

Nutritional strategies to improve gastrointestinal and metabolic health

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Impact paragraph

Over the last century, the mean age and the number of elderly individuals in the general population has increased substantially, in parallel with a global increase in adherence to the Western diet and lifestyle.¹ Both factors have been associated with an increased prevalence of chronic conditions and disorders such as obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease and liver disease.^{2,3} In addition, nutrition and lifestyle related factors can also contribute to the onset and progression of diseases of the gastrointestinal (GI) tract, such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS).^{4,5} These chronic metabolic and/or inflammatory diseases are associated with a lower quality of life and an increased risk of disease-related comorbidity.^{6,7}

On the one hand, diet can be a risk factor, while on the other hand, nutrition can also be used as a strategy to improve general health, well-being and the course of chronic diseases. A class of nutrition specifically designed to improve health by targeting one or more of the processes involved in disease development and progression are the functional foods. These are foods that offer health benefits beyond their nutritional value. In this thesis, we assessed the effects of two different classes of functional food supplements on intestinal and metabolic health, *i.e.* probiotics and polyphenol-rich extracts. Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”.⁸ Polyphenols are naturally occurring metabolites found in plants with known anti-inflammatory and anti-oxidant effects, of which flavonoids are the largest and most studied group. These interventions were chosen as they have the potential to improve GI and metabolic health via various mechanisms of action. The main mechanistic targets we focused on were intestinal barrier function, microbiota composition, inflammation and blood lipid profiles. Functional foods are merely used as strategy to improve health and well-being or to reduce disease risk. To study the effects in humans, we chose to include elderly individuals and overweight/obese subjects, as they are (relatively) healthy, but at risk for mild disturbances in these outcomes. Furthermore, we included IBS patients with low-grade intestinal inflammation and performed *in vitro* experiments using a model that mimics disruption of intestinal barrier function, which is induced by inflammation.

The studies we performed can contribute to further insight into the health effects of the products we focused on and can provide leads for future studies that are relevant to scientists. In addition, by studying various mechanism related to chronic metabolic and inflammatory diseases, these types of studies can also provide more general insight into the factors that can contribute to the development of certain (pre-) disease conditions,

which is valuable information for researchers but also for healthcare workers involved in direct patient care.

Scientific impact

In the current thesis, we provided an extensive overview of the currently available evidence on citrus flavonoids and their effects on intestinal health (**Chapter 2**). We concluded that citrus flavonoids and their metabolites may contribute to improved GI functioning and health, likely due to a combined effect of the original compounds, of their metabolites, and an interaction with the intestinal microbiome. So far, most of the currently available evidence comes from animal and *in vitro* studies. To improve our understanding of these effects in the human gut, more research, especially in human subjects, is needed. Furthermore, studies are needed that directly compare the effect size of the flavonoids with the metabolites formed during intestinal breakdown, to provide more insight into their relative contribution to the beneficial effects.

In this thesis, we performed four randomised, placebo-controlled clinical trials with functional food supplements in subjects with a mild metabolic or inflammatory disturbance (**Chapters 4-7**). These well-controlled trials are the first step in translating the beneficial effects found in *in vitro* and animal studies into clinical practice. So far, many human studies have selected study populations that are convenient, but not necessarily the target population for the final application, while we wanted to study the effects of food interventions in populations that could ultimately benefit from such products. We performed these studies in subjects that were mainly at risk for metabolic or GI diseases and asked them to maintain their dietary and lifestyle habits. With these studies, we aimed to mimic the real-world settings as closely as possible, providing evidence of effects that can realistically be expected. Because we wanted to gain more insight into several different processes that may be involved, we made use of a combination of various non-invasive measurements in these studies. Overall, the observed effects were modest, but still do provide valuable information. In **Chapter 6**, we found that the carotenoid-producing *Bacillus* strain PD01 did not significantly affect GI permeability in overweight/obese subjects. However, we were able to show that PD01 survived transit through the GI tract and resulted in systemic carotenoid accumulation, without causing adverse events. In **Chapters 4, 5 and 7**, we did not find significant effects of the interventions (Citrus extract and olive leaf extract) on the main outcome parameters studied. All these studies had in common that the subjects included were still relatively healthy or had only mild disturbances. To determine whether these interventions, but also other functional foods, can contribute to improved metabolic or GI health, we advise future studies to test the application of these interventions in populations with

more pronounced disturbances and to consider using more mechanistic and clinical outcomes.

In addition to performing human studies, we wanted to focus in more detail on the relative contribution of citrus flavonoids and their metabolites to the observed effects. Therefore, we studied the effects of the two main citrus flavonoids hesperidin and naringin and their main metabolites formed during intestinal metabolism on immune-mediated barrier disruption in a well-controlled environment (**Chapter 3**). In this study, we showed that *in vitro*, the flavonoids as well as their metabolites were indeed able to exert comparable anti-inflammatory effects. These findings combined with what we already know about intestinal citrus flavonoid metabolism, provide additional information about where effects can be expected in the intestine after oral intake. Citrus flavonoids are rapidly metabolised by the intestinal microbiota once they reach the colon, with the highest levels being produced in the proximal colon. Therefore, anti-inflammatory effects, due a combination of direct effects of the (metabolised) compounds themselves and those mediated by the microbiota, will likely be most pronounced in the proximal colon. Human intervention studies applying methods to confirm these local effects, *e.g.*, by sampling biopsies or faecal material in the different intestinal compartments, are needed. In addition, further studies should also focus on how these effects can be influenced by the composition of the microbiota and potential other (host related) factors (*e.g.*, disease status, intestinal transit time and age).

Societal impact

In the Netherlands, on average more than 50% of the population suffers from one or more chronic disease(s) and this number rises to more than 95% in adults aged 75 years and older.⁹ This poses a major public health concern, as the costs associated with treatment of these diseases and societal costs, such as loss of productivity and increased disability, place a large burden on society.⁶ The use of functional foods is often preferred as treatment option over pharmaceutical drugs, in part because of their natural origin and the lower risk for side effects. In addition, consumers have become increasingly interested in how food and lifestyle can contribute to their health and well-being. Especially in those cases where it proves difficult to maintain lifestyle changes, such as strict dietary regimen long-term, intake of functional foods may be a more feasible option for consumers. Thereby, effective functional food products can have a significant impact on individual consumer well-being, but also on society in general, by contributing to a healthy lifestyle and the prevention of chronic diseases.

An important aspect contributing to the societal impact of research is effective communication and dissemination of study findings. The findings of studies in this

thesis have been presented during both national and international meetings and congresses. Furthermore, the articles presented in this thesis were all published in peer-reviewed open access journals, ensuring that the study findings are accessible not only to scientists within the field, but also to the general public. This was also the case for the clinical trials with final results that did not confirm or were not in line with our conceived hypothesis. However, we do feel that it is also very important to learn from negative findings. Findings described in this thesis have also been covered by an online news source for the nutrition industry (NutraIngredients) and in press releases of BioActor (the ingredient supplier and funder of the research), which both summarize newly published research in layman's terms. Communication about the effects of functional foods may even improve the awareness of consumers about the importance of nutrition and the role certain foods can play in health and disease in general.

Performing studies with functional foods and publishing the results of these studies is also important for companies focusing on the development of these products and the food industry as a whole. On one hand, scientific evidence, for example from well-controlled intervention studies, supporting the safety and clinical efficacy of products is important for companies to be able to comply with regulations (*e.g.*, to be allowed to substantiate and claim a certain health effect), but also for marketing and product development. On the other hand, collaboration of science and industry will contribute to the translation of scientific findings to successful products by taking factors into account that will impact the applicability of the intervention. This thesis is a typical example of a long-term collaboration between industry and academic partners, providing us with the opportunity to perform several well-designed clinical trials with relevant products. A crucial factor that determines how successful functional foods can become at preventing or improving a disease course, is consumer acceptance. This factor was taken into consideration by us already in the conceptualisation phases of the research performed within this thesis. Not only by performing consumer research in parallel to the clinical trial, but also by choosing a study product that can realistically be ingested on a daily basis (both in terms of convenience and price). The polyphenol interventions in particular are suitable for the development of products with high compliance and consumer acceptance rates. By using extracts with a standardized high content of the bioactive compounds, the total volume can be kept low. Furthermore, the extracts we used can be stored at room temperature for extended periods of time. Together, this will increase the potential product applications as the extract can be easily offered as capsules, effervescent tablets or added to products such as drinks with limited impact on palatability.

Conclusion

In this thesis steps have been taken in the search for effective nutritional strategies to improve GI and metabolic health, by performing several trials with different functional food supplements in relevant populations and models and by communicating these findings via various channels accessible to both scientists and the general public. This thesis has shown that more human studies with food interventions are needed, not only in populations with mild but also with more pronounced health disturbances, and should include more mechanistic and clinical outcomes.

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