Functional Foods and Beverages with Promising Gut-Health-Related Outcomes

Subjects: Food Science & Technology

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The notion of food as medicine can be traced back thousands of years, when the use of plants, herbs, and foods to treat disease and restore health was commonplace. Today, it is well understood that diet interacts with human physiology and health. Healthy dietary patterns that favour plant-based foods have been shown to offset the risk of chronic disease. Furthermore, components of plant-based diets have been shown to influence human physiology via effects on the gut microbiome. The innovation opportunity to design functional foods to support a resilient gut microbiota with a view to safeguarding against wider pathologies associated with gut dysbiosis extends the concept of functional foods into a new sphere. Bioactive food ingredients, through their interactions with the gut microbiota, may contribute to microbiota resilience, thus supporting the body's adaptive capacity.

microbiota resilience functional foods gut health hormesis

1. A Multi-Pronged Approach to the Design of Functional Foods for Gut and Systemic Health

How, then, might functional food developers set about selecting ingredients with the highest probability of influencing the functional parameters of gut and systemic health and shaping the microbiota towards a healthy state? In recent history, the field of nutrition science evolved from focusing on how intakes of individual nutrients impact the risk of disease, to examining dietary patterns and their influence on health. Global dietary guidelines today also tend to emphasise the notion of varied and diverse diets, favouring fruits, vegetables, and wholegrains, the consumption of which must be maintained over the life course.

Despite nutritional strategies to modulate the gut microbiota towards a resilient state being an emerging field of study, it is theoretically possible to design food-based interventions that may act on functional parameters of gut health along with shaping the gut microbiota towards a resilient, healthy state [1]. Although product developers may be well-equipped to select ingredients that pose the required technical properties for incorporation into their product matrix, choosing the right bioactives that impact the gut microbiota and beyond can be challenging. Despite the growing body of evidence supporting the relationship of specific functional ingredients with gut health, the field itself is a complex one, as the gut holds a bidirectional relationship with other organs and systems in the body. Consequently, different bioactive ingredients may act directly or indirectly on different gut outcomes, having local effects or broader systemic effects. Developing an understanding of how certain bioactive components may act

locally, or systemically, would help product developers to innovate in the gut health field. This could be particularly useful for innovation purposes when new concepts are developed for testing with consumers.

2. The Functional Relevance of Microbiota

Accumulating evidence suggests that the gut microbiota plays a key role in the initiation and progression of metabolic diseases [2]. A transplantation of gut microbes from conventionally reared mice into germ-free mice resulted in an increased accumulation of adipose tissue in the germ-free mice, despite controlling their food intake, thus demonstrating that gut microbiota transplantation is capable of leading to an increased body fat content in mouse models [3][4]. Moreover, the intestinal microbial composition was shown to be different between obese and lean individuals, with obese persons having a lower prevalence of Bacteroidota but a higher prevalence of Bacillota [5]. Compositional variation in the intestinal microbiota has also been observed when comparing faecal samples from type 2 diabetes (T2D) patients versus healthy individuals [6]. The T2D samples had a lower abundance of bacteria from the genus *Lactobacillus* and higher abundance of *Bifidobacterium*. These studies illustrate the significance of microbiota for potentially offsetting the risk of chronic disease.

Beyond specific diseases, evidence suggests that the gut microbiota significantly contributes to general well-being, especially in later life. Research across various model organisms, as well as in humans, demonstrates the role of the gut microbiome in well-being and longevity. Generally, as organisms age, the diversity of their gut microbiota decreases and health-promoting bacteria decline, while opportunistic bacteria and overall microbial numbers increase [7]. Human studies also indicate age-related compositional changes in the microbiota, suggesting a potential causal role in late-life health [8]. Centenarians were shown to overcome those changes by maintaining gut microbiota diversity and by increasing the prevalence of health-associated groups (e.g., *Akkermansia* and *Bifidobacterium*) [9]. These studies suggest that the gut microbiota shows compositional changes that correlate age and disease, implying that interventions which target the gut microbiota have the potential to improve both health span and lifespan.

3. What Is a “Healthy” Gut Microbiota? A Holistic Exploration of Dysbiosis-Induced Pathogenesis

Substantial research is dedicated to defining a “healthy” gut microbiota and understanding its connection to host physiological functions. However, the concept of a “healthy” gut microbiota remains complex and evolving within scientific discourse, lacking a universally agreed-upon definition due to variations among individuals. Nevertheless, certain characteristics associated with gut microbiota composition are often considered indicative of a potential state of health. Under healthy conditions, the gut microbiota exhibits stability, resilience, and a symbiotic relationship with the host [10]. A “healthy” gut microbiota is generally characterised by a balanced and diverse microbial community, essential for maintaining gut barrier integrity, nutrient metabolism, and immune system modulation [10].

In a state of homeostasis, the gut microbiota performs essential functions, such as aiding in the digestion of complex carbohydrates, the extraction of nutrients from food, and the biosynthesis of bioactive molecules, including vitamins, amino acids, lipids, or short-chain fatty acids [3]. Moreover, the gut microbiota not only shields the host from external pathogens by producing antimicrobial substances, but also contributes significantly to the development of intestinal mucosa and the immune system [11]. Dysbiosis can instigate disease processes through multiple mechanisms. Disruption of the gut barrier, altered immune responses, and dysregulation of metabolic pathways are among the key contributors [12][13].

But how might gut-confined microbes have such systemic effects on health? The gut microbiota can produce and regulate signals that reach the circulation and modulate whole-organism physiology. These signals can be either microbiota-derived or host-derived. Microbial signals can be structural components of bacteria or metabolites. Structural components such as lipopolysaccharide (LPS), peptidoglycan, and flagellin are recognised by pattern-recognition receptors on epithelial and immune cells and they are generally not diffused across the epithelial barrier [14]. It has been reported that LPS might reach the circulation via co-transport with chylomicrons, which was suggested to have implications for inflammation and obesity [15]. An altered composition of gut bacteria has also been shown to catabolise tryptophan into the metabolite indole-3-aldehyde, which has been associated with inflammatory bowel disease [16]. Moreover, SCFAs, such as butyrate, propionate, and acetate, generated from the saccharolytic fermentation of dietary fibre, can act as signalling molecules at distant body sites. For example, acetate, produced from dietary fructose, is a source for supplying acetyl-CoA, which can then trigger hepatic de novo lipogenesis [17]. Thus, bacterially sourced molecules can systemically affect host health.

As well as containing bacteria that produce signals, the gut is the largest endocrine organ in the human body, containing specialised hormone-producing enteroendocrine cells [18]. In mice, SCFAs have been shown to activate receptors on those cells, which then triggers the secretion of gut peptides such as glucagon-like peptide (GLP-1) and peptide YY (PYY) [19]. GLP-1 is known to regulate pancreatic function, insulin release, and appetite, while PYY has been shown to increase energy harvest from the diet [20][21]. Human studies have demonstrated that the administration of fermentable fibres induces changes in the gut microbiome, which, when modulated by fructooligosaccharides (FOS), is suggested to enhance satiety, reduce hunger, and elevate GLP-1 and PYY levels [22]. Thus, microbes that reside in our gut generate molecules that can influence host endocrine signalling, and this may have consequences for wider systemic health.

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