Dietary polyphenols: modulators of energy and substrate metabolism in obese humans

Valorization

Dutch universities are obliged by law to ensure that their research findings impact society. The following chapter is dedicated to the valorization of the findings in the present thesis, which is defined as 'process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities'. In other words, this chapter covers (a) the social and economic relevance of the investigated problem, (b) the possible implementations for target groups and further research, and (c) possible applications with respect to industrial development and marketing of the combined polyphenol-approach, as investigated in this thesis, and to dietary intervention studies in general.

Social and economic relevance

The prevalence of obesity has reached an epidemic dimension and is continuously increasing all over the world. Overweight and obesity have been defined by the World Health Organization as 'abnormal or excessive fat accumulation that may impair health', indicating that obesity relates and predisposes to a variety of diseases such as type 2 diabetes mellitus, cardiovascular diseases, certain types of cancer and depression. Consequently, obesity reduces the quality of life and causes around 2.8 million deaths each year worldwide [1].

The European Commission estimated that obesity costs represented 7 % of its total health care spending in 2006, which equates to around €81 billion per year in 2012 [2]. Another 10 % of healthcare expenditures were spent on type 2 diabetes mellitus, estimated by the London School of Economics [3]. Taking into account absenteeism, early retirement and social benefits, the costs of obesity- and diabetes-related health impairments in the European Union added up to around €400 billion in 2010 [4].

Approximately 30-40 % of the European population is using dietary supplements, of which half are non-vitamins [5]. The retail value in 2009 was already €4 billion in Europe and increasing, creating 500.000 jobs. However, the scientific evidence for health benefits of such supplements is poor as compared to their marketing claims. This is indicated by the great inconsistency in scientific studies and the lack of approved health claims for polyphenolic supplements on energy and substrate metabolism by the European Food Safety Association. Thus, it remains to be investigated how effective this money is spent.

Target groups

The aim is to make all results described in this thesis available for the scientific community through publication in international peer-reviewed journals. Beyond academia and academic journals, newspaper articles have been published on our research, which has enabled a broader audience to take notice of our findings.

By performing randomized, clinical trials with human subjects, scientific evidence can be acquired on specific supplements and their effects in different groups of subjects. These studies are inevitable in order to organize, control and align the overwhelming amount of information on nutrition, diets and supplements that is presented by the media every day. Evaluation of such studies by independent institutions, non-profit organization or others (e.g. European Food Safety Authority, Netherlands Nutrition and Health Council) may help to generate a synergistic database. In that manner, dietary recommendations can be evidence-based and communicated to target groups. As an example for the necessity of the mentioned institutions, that communicate science to the media and the public, the beneficial effects of E+R that we describe in this thesis might be taken. Our findings of 'increased fat oxidation after E+R supplementation as compared to placebo' might be misinterpreted by the media or cause false hope for consumers (e.g. the idea that it may lead to weight loss). However, neither energy expenditure nor body composition or food intake were changed after long-term E+R supplementation, as described in this thesis, to scientifically support such hopes. It is highly relevant that results are critically reviewed and communicated into the right context.

Activities and products

In the present thesis, it is described that polyphenol supplementation improved risk factors for the development of chronic metabolic diseases (e.g. oxidative capacity, fat oxidation, plasma lipids), which led us to conclude that polyphenol supplementation may prevent or delay the development of cardiometabolic diseases. Importantly, studies that assess the possible benefit of polyphenol supplementation over years need to confirm such claims. The diversity in the effects that we have demonstrated in the present thesis (e.g. gender-specific effects, microbiota-related effects or tissue-specific effects on gene and protein expression) indicates that E+R may not be evenly effective in all consumers, or may not exclusively exert beneficial effects at all organs.

The results of the present studies have provided additional insight in the potential of polyphenol supplementation to stimulate whole-body fat oxidation and skeletal muscle oxidative capacity. However, we have found that the average effect size is limited due to variation in effect between subjects. A valuable approach to increase the beneficial impact of polyphenols might be the identification of biomarkers that can predict the susceptibility to supplementation. Possible biomarkers may be identified in the human and microbial genotype, phenotype and metabolome. Moreover, metabolites of polyphenols may offer additional biomarkers due to the possibly extensive metabolism of polyphenols in the gastrointestinal system and the liver and their diverse effects.

With respect to the investigated supplements, it has been suggested that people with metabolic impairments or under metabolic challenges may benefit the most from polyphenol supplementation. For example, polyphenol-supplementation for 8 weeks had no effect on hepatic insulin sensitivity in humans, whereas it prevented fructose-induced hepatic insulin resistance, which was observed in the placebo-group after another week [6]. This preventive effect may be applied to conditions of metabolic impairment and/or in situations in which metabolic health deteriorates rapidly.

In the present thesis, we performed microbiota analysis in a dietary intervention study, designed to investigate effects on energy and substrate metabolism. Since we and others have shown that the microbiota may have a profound modulatory impact on dietary polyphenol interventions, it is highly important to consider the impact of alterations in the gut microbiota on energy and substrate metabolism in future dietary intervention studies.

The benefit of this combined approach is supported by the results of the present thesis and may generate broad applicability and perspective for the food supplement industry. The combined polyphenol-approach may translate into indefinite market opportunities by developing new indication-specific combinations of supplements, or treatment regimens in general.

In general terms, it might be considered to produce polyphenol-enriched foods (e.g. resveratrol-enriched rice has been developed [7]), rather than distributing encapsulated supplements. In this manner, aversions against taking pills can be circumvented.

Innovation

Although various multi-ingredient supplements have been developed and promoted, the claims on these supplements are almost exclusively based on their antioxidant potential. To specifically determine the effects of combined polyphenols on energy and substrate metabolism is however novel. By using state-of-the-art methodologies for both *in vivo* measurements and laboratory analyses, we were able to investigate effects on whole-body, organ-specific and cellular level. Moreover, the inclusion of the gut microbiota analysis allowed to account for a new dimension to the field of nutritional and health sciences, which is described in Chapters 6 and 7 of this thesis.

The work described in this thesis is the result of several (inter)national collaborations with both academic and industrial partners. Without the contributions of these partners, it would not have been possible to achieve the results described in this thesis, and as such it would not have been possible to achieve the scientific advancement that has been made.

Implementation

The increased fat oxidative capacity as result of chronic E+R supplementation may be of importance in the prevention of chronic metabolic diseases, often characterized by impairments in oxidative capacity. This remains to be determined in future studies. As discussed above, dietary polyphenol supplementation may be rather applicable as a subgroup-based approach as compared to a population-wide approach since intervention response may depend on initial metabolic status, gender and possibly other, yet unknown factors. In general, prevention is known to be less intensive and less expensive than treatment. However, to prevent a disease that develops over decades would require decades of supplementation. Obviously, this is not feasible. To prevent unnecessary and unsuccessful supplementation regimens, the identification of biomarkers may offer an extremely valuable approach to be able to predict effectiveness to polyphenol supplementation. By that means, subjects can be characterized by their disease risk profile and by their susceptibility to an intervention. We have shown in the present thesis that polyphenol supplementation may have the potential to reverse disturbances in lipid metabolism, thereby contributing to a reduced risk of developing type 2 diabetes mellitus and cardiovascular diseases. The analysis of the gut microbiota may further add to improve a more targeted intervention approach.

References

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