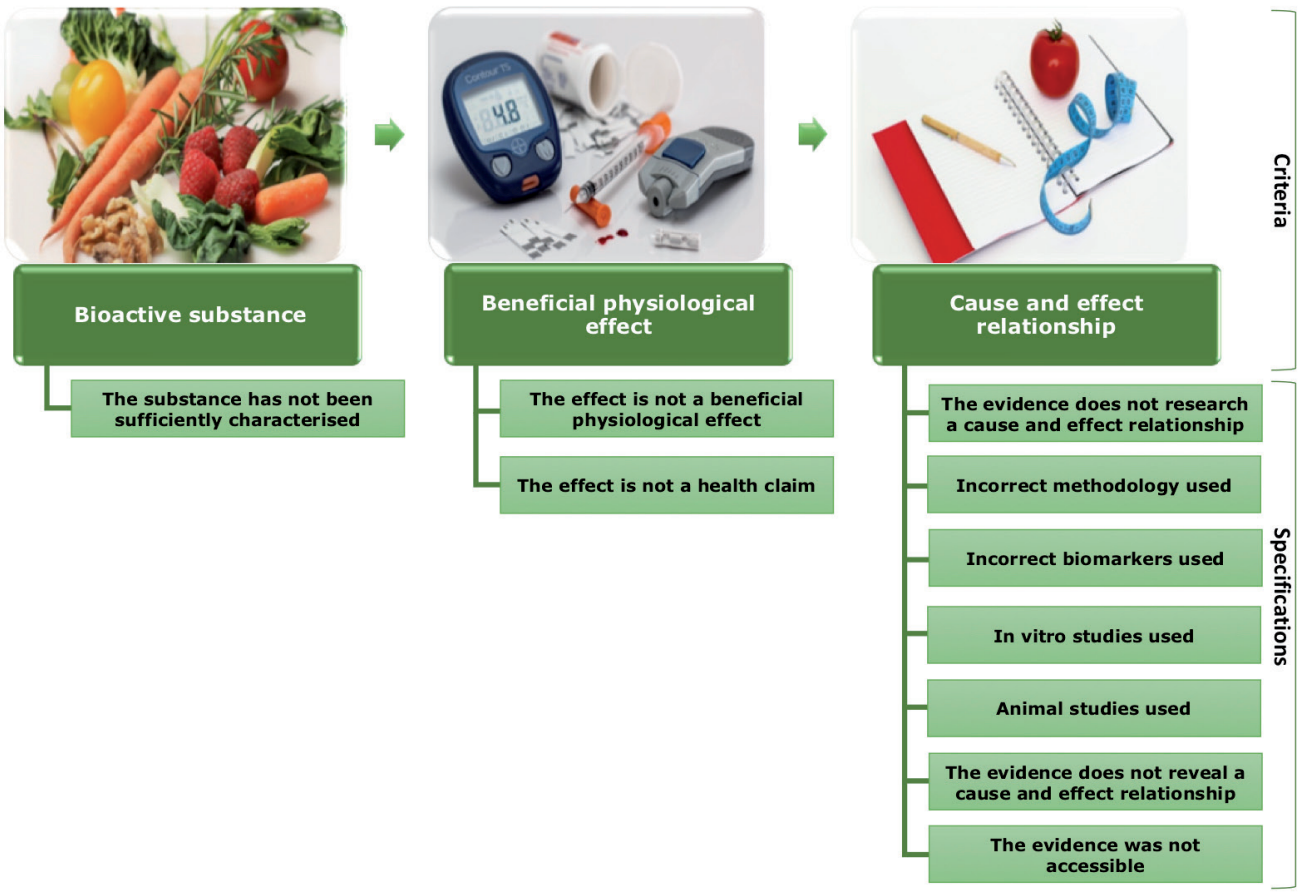
All the EC's requests to EFSA for scientific and technical advice are publicly available in the register of questions, which contains both identification numbers for questions related to health claim evaluations, as well as EFSA's scientific opinions in which the outcome of the evaluation is published (19). The initial search strategy used in the register of questions was 'antioxidant' within Food Sector Area: 'Health Claims Art 13/2', which refers to Art. 13.1 health claims. To prevent incomplete analyses, additional searches were conducted with the keywords 'oxidative stress', 'oxidative' and 'ageing'. Claims related to ageing were only taken into consideration when the claim was related to the ageing of cells. Scientific opinions explicitly mentioning that a cause and effect relationship had been researched and reported upon in a previous scientific opinion, were excluded.

7.2.2 Data collection from scientific opinions on antioxidant health claims

For the analysis, data was collected from all scientific opinions on submitted antioxidant health claims. The terminology as used by EFSA was used in both the collection and the analysis of the data. The following information was obtained from the scientific opinions:

(I) Date of publication, to provide information on changes in the procedure over time.
(II) Number of studies included in the scientific dossier, used to determine the size of the various scientific dossiers.
(III) Bioactive substances of interest and the related proposed claims.
(IV) Outcome of the three criteria upon which an evaluation is based: (1) bioactive substance, (2) beneficial physiological effect and (3) cause and effect relationship between substance and health benefit.
(V) Wording used by EFSA for criterion 2 (beneficial physiological effect), to determine the communication of EFSA towards the applicant.
(VI) For scientific opinions with a negative evaluation, the specifications used to describe any missing scientific evidence consequently resulting in a negative evaluation of one of the three criteria were obtained. Figure 1 displays for the evaluation procedure the possible specifications for rejection per criterion. Not all specifications immediately lead to rejection: animal studies and *in vitro* studies can for example be used as supportive evidence, but they clarify why the scientific evidence is not explicitly supporting the proposed health claim.

Figure 1. Evaluation process with specifications for rejection per criterion (9).



The evaluation procedure of health claims by EFSA. The figure displays, per criterion, which specifications for rejection can be provided in a scientific opinion.

7.2.3 Data analysis

7.2.3.1 Consistency

The collected data was based upon the requirements in the guidance documents provided by EFSA and collected systematically (10). The systematic collection provides insights into whether all published health claim evaluations are consistently conducted and reported. As the data collection was based on EFSA's published guidance documents, subsequent analysis evaluated whether the evaluation procedure was based on EFSA's set standards.

7.2.3.2 Assessment of the rejection criterion and specifications

As the analysis does not only include health claims related to the protection from oxidative damage but includes all physiological conditions related to oxidative stress, the claims were categorised in one of eight physiological conditions based on EFSA's terminology, being: 'ageing of cells', 'cardiovascular', 'immune system', 'inflammatory reactions', 'oxidative damage/antioxidant', 'UV-induced oxidative damage', 'vision', and 'other oxidative stress-related physiological conditions'. These conditions were identified according to physiological processes associated with oxidative stress, as exemplified in the role of reactive oxygen species in the NF-kB pathway and in the development of atherosclerosis (20,21).

A descriptive statistical analysis was conducted to distinguish the evaluation criterion upon which most putative health claims received negative opinions. First, the totality of claims was analysed based upon the three evaluation criteria as described. Health claims of which the evaluation outcome of criterion 1 (bioactive substance) was missing in the scientific opinion were categorised separately. The analysis resulted in percentages defining the proportion of the total claims rejected on the specific criterion (section 'evaluation criteria).

After assessing the total number of claims, the health claims categorised per physiological condition were analysed likewise.

Subsequent to the analysis on the evaluation criteria, argumentation to reject a claim on one of the three criteria, here referred to as specifications, was studied. As in the initial analysis, first the totality of claims was studied followed by the separate categories on the physiological conditions. In order to determine the relative importance of a specification, the number of health claims that was given a certain specification was compared to the total number of claims.

7.2.3.3 In-depth interpretation of the health claim evaluation

A subset of scientific dossiers that underlie a scientific opinion was analysed qualitatively to gain in-depth understanding of the evaluation procedure of the submitted scientific dossiers.

7.2.3.3.1 Dossier selection

The five dossiers were selected based upon the outcomes of the scientific opinion analysis by selecting dossiers of health claims that were of average size and of which the evaluation outcome was published in the years 2009-2011 (22–25).

Two dossiers with the same bioactive substance, kaki fruit, were chosen, of which the evaluation outcome of criterion 1 (bioactive substance) was published for one but not the other (22,24). Although, this was also observed for two other selected dossiers with honey as bioactive, when the evaluation outcome of the bioactive substance was published, kaki fruit was considered a bioactive substance whereas honey was not (22,24,25). One additional dossier was selected with cocoa flavanols as bioactive substance, also because of the later authorisation of an Art. 13.5 health claim with that same bioactive substance (13).

7.2.3.3.2 Collection of references in the selected dossiers

The reference lists of the dossiers submitted to substantiate the selected proposed health claims were obtained from the EFSA website and all studies presented in these lists were collected (26). Only full text English studies were taken into consideration for the analysis.

Table 1. Selection of dossiers.

Health Claim	Criterion 1	Criterion 2	Criterion 3
Honey and antioxidant properties	✗	-	-
Honey and protection of DNA proteins and lipids from oxidative damage	N/A	✓	✗
Kaki fruit and maintenance of vision	✓	✓	✗
Kaki fruit and protection of DNA, proteins and lipids from oxidative damage	N/A	✓	✗
Cocoa flavanols and protection of lipids from oxidative damage	✓	✓	✗

The table displays per dossier the criterion the health claim is rejection upon which was the base for selecting the scientific dossier for the qualitative analysis. Criterion 1: the bioactive substance is sufficiently characterised. Criterion 2: the proposed claim is a beneficial physiological effect. Criterion 3: a cause and effect relationship has been established between bioactive substance and beneficial physiological effect.

Various scientific opinions describe the evaluation of a health claim which was subject of several submitted scientific dossiers. For these evaluations, EFSA combined the scientific dossiers and in the scientific opinion, references were made to studies from all scientific dossiers under review. All referred studies, including studies that were not part of the original dossier, were taken into account for this in-depth analysis. Some scientific opinions referred to scientific literature discussing the appropriate biomarkers for oxidative stress, and were therefore not explicitly related to the health claim itself. These references were excluded from the analysis.

7.2.3.3.3 Data collection and analysis

Scientific dossiers referred to both original research articles and other scientific sources such as review articles and books. The methodological requirements for studies supporting a health claim are described in the guidance documents published by EFSA (27,28). The types of data collected from the obtained references are based on these methodological requirements. From the original research articles, the following information was obtained: (I) objective of the study; (II) summary of the study results; and (III) methodology of the conducted study. Other scientific sources were analysed based on: (I) the objective; (II) the bioactive substance of interest or another main subject (being e.g. a disease or condition); (III) details on how information was obtained; (IV) types of studies used to review the subject; and (V) the overall outcome of the review according to the authors. The systematic review of the studies alongside the requirements described in the published guidance documents provides understanding as to why studies were not regarded to be substantiating putative health claims, which allows for a deeper understanding of the evaluation procedure conducted by EFSA.

7.3 Results

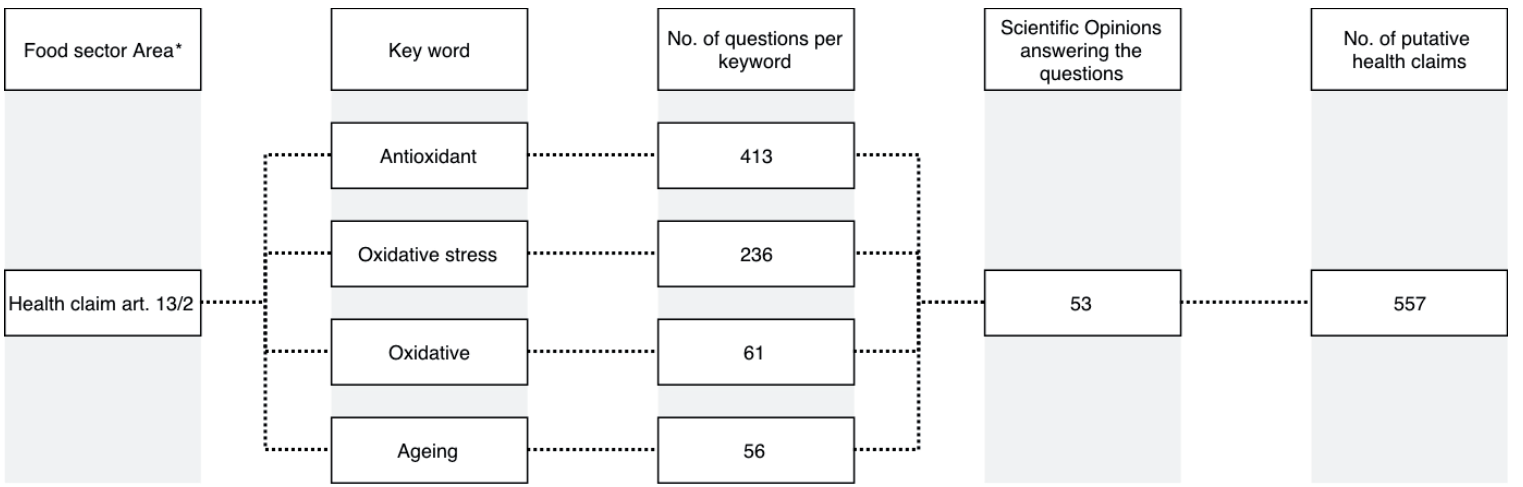
7.3.1 Consistency of the evaluation procedure

The 557 questions excluding duplicates resulting from the search strategy, were answered in 53 scientific opinions (Figure 2). Since in one scientific opinion multiple questions of the EC can be answered, the number of questions exceeds the number of scientific opinions.

7.3.1.1 High numbers of claims evaluated in one scientific opinion

Various scientific opinions encompass evaluations of multiple proposed health claims. Some scientific opinions combine proposed claims on the same bioactive substance and the same beneficial physiological effect resulting in one overall

Figure 2. search strategy in the Register of Questions to obtain putative antioxidant Article 13.1 health claims.



The figure shows the search strategy conducted in the European Food Safety Authority's Register of Questions and its outcome. The number of questions per key word include duplicates and excluding duplicates results in the final number of 557 unique putative health claims.
**The food sector area is a field in the register of questions. Health claim Art. 13/2 will provide you with all questions asked to the European Food Safety Authority concerning Article 13.1 health claims.*

conclusion on one health claim. However, other opinions evaluate different bioactive substances related to one beneficial physiological effect.

Scientific opinion numbers 1489, 1752 and 1799 are examples of opinions displaying the evaluation outcome of high numbers of substances for a few beneficial physiological effects (24,29,30). Scientific opinion 1489 presents one evaluation outcome of 145 different substances and their relation to the protection of DNA, proteins and lipids from oxidative damage. For all these putative health claims the evaluation of criterion 1 (bioactive substance) was unavailable and they were rejected upon criterion 3 (cause and effect relationship), as the scientific dossiers did not reveal a cause and effect relationship (24).

7.3.1.2 Wording of the beneficial physiological effect

The systematic analysis of the scientific opinions demonstrated that for some proposed health claims, the effect is considered to be a beneficial physiological effect, whereas for others the health claim may be a beneficial physiological effect. Maintenance of normal blood pressure for example is a beneficial physiological effect, while improvement of endothelium dependent vasodilation may be a beneficial physiological effect (31,32).

Throughout the evaluation of the Art. 13.1 claims, the wording of criterion 2 (beneficial physiological effect) for oxidative stress related claims is shown to be changed from 'protection of DNA, proteins and lipids from oxidative damage is a beneficial physiological effect' to 'protection of DNA, proteins and lipids from oxidative damage may be a beneficial physiological effect'. The latest scientific opinion using 'is' was published in October 2009, the first using 'may be' was published in February 2010 (31,33). Scientific opinions provide a short explanation on the beneficial physiological effect, which is identical in these scientific opinions, except for the words 'is' and 'may be'.

7.3.1.3 Defining the bioactive substance

The bioactive substance honey was not considered sufficiently characterised, as the composition of honey can vary due to environmental factors (25). Kaki fruit is described to be sufficiently characterised (22). Additional information provided in the scientific opinion focussed on the species but does not describe the potential bioactive ingredient.

When authorised by the EC, a health claim is included in Regulation 432/2012 (Art. 1) describing authorised Art. 13.1 and Art. 13.5 claims (13). The regulation also presents the conditions of use for each claim. An example of the conditions

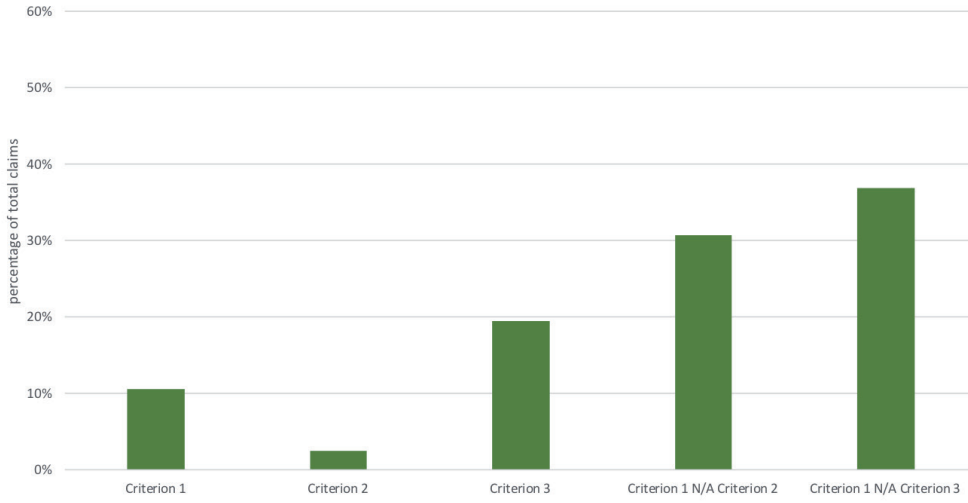
of use for the authorised antioxidant health claim of which the bioactive substance is not a mineral or a vitamin, is the claim 'olive oil polyphenols contribute to the protection of blood lipids from oxidative stress'. The conditions of use are specified for the claim to only be used when 20 grams of olive oil contains at least 5 milligrams of hydroxytyrosol and its derivatives. Hence, the claim may not be used for other products also containing hydroxytyrosol (34).

7.3.2 Quantitative analysis on rejection

7.3.2.1 Evaluation criteria

Descriptive statistics were applied to the total number 557 putative Art. 13.1 health claims with a negative evaluation and the subsequent physiological related categories. The majority of the studied claims, 320 (57.5%), were related to oxidative damage or antioxidant activity. Figure 3 displays the descriptive analysis on the total number of claims of EFSA's three evaluation criteria.

Figure 3. Total claims: rejection per criterion.



The figure displays on which evaluation criterion a health claim application is rejected for the total number of antioxidant claims. Criterion 1: the bioactive substance is not sufficiently characterised. Criterion 2: the proposed claim is not a beneficial physiological effect. Criterion 3: A cause and effect relationship between bioactive substance and physiological effect has not been established. Criterion 1 N/A Criterion: the evaluation outcome of criterion 1 was not published, the health claim is rejected on criterion 2. Criterion 1 N/A Criterion 3: the evaluation outcome of criterion 1 was not published, the health claim is rejected on criterion 3.

Analysis of the claims categorised upon the oxidative stress related physiological conditions demonstrates that claims related to 'ageing of cells' and 'inflammatory responses' are not considered to be describing a beneficial physiological effect (Table 2). Claims describing such effects were, irrespective of the evaluation of criterion 1 (bioactive substance), rejected upon criterion 2 (beneficial physiological effect) and, hence, were never evaluated on a cause and effect relationship.

7.3.2.2 Missing evaluation of criterion 1

As displayed in Figure 3, in 67.5% of the total number of claims, EFSA's assessment outcome on criterion 1 (bioactive substance) was not published. Categorisation (Table 2) shows that the majority of claims in the categories, 'ageing of cells', 'claims related to the immune system', 'inflammatory responses', 'oxidative damage/antioxidant activity', and 'other oxidative stress-related physiological conditions', were not evaluated on this specific criterion.

Comparing scientific opinions describing the evaluation of health claims with the same bioactive substance reveals that the missing evaluation of criterion 1 does not imply that the bioactive substance is considered sufficiently characterised. This is exemplified by health claims on honey and kaki fruit, which were evaluated in various scientific opinions (22,24,25,35). Three scientific opinions on health claims involving honey as bioactive substance were published in February 2010: the first scientific opinion evaluates criterion 1 with a negative outcome, but the second does not present this evaluation outcome (24,35). The third scientific opinion again presents the negative evaluation of the first criterion, the bioactive substance (published in 2011) (25). In the example of kaki fruit, one scientific opinion does not present the evaluation outcome of criterion 1 (2010) and the other scientific opinion states (2009) that the bioactive substance is considered sufficiently characterised (22,24).

7.3.2.3 Specifications for rejection

Figure 4 shows the results of the rejection specification analysis (the argumentation to reject a claim on one of the three criteria).

Two out of 557 analysed health claims were given additional reason 'the evidence was not accessible', indicating that the majority of the studies presented in the scientific dossier were available for review by EFSA.
Subsequent categorisation demonstrates that 'ageing of cells' and 'inflammatory responses' are never considered to be beneficial physiological effects (Figure 4). They were only provided with the specifications 'not a beneficial physiological

Table 2. Oxidative stress related physiological conditions: rejection per criterion.

Category	Evaluation criteria	Rejected claims (% of total)
Ageing (19 = 100%)	Criterion 1	0 (0,0%)
	Criterion 2	2 (10,5%)
	Criterion 3	0 (0,0%)
	Criterion 1 N/A, criterion 2	17 (89,5 %)
	Criterion 1 N/A, criterion 3	0 (0,0%)
Cardiovascular (36 = 100%)	Criterion 1	10 (27,8%)
	Criterion 2	2 (5,5%)
	Criterion 3	9 (25,0%)
	Criterion 1 N/A, criterion 2	10 (27,8%)
	Criterion 1 N/A, criterion 3	5 (13,9%)
Immune system (70 = 100%)	Criterion 1	7 (10,0%)
	Criterion 2	5 (7,1%)
	Criterion 3	3 (4,3%)
	Criterion 1 N/A, criterion 2	55 (78,6%)
	Criterion 1 N/A, criterion 3	0 (0,0%)
Inflammatory responses (8 = 100%)	Criterion 1	0 (0,0%)
	Criterion 2	1 (12,5%)
	Criterion 3	0 (0,0%)
	Criterion 1 N/A, criterion 2	7 (87,5%)
	Criterion 1 N/A, criterion 3	0 (0,0%)
UV-induced damage (23 = 100%)	Criterion 1	1 (4,3%)
	Criterion 2	0 (0,0%)
	Criterion 3	20 (87,0%)
	Criterion 1 N/A, criterion 2	0 (0,0%)
	Criterion 1 N/A, criterion 3	2 (8,7%)
Oxidative damage / antioxidant activity (320 = 100%)	Criterion 1	25 (7,8%)
	Criterion 2	2 (0,6%)
	Criterion 3	52 (16,3%)
	Criterion 1 N/A, criterion 2	46 (14,4%)
	Criterion 1 N/A, criterion 3	195 (60,9%)
Vision (17 = 100%)	Criterion 1	3 (17,6%)
	Criterion 2	0 (0,0%)
	Criterion 3	12 (10,6%)
	Criterion 1 N/A, criterion 2	0 (0,0%)
	Criterion 1 N/A, criterion 3	2 (11,8%)

Table 2. Continued

Category	Evaluation criteria	Rejected claims (% of total)
Other related claims (64 = 100%)	Criterion 1	13 (20,3%)
	Criterion 2	2 (3,1%)
	Criterion 3	12 (18,8%)
	Criterion 1 N/A, criterion 2	36 (56,2%)
	Criterion 1 N/A, criterion 3	1 (1,6%)

The table displays the number of health claims that were rejected upon each criterion, and its percentage of the total antioxidant claims. Criterion 1: the bioactive substance is not sufficiently characterised. Criterion 2: the proposed claim is not a beneficial physiological effect. Criterion 3: A cause and effect relationship between bioactive substance and physiological effect has not been established. Criterion 1 N/A Criterion: the evaluation outcome of criterion 1 was not published, the health claim is rejected on criterion 2. Criterion 1 N/A Criterion 3: the evaluation outcome of criterion 1 was not published, the health claim is rejected on criterion 3.

effect' or 'not a health claim', the latter being provided when a claim is indicating, for example, medicinal purposes of the substance.

7.3.2.4 Studies not related to the health claim presented in the scientific dossier

The analysis of the total number of claims showed that claims rejected upon criterion 3 (cause and effect relationship) were more often linked to the specification 'the evidence does not research a cause and effect relationship' than 'the evidence does not reveal a cause and effect relationship' (Figure 4). Categorisation of physiological conditions related to oxidative stress demonstrates this observation in the categories 'UV-induced oxidative damage', 'cardiovascular' and 'oxidative damage/antioxidant'.

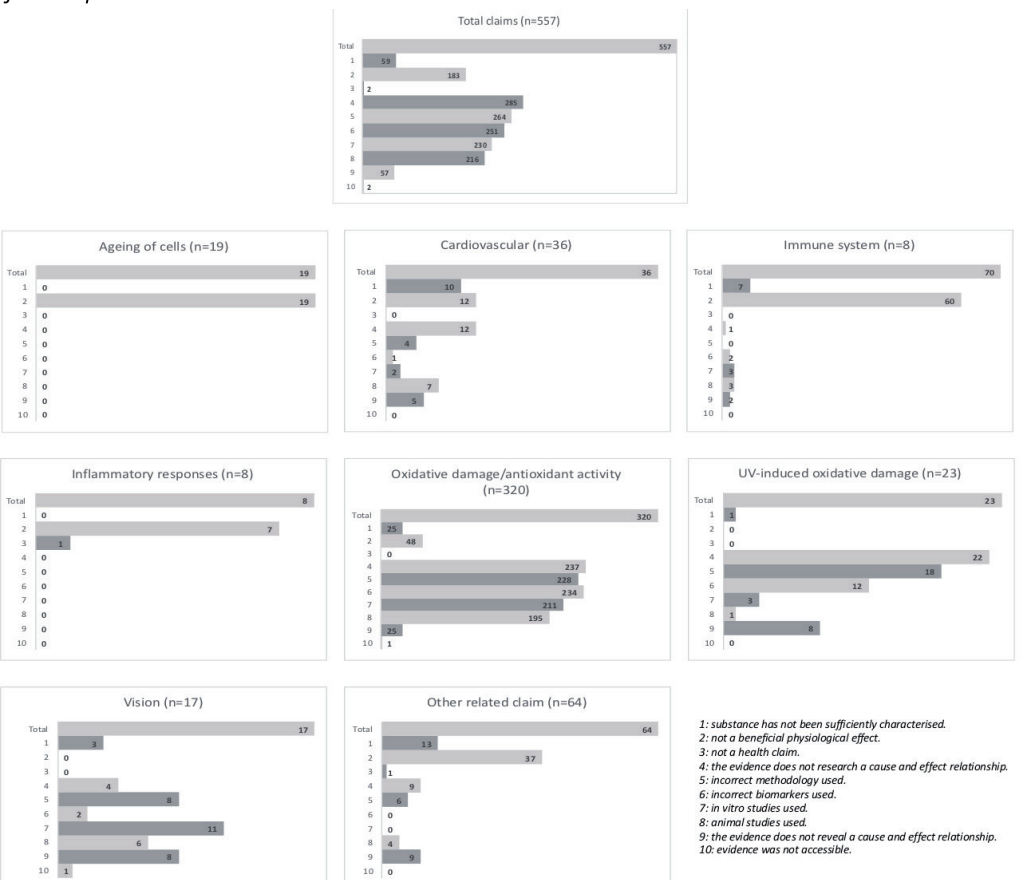
7.3.3 Interpreting the scientific opinions with the submitted scientific dossiers

Five proposed health claims were selected for the qualitative dossier analysis. Table 3 shows the composition of the scientific dossiers studied for this analysis.

7.3.3.1 Studies not related to the health claim presented in the scientific dossier

The in-depth scientific dossier analysis underlines the observation that the specification 'the evidence does not research a cause and effect relationship' was more often concluded rather than 'the evidence does not reveal a cause and effect relationship' (3.2.4) The studied scientific dossiers on kaki fruit and honey merely present studies not related to the proposed health claim: the studies in the two dossiers on kaki fruit do not research the effect of kaki fruit, but focus on lutein, zeaxanthin or a combination of both, on the proposed physiological effect

Figure 4. specifications for rejection upon a criterion.



The figure shows for the total claim and per oxidative stress related physiological condition the number of claims provided with a specification. The bars demonstrate the specification relative to the total number of claims or to the total claims in a category in order to determine the importance of that specifications.

Table 3. Composition of dossiers.

ID number	Bioactive substance	Claim	References in dossier	Reference not available in English	References not accessible	References reviewed
1159	Honey	Antioxidant properties	37	1	4	29 original research articles 3 reviews
1321	Honey	Protection of DNA, lipids and proteins from oxidative damage	3+8*	0	0	3 original research articles 0 reviews
1260	Kaki fruit	Protection of DNA, lipids and proteins from oxidative damage	19	3	2	6 original research articles 8 reviews
1261	Kaki fruit	Maintenance of vision	78	3	10	46 original research articles 19 reviews
1506	Cocoa flavanols	Protection of lipids from oxidative damage	54+1*	0	0	32 original research articles 23 reviews

The table displays the information on the health claims studied in the dossiers analysis. Included is also information on the availability of the references and the final numbers and types of references studied in the qualitative analysis. References which were not accessible include the studies which could not be obtained by the researcher, these were available for review by EFSA.
** The study was not mentioned in the dossier, but included in EFSA's scientific opinion.*

(36). One in vitro study is conducted on persimmon genotypes which includes kaki fruit (37). The scientific dossier on honey and its antioxidant properties mainly includes in vitro studies on the antibacterial properties of honey, not on the antioxidant activity of honey (36). One intervention study with buckwheat honey on antioxidant capacity of serum is presented, but this study did not use biomarkers considered reliable by EFSA (38).

7.3.3.2 Study design

The dossier presenting studies on the effect of cocoa flavanols on the protection of lipids from oxidative damage demonstrates the importance of using the appropriate study design for health claim substantiation. The scientific dossier contains 26 human intervention studies (36). All studies researched the effect of either flavanols or chocolate on various outcomes.

The guidance document on oxidative stress-related claims describes the biomarkers for oxidative damage on lipids considered reliable by EFSA: F2a–isoprostanes in urine, oxidised LDL particles in blood, and phosphatidylcholine hydroperoxides in blood or tissue (27). In the dossier on cocoa flavanols, six studies used one of the biomarkers proposed by EFSA (39–44). Four of these six studies did not show statistically significant results (40–43). The other two studies describe a statistically significant difference between the intervention and the control group, of which one study was in heart transplant patients and one study used a bicycling ergometer to induce oxidative stress (39,44). In five out of six studies the biomarkers were measured in blood instead of urine. As the scientific opinion does explicitly specify studies not supporting a cause and effect relationship as they were conducted with biomarkers not considered reliable by EFSA, measuring the biomarkers in a different medium than specified in the guidance did not contribute to the negative opinion (23).

The scientific opinion states that administration of cocoa flavanols shows an acute effect on the protection of lipids, but long-term effects are not substantiated (23).

7.4 Discussion

This study aims to identify the effect of EFSA's evaluation procedure of Art. 13.1 health claims on the perception of future functional food innovation. To this end, 53 scientific opinions were analysed quantitatively and five of the scientific dossiers were studied in-depth. The scientific opinion analysis shows that the evaluation was not always done according to the criteria EFSA states in their guidance document (10,45–47). The evaluation of large numbers of claims in one scientific opinion, not publishing the evaluation outcome for the bioactive substance and the changed wording for the beneficial physiological effect indicates the procedure was not always followed. The limitations because the study design requires to be a randomised controlled trial (RCT) and the varying requirements for the characterisation of the bioactive substance, might add to the negative perception of the NHCR. On the contrary, the scientific dossiers submitted to EFSA to substantiate the proposed health claims, often present studies not related to proposed health claim.

7.4.1 Inconsistency in the evaluation process

The evaluation of high numbers of claims in one scientific opinion, the missing evaluation outcome of criterion 1 (bioactive substance) in many opinions, and

the varying wording for criterion 2 (beneficial physiological effect) have affected the perception of future functional food innovation of food business operators.

Publishing the outcome of a high number of evaluated claims in one scientific opinion provides no clarity as to whether the provided specifications apply to all claims. When the evaluation does not indicate which elements are missing in the scientific dossier for a specific claim, future studies for health claim substantiation might still lack these necessary elements.

The majority of the reviewed health claims is shown to not include the evaluation outcome of criterion 1 (the bioactive substance), indicating this was not evaluated by EFSA. The evaluation of criterion 1 is the first step in the assessment process that EFSA uses to finalise their scientific opinion. If the bioactive substance is not considered sufficiently characterised, the evaluation process is terminated (11). Previous studies showed that food companies have invested additional resources in analysing the nutritional value of their products (48). Scientific opinions not disclosing the outcome evaluation of this bioactive substance, do not provide information on whether the substance is sufficiently characterised. Hence, if the analysis conducted by food companies has revealed potentially bioactive substances, these scientific opinions do not confirm nor deny whether this substance is sufficiently characterised.

Finally, the terminology used to define the beneficial physiological effect differs between scientific opinions: the word 'is' ('… is a beneficial physiological effect) is adjusted to 'may be'. Some claims are phrased as '… is a beneficial physiological effect' whereas other are defined as '… may be a beneficial physiological effect'. For the health claim related to 'protection of DNA, proteins and lipids from oxidative stress', the wording of the beneficial physiological effect was adjusted from 'is' to 'may be' during the evaluation procedure. When comparing the final permitted health claims however, the wording of the claims does not vary (13, Annex). It is unclear whether the wording used for the beneficial physiological effect affected the assessment of the evidence. A potential explanation of this adjustment however is that the development of the guidance document for oxidative stress claims, which was published in November 2011, influenced the view of EFSA on these claims (27). Still, the guidance document does not provide any insights into how its development has led to the change of words.

Previous research already showed that the perception of the industry towards the NHCR is negative (7,12,16–18). This was mainly attributed to a lack of transparency of the evaluation procedure. Publishing high numbers of health claims

in one scientific opinion and not publishing the evaluation outcome of the bioactive substance itself indicates that EFSA does not follow its own evaluation procedure. Varying words and changing the words for the beneficial physiological effect while the health claims are under review suggest EFSA can alter their view on a claim without providing further clarity. If food companies want to apply for an Art. 13.5 claim, which should be based on newly developed scientific evidence, a scientific opinion might aid in setting up the additional research (48,49). When a scientific opinion does not describe the full evaluation of all proposed claims, future studies might be conducted with similar study designs used before, as it was not clear why the study was not considered to substantiate the health claim. This increases the risk for a future negative opinion by EFSA. A negative opinion most often results in non-authorised health claims, so the product presents no added value to the customer (50). The return on investments for the R&D of the product, will thus be lower. Together, these risks will negatively impact investments done into new functional food products and therefore decrease functional food innovation, as risks are partly decisive for future company strategies (49). Such risks also increase when EFSA apparently can alter the evaluation procedure without any communication on these changes to the industry.

EFSA aimed to clarify the evaluation process and methodological requirements by publishing guidance documents. The guidance documents on the general requirements were already revised by EFSA multiple times, indicating EFSA continuously aims to clarify the procedure for the industry (10,46,47). To support the industry even more, guidance documents on specific types of beneficial physiological effects have been developed and published, in which the development included a consultation with industry stakeholders (27,28).

It should however be noted that a scientific opinion is not depicted to aid companies in setting up further research. EFSA's objective is to only give an independent scientific risk assessment and does this based on the submitted scientific dossier (Art. 22.2) (51). The European Medicines Agency (EMA) is, on the contrary, involved in the during the scientific dossier development, by means of scientific advice on the required scientific substantiation. EMA is the responsible authority for evaluation marketing authorisation applications for medicines (Art. 5.2) (52). The legislation in which EFSA (Art. 22.2) and EMA (Art. 5.2) are established, both refer to the duty to provide scientific advice (51, 52). However, the execution of this duty varies between the two authorities. Research has showed that, when the scientific advice provided by the EMA during the scientific dossier development, is implemented by a company, scientific advice increases the chance of approval of a new medicine (53). It can hence be argued that consultation possibilities, if

EFSA implements a similar strategy as EMA, can provide substantial aid for food companies, which will decrease the risk of a negative opinion and can stimulate functional food innovation. The proposed adjustments to Regulation 178/2002, responsible for establishing EFSA, following from its evaluation as conducted by the EC include, amongst other things, the possibility to have pre-assessment meetings with supporting staff of EFSA (54). As these meetings can clarify the requirement for a positive health claim evaluation, it will be highly valuable for food innovation.

7.4.2 Methodological requirements

The strict requirements regarding the study design and the varying requirements concerning characterising the bioactive substance also pose obstacles for food companies (34,55). The dossier on cocoa flavanols and protection of lipids from oxidative damage demonstrates the need for studies to be conducted with certain biomarkers and being set up in a specific study design, an RCT. The only scientific consensus on biomarkers for lipid oxidation is that measuring at least two different biomarkers is appropriate without considering any biomarker the gold standard (56). EFSA published a guidance document disclosing the biomarkers appropriate for measuring effects of food on oxidative stress (27). It thereby provides scientific boundaries upon which no agreement is in science. Setting such boundaries can lead to the exclusion of all other biomarkers in nutrition and health related studies. It might also be possibly resulting in less efforts for the development and validation of new biomarkers, as the risk exists of EFSA not considering them reliable and therefore unsuitable for health claims related research.

Besides the biomarkers, the observed requirement for an RCT, in the analysis of the scientific dossiers, poses various difficulties when it comes to nutrition and health related research, as it focusses on one effect of one compound, whereas foods are expected to subtly effect multiple outcome measures (9,55). Additionally, many diseases for which its relation to nutrition is researched, develop over years, and effects of consumption of food will therefore manifest after a long period of time (57). The current legal framework on health claims is in literature described to be focussing on the single substance – single outcome (9,57). In this framework, the RCT seems to be the only suitable study design for health claims substantiation research. It should thus be reconsidered whether the single substance – single outcome approach is the most suitable in the legal framework of health claims.

The results indicate that, for some health claims, evidence should clearly provide the singular substance responsible for the health benefit, whereas for other this is not necessary. This has been shown in previous research: the claim of olive oil and its effect on the protection of blood lipids is only authorised for olive oils of which 20 grams contain at least 5 milligrams of hydroxytyrosol and its derivatives (34). These findings are confirmed in the conducted analysis presented in this paper, studying honey and kaki fruit (section 'defining the bioactive substance'). This demonstrates that for some foods the bioactive substance should be explicitly defined, illustrated by the conditions of use for the authorised claim with olive oil and the rejection of the claim with honey on the bioactive substance, whereas for others the complete food is considered sufficient to obtain a positive evaluation on criterion 1, as observed for kaki fruit (22,25). It therefore remains unclear in what detail the bioactive substance should be characterised to obtain a positive evaluation on the first criterion (bioactive substance).

Within nutritional science, the impact of the food matrix on bioavailability and the effectiveness of a bioactive substance in the human body is acknowledged (58,59). An example of a claim of which the bioactive substance is known to be affected by the food matrix and also processing, is the claim on β-glucans contributing to the maintenance of normal blood cholesterol levels (60). In the case of olive oil phenols, it is known that hydroxytyrosol is also present in other products such as olive leaves (34,61). The main aspect would be the bioaccessibility and bioavailability of the substance in the human body, as this is important to determine if the substance can have an effect in the human body (59). Bioavailability data on the food constituent is also required for a health claim authorisation (10). For olive oil, the studies in the scientific dossier determine that the bioavailability of hydroxytyrosol is sufficient, for other products this might not be verified by the studies presented in the dossier. As the studies further determine hydroxytyrosol has a favourable effect on the protection of lipids from oxidative damage, proving the bioavailability of the food constituent in a different food matrix should thus be sufficient to determine it has a positive effect on health. EFSA might therefore consider a simplified procedure for determining the bioavailability of food constituents of authorised health claims in a different food matrix.

In summary, getting a health claim authorised is difficult as proving the effect of a product in an RCT might not reflect the actual effect of a food product. Additionally, it remains uncertain to what extent the bioactive substance responsible for the effect should be characterised as exemplified by the opinions issued upon honey and kaki fruit. This increases the risk of a negative opinion or an unsuitable

authorised health claim and makes the decision to aim for a health claim risky for food companies and hence, will decrease the investments done towards new functional food products (48,49). Considering supporting other study designs such as the challenge model, and a simplified procedure for determining the bioavailability of authorised claims within different food matrices might proof useful to stimulate functional food innovation (34).

7.4.3 Studies not related to the health claim presented in the scientific dossier

The qualitative analysis of the scientific dossiers shows that at least in some scientific dossiers, studies are presented that either do not analyse the bioactive substance that is subject of the claim, or do not research the effect of the bioactive substance on outcomes related to the beneficial physiological effect. These studies do not contribute to providing evidence on the proposed health claim presented in the dossier which explains the negative opinion issued by EFSA.

All Art. 13.1 claims needed to be substantiated by generally accepted scientific evidence (Art. 13.1.i) (6). The studies included in the scientific dossiers were not executed primarily for health claim substantiation and the definition of generally accepted scientific evidence is considered difficult, explaining why these studies do not all research a direct cause and effect relationship (16). However, the examples presented in this study demonstrate that some dossiers contain no, or only a very limited amount of studies that do investigate the effect of the substances of interest on reliable outcomes. Whereas this has resulted in the majority of health claims receiving a negative opinion, contributing to the negative perception towards health claims, there is still interest in claims related research today (62). Industrials state that even though their expectations of the regulation differed from their experience, knowing now what is expected will improve future studies that are conducted for health claim substantiation (12). This difference between expectations and actual situation can also partly explain the high number of studies in the submitted dossiers related not directly to the health claim. The published guidance documents and additional scientific papers on the design of claims related research, might benefit food companies further by decreasing uncertainty (47,62). When uncertainty regarding the required research is lower, industrials will perceive a decreased risk for a negative opinion which might lead to increasing R&D budgets for functional food products (49).

7.4.4 Strengths and limitations

The presented study is the first analysing the evaluation procedure quantitatively and so identified this procedure has created for functional food innovation.

Whereas previous studies mainly focussed on stakeholders' perception of the NHCR, the current study identifies how this perception came about.

The study does however only include health claims related to oxidative stress, which represents only a small percentage of the more than 44,000 health claims submitted to the EC. Still, the findings of this study are expected to be relevant for other health claim categories as well because the assessment procedure has been executed likewise for these other categories.

The study does not determine the influence of the NHCR on the number of new food innovations marketed. However, as the industry is the responsible stakeholder for putting new innovative food products on the market, it is expected that by identifying the main aspects which contributed to the negative perception, this study did identify that the evaluation procedure influenced functional food innovation.

Future studies should aim to determine if the NHCR influenced the number of new functional food products put on the market. The assumption that the NHCR has a negative impact on functional food innovation, mainly based on the perception of the stakeholders, should be analysed quantitatively. Such research will also be useful to determine if clarifying the health claim assessment procedure stimulates functional food innovation.

7.5 Conclusion

The scientific assessment of the Art. 13.1 claims by EFSA has given rise to uncertainties for food companies. As uncertainties create financial risks, the evaluation procedure is considered to have negatively impacted the perception of future functional food innovation. Although currently more guidance is available which already abates some of the identified uncertainties, this study shows that certain concerns still exist that influence the application for an Art. 13.5 health claim. Elucidation of the discussed issues, such as the missing evaluation of the bioactive substance, will stimulate future functional food innovation by increasing the potential for using health claims. To this end, a more standardised approach of EFSA based on their own procedure is encouraged, as well as increased transparency in the decision-making process. Additionally, the approach of EMA, providing scientific advice to applicants during the development of the dossiers, is shown to positively influence the outcome of a scientific assessment. Such an approach could hence improve the perspective of the industry towards

the NHCR. Nonetheless, when applying for an Art. 13.5 claim, the industry should not disregard the efforts EFSA already put into clarifying the procedure. Future studies for health claim substantiation require to be based on the available guidance documents.

Clarification of the evaluation procedure by EFSA and implementation by the industry of the already available requirements for health claim substantiation will improve functional food innovation.

7.6 References

1. Avermaete T, Viaene J, Morgan E. Determinants of innovation in small food firms. Eur J Innov Manag. 2003;6(1):8–17.
2. Archibugi D, Evangelista R, Simonetti R. Concentration, firm size and innovation: evidence from innovation costs. Technovation. 1995;15(3):153–63.
3. Costa A, Jongen W. New insights into consumer-led food product development. Trends Food Sci Technol. 2006;17(8):457–65.
4. Bigliardi B, Galati F. Innovation trends in the food industry: the case of functional foods. Trends Food Sci Technol. 2013;31(2):118–29.
5. Menrad K. Market and marketing of functional food in Europe. J Food Eng. 2003;56:181–8.
6. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
7. Moors E. Functional foods: regulation and innovations in the EU. Innov Eur J Soc Sci. 2012;25(4):424–40.
8. Smith A, Terry S, Detken D. 10 Years of the European Food Safety Authority (EFSA) and the EU food safety system. Eur Food Feed Law Rev. 2012;3:111–6.
9. de Boer A, Vos E, Bast A. Implementation of the nutrition and health claim regulation–The case of antioxidants. Regul Toxicol Pharmacol. 2014;68(3):475–87.
10. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of the application for authorisation of a health claim. EFSA J. 2007;530:1–44.
11. Verhagen H, Loveren H van. Status of nutrition and health claims in Europe by mid 2015. Trends Food Sci Technol. 2016;56:39–45.
12. de Boer A, Bast A. Stakeholders' perception of the nutrition and health claim regulation. Int J Food Sci Nutr. 2015;66(3):321–8.
13. European Commission. Consolidated version of commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. Off J Eur Union L. 2012; 22-08-2017.
14. Richardson DP, Eggersdorfer M. Opportunities for product innovation using authorised European Union health claims. Int J Food Sci Technol. 2015;50(1):3–12.
15. Roberfroid M. Concepts and strategy of functional food science: the European perspective. Am J Clin Nutr. 2000;71(6):1660s-1664s.
16. Bröring S, Khedkar S, Ciliberti S. Reviewing the Nutrition and Health Claims Regulation (EC) No. 1924/2006: What do we know about its challenges and potential impact on innovation? Int J Food Sci Nutr. 2017;68(1):1–9.
17. Khedkar S, Bröring S, Ciliberti S. Exploring the Nutrition and Health Claims Regulation (EC) No. 1924/2006: What is the impact on innovation in the EU food sector? Int J Food Sci Nutr. 2017;68(1):10–7.
18. Khedkar S, Ciliberti S, Bröring S. The EU health claims regulation: implications for innovation in the EU food sector. Br Food J. 2016;118(11):2647–65.
19. EFSA. Register of Questions [Internet]. 2017. Available from: http://registerofquestions.efsa.europa.eu/roqFrontend/login?0
20. Baker RG, Hayden MS, Ghosh S. NF-κB, Inflammation, and Metabolic Disease. Cell Metab. 2011;13(1):11–22.

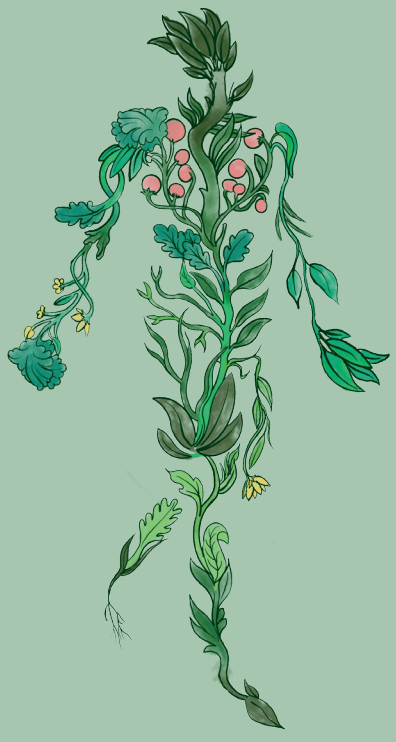
21. Hajjar DP, Gotto AMJ. Biological Relevance of Inflammation and Oxidative Stress in the Pathogenesis of Arterial Diseases. Am J Pathol. 2013;182(5):1474–81.
22. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to kaki fruit and maintenance of vision (ID 1261) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2009;7(9):1275.
23. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to cocoa flavanols and protection of lipids from oxidative damage (ID 652, 1372, 1506, 3143), and maintenance of normal blood pressure (ID 1507) pursuant to Article 13(1) of Regulation (EC No 1924/2006). EFSA J. 2010;8(10):1792.
24. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to various food(s)/food constituent(s) and protection of cells from premature aging, antioxidant activity, antioxidant content and antioxidant properties, and protection of DNA, proteins and lipids from oxidative damage pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2010;8(2):1489.
25. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to: dairy products (ID 1140, 1141, 1191), raw or processed food products of animal origin, plus bread and panification products (ID 1193, 1194), herbal yeast plasmolysate (ID 1815, 1816), apple polyphenols (ID 2713), rye flour (ID 1266), tomato juice (ID 1202), whey protein and alphal-actalbumin (ID 424, 430, 432, 725, 1433), brocco shoots, broccoli sprout powder and brassica oleracea var. italica (broccoli) (ID 1362, 1481, 2844, 2845), honey (ID 1159, 1160, 1318, 4678, 4679), and Cucurbita pepo L. (pumpkin) seeds and seed extracts (ID 2029, 2365) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2011;9(6):2243.
26. EFSA. General function health claims under Article 13 | European Food Safety Authority. 2017. Available from: https://www.efsa.europa.eu/en/topics/topic/article13
27. EFSA NDA Panel. Scientific Opinion – Guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health. EFSA J. 2011;9(12):2474.
28. EFSA NDA Panel. Scientific Opinion – Guidance on the scientific requirements for health claims related to functions of the nervous system, including psychological functions. EFSA J. 2012;10(7):2816.
29. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to various food(s)/food constituent(s) and protection of cells from premature ageing (ID 1668, 1917, 2515, 2527, 2530, 2575, 2580, 2591, 2620, 3178, 3179, 3180, 3181, 4329, 4415), antioxidant activity, antioxidant content and antioxidant properties (ID 857, 1306, 2515, 2527, 2530, 2575, 2580, 2591, 2629, 2728, 4327, 4365, 4380, 4390, 4394, 4455, 4464, 4507, 4694, 4705), protection of DNA, proteins and lipids from oxidative damage (ID 1196, 1211, 1216, 1306, 1312, 1440, 1441, 1666, 1668, 1692, 1900, 1914, 1948, 2023, 2158, 2517, 2522, 2527, 2575, 2591, 2620, 2637, 2639, 2663, 2860, 3079, 3276, 3564, 3818, 4324, 4329, 4351, 4397, 4416, 4424, 4507, 4527, 4528, 4542, 4611, 4629, 4659) and bioavailability of anthocyanins in black currants (ID 4220) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2010;8(10):1752.
30. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to various food(s)/food constituents(s) and "immune function/immune system" (ID 433, 605, 645, 791, 1384, 1451, 1624, 1743, 1776, 1838, 1851, 1854, 1891, 1895, 3074, 3191, 3211, 3218, 3336, 3341, 3450, 3514, 3658, 3756, 3802, 3805, 3814, 3935, 3979), "contribution to body defences against external agents" (ID 2344, 3208, 3213, 3270, 3278, 3285, 3294, 3309, 3387, 3424, 3428, 3536, 3537, 3539, 3575, 3577, 3579, 3582, 3603, 3618, 3755, 3776, 3777, 3778, 3801, 3804, 3840, 4367, 4472), reduction of inflammation (ID 1327, 1391) and decreasing potentially

pathogenic gastro-intestinal microorganisms (ID 2362, 2730, 4064) pursuant to Article 13(1) of Regulation (EC) No 1924/2006,. EFSA J. 2010;8(10):1799.

31. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to Camellia sinensis (L.) Kuntze (tea), including catechins in green tea and tannins in black tea, and protection of DNA, proteins and lipids from oxidative damage (ID 1103, 1276, 1311, 1708, 2664), reduction of acid production in dental plaque (ID 1105, 1111), maintenance of bone (ID 1109), decreasing potentially pathogenic intestinal microorganisms (ID 1116), maintance of vision (ID 1280), maintanence of normal blood pressure (ID 1546) and maintanence of normal blood cholesterol concentration (ID 1113, 1114) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2010;8(2):1463.
32. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to rutin and improvement of endothelium□dependent vasodilation (ID 1649, 1783) and protection of DNA, proteins and lipids from oxidative damage (ID 1784) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2010;8(10):1751.
33. EFSA NDA Panel. Scientific opinion on the substantiation of health claims related to Justicia adhatoda L. and protection of DNA, proteins and lipids from oxidative damage (ID 2508) and function of the upper respiratory tract (ID 3970) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2009;7(9):1294.
34. de Boer A, Urlings M, Bast A. Active ingredients leading in health claims on functional foods. J Funct Foods. 2016;20:587–93.
35. EFSA NDA Panel. Scientific Opinion on the substantiation of health claims related to honey and "respiratory health through presence of antioxidant phytochemicals" (ID 1161), "the unique composition and ratio of effective substances adds energy to the human body" (ID 3188), and "it stimulates the whole metabolism and the immune system" (ID 3189) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J. 2010;8(2):1484.
36. EFSA. Consolidated list of Article 13 health claims - List of references received by EFSA - Part 2 IDs 1001-2000. 2011;1–856.
37. Ercisli S, Akbulut M, Ozdemir O, Sengul M, Orhan E. Phenolic and antioxidant diversity among persimmon (Diospyrus kaki L.) genotypes in Turkey. Int J Food Sci Nutr. 2008;59(6):477–82.
38. Gheldof N, Xiao-Hong, Wang A, Engeseth NJ. Buckwheat Honey Increases Serum Antioxidant Capacity in Humans. J Agric Food Chem. 2003;51(5):1500–5.
39. Flammer AJ, Hermann F, Sudano I, Spieker L, Hermann M, Cooper KA, Serafini M, Lüscher TF, Ruschitzka F, Noll G, Corti R. Dark chocolate improves coronary vasomotion and reduces platelet reactivity. Circulation. 2007;116(21):2376–82.
40. Mathur S, Devaraj S, Grundy SM, Jialal I. Cocoa products decrease low density lipoprotein oxidative susceptibility but do not affect biomarkers of inflammation in humans. J Nutr. 2002;132(12):3663–7.
41. Murphy KJ, Chronopoulos AK, Singh I, Francis MA, Moriarty H, Pike MJ, Turner AH, Mann NJ, Sinclair AJ. Dietary flavanols and procyanidin oligomers from cocoa (Theobroma cacao) inhibit platelet function. Am J Clin Nutr. 2003;77(6):1466–73.
42. Mursu J, Voutilainen S, Nurmi T, Rissanen TH, Virtanen JK, Kaikkonen J, Nyyssönen K, Salonen JT. Dark Chocolate Consumption Increases HDL Cholesterol Concentration and Chocolate Fatty Acids May Inhibit Lipid Peroxidation in Healthy Humans. Free Radic Biol Med. 2004;37(9):1351–9.
43. Wang JF, Schramm DD, Holt RR, Ensunsa JL, Fraga CG, Schmitz HH, Keen CL. A dose-response effect from chocolate consumption on plasma epicatechin and oxidative damage. J Nutr. 2000;130(8S Suppl):2115S-9S.

44. Wiswedel I, Hirsch D, Kropf S, Gruening M, Pfister E, Schewe T, Sies, H. Flavanol-rich cocoa drink lowers plasma F2-isoprostane concentrations in humans. Free Radic Biol Med. 2004;37(3):411–21.
45. EFSA NDA Panel. Scientific Opinion - General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA J. 2011;9(4):2135.
46. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (revision 1). EFSA J. 2011;9(5):2170.
47. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of a health claim application (revision 2). EFSA J. 2017;15(1):4680.
48. Brandenburger S, Birringer M. European health claims for small and medium-sized companies–Utopian dream or future reality? Funct Foods Heal Dis. 2015;5(2):44–56.
49. Bremmers HJ, van der Meulen BMJ, Purnhagen K. Multi-stakeholder responses to the European Union health claims requirements. J Chain Netw Sci. 2013;13(2):161–72.
50. Siro I, Kápolna E, Kápolna B, Lugasi A. Functional food. Product development, marketing and consumer acceptance□A review. Appetite. 2008;51(3):456-467.
51. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Off J Eur Union. 2002;31:1–44; 01-07-2018.
52. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and vetrinary use and establishing a European Medicines Agency. Off J Eur Union. 2004;136:1–70; 05-06-2013.
53. Regnstrom J, Koenig F, Aronsson B, Reimer T, Svendsen K, Tsigkos S, Flamion B, Eichler H-G, Vamvakas S. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur J Clin Pharmacol. 2010;66(1):39–48.
54. European Commission. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the transparency and sustainability of the EU risk assessment in the food chain amending Regulation (EC) No 178/2002 [on general food law], Directive 2001/18/EC [on the deliberate release into the environment of GMOs], Regulation (EC) No 1829/2003 [on GM food and feed], Regulation (EC) No 1831/2003 [on feed additives], Regulation (EC) No 2065/2003 [on smoke flavourings], Regulation (EC) No 1935/2004 (on food contact materials], Regulation (EC) No 1331/2008 [on the common authorisation procedure for food additives, food enzymes and food flavourings], Regulation (EC) No 1107/2009 [on plant protection products] and Regulation (EU) No 2015/2283 [on novel foods]. Brussels; 2018.
55. Bast A, Briggs W, Calabrese E. Scientism, legalism and precaution-contending with regulating nutrition and health claims in Europe. Eur Food Feed Law Rev. 2013;6:401–9.
56. Carocho M, Ferreira ICFR. A review on antioxidants, prooxidants and related controversy: Natural and synthetic compounds, screening and analysis methodologies and future perspectives. Food Chem Toxicol. 2013;51:15–25.
57. Todt O, Luján J. The role of epistemic policies in regulatory science: scientific substantiation of health claims in the European Union. J Risk Res. 2017;20(4):551–65.

58. Binns N, Howlett J. Functional foods in Europe: international developments in science and health claims. Eur J Nutr. 2007;1:3–13.
59. McClements DJ. Enhancing nutraceutical bioavailability through food matrix design. Curr Opin Food Sci. 2015;4:1–6.
60. Kerckhoffs DAJM, Hornstra G, Mensink RP. Cholesterol-lowering effect of beta-glucan from oat bran in mildly hypercholesterolemic subjects may decrease when beta-glucan is incorporated into bread and cookies. Am J Clin Nutr. 2003;78(2):221–7.
61. de Bock M, Thorstensen EB, Derraik JGB, Henderson H V., Hofman PL, Cutfield WS. Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (Olea europaea L.) leaf extract. Mol Nutr Food Res. 2013;57(11):2079–85.
62. Lucey A, Heneghan C, Kiely ME. Guidance for the design and implementation of human dietary intervention studies for health claim submissions. Nutr Bull. 2016;41(4):378–94.



Chapter 8

The complexity of 'traditional use' to prove health effects: a critical perspective on botanical health claim substantiation

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Abstract

Background

There is considerable interest among consumers in using 'natural', plant-based nutritional supplements for their purported health benefits. However, the data required to support health claims on these so-called botanicals is subject to an ongoing debate, especially in Europe. Remarkably, pharmaceutical regulations have a provision that sometimes makes it possible to include data on 'traditional use' in the approval process.

Scope and approach

In this critical perspective, we elaborate why substantiation of health benefits with evidence on traditional use is not easy to apply for food products. This is highlighted by the examples of recent incidents with traditional herbal substances such as kava kava and ephedra. These examples demonstrate that safety considerations, which are explicitly considered in the assessment of traditional herbal medicinal products, deserve special attention, and cannot be disregarded in food products that have health claims based on traditional use.

Key findings and conclusions

Unexpected safety-related problems may arise when consumers combine botanicals with (prescribed) pharmaceutical products or specific nutrients, as it is often unlikely that such interactions will have been identified during traditional use. Information on both the safety and the health benefits are key to enable consumers to make the best decision for their personal health.

As current legislative requirements for food products do not provide the opportunity to include both effectiveness and safety in the assessment, it is questionable whether and how traditional use evidence can be used under the current regulatory framework for health claims on foods.

8.1 Introduction

With a growing interest of consumers in maintaining and improving health (1) and a trend to self-medicate (2, the market for products with presumed health-promoting properties such as food supplements is large and ever-growing (2,3,4). Next to using products that contain conventional nutrients or pharmaceutical ingredients, various consumer products used for health promotion (especially food supplements) include botanicals as main ingredient: substances, often extracts, that are made from plants, algae, fungi, or lichens (2,5) (. Whereas botanicals are in the US separately regulated by the Dietary Supplement and Health Education Act (DSHEA), in the European Union, some plant-derived products find their way both to the food and pharmaceutical markets (2,6).

Producers of these products can voluntarily provide information to consumers about potential health effects of the products, also referred to as claims. Claims referring to the relationship between health and (a constituent of) a food product are considered to be health claims (Art. 2.2.5), which are in Europe regulated by the Nutrition and Health Claim Regulation (NHCR, Regulation (EC) No 1924/2006) (7). By only authorising health claims that are substantiated by scientific evidence (Art. 1.c), the NHCR aims to ensure that consumers cannot be misled by unsubstantiated, false or medicinal claims (Art. 3.a) (7,8). Health claims will only be evaluated positively, and subsequently authorised, when a cause-and-effect relationship is has been established in a human intervention trial (9,10). Statements on medicinal products conveying the efficacy of a product also need to be based on evidence, but for some products, for which a long history of use can be demonstrated, the efficacy does not necessarily need to be proven with intervention studies. As defined in Directive 2004/24/EC, next to the authorisation procedure for newly developed pharmaceutical products, pharmaceutical ingredients whose composition, production process, safety and effect are described in 'traditional evidence', can be authorised as traditional herbal medicinal products (Art. 16.a) (THMPs)(6,11). Evidence on the traditional use of a product for a specific health benefit, hereafter referred to as 'traditional use evidence', thus has a prominent position in the substantiation of efficacy and safety of THMPs. Various stakeholders within the food sector have suggested that this approach could also be used to support health claims on botanical food products (12,13,14,15). This because botanicals are present in both food and pharmaceutical products, but the substantiation requirements differ to the extent that the substantiation requirements are more clarified for pharmaceutical products, including THMPs. The different position of data on traditional use in the legal frameworks of food and medicine has therefore been described as

discriminatory (16). Whether such traditional use evidence can and should be applied in substantiating food health effects, specifically those of botanicals, is however highly debated and the review process of the substantiation of botanical health claims has been put on hold by the Commission in 2010 (17,18). This review process, and the authorisation procedure as a whole, are not expected to be resumed before consensus is reached regarding the use and applicability of traditional use evidence.

Various authors have made suggestions on how to use traditional use evidence for the support of health claims (12,15). They thereby often relate to the use of such evidence in supporting efficacy of THMPs (18). In this critical perspective, we however outline the complexity of applying traditional use evidence to support health benefits claimed on botanical containing food products. Previous research has shown that there are essential differences between the application of data on 'traditional use' in medicine, where such information underlies both the safety and efficacy assessment, and its potential for use in health claim evaluations, where only the beneficial effect on health needs to be demonstrated. The focus of this review is therefore not on the type of data required to establish a beneficial health effect of botanical by traditional use evidence, but to understand the underlying difficulties that may arise when this type of evidence is used in risk assessment. Additionally, we concentrate on the role of the risk manager in specifying the objectives of EU food law, to allow the risk assessor to assess the (scientific) evidence to adhere to these objectives.

We therefore evaluate the legal framework of food and pharmaceutical products, to analyse which essential considerations should be explored when assessing the potential application of data on the traditional use of a product to support health benefits of such a product.

8.2 Traditional use evidence for health claim substantiation

Traditional use evidence has a role in various international frameworks dealing with foods and medicinal safety and efficacy (6). Even though it is currently not considered sufficient to support a health claim authorisation request in the EU, it does play a role in various European legal frameworks that deal with the authorisation of chemical products, including THMPs and novel foods.

8.2.1 Defining 'traditional use evidence' in Europe

There are two main elements in defining a THMP under Directive 2004/24/EC. Firstly, a herbal product should be used for at least 30 years of which 15 years within the European Union to treat, alleviate or cure (symptoms of) a specific disease (Art. 16c.1.c)(11). Secondly, it should be possible to use the product without the supervision of a medical expert (Art. 16a.1.a) (11). Through a simplified procedure which will be discussed in more detail later in this section, market authorisation and recognition of a product as THMP, can be obtained for such a product. In order for the product to be eligible for authorisation under the simplified procedure, it must meet certain specific criteria. As defined in Article 16a of the human medicine's directive, Directive 2001/83/EC, the product can be taken orally or is for external use or inhalation (it is not administered intravenously), and the specifics regarding the posology are indicated. Most importantly, 'sufficient' data regarding the traditional use of the product (Article 16a.1.e) must prove that the product is 'not harmful in the specified conditions of use and the pharmacological effects (…) are plausible' (Art. 16a.1.e) (20). For obtaining a traditional use registration, the applicant needs to submit the application to a national competent authority. Article 16c.1.c further specifies that this traditional use evidence consists of bibliographical or expert evidence related to the specific medicinal product or a corresponding product (having the same active ingredients and the same or similar intended purpose), and defines that data should be provided 'throughout a period of at least 30 years preceding the date of the application', of which at least 15 years within the European Union (Art. 16c.1.c) (11). As put forward in Art. 16c.1.d, the Member State authority can request not only the bibliographic review of safety data together with an expert report, but can also require additional data that is deemed necessary to assess the safety of the pharmaceutical product. After submitting this application for authorisation for traditional use registration at the competent authority of a Member State, this Member State can request the Committee for Herbal Medicinal Products to draw up an opinion on whether the provided evidence is adequate in supporting the 'long-standing use of the product' (Article 16c.1.c). When a product is authorised based on such traditional use evidence, a manufacturer is required to place information on the label and/or leaflet for users that the use of the THMP for the specific indication is exclusively based on long-standing use (Article 16g.2.a), and when symptoms persist or adverse effects are experienced by users, they should consult a health care professional (Article 16.g.2.b) (20). Only 'minor claims' can be permitted on THMPs, and next to showing their efficacy based on traditional use (17,21), no further requirements for the demonstration of efficacy are needed to be fulfilled (22). Specific therapeutic indications, including those referring to cancer, infectious diseases, or diabetes,

are not allowed for THMPs (21,23). Additionally, in the claim it must be specified what the nature and type of tradition is and in general, no terminology that is related to pharmacological actions can be used. For example, a claim related to clinically relevant biomarkers such as cholesterol levels, needs to be scientifically measured and can thus not be used on THMPs (21). Finally, in communicating the indicated use to a consumer, it is required to introduce the indication as follows: "Herbal medicinal product traditionally used…" (21). This means that the claims that are placed on these THMPs are not completely comparable to efficacy claims on regular pharmaceutical products.

The Committee on Herbal Medicinal Products is one of the scientific committees of the European Medicines Agency, EMA, who provides scientific opinions on herbal substances and preparations and provides information on the recommended uses and safe conditions of such herbals (Art. 16e.1) (11). Manufacturers who seek to obtain a traditional use registration for their product, are encouraged by Directive 2004/24/EC to make use of EU herbal monographs that are established by this Committee, in which the therapeutic uses and safe conditions for both well-established and traditional herbal substances and preparations are described. Additionally, scientific guidance documents issued by the Committee describe how to prepare marketing applications and for example detail quality aspects of (traditional) herbal medicinal products (24) and provide specifications regarding test procedures for herbal substances, preparations and (traditional) medicinal products (25).

As indicated above, such preparations of plants (and other substances) can sometimes also be used in food products in the EU. Generally referred to as 'botanicals', such constituents can only be used in foods when they are considered to be safe for human consumption, similar to other food ingredients. Before a new food ingredient (that has not been used as food ingredient before May 1997) can be sold on the EU market, a notification or authorisation request (depending on whether these foods are known outside the EU) needs to be submitted to the European Commission (Art. 10&14) (26,27). This is regulated under the Novel Foods Regulation (Regulation (EU) No 2015/2283), that defines two types of novel foods: (a) foods that are new ingredients and fall within one of the ten predefined categories such as ingredients that have a new molecular structure or resulting from a new production process; or (b) those food products or ingredients that are already consumed as food products in countries outside the EU, and have a 'history of safe use' in such a third country, also known as a 'traditional food from a third country' (Art. 3.2.c.) (26). For completely new ingredients, an authorisation request must be submitted that contains scientific

evidence to demonstrate that a food is not posing a safety risk to human health (Article 10), often including nutritional, toxicological and allergenic information (Art. 5) (27,28,29). This 'history of safe use' can however again be established with traditional use evidence (Art. 15) (26). For traditional foods, data need to be provided regarding the composition of the product, the experience of continued use and what the proposed conditions of use are (28). For the safety assessment, especially this experience of continued use is important, which should provide insights into how the food is used in a third country and proposed conditions of use within the EU: the extent of the use, the population group, how the product is prepared and handled, as well as relevant insights into precautions for the use of the ingredient or food product. The EFSA guidance on traditional foods suggests combining information from scientific publications (preferably by conducting a literature review of human studies), with scientific expert and organisational opinions, monographs, governmental documents, data on cultivation and harvesting as well as sales and trade figures. Even the use of cookbooks, recipes and anecdotal data may be considered, although the reliability of the data will be critically assessed (28). Previous research into the use of traditional use evidence for supporting safety assessments of functional foods that contain botanicals, has highlighted the delicacies in this process, for example related to the variability of composition (30).

8.2.2 Traditional use for health claims

Whereas for pharmaceutical products, the authorisation deals with safety and efficacy, for foods it merely needs to be proven that these are not unsafe before it is placed on the market. Only food products that are not unsafe are allowed on the market (as defined by the General Food Law, Regulation (EC) No 178/2002) (Art. 14.1), but communicating the potential beneficial health effects of a food (ingredient) is considered voluntary information provision (7,31). Such communication is regulated as health claim: when information is provided regarding the efficacy of a food ingredient, that consuming such a food results in a specific health benefit, scientific evidence needs to be provided to support this claim (8,9). The by the applicant provided evidence is evaluated based on three criteria: (I) the bioactive substance is sufficiently characterized, (II) the claimed effect is a beneficial physiological effect and (III) a cause-and-effect relationship is established between the substance and the beneficial physiological effect (8,9,32). The evaluation is also done in that specific order: only when the evidence is considered sufficient for proving this claimed relationship between ingredient and benefit, proven through human intervention studies, the claim can be authorised for use by the European Commission (8,33,34). EFSA furthermore provides

guidance on the methodologies of the human intervention studies by means of specifying adequate outcome measures (35,36).

In 2012, merely 222 of the over 44,000 submitted claims were authorised for use (Art. 1.2) (8,37). The majority of the claims that were initially submitted, received a negative opinion because the underlying scientific evidence did not show a cause-and-effect relationship (9). A more in-depth analysis of the various scientific dossiers revealed that the study designs were often not researching either the cause, or the effect, and so no conclusion could be drawn on the claimed effect of the putative health claim (9).

Besides the authorised and unauthorised health claims, there are currently still approximately 1,500 submitted claims on-hold (34,38): claims that describe putative health effects of botanicals. The underlying evidence for these claims is not yet evaluated by EFSA, whereas these claims are allowed to be used in the communication towards consumers pending authorisation by the European Commission (39). Even though human intervention studies are considered essential for proving health claims (Art. 5) (32,40), stakeholders have started the debate whether also traditional use evidence should be allowed to support health claims (34).

Various authors have analysed what data could be used as evidence to support such traditional use claims for health claims on foods, including but not limited to Coppens et al. (2006), Nicoletti (2012), Schwitters et al (2012), Anton et al. (2013) and Anton et al. (2019) (15,18,41,42). Suggestions have been made to focus on quality requirements described in pharmacopoeias, and to, for example, phrase claims that are substantiated with traditional use data differently to allow consumers to distinguish these claims from claims that are proven by human intervention studies (43). Previous research has furthermore analysed the substantiation requirements in other legal jurisdictions to assess the applicability of the requirements in the European Union. In these jurisdictions such as from China or Japan, traditional use evidence is often based on traditional medicinal systems (6). As there is no traditionally recognised medicinal system in place in the European Union, implementing such an approach has been previously considered as a complex endeavour (6). Even harmonising a list of allowed botanicals and botanical preparations, as suggested within the BELFRIT project, has not yet resulted in a list of substances recognised across European Member States (44).

8.3 The traditional use issue for botanical products

Insights that are gained through traditional use may have a well-established position in substantiating THMPs (Art. 16a.2) and in supporting the safety of traditional food products (Art. 14) (11,26). When considering their application in the substantiation of health benefits of food products, it is however essential to consider the use of the product that will be promoted by this type of health claim. It is important to realise that experience with traditional use of botanicals is – obviously – frequently gained in a different timeframe and perhaps even in a different cultural setting. Parents or grandparents lived closer to their children: information on the correct use of botanicals could be communicated easily and proper use could be learned and supervised. Possible side-effects (safety issues) were probably known within the community and could be detected. This can be exemplified by a study conducted in Tanzania, where elderly family members are still considered to be a valuable source of information when it comes to using medicinal products (45). It is questionable whether the traditionally expected effects of using such a botanical product still fits its use in today's society.

Even though nutrition had already been an important part of many traditional medicinal systems (46), the development of pharmacological preparations from synthetic sources resulted in the development of food and medicine as two distinct fields (47,48). Over the last few decades, the increased attention for nutrition and lifestyle to maintain and improve health has however also resulted in a rising interest in the use of botanical preparations for their health enhancing effects (49). At the same time however, the information about foods, medicines and (healthy) ingredients in general in modern society seem to be more elaborate and additionally food supplement users are known to be higher educated (50). It can however be questioned whether individual scrutiny also has increased. Nowadays, the individual experience with botanicals recognising the beneficial effect as well as side-effects within a social coherent group is less. In other words, although we might rely on the reported health effects based on traditional use, modern man resides in a different societal context. This is also reflected in the reported increased uncertainty of consumers when it comes to food and food safety (51).

During the last decades, we are exposed to a wide variety of compounds, many more than 20-50 years ago, due to e.g. food intake, the use of pharmaceuticals, as well as the use of cosmetic products. With consumers actively looking into ways to maintain and optimise their health, new pharmaceutical products have been developed and are used together with botanicals (52). This results in a

completely different situation when compared to the past and might give rise to unexpected pharmacokinetic as well as pharmacodynamic interactions. A good illustration is kava kava (Piper methysticum). The root of kava kava has been used for centuries by inhabitants of the Polynesian islands in the Pacific for its tranquillizing and pain killing effect. In the Western world it was subsequently processed in various pharmaceutical formulations as capsules, tablets and potions (53). This broad use revealed serious liver and nerve damage of kava kava and it was consequently banned in the USA and Europe in the beginning of this century (53). It is however still obtainable online. Another example is ephedra (in Chinese called Ma Huang) which contains the bioactive substance ephedrine and has been used for centuries in folk medicine in the treatment of lung disease. Until 2004 ephedra was widely used, for example among others by body builders (54). After that, producing and selling ephedra was prohibited because of the reported serious side effects among others on blood pressure (55). Many of the effects are similar to those of amphetamine. The side effects of ephedra are aggravated when MAO-inhibitor medication is used simultaneously.

It will be very difficult to warn the consumer or patient for all possible interactions between for example botanicals used in foods or food supplements, and conventional drugs. Patients are used to receiving indications for proper use of medication and should be warned for simultaneous use of certain nutritional products, which could affect the action of the medication. Even though it is already questionable to what extent consumers are informed by for example retail clerks (56), if there is information provided to a consumer, only the most important interactions are communicated. A nice illustration is formed by the inhibitory effects of components in grapefruit juice on cytochrome P450 3A4 and P-glycoprotein which may lead to a detrimental food-drug interaction (52). Notifications to consumers however are generally limited to grapefruit juice, although other juices could have similar effects (57). And even though it may be useful to provide such information on food products as well, the individual diversity in using prescriptive medicines and additional health affecting compounds increases the difficulty to add package inserts to foods. Even though part of food safety is providing (mandatory) information on how to use a food (Art. 3), which is described in the Food Information to Consumers Regulation (Regulation (EU) No 1169/2011) (58), this mandatory information mainly deals with product and ingredient particulars. Merely allergen information can be considered as warning consumers for potential health risks and thereby protecting certain health sensitive consumers. Additional information on e.g. interactions with other foods or pharmaceuticals could also be expected to confuse consumers: if products are safe for use, why should they receive information about potential unsafety?

Hence, potential interactions between food products and medicinal products are communicated in the leaflets of medicinal products and not on the label of the food product.

The presumption of safety of botanicals in foods would result in not needing to provide additional information to protect from any health risks following consumption. Still, gaining insights into potential differences in how products are used today, when compared to their traditional use, may provide insights into which combinations of products should explicitly be discouraged. Employing a nutrivigilance scheme, a system in which adverse events that are attributed to food intake can be reported, would allow for the identification of such products and interaction effects (59,60). This would however require further instructions on reporting, as provided on leaflets with medicinal products, and an authority collecting and reviewing all adverse event reports.

This leads us to believe that in the current European approach to health claims for foods, it will be difficult and perhaps impossible to simply extrapolate traditional use data to the safe and conscious use of food supplements and to substantiate their health claims. Before applying traditional use evidence in health claim applications, the consumer must understand how to weigh the evidence coming from clinical studies and evidence of traditional use and how this may impact one's health. Whether the consumer can do so, and therefore interpret the information on the product correctly, is for the risk manager to decide. If the risk manager decides to allow traditional use evidence as support for health claims, it could potentially result in allowing two types of claims on food products, similarly to the distinct types of efficacy claims on medicinal products: firstly, the currently authorised claims, which clearly reflect the scientifically substantiated causal relationship between intake and beneficial effect; and secondly, a specific type of claim that will reflect in its wording that it is based on traditional use evidence. It would be the responsibility of the risk assessor to set the criteria for assessing the evidence in order to meet the objectives set by the risk manager (Art. 22) (31). Hence, the risk manager and risk assessor have two different duties which require different actions in order to resume the evaluation of the botanical health claims (31).

8.4 Conclusion and future perspectives

As displayed in this critical review, the suggested approach of stakeholders for allowing 'traditional use evidence' to support putative health claims on botanical ingredients or botanical containing food products, seems based on the assumption that their use today is similar to the traditional usage of botanicals and botanical preparations. This however seems to be an overly simplistic representation of reality: even though plant-derived products have been used in maintaining and improving health for centuries, today's society and consumption patterns bring about new challenges in which traditional use evidence that promotes the intake of a specific product might result in ignoring or even creating potential risks such as adverse effects due to interactions. Even though consumers are already able to buy botanical products that are supposed to not be unsafe, the promotion of such products should not be based on outdated insights from traditional use when these are not applicable anymore, thus potentially contributing to the occurrence of adverse events.

The comparison of using evidence on traditional use for health claim substantiation to its role in substantiating traditional herbal medicinal products is therefore an incomplete comparison: for THMPs, traditional use evidence would be used for conducting a full benefit/risk assessment (11), whereas for foods (which are safe for use) this would merely be a benefit assessment (Art. 15.1.3.e) (7). The increased use of (prescription) medication and other substances to maintain and improve our health, as well as treat symptoms of diseases, has resulted in greater and a more varied exposure to various bioactive substances (61). Traditional use evidence may therefore be a useful information source for consumers to generate insights into potential health effects, but the weight of this type of evidence cannot be considered similar as to scientific evidence on which is a consensus is reached that it substantiates a health effect in humans.

Whereas the discussion amongst stakeholders seems to address the role and applicability of traditional use evidence to support potential health benefits of botanical products, this debate cannot be seen separately from the discussion on what type of information should be available to consumers. One of the main aims of EU food legislation, is to ensure that the 'highest level of consumer protection' is achieved (Art. 1) (31). To achieve that level of protection, specific information requirements have been defined in legislation, for example related to mandatory food information (in the FIC Regulation) (Art. 4) and requiring scientific evidence before a health claim can be voluntarily used by food businesses (Art. 4.1.c) (following Regulation 1924/2006) (7,58). The two most extreme views

in this debate describe on the one side that these strict scientific requirements for health claims could be seen as 'censoring' food business operators in their marketing strategies, whereas others believe that consumers must be protected from information upon which no consensus is reached yet, or that is not scientific but rather originating from tradition. Determining how the objectives of food law are supposed to be met is the responsibility of the risk manager. Although previous research mainly discussed data requirements, it seems to address predominantly the risk assessor. This risk assessor can however only act when the goals and objectives are clearly set by the risk manager, which is, in the case of botanicals, still to be done.

As put forward however in this critical reflection, we believe that when discussing these information requirements for foods, even though it addresses health benefit insights, it is essential to also consider the safety of consuming such products. Only when the consumer is fully informed about the differing substantiation of this type of claim, the information on how to use the botanical containing product safely is clearly displayed, and producers are required to collect information on adverse events (nutrivigilance), traditional use evidence may contribute to supporting the consumer in choosing healthy food products to supplement their diet.

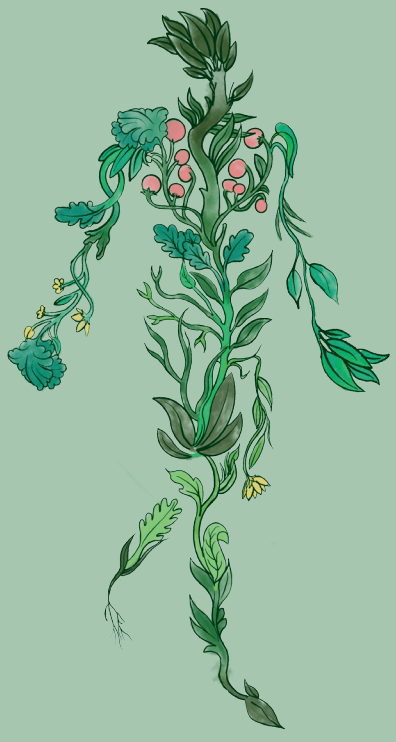
8.5 References

1. Egan B, Hodgkins C, Sheperd R, Timotijevic L, Raats M. An overview of consumer attitudes and beliefs about plant food supplements. Food Funct. 2011;2(12):747–52.
2. Schieber A. Botanicals- challenges abound, solutions in sight? Curr Opin Food Sci. 2020;32:144–8.
3. Euromonitor International. Herbal/Traditional Products. Market Sizes | Historical. 2018.
4. Euromonitor International. Vitamins and Dietary Supplements. Market Sizes | Historical. 2018.
5. EFSA. Botanicals [Internet]. 2018. Available from: https://www.efsa.europa.eu/en/topics/topic/botanicals
6. Lenssen KGM, Bast A, de Boer A. International perspectives on substantiating the efficacy of herbal dietary supplements and herbal medicines through evidence on traditional use. Compr Rev Food Sci Food Saf. 2019;18(4):910–22.
7. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
8. de Boer A, Vos E, Bast A. Implementation of the nutrition and health claim regulation–The case of antioxidants. Regul Toxicol Pharmacol. 2014;68(3):475–87.
9. Lenssen KGM, Bast A, de Boer A. Clarifying the health claim assessment procedure of EFSA will benefit functional food innovation. J Funct Foods. 2018;47:386–96.
10. Todt O, Luján J. The role of epistemic policies in regulatory science: scientific substantiation of health claims in the European Union. J Risk Res. 2017;20(4):551–65.
11. European Parliament and the Council of the European Union. Consolidated version of directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;136:85–90; 30-04-2004.
12. Anton R, Serafini M, Delmulle L. Traditional knowledge for the assessment of health effect for botanicals - a framework for data collection. Eur Food Feed Law Rev. 2012;74–80.
13. Coppens P. The future of botanicals in the EU. Nutrafoods. 2011;10:2–3.
14. Geurts S. Health claims and botanicals: how to proceed with European harmonisation. Eur Food Feed Law Rev. 2018;13(29).
15. Schwitters B. Want to harmonise botanicals: take the broader perspectives of traditional health claims and other substances. Eur Food Feed Law Rev. 2012;6:328–40.
16. Schwitters B. EU health claim laws cannot be bent for botanicals. Nutraingredients [Internet]. 2014; Available from: https://www.nutraingredients.com/Article/2014/10/28/Author-EU-health-claims-laws-cannot-be-bent-for-botanicals
17. Anton R, Serafini M, Delmulle L. The substantiation of claims for botanical food supplements in relation to traditional use. Eur Food Feed Law Rev. 2013;5:321–8.
18. de Boer A, Bast A. Stakeholders' perception of the nutrition and health claim regulation. Int J Food Sci Nutr. 2015;66(3):321–8.
18. Coppens P, Delmulle L, Gulati O, Richardson D, Ruthsatz M, Sievers H, Sidani S. Use of botanicals in food supplements. Ann Nutr Metab. 2006;50(6):538–54.
20. European Parliament and the Council of the European Union. Consolidated version of directive 2001/83/EC of the European Parliament on of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J Eur Union. 2001;311:1–188; 26-05-2021.

21. Committee on Herbal Medicinal Products. Guideline on the assessment of clinical safety and efficacy in the preparation of community herbal monographs for well-established and of community herbal monographs;entries to the community list for tradtional herbal medicinal products/substances/preparations. 2006;EMEA/HMPC/104613/2005:1-13.
22. Routledge P. The European Herbal Medicines Directive - Could it have saved the lives of Romeo and Juliet? Drug Saf. 2008;31(5):416–8.
23. Committee on Herbal Medicinal Products. Questions & answers on the EU framework for (traditional) herbal medicinal products, including those from a "non-European" tradition. 2013;EMA/HMPC/402684/2013:1-20.
24. European Medicines Agency. Guideline on quality of herbal medicinal products/traditional herbal medicinal products. 2011;EMA/HMPC/201116/2005;1-13.
25. European Medicines Agency. Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products. 2022;EMA/HMPC/162241/2005 rev 3:1-25.
26. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel food, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Off J Eur Union. 2015;327:1–22; 27-03-2021.
27. de Boer A, Bast A. Demanding safe foods - safety testing under the novel food regulation (2015/2283). Trends Food Sci Technol. 2018;72:125–33.
28. EFSA NDA Panel. Guidance on the preparation and presentation of the notification and application for authorisation of traditional foods from thrid countries in the context of Regulation (EU) 2015/2283. EFSA J. 2016;14(11):1–16.
29. European Commission. Consolidated version of commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. Off J Eur Union. 2017;351:64–71; 20-12-2017.
30. Kroes R, Walker R. Safety issues of botanicals and botanical preparations in functional foods. Toxicology. 2004;198(1–3):213–20.
31. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Off J Eur Union. 2002;31:1–44; 26-05-2021.
32. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of a health claim application (revision 2). EFSA J. 2017;15(1):4680.
33. Verhagen H, Vos E, Francl S, Heinonen M, van Loveren H. Status of nutrition and health claims in Europe. Arch Biochem Biophys. 2010;501(1):6–15.
34. Verhagen H, Loveren H van. Status of nutrition and health claims in Europe by mid 2015. Trends Food Sci Technol. 2016;56:39–45.
35. Martini D, Rossi D, Biasini B, Zavaroni I, Bedogni G, Musci M, Pruneti C, Passeri G, Ventura M, Di Nuzzo S, Galli D, Mirandola P, Vitale M, Dei Cas A, Bonadonna RC, Del Rio D. Claimed effects, outcome variables and methods of measurement for health claims proposed under European Community Regulation 1924/2006 in the framework of protection against oxidative damage and cardiovascular health. Nutr Metab Cardiovas. 2017;27(6):473-503.

36. Martini D, Biasini B, Rossi S, Zavaroni I, Bedogni G, Musci M, Pruneti C, Passeri G, Ventura M, Galli D, Mirandola P, Vitale M, Dei Cas A, Bonadonna RC, Del Rio D. Claimed effects, outcome variables and methods of measurement for health claims on foods proposed under European Community Regulation 1924/2006 in the area of appetite ratings and weight management. Int J Food Sci Nutr. 2018;69(4):389-409.
37. European Commission. Consolidated version of commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring. Off J Eur Union L. 2012; 17-05-2021.
38. de Boer A. (2021). Fifteen years of Regulating Nutrition and Health Claims in Europe: The Past, the Present and the Future. Nutrients. 2021;13(5):1725.
39 European Commission. Commission staff working document - evaluation of the Regulation (EC) No 1924/2006 on nutrition and health claims made on foods with regard to nutrient profiles and health claims made on plants and their preparations and of the general regulatory framework for their use in foods. 2020;Brussels;SWD(2020) 95 final:1-87.
40. European Commission. Consolidated version of commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. Off J Eur Union. 2008;109:11–6;21-12-2009.
41. Nicoletti M. Nutraceuticals and botanicals: overview and perspectives. Int J Food Sci Nutr. 2012;63(S1):2–6.
42. Anton R, Mathioudakis B, Pramono S, Sezik E, Sharma S. Traditional use of botanicals and botanical preparations. Eur Food Feed Law Rev. 2019;14(2):132–41.
43. Gulati O, Ottaway P. Legislation relating to nutraceuticals in the European Union with a particular focus on botanical-sourced products. Toxicology. 2006;221(1):75–87.
44. Cousyn G, Dalfra S, Scarpa B, Geelen J, Anton R, Serafini M, Delmulle L. Project BELFRIT. Harmonizing the use of plant food supplements in the European Union: Belgium, France and Italy - A first step. Eur Food Feed Law Rev. 2013;3:187–96.
45. Stanifer JW,Pater UD, Karia F, Thielman N, Maro V, Shimbi D, Kilaweh H, Lazaro M, Matemu O, Omolo J, Boyd D. The determinants of traditional medicine use in Northern Tanzania: a mixed-method study. PLoS One. 2015;10(4):e0122638.
46. Georgiou N, Garssen J, Witkamp R. Pharma–nutrition interface: the gap is narrowing. Eur J Pharmacol. 2011;651:1-8.
47. de Boer A. Interactions between nutrition and medicine in effect and law. 2015.
48. Witkamp R, Norren van K. Let thy food be thy medicine....when possible. Eur J Pharmacol. 2018;836:102–14.
49. Samojlik I, Mijatovic V, Gavaric N, Krstin S, Bozin B. Consumers' attitude towards the use and safety of herbal medicines and herbal dietary supplements in Serbia. Int J Clin Pharmacol. 2013;35:835–40.
50. Garcia-Alvarez A, Egan B, Klein de S, Dima L, Maggi F, Isoniemi M, Ribas-Barba L, Raats MM, Meissner EM, Badea M, Bruno F, Salmenhaara M, Milà-Villarroel R, Knaze V, Hodgkins C, Marculescu A, Uusitalo L, Restani P, Serra-Majem L. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. PLoS One. 2014;9(3):1–18.
51. Verbeke W, Frewer LJ, Scholderer J, De Brabander HF. Why consumers behave as they do with respect to food safety and risk information. Anal Chim Acta. 2007;586(1–2):2–7.
52. de Boer A, van Hunsel F, Bast A. Adverse food-drug interactions. Regul Toxicol Pharmacol. 2015;73:859–65.

53. White CM. THe pharmacology, pharmacokinetics, efficacy, and adverse events associated with kava. J Clin Pharmacol. 2018;58(11):1396–405.
54. Shekelle PG, Hardy ML, Morton SC, Maglione M, Mojica WA, Suttorp MJ, Rhodes SL, Jungvig L & Gagné J. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. JAMA. 2003;289(12):1537–45.
55. Soni MG, Carabin IG, Graffiths JC, Burdock GA. Safety of ephedra: lessons learned. Toxicol Lett. 2004;150(1):97–110.
56. Lenssen KGM, Bast A, de Boer A. How does scientific information reach the consumer? A case study among students into providing verbal information on dietary supplements at point of purchase. Int J Food Sci Nutr. 2020;72(3):402-417.
57. Chen M, Zhou S-Y, Fabriaga E, Zhang P-H, Zhou Q. Food-drug interactions precipitated by fruit juices other than grapefruit juice: an update review. J Food Drug Anal. 2018;26(2):S61–71.
58. European Parliament and the Council of the European Union. Consoldiated version of regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the Eruopean Parliament and of the Council, Commission Directive 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Off J Eur Union. 2011;304:1–60;01-01-2018.
59. de Boer A, Bast A, Godschalk R. Dietary supplement intake during pregnancy; better safe than sorry? Regul Toxicol Pharmacol. 2018;95:442–7.
60. Rihouey-Robini L, Amat E. New report on the French" nutrivigilance" mission since 2010. Eur Food Feed Law Rev. 2014;9(6):421.
61. Williams S, Martin P, Gabe J. The pharmaceuticalisation of society? A framework for analysis. Sociol Health Illn. 2011;33(5):710–25.



Chapter 9

Summary and general discussion

The aim of this dissertation was to determine whether there is a potential role for traditional use evidence in the risk analysis of botanicals. The studies described in this thesis indicate that it is possible but not expedient. In the remainder of this chapter, first the main findings of this thesis are briefly listed, after which it is argued why exactly – in light of these findings – traditional use evidence should not play a role in the assessment of botanical health claims.

9.1. Main findings

In **chapter 2**, policy documents and scientific literature were analysed to define the concept of 'traditional use evidence' when considering its potential role in both substantiating safety and health efficacy of botanicals. The analysis highlights that for traditional herbal medicinal products and novel food products with a history of safe use in a third country, guidelines on the data and source requirements are already available. The assessment criteria for substantiation of botanical health claims with evidence on traditional use can be based upon the criteria for assessing efficacy for traditional herbal medicinal products. Traditional use evidence then can be defined as a collection of sources that plausibly establish a history of safe and efficacious use over one or two generations, for a purpose in line with the botanical health claim.

In **chapters 3** and **4**, it was explored how the provision of risk-benefit information for a botanical affects the consumer's intention to purchase the botanical product. An online questionnaire study (**chapter 3**) allowed for determining whether different types of front-of-pack risk-benefit information would influence the intention to use a Guarana containing dietary supplement. Providing detailed risk-benefit information increased the intention to use the product, but no significant differences were found between different types of front-of-pack information. **Chapter 4** presents an explorative case study in which participants were instructed to purchase a St. John's wort supplement in various stores after which they were asked whether they were provided with risk-benefit information, and if so, how detailed, and how reliable they believed this information to be. Verbal information provision was inconsistent but results also showed that the perceived reliability of the information was influenced by spurious attributes, such as the perceived authority of the store employee providing the information.

The evaluation of botanical health claims was put on hold to determine whether traditional use evidence is sufficient to substantiate these health claims. Industry stakeholders provide arguments as to why traditional use evidence should

or should not be allowed. In **chapter 5**, a social network analysis shows that stakeholders' individual arguments for traditional use evidence frequently overlap, but that these stakeholders interpret consumer protection (in relation to misleading practices) differently.

The review of international jurisdictions in **chapter 6** unveiled that traditional use evidence can be used as substantiation of safety and efficacy of herbal medicinal products and health claims. Two additional ways were identified that could support moving forward with botanicals and their claims in the EU. Either establish (i) a legal category of products on the borderline of foods and medicinal products or create (ii) a separate category of health claims within the NHCR.

The current risk assessment procedure for food health claims was scrutinized in **chapter 7**, by reviewing the publicly available scientific opinions published by EFSA. The evaluation by EFSA was not conducted consistently; that is, the three criteria for health claim evaluation were not always addressed for every individual food product or ingredient in the scientific opinion. An in-depth review of the selected scientific dossiers however showed that these dossiers often referred to studies unrelated to the health claim. The procedural inconsistency (even if justified) nonetheless creates uncertainties among food business operators. Furthermore, errors in submitted dossiers suggest that for many food business operators, the evaluation criteria are not sufficiently clear yet.

Finally, **chapter 8** provides a critical reflection illustrating the complexity of substantiating health claims on food products with evidence on traditional use. If historical use data is considered to potentially support evidence of health benefits of a modern botanical, it is essential that modern botanicals (and botanical preparations) are used in a similar way and with a similar purpose as traditional use. For example, extraction methods may be modernised leading to more concentrated forms of botanical ingredients, which would also increase the concentration of potentially toxic substances in a botanical.

9.2 Methodological considerations

The first two studies of this thesis illustrate the difficulties in providing information to consumers. The quantitative survey and the qualitative, explorative case-study approach used in these studies allowed for showing the potential internal and external factors that may have an effect on information use. The main limitation of the quantitative study in chapter 3 is the use of a fictive case

and a relatively homegeneous sample. This methodology created a standardised situation in which the use information could be assessed, but does not reflect the use of information by actual consumers of food supplements among the general population. The qualitative case-study allowed for exploring the provision of information in more real-life circumstances, but is limited in generalisability due to the sample and the instruction given to the participants. To potentially confirm and deepen these findings, additional qualitative and quantitative research is necessary. Qualitative research with participants that have a habit of consuming food supplements could provide further in-depth insights into the reasons for consuming these products. Such methods could also allow to understand how information consciously and unconsciously influences a consumer's behaviour. Further quantitative studies are needed to study the causal relationships between the factors that influence how people perceive the information they receive, and the significance of these different factors. And although the studies in chapter 3 and 4 cannot be generalised to fully understand consumer behaviour, they could serve a starting point for such studies.

Even though the research questions of the different studies in chapters 5, 6 7 and 8 are focused on future perspectives on risk analysis, the conducted studies mainly involve retrospective data analysis. Although the results obtained in the different studies provide valuable insights into the risk analysis procedure as it is used within EU food law, they do not reflect a procedure in which traditional use evidence has a role in health claim substantiation. The findings show potential barriers and opportunities for traditional use evidence, assuming that these would be implemented in currently existing regulatory procedures. That also means that legislative changes could alter the observations resulting from these studies.

Regardless of the discussion on traditional use evidence, regulatory procedures and legislation are adjusted and amended regularly. Conducting critical scientific studies as done in this thesis, as well as setting up new research is needed when changes are made in either the legislation or the risk analysis. The findings from such future research can build upon the findings that are presented in this thesis, to further understand the true impact of traditional use evidence in risk analysis on its different components.

9.3 A role for traditional use evidence?

One of the consequences of the evaluation of botanical health claims being put on hold is that consumers are currently exposed to inconsistent, unsubstantiated and potentially misleading information (2). Communicating affirmed risks and benefits of botanicals is important for health and consumer protection as it empowers consumers to make informed purchasing decisions and protects them from misleading information (2). It is important too for businesses – the manufacturers and sellers of botanicals – as it appears that providing detailed information to the consumers on both risks and benefits of the product may promote the intention to use (chapter 3) and hence purchase the product over time. Obviously, the enduring regulatory impasse is an unwanted state of affairs. However, stakeholders are divided on whether the current potential for misleading practices provides an argument for or against allowing traditional use evidence to be used as support for putative health claims (chapter 5).

Interestingly, 'traditional use evidence' was not merely an issue discussed in food legislation, but already the European medicines directive was amended to address this (3,4). An adjusted authorisation procedure for traditional herbal medicinal products was adopted when it became apparent that harmonization issues for these products emerged in the EU (Art. 16a) (5,6). In the context of the authorisation procedure of these types of products, traditional use evidence refers to historical sources (e.g., archives) or acknowledged sources (e.g., monographs) that plausibly describe a history of safe and effective use (7). Using a similar definition, traditional use is already allowed to substantiate the presumed safety of food products used traditionally in a third country (Art. 14-19) (8). However, Regulation (EC) No 1924/2006 on nutrition and health claims (NHCR; article 6) mandates that health claims are substantiated with generally accepted scientific evidence (9). Traditional use evidence is not *generally* accepted scientific evidence of efficacy. Nonetheless, it is accepted as such in the context of evaluating traditional herbal medicinal products (Art. 16) (5). Furthermore, traditional use evidence is allowed as a form of support for botanical health claims in various jurisdictions outside the EU (chapter 6). In the case of EU food law, allowing traditional use evidence would require an amendment of the NHCR and clear agreement on the criteria for what sources can be considered as traditional use evidence of both safety and health benefit (chapter 7 & 8). Based on the findings in chapter 6, it would need either (i) creating an additional category of health products 'in between' food products and medicinal products; or (ii) creating a separate category of health claims within the NHCR. Implementing these options would however require amendments to the current EU regulatory frame-

work and may give rise to new difficulties. Firstly, defining a separate category in between food and pharmaceutical products may resolve categorization issues that result from the current framework (10), but at the same time new grey areas will emerge and may well introduce new categorization issues. When exactly is a botanical product to be considered a form of medicine, an 'in-between' health product, or a food product? Furthermore, when limiting the substantiation of health claims with traditional use evidence to only botanicals, these botanical health claims are evaluated with greater leniency than food health claims are. This can be exemplified with comparing garlic supplements with vitamin D supplements. If one wishes to argue that Q10 supports the maintenance of normal cholesterol levels, authorisation of that claim would require two separate randomized controlled trials substantiating that claim. However, when the similar claim for garlic supplements were to be made, it would only require the suggestion of its efficacy through a history of use. Historical documentation from archives or expert evidence showing the plausible efficacy over one or two generations would be sufficient.

Secondly, when traditional use evidence would be allowed as substantiation for botanical health claims within the NHCR, separate criteria for the substantiation should be defined. These criteria should clearly state what types of sources are required as traditional use evidence. In principle, the same criteria could be used as already defined in the context of the authorisation procedure for traditional herbal medicine (5,7). The difficult discussion that then remains is how the risks and benefits of a modern innovation such as highly processed and consequently concentrated botanical supplements can be expected to be substantiated by a certain history of use, even if that history can be as brief as 30 years (see chapters 2 and 8). However, this latter difficulty also does not preclude the possibility of incorporating traditional use evidence for botanical health claims (in some form or another) within the NHCR, as this is only focused on the benefits of a product. The real question, then, is whether traditional use evidence should have a role in the assessment of botanical health claims.

The authorisation procedure for nutrition and health claims serves an important dual purpose: protecting the consumer against fraud and misleading practices and by doing so, protecting food businesses (and food business operators) from unfair competition (Art. 1.1) (9). The objective of the procedure then benefits from being as transparent and straightforward as possible. Creating a specific category for botanicals in the NHCR would likely necessitate a weighted approach to evaluating health claims, as it cannot be considered equal to scientific evidence (chapter 8). A graded evidence approach, in which the 'level' of evidence

is reflected in the wording of the claim ('may support' or 'traditionally used to support'), has been proposed in previous research to replace the current criteria (11) (see also chapter 2). This would allow to communicate different weights of support for a given health claim – with independent, peer-reviewed randomized controlled trials representing top tier evidence and traditional use evidence representing the lowest tier of support (11,12). In the United States of America (US), it is already possible to use a qualified health claim on foods (13). These are claims that are not authorized by the US Food and Drug Administration, but for which scientific evidence exists that supports the claim (13). The wording of these claims must show that the cause-and-effect relationship is not formally assessed by the US Food and Drug Administration, for example using the wording 'product x may support effect y'. Previous research into these qualified health claims found that consumers experienced difficulties in distinguishing the different types of claims (14), and understanding the different levels of scientific evidence underlying these claims (14,15). This is problematic from the perspective of current EU food law. The average consumer cannot be expected to perceive that a graded health claim such as 'traditionally used to support …' represents a relatively weak health claim. Implementing such graded health claims would thus accommodate the interests of botanical businesses but potentially erode consumer protection.

As stated in the General Introduction, EU food law was extensively revised in the wake of the BSE crisis and other food scares (16). The EC aspired a high level of health and consumer protection and by doing so aimed to regain and maintain consumer trust (16). Lowering the bar for evaluating botanical health claims could erode consumer protection and consumer trust. That need not be much of a concern if consumer trust is very high. However, with the current high level of consumer protection within the context of the GFL, consumer trust in food products is moderate at best (17). A recent report indicates that a mere 40% of EU consumers is confident that food products are authentic, that these products are genuinely what food business operators say they are (18). Of course, one might argue that a contributing factor to this moderate degree of consumer trust is precisely the enduring pause of evaluating botanical health claims (2). That is conceivable but it is difficult to argue that resuming the evaluation of these specific claims with more lenient criteria for its substantiation would be conducive to promoting that consumer trust, at least not above and beyond the more stringent evaluation of food health claims. Moreover, adopting traditional use evidence in the evaluation of botanical health claims faces several hurdles (as detailed above) which will take time to clear, time during which the evaluation of these health claims will be on hold even longer. In other words, adopting

traditional use evidence in the evaluation of botanical health claims is possible but not expedient.

It is known that establishing a cause-and-effect relationship between a food product and a health benefit is difficult in nutritional sciences, even though there are animal or *in vitro* studies that indicate a beneficial health effect (19,20). It could be argued then that the criteria for substantiating a food/botanical health claim should differ from the assessment criteria of the benefit assessment of medicinal products. At present, for both food and medicinal products, it must be clear which exact substance is causing the beneficial health effect and the effect must be established in human intervention trials (21). According to critics (19,22) this methodology is suitable for pharmaceuticals in which the effect of one substance on one outcome is assessed but unsuitable for food products. It is argued that food products have more complex matrices that can influence the effect that the substance has in the body, or that it may be unknown which specific substance in the product causes the beneficial physiological effect (19,23,24). Some products are known to contain multiple bioactive substances that can have synergistic effects which can be considered beneficial (19,20,25). One substance can furthermore have subtle effects on multiple targets, also known as the pleiotropic effect (19,20,25). This is a viable argument for reconsidering criteria for indicating a plausible mechanism for a putative health benefit. Indeed, it is possible to demonstrate a reliably beneficial health effect of a given product without (yet) fully understanding the precise mechanism underlying this effect. But this argument alone does not justify abandoning the requirement of human intervention trials.

A frequently used argument against the requirement of human intervention trials is that resources (financial resources and expertise) are often lacking to enable small business operators to acquire and provide the required research for substantiating a health claim for their product (chapter 5). But just because research is expensive does not disqualify this requirement as proportionate. The requirement also does not withhold a small business from using health claims for nutrients, substances or foods contained in their product, as any food business operator (big and small) can use authorised and registered health claims when respecting conditions of use and potential restrictions (GFL, Art. 17.2) (Art. 1.2) (9,26). If lack of resources is still a problem, then that problem might be resolved best by providing those resources to small businesses, rather than weakening consumer protection.

One might still argue that there is inconsistency in the risk assessment of traditional herbal medicine and botanicals. There clearly is overlap in the types of products. Botanicals are sold as food products, food supplements or indeed medicinal products. Traditional use evidence is allowed in the substantiation of both safety and efficacy for traditional herbal medicinal products, so why not also allow it for substantiating health claims for botanicals? The answer is simple. One of the main objectives of current EU food law is a high level of consumer protection and that requires stringent assessment of any food claim, including health claims.

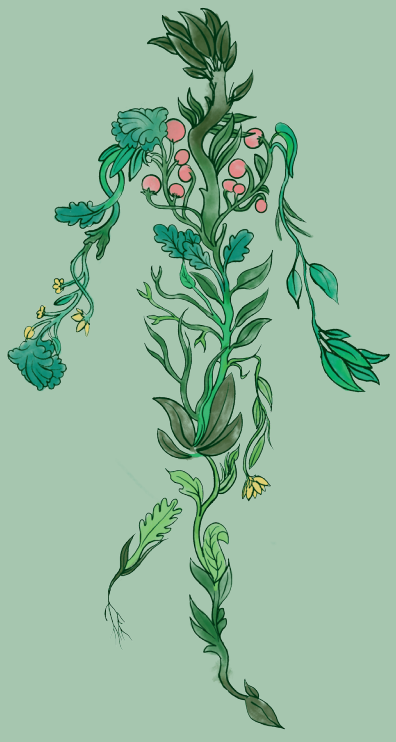
9.4 Conclusion

The research presented in this thesis was aimed to determine the potential role of traditional use evidence in EU risk analysis by studying the botanical health claims for which the evaluation is currently on hold. Recognising traditional use evidence as substantiation for benefits of food products is possible, as observed in international jurisdictions. Within the EU this would require an amendment of article 6 of the NHCR. This amendment and its consequences pose regulatory hurdles that would significantly extend the current regulatory impasse on assessing botanical health claims. Further, the required changes in communicating health benefits (i.e., qualifying health claims supported by traditional use only) would put the consumer at greater risk of being misled. Traditional use is much weaker evidence for a purported health benefit than results from multiple independent randomized controlled trials are. The likelihood that a health claim based on traditional use evidence may prove to be false with further scientific research, is much bigger than when the claim is based on science to begin with. In other words, allowing traditional use evidence as support for botanical health claims is possible but not expedient. As long as it is not proven that weighted claims do not mislead consumers, it should not be part of EU risk analysis. This conclusion, which ultimately addresses a political decision, allows for immediate resumption of the authorisation procedure for botanical health claims, upholding a high level of consumer protection, and offering the clearest possible criteria for consumers, business operators, and risk managers.

9.5 References

1. Pajor EM, Eggers SM, Curfs KCJ, Oenema A, de Vries H. Why do Dutch people use dietary supplements? Exploring the role of socio-cognitive and psychosocial determinants. Appetite. 2017;114:161–8.
2. European Commission. Commission staff working document - evaluation of the Regulation (EC) No 1924/2006 on nutrition and health claims made on foods with regard to nutrient profiles and health claims made on plants and their preparations and of the general regulatory framewor. Brussels; 2020.
3. Jütte R, Heinrich M, Helmstädter A, Langhorst J, Meng G, Niebling W, Pommering T, Trampisch HJ. Herbal medicinal products - evidence and tradition from a historical perspective. J Ethnopharmacol. 2017;207:220–5.
4. Quintus C, Schweim H. European regulation of herbal medicinal products on the border area to the food sector. Phytomedicine. 2012;19:378–81.
5. European Parliament and the Council of the European Union. Consolidated version of directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;136:85–90; 30-04-2004.
6. European Parliament and the Council of the European Union. Consolidated version of directive 2001/83/EC of the European Parliament on of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off J Eur Union. 2001;311:1–188; 01-01-2022.
7. Committee on Herbal Medicinal Products. Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products - Final. 2017. Report No.: EMA/HMPC/104613/2005 – Rev. 1.
8. European Parliament and the Council of the European Union. Consolidated version of regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel food, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. Off J Eur Union. 2015;327:1–22; 27-03-2021.
9. European Parliament and the Council of the European Union. Consolidated version of regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Off J Eur Union. 2006;49:9–25; 13-12-2014.
10. Melcher SR, Timmermans L. It's the dosage, stupid: the ECJ clarifies the border between medicines and botanical food supplements. Eur Food Feed Law Rev. 2009;3:185–91.
11. Chevallier H, Herpin F, Kergosien H, Ventura G, Allaert F-A. A graded approach for evaluating health claims about plant-based food supplements: application of a case study methodology. Nutrients. 2021;13(8):2684.
12. European Federation of Associations of Health Product Manufacturers. Botanical health claims on foods and food supplements in the EU - EHPM proposal. 2021.
13. U.S. Food & Drug Administration. Guidance for industry: evidence-based review system for the scientific evaluation of health claims [Internet]. 2009. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims

14. Kapsak WR, Schmidt D, Childs NM, Meunier J, White C. Consumer perceptions of graded, graphic and text label presentations for qualified health claims. Crit Rev Food Sci Nutr. 2005;48(3):248–56.
15. Teratanavat RP, Hooker HN, Haugtvedt CP, Rucker DD. Consumer understanding and use of health information on product labels: marketing implications for functional food. Res Agric Appl Econ. 2004;No. 377-20:1–21.
16. Vos E. EU food safety regulation in the aftermath of the BSE crisis. J Consum Policy. 2000;23(3);227-255.
17. Murphy B, Benson T, Lavelle F, Elliott C, Dean M. Assessing differences in levels of food trust between European countries. Food Control. 2021;120:107561.
18. EIT Food. The EIT Food trust report - sustainable food choices and the role of trust in the food chain. 2022.
19. Bast A, Briggs W, Calabrese E. Scientism, legalism and precaution-contending with regulating nutrition and health claims in Europe. Eur Food Feed Law Rev. 2013;6:401–9.
20. Heaney R. Nutrition, chronic disease, and the problem of proof. Am J Clin Nutr. 2006:471-472.
21. EFSA NDA Panel. Scientific Opinion - Scientific and technical guidance for the preparation and presentation of a health claim application (revision 2). EFSA J. 2017;15(1):4680.
22. de Boer A, Vos E, Bast A. Implementation of the nutrition and health claim regulation–The case of antioxidants. Regul Toxicol Pharmacol. 2014;68(3):475–87.
23. Binns N, Howlett J. Functional foods in Europe: international developments in science and health claims. Eur J Nutr. 2007;1:3–13.
24. McClements DJ. Enhancing nutraceutical bioavailability through food matrix design. Curr Opin Food Sci. 2015;4:1–6.
25. van Steenwijk H, Bast A, de Boer A. The Role of Circulating Lycopene in Low-Grade Chronic Inflammation: A Systematic Review of the Literature. Molecules. 2020;25(19):4387.
26. European Commission. Consolidated version of commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. Off J Eur Union L. 2012; 17-05-2021.



Chapter 10

Impact paragraph

The main conclusion of this thesis is that the use of non-scientific information coming from traditional use in risk analysis is possible, but creates many new problems. First and foremost, it would require an amendment of current or new legislation, which would cost time in which potentially misleading claims are still to be found on the market. It would also require the implementation of a graded evidence approach in which the wording would reflect the 'strength' of the evidence. This graded evidence is expected to have an influence on consumer trust, which would impact the objective of European Union (EU) food law negatively. After all, we have learned that the provision of information on botanical products, and food products in general, goes beyond merely the *content* of the presented information. Personal and societal aspects influence the perception of the provided information. Because of this, it is of utmost important that the information provided on or along with the product is visible, clear, and unambiguous. Whilst the evaluation of botanical health claims is on hold, Dutch authorities require the use of a disclaimer along with the botanical health claim. This disclaimer must indicate that the evaluation of the evidence underlying the health claim is pending. Although this shows the effort to be transparent in the provision of information, it is questionable whether consumers understand the content and implication of this disclaimer. Additionally, the use of this mandatory disclaimer is a requirement set by the Dutch institutions, and may consequently result in unequal competition among member states which do not mandate the use of this disclaimer. Together, it is very much debatable whether the use of such a disclaimer is in line with the objectives of EU food law.

Since it is impossible to control for every factor that may influence the perception of provided information, it would be detrimental if the content itself already allows for varying interpretation just by the wording of it. This could be a result when a graded evidence approach would be used in the EU. Given that member states are implementing new rules for the botanicals now, it is of utmost importance that the evaluation of the botanical health claims is resumed, with the existing evaluation criteria. By doing so, food business operators, consumers and other stakeholders involved will finally have an answer to the current impasse.

10.1 Beyond botanicals

A secondary conclusion from this thesis is that the full risk analysis cycle should be involved when adjustments are required in one aspect of it. Previous research on botanical health claims mainly focused on risk assessment and the criteria for substantiation with traditional use evidence. This may have resulted in stake-

holders believing that such adjustments would be easy to accomplish. When considering risk management, risk communication and risk assessment together, the complexity and barriers become apparent and the conclusion on the implementation of traditional use evidence for substantiation health claims shifts.

The provision of information on health benefits of a product is voluntary. Even though the nutrition and health claims regulation only lays down the provision for providing information on the relationship between food and health, different types of voluntary information are provided on food products these days. Messages regarding sustainability, animal welfare or production circumstances are visible both on packaging and in advertisements of (food) products. Even though these messages should in general not be misleading, there is no formal EU evaluation procedure in place that evaluates the underlying evidence of such statements. Since 2021, the European Commission started the Sustainable EU food system initiative in which setting rules for sustainability labelling is one objective. If a formal evaluation procedure would be instated using the principles of risk analysis, the lessons from the thesis can aid in setting up the procedure and defining the necessary framework up front. Important aspects which would need specific attention are, for example, that the provided information to consumer is unambiguous, and the roles and responsibilities of the different actors in the evaluation procedure are clear. The data requirements which allow for clear and transparent communication of sustainability information should be determined before the implementation of a legal framework on the provision of such sustainability information. Although the initiative is still in its early phase, it does show that providing more information on food products is important, but also that centralisation of the regulation of such information is strived after. As a consequence, food business operators as well as risk managers, risk assessors and risk communicators need to deal with these existing and new legislation covering the provision of information. They would benefit from transparent rules and clear guidelines. Consumers are potentially confronted with more and potentially different information on products they intent to purchase. It is therefore of utmost importance that they understand the content information, and ideally, the underlying rules and regulations.

10.2 The role of science in law

Scientific studies have a dominant role in EU food law as they are used for showing a product's health benefits and demonstrating there are not adverse effects. By requiring human intervention trials as evidence for the substantiation of health

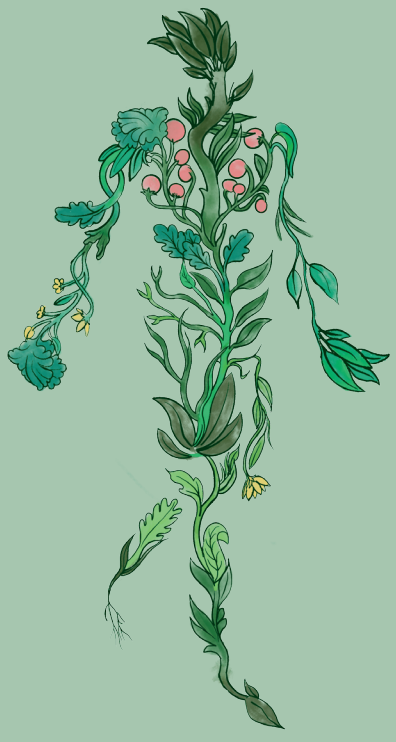
claims, there is as much certainty as possible with regards to the cause-and-effect relationship of food products and health benefits. Science consequently becomes an inevitable part of society: if it cannot be proven scientifically, a statement will not be authorized and consequently such statements cannot be used in the communication towards the general public. Although implemented to protect the general public, this regulatory framework also results in a limited information supply and a tremendous pressure on nutritional sciences to broaden this information supply. This may in the end also lead to scientism in society: decision making purely based on the results of scientific studies. This is also the conclusion of this thesis: within the current regulatory framework, evidence on traditional cannot play a role without major changes in the legislation. The case on botanicals does show that it sometimes becomes difficult to defend that everything should be based on scientific studies. Other information sources including studies using an *in vitro* or longitudinal research methodology may provide an indication of a beneficial health effect. These sources can now solely be used as supporting evidence within the authorisation procedure. Even though it is known that showing beneficial effects of food products in human intervention trials is difficult, it is the only way to show a cause-and-effect relationship. And since authorisation will only occur when a cause-and-effect relationship between food product and health benefit is established, the human intervention trial is the only way to go in the current regulatory framework.

In deciding upon the role of science in food law, one must find the perfect equilibrium in providing sufficient information and the certainty that the information is truthful. In the current legal framework, the scale moves towards certainty. If there is a desire to also increase the amount of information provided to consumers, the level of certainty must decrease, simply because sources beyond human intervention trials must be considered. This does however require further research into consumer understanding of information, consumer use of information and validation of scientific and non-scientific sources of information. When the ambition is to increase the provision of information, science, policy-makers and food business operators must work together to cover these topics.

10.3 Conclusion

The research presented in this thesis allowed for obtaining a broader perspective on risk analysis and the provision of information to consumers. The conclusions from this thesis firstly shed light on the underlying argumentation in the discussion on botanical health claims; and additionally allow for understanding

the complexities of risk analysis for voluntary information provision. With new societal challenges these days and a food system that may be asked to deliver sufficient, nutritious, healthy as well as sustainable food products, also other messages beyond health effects may become regulated. Risk analysis – or a more broadly defined term better suitable for its use in EU food law, for example scientific analysis - may again be implemented to assess the underlying evidence of these messages. The findings from this thesis may aid in shaping the framework for the evaluation of that information.



Appendices

Nederlandse samenvatting

In de jaren 90 waren er verschillende voedselcrises, waaronder de BSE-crisis. Mede hierdoor ontstond er een oproep voor uitbreiding en herziening van de bestaande levensmiddelenwetgeving binnen de Europese Unie (EU). Eén van de veranderingen die werd geïmplementeerd, was de risicoanalyse: een procedure waarin risicomanagement, risicobeoordeling en risicocommunicatie van elkaar zijn gescheiden. Deze procedure moet onder andere gevolgd worden voor het op de markt brengen van nieuwe voedingsproducten en bij het beoordelen van de veiligheid van mogelijke additieven voor voedingsproducten. Ook voor de beoordeling van gezondheidsclaims wordt de risicoanalyse gebruikt, hoewel hier niet de risico's maar de gezondheidseffecten van voedingsproducten moeten worden bewezen.

Een belangrijke voorwaarde voor de risicoanalyse binnen levensmiddelenwetgeving is dat de *risicobeoordeling* gebaseerd is op een wetenschappelijke onderbouwing. Dit geldt voor zowel het vaststellen van de veiligheid van voedingsproducten als voor de gezondheidseffecten zoals voorgesteld in claims. De voornaamste focus van dit proefschrift is de onderbouwing van gezondheidsclaims op kruiden.

De risicobeoordeling in het algemeen en dus ook die van de gezondheidsclaims, wordt gedaan door de Europese voedselveiligheidsautoriteit (EFSA). Er is één groep gezondheidsclaims die nog niet beoordeeld is en momenteel 'on-hold' staan: de gezondheidsclaims op kruiden. De reden van het on-hold zetten van de beoordeling is de centrale vraag of gezondheidsclaims onderbouwd kunnen worden op basis van bewijs van traditioneel gebruik. Dit is, via een speciale procedure, mogelijk voor traditionele kruidengeneesmiddelen, maar is op dit moment niet voldoende onderbouwing voor gezondheidsclaims op voeding. Verschillende wetenschappelijke publicaties hebben betrekking op de gezondheidsclaims op kruiden en de individuele componenten van de risicoanalyse. Er mist echter een wetenschappelijke benadering van de gezondheidsclaims op kruiden, bewijs van traditioneel gebruik en de gehele risicoanalyse. De onderzoeksvraag van dit proefschrift is daarom: wat is de mogelijke rol van bewijs van traditioneel gebruik in de risicoanalyse van kruiden?

Hoofdstuk 1 geeft een algemene introductie in het onderwerp en de voorbeschouwing van de onderzoeksvraag. Om 'bewijs van traditioneel gebruik' verder te definiëren, zijn in **hoofdstuk 2** verschillende beleidsdocumenten en wetenschappelijke publicaties geanalyseerd. Het doel van deze analyse was om te

bepalen welke rol 'bewijs van traditioneel gebruik' kan spelen in het onderbouwen van gezondheidseffecten van kruiden. Voor traditionele kruidengeneesmiddelen en nieuwe voedingsproducten, waarvan veilig gebruik in een land buiten de EU bekend is, bestaan er al procedures voor het onderbouwen met bewijs van traditioneel gebruik. Voor gezondheidsclaims op voeding bestaat een dergelijke uitzonderingspositie niet. Wetenschappelijke literatuur, die gaat over de onderbouwing van gezondheidsclaims met bewijs van traditioneel gebruik, geeft wel suggesties voor beoordelingscriteria. Deze beoordelingscriteria zijn met name gebaseerd op bestaande procedures voor traditionele kruidengeneesmiddelen en nieuwe voedingsproducten. Als bron voor goed traditioneel gebruik geldt dat aannemelijk moet worden gemaatk dat een product al veilig wordt gebruikt en een positief gezondheidseffect heeft, gedurende een periode van één of twee generaties. Ook worden er suggesties gedaan voor een systeem waarbij de formulering van de claim, de sterkte van het bewijs weergeeft. Volgens deze redenering, zouden er drie verschillende typen claims op de markt kunnen komen, namelijk: product x zorgt voor effect y, product x kan zorgen voor effect y, of product x wordt traditioneel gebruikt voor effect y. De centrale vraag blijft echter of middels het implementeren van nieuwe beoordelingscriteria, danwel een heel nieuw systeem, de doelen van de wete nog behaald kunnen worden. Deze doelen richten zich onder andere op het beschermen van de consument tegen misleidende informatie. Op deze vraag wordt tot op heden nog geen antwoord gegeven. Hierdoor is het veranderen van het huidige wettelijke kader, inclusief de bijbehorende procedures, minimaal ingewikkeld, maar zelfs ook problematisch te noemen.

In hoofdstukken 3 en 4 is gekeken naar het verschaffen van informatie over voordelen en risico's van een product aan consumenten.

In een online vragenlijst (**hoofdstuk 3**) zijn deelnemers blootgesteld aan verschillende typen risico- en voordeelinformatie op het etiket van een voedingssupplement dat guarana bevat. Er is gemeten of deze informatie invloed heeft op de intentie om het voedingssupplement te gebruiken. De deelnemers kregen daarbij ook gedetailleerde uitleg over de voordelen en risico's van het product waarbij er werd bijgehouden hoelang de deelnemers naar deze informatie keken.

Hoewel de verschillende informatie op het etiket geen effect had op de intentie om het product te gebruiken, was wel een effect zichtbaar nadat deelnemers de gedetailleerde informatie hadden gezien. De intentie om het product te gebruiken ging omhoog nadat deelnemers deze uitgebreide informatie over de

voordelen en risico's konden lezen. Hoelang men naar de informatie keek, leek echter geen directe invloed te hebben.

Deze bevindingen geven inzicht in de complexiteit van informatievoorziening, mede doordat niet duidelijk is of de informatie op het etiket gezien en/of gebruikt wordt door een consument. Het is daarom ook lastig vast te stellen, wat een eventuele verandering in de informatievoorzeniening, teweeg gebracht door een verandering in de risico analyse, voor invloed heeft op de consument. Om tot een sluitende oplossing te komen voor de gezondheidsclaim op kruiden, zal hier eerst meer duidelijkheid over moeten komen.

Hoofdstuk 4 beschrijft een verkennende casestudie over de informatieverschaffing in Nederlandse drogisterijen. Deelnemers werden geïnstrueerd om Sint Janskruid te kopen in een drogisterij of gezondheidswinkel waarna zij meededen in een kwalitatief onderzoek over de informatie die zij ontvingen in de winkel.

De verbale informatie was niet consistent en verschilde per drogisterij. De betrouwbaarheid van de informatie werd beïnvloed door andere kenmerken zoals de autoriteit van de medewerker of winkel. Deelnemers verkregen daarbij ook informatie uit de winkelomgeving door bijvoorbeeld thematische schappen. Hoewel deze case studie niet direct te generaliseren valt door de kleine populatie en studie opzet, geeft het wel inzicht in de complexiteit van informatieverschaffing. Veel verschillende factoren kunnen invloed hebben op de perceptie van een consument aangaande de gekregen informatie. Dit laat zien dat er buiten de inhoud van de informatie, ook andere aspecten invloed hebben op de ervaren betrouwbaarheid van de informatie door consumenten.

Sinds de evaluatie van de gezondheidsclaims op kruiden 'on-hold' staat, zijn er verschillende publicaties waarin argumenten van voor- en tegenstanders van bewijs van traditioneel gebruik uitgelicht worden. In **hoofdstuk 5** zijn de relaties van belanghebbenden geanalyseerd middels een netwerkanalyse en zijn de verschillende argumenten nader wetenschappelijk getoetst.

De resultaten lieten zien dat een aantal onderwerpen, zoals consumentenmisleiding, door zowel voor- als tegenstanders aangehaald worden. Deze onderwerpen moeten wellicht verder gedefinieerd worden om helder te krijgen wat ze betekenen binnen de EU-levensmiddelenwetgeving. Andere argumenten zijn gebaseerd op aannames die niet kunnen worden geverifieerd omdat dit gevolgtrekkingen zijn van definitief besluit over de beoordeling van gezondheidsclaims op kruiden. De analyse van de netwerk van de belanghebbenden liet zien dat er

vaak een connectie is tussen belanghebbenden die eenzelfde argument uiten. Een argument dat door verschillende partijen wordt geuit, kan dus voortkomen uit eenzelfde belang.

In **hoofdstuk 6** zijn verschillende internationale jurisdicties onderzocht, om te bepalen welke rol bewijs van traditioneel gebruik in de wetgeving van geneesmiddelen en voedingsproducten speelt. Er wordt binnen de EU uitgegaan van twee opties die de huidige impasse rondom de beoordeling van gezondheidsclaims op kruiden kunnen oplossen, namelijk: (i) doorgaan met de huidige beoordelingscriteria of (ii) bewijs van traditioneel gebruik toestaan als onderbouwing van gezondheidsclaim. Uit deze analyse kwam naar voren dat er nog twee andere opties zijn, te weten: (iii) een aparte categorie specificeren binnen de gezondheidsclaims verordening of (iv) een aparte juridische categorie creëren tussen geneesmiddelen en voedingsproducten. Een selectie van één van deze procedures blijft een politieke keuze die gemaakt dient te worden door de risicomanager. Zowel de risicobeoordelaar als de risicocommunicator dienen geraadpleegd te worden, gezien een verandering in het wettelijk kader of de procedure verstrekkende gevolgen kan hebben voor het uitvoeren van hun taken.

Hoewel de evaluatie van de gezondheidsclaim op kruiden 'on-hold' staat, is deze voor andere gezondheidsclaims wel al afgerond. De door EFSA gepubliceerde wetenschappelijke opinies, alsmede een aantal wetenschappelijke dossiers, over gezondheidsclaims met als gezondheidseffect antioxidant activiteit, zijn geanalyseerd in **hoofdstuk 7**. Uit deze analyse kwam naar voren dat de evaluatie van het aangeleverde wetenschappelijke bewijs niet altijd volgens de door EFSA vastgestelde criteria werd uitgevoerd. De analyse van de aangeleverde, onderliggende wetenschapplijke dossiers liet echter zien dat het merendeel van de studies niet de relatie onderzocht tussen het voedingsproduct of ingrediënt en het gezondheidseffect.

De inhoud van de dossiers suggereert dat de beoordelingscriteria niet duidelijk waren. Daarbij werd de beoordeling niet altijd volgens de door EFSA vastgestelde criteria uitgevoerd (karakterisren van stof/ingredient, definieren van gezondheidseffect en vaststellen van causaal verband tussen ingredient en gezondheidseffect). Dit leidt tot onzekerheid en remt innovatie. De beoordelingscriteria zijn echter recent aangescherpt. De belangrijkste bevinding van dit onderzoek is dat de beoordelingscriteria voor een risicobeoordeling duidelijk moeten zijn. Eventuele veranderingen met betrekking tot de gezondheidsclaims op kruiden zullen daarom helder moeten zijn richting levensmiddelenbedrijven.

Onduidelijkheid kan leiden tot onzekerheid en dat kan vervolgens resulteren in minder innovaties.

Tenslotte wordt in **hoofdstuk 8** een kritische reflectie gegeven over de complexiteit van het onderbouwen van gezondheidsclaim met bewijs van traditioneel gebruik. Als bewijs van traditioneel gebruik een rol gaat spelen in de onderbouwing van gezondheidseffect van kruiden, dan moet men er zeker van zijn dat de productiemethoden en gebruikscondities deze tradities ook reflecteren. Modernere methoden kunnen bijvoorbeeld zorgen voor een geconcentreerder product, waarbij ook mogelijk toxische stoffen in grotere hoeveelheid aanwezig kunnen zijn. Daarbij moet ook helder blijven dat bewijs van traditioneel gebruik niet hetzelfde gewaardeerd kan worden als wetenschappelijk bewijs voortkomend uit geblindeerde, gerandomiseerde klinische studies.

Het doel van het onderzoek in dit proefschrift was om de mogelijke rol van bewijs van traditioneel gebruik als onderbouwing van gezondheidsclaims op kruiden te onderzoeken. Het toestaan van bewijs van traditioneel gebruik als onderbouwing van gezondheidsclaims is mogelijk, maar niet raadzaam.

Hoewel de analyse van de internationale jurisdictie laat zien dat bewijs van traditioneel gebruik gebruikt kan worden als onderbouwing, vereist dat binnen de EU grote aanpassingen aan het bestaande juridische kader. Daarbij moet gekeken worden naar de invloed van de aanpassingen op de doelen van de gezondheidsclaimsverordening. Het onderbouwen van een gezondheidsclaim met bewijs van traditioneel gebruik is niet alleen veel zwakker dan een onderbouwing met klinische studies, er is ook een risico van het autoriseren van meer vals positieven: claims waar een gezondheidseffect aangetoond lijkt maar die er niet is.

Zo lang niet duidelijk is of een consument vaker misleid wordt door gezondheidsclaims onderbouwd met bewijs van traditioneel gebruik, kan deze onderbouwing niet geïmplementeerd worden in de EU. Hoewel deze conclusie uiteindelijk een politieke keuze is, zou een snelle beslissing er wel voor zorgen dat de gezondheidsclaims die nu ‘on-hold’ staan, meteen beoordeeld kunnen worden met de bestaande beoordelingscriteria. Dit zou zorgen voor een betere consumentenbescherming en geeft de meest duidelijke criteria voor consumenten, bedrijven en risicomanagers.

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En als laatste **Nard**, lieve Nard. Ik leerde jou kennen toen ik al in de afrondende fase zat. Aangezien deze wat langer duurde, heb je toch een aanzienlijke periode van mijn PhD naast me gestaan. En dat was toch echt een leukere tijd dan de tijd daarvoor. Hoewel ik altijd blijf zeggen dat ik 'het wel zelf kan', is het toch fijn om te weten dat dat niet meer hoeft. Vanaf nu gaan we samen verder, in ons huisje in Hegelsom. Ik weet nu dat ik met jou elke storm aan kan, maar dat ik het ook heerlijk met je vind en rustig en kalm weer. Bedankt moppie, uit de grond van mijn hart.

Curriculum Vitae

Karin Lenssen was born on the 12th of February, 1993 in Hegelsom, the Netherlands. After completing her high school education with a VWO diploma in the Nature & Health profile she started her bachelor study European Public Health at Maastricht University. She received her BSc diploma in 2014 after which she took a gap year to prepare for her master in a different discipline. She started the Master's programme Health Food Innovation Management in 2015 and graduated in 2017. During her internship she did research into the influence of the health claim evaluation process on functional food innovation which was published in 2018.

After graduating Karin started her PhD project on the 'Risks & benefits of botanicals' at the Food Claims Centre Venlo of Maastricht University Campus Venlo. Besides the interdisciplinary research into the subject she was also teaching in various courses in the bachelor's programme University College Venlo and master's programme Health Food Innovation Management. She managed to obtain her 'university teaching qualification' during her time as a PhD student. Karin was a member of the Education Programme Committee of Maastricht University Campus Venlo as well.

During her time at Maastricht University Campus Venlo, she also visited multiple fairs and network events to create awareness for the research and education activities that were taking place in Venlo.

After finishing her PhD project, Karin will remain at Maastricht University Campus Venlo as a teacher for both the bachelor's programme University College Venlo and the master's programme Health Food Innovation Management. She will be teaching and coordinating courses as well as remain a member of the Educational Programme Committee and guide students in writing their theses.

List of publications

Published manuscripts

Lenssen, K. G. M., Bast, A., Garcia-Fuentes, A., van Osch, F. H. M. & de Boer, A. (2022). Assessing the influence of information on dietary supplement use: an online questionnaire study. *Journal of functional foods, 92,* 105017.

Lenssen, K.G.M., Bast, A. & de Boer, A. (2022). The complexity of 'traditional use' to prove health effects: a critical perspective on supporting botanical health claims. *Trends in Food Science & Technology, 120,* 338-343

Lenssen, K. G. M., Bast, A. & de Boer, A. (2021). How does scientific evidence reach the consumer: a qualitative study into providing information on dietary supplements. *International Journal of Food Sciences and Nutrition, 72*(3), 402-417.

Lenssen, K. G. M., Bast, A. & de Boer, A. (2020). Should botanical health claims be substantiated with evidence on traditional use? Reviewing the stakeholders arguments. *PharmaNutrition, 14*, 100232.

Lenssen, K. G. M., Bast, A. & de Boer, A. (2019). International perspectives on substantiating the efficacy of herbal dietary supplements and herbal medicines through evidence on traditional use. *Comprehensive Reviews in Food Science and Food Safety*, *18*(4), 910–922.

Lenssen, K. G. M., Bast, A. & de Boer, A. (2018). Clarifying the health claim assessment procedure of EFSA will benefit functional food innovation. *Journal of Functional Foods*, *47*, 386–396.

Published book chapter

Lenssen, K.G.M. & de Boer, A. (2022). The regulatory aspects of substantiating health benefits of foods containing antioxidants. In B. Hernández-Ledesma & C. Martínez-Villaluenga (Ed.) *Current Advances for Development of Functional Foods Modulating Inflammation and Oxidative Stress.* London: Academic Press.

Presentations at conferences

The influence of front-of-pack risk-benefit information on the intention to use dietary supplements. Nutritional Science days, Nederlandse Academie van Voedingswetenschappen, Heeze, the Netherlands, 2019

International perspective on substantiating the efficacy of herbal dietary supplements and herbal medicines through evidence on traditional use. Global harmonization initiative. 1st world congress on food safety and security, Leiden, the Netherlands, 2019.

Other presentation

NPN workshop on botanicals, Venlo, the Netherlands, 2019.

Completed courses and trainings

Cambridge Proficiency in English, Eindhoven, the Netherlands, 2018.

Parma Summer School, EFSA, 2021

University Teaching Qualification, Maastricht, The Netherlands, 2020.

European Nutrition Leadership Platform, Essentials Seminar, 2021.