Journal of Functional Foods 81 (2021) 104466

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Re-thinking functional food development through a holistic approach

Marilisa Alongi [*], Monica Anese

Department of Agricultural, Food, Environmental and Animal Sciences, University of Udine, via Sondrio 2/A, 33100 Udine, Italy

ARTICLE INFO

Keywords:
Functional food
Food design
Sustainability
Communication
Multidisciplinary approach
Iterative process

ABSTRACT

Although the interest towards functional food has dramatically increased, several factors jeopardize their effective development. A univocally recognized definition and a dedicated regulation for this emerging food category is lacking, and a gap exists between the technological and the nutritional viewpoints. Involved actors speak different languages, thus impinging the progression towards an integrated approach for functional food development.

A holistic approach to rationalize functional food development was here proposed, *i.e.,* the "Functional Food Development Cycle". First regulation and definitions were reviewed. The technological approaches for functional food design were then described, followed by the efficacy evaluation ones. Merging the technological and the evaluation viewpoints, by identifying the best compromise between quality and functionality, is pivotal to develop effective functional foods. Finally, delivering functional food on the market requires dedicated communication strategies. These in turn can provide information about consumer needs, thus representing an input for regulatory bodies to drive the development of functional food, feeding it within an iterative and virtuous holistic cycle.

1. Historical overview of functional food

The term "functional food" firstly appeared in Japan in 1984. The Japanese government defined a new product category, Food for Specific Health Uses (FOSHU), as "food containing an ingredient with functions for health and officially approved to claim their physiological effects on the human body" and produced a dedicated legislative framework. Japan was followed by the United States that in the '90s developed the first health claim act, but without providing a formal definition of functional food (Martirosyan & Singh, 2015). European countries acquired the functional food concept more than 10 years later when the European Parliament and Council introduced the regulation on nutritional and health claims (Reg. (EU) n. 1924/2006); but also in this case no formal definition was mentioned.

The research interest towards functional food experienced a steep increase only in the 21st century (Fig. 1a) and this globally growing attention has tremendously influenced their market (Kaur & Das, 2011), the size of which was estimated at USD 162 billion in 2018 and was projected to reach USD 280 billion by 2025 with an annual growth rate of around 8% (Grand View Research, 2019b, 2019a).

2. Functional food issues

2.1. Definition: What are we talking about?

Although the research interest and the market of functional food are exponentially growing, many stakeholders in the European Union are disoriented, due to the lack of a comprehensive picture on this topic, which jeopardizes their effective development. This has produced a debate on the functional food definition that has been ongoing for more than 20 years and is still opened. The term "functional food" generally refers to products providing a specific health benefit, beyond basic nutrition. Although different terms in the field of food providing health benefits have been univocally defined by EU and extra-EU legislation, as in the case of food supplements and food for medical use, still no common and exhaustive definition has been recognized for functional food yet (Table 1). Actually, the terms nutraceutical and functional foods are often confused and interchanged.

Different attempts have been made to propose a commonly agreed definition. The last proposal was that presented by the Functional Food Center (FFC) in 2018 (Table 1), describing functional foods as "natural or processed foods that contain biologically active compounds; which, in defined, effective, and non-toxic amounts, provide a clinically proven

---

[*] Corresponding author.
E-mail address: marilisa.alongi@uniud.it (M. Alongi).

https://doi.org/10.1016/j.jff.2021.104466
Received 29 December 2020; Received in revised form 12 March 2021; Accepted 28 March 2021

and documented health benefit utilizing specific biomarkers for the prevention, management, or treatment of a chronic disease or its symptoms" (Gur, Mawuntu, & Martirosyan, 2018).

Based on this definition, a conventional product ("natural or processed food") containing components positively affecting health should be regarded as a functional food as well (Gur et al., 2018). However, such a definition is not fully accepted, as other authors excluded from the functional food category those products naturally containing bioactive compounds (Kaur & Das, 2011). In particular, they stated that foods can be defined as functional only if belonging to the following classes:

- products fortified with ingredients having a positive health influence;
- products cleared from anti-nutritional compounds;
- raw materials improved/fortified/cleared by changing agricultural practices (*i.e.,* animal feeding and vegetable breeding) or postharvest treatments (fruits and vegetables);
- novel foods with an improved health benefit.

On the other hand, the definition by Gur et al. (2018) does not include those products cleared from some components (*i.e.,* light foods), although these are generally intended as foods carrying a health-promoting effect.

As a result, when dealing with functional food there is a high risk of confusion and misunderstanding, and this term is currently used mostly as a marketing idiom (Martirosyan & Singh, 2015), pointing out the urgent need for a standard functional food definition approved by governments.

In fact, the absence of an agreed definition brings about the lack of a dedicated legislative framework in Europe. Currently, several regulations relevant to the food field apply to this category. However, a dedicated regulation establishing functional food as a separate category is urgently needed (Gur et al., 2018) to guide and control the innovation in the functional food field by setting rules and standards (Moors, 2012). These are essential to reduce the fear of working in a grey area and increasing the investments in functional food R&D (Kaur & Das, 2011).

Another key aspect to be considered is the need for rules to assess functional food efficacy. This issue has already been brought about by the Reg. (EU) n. 1924/2006 concerning nutritional and health claims, and more in detail by the Reg. (EU) n. 353/2008 that establishes the requirements for health claims to be authorized. These cover a broad range of effects, including immune system protection, prevention of oxidative damage and cardiovascular diseases, control of blood glucose levels, the health of bones and skin, protection of nervous system, and overall improvement of physical performances. However, demonstrating such effects is challenging and claims are often rejected by EFSA. In fact, food matrix complexity hinders making clear cause-effect

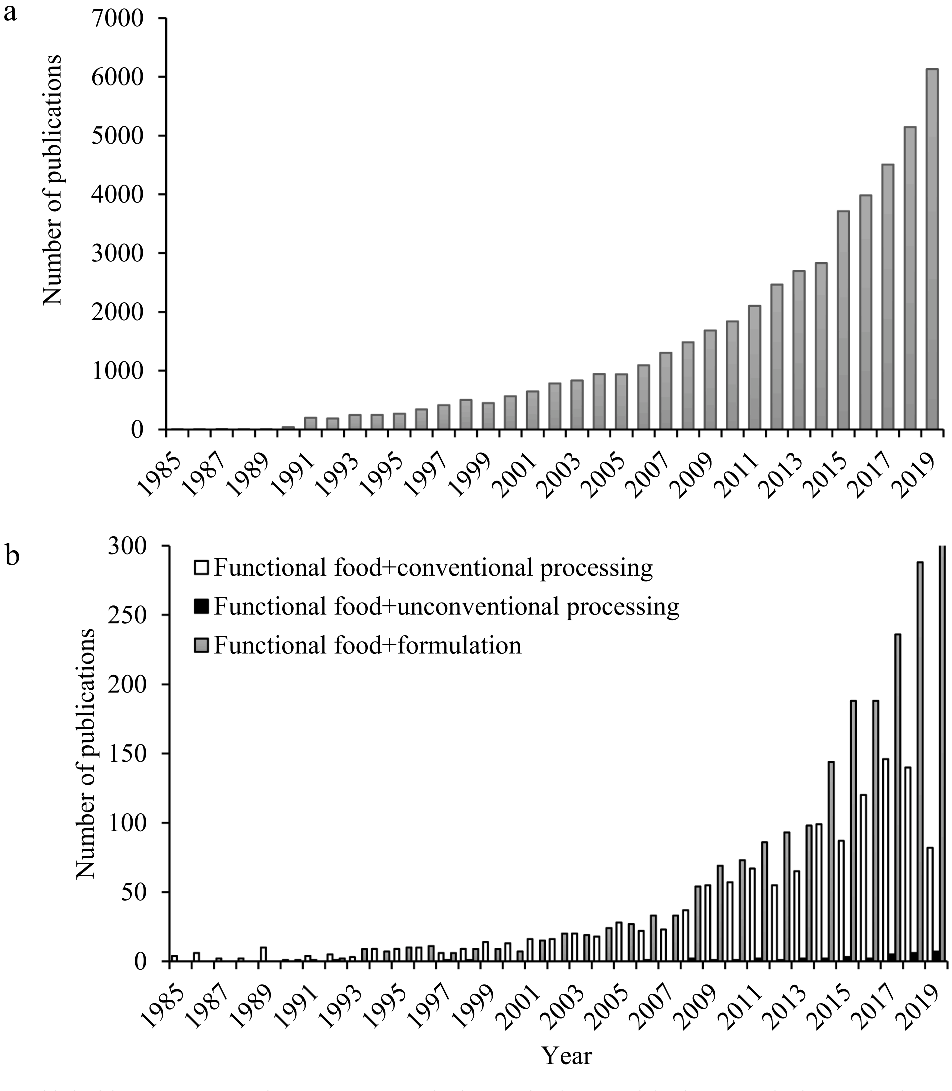

Fig. 1. Number of papers published between 1985 and 2019 containing the keywords "functional food" (a), or the keywords "functional food" associated with "unconventional processing", "conventional processing" or "formulation" (b).

Table 1
Definitions of functional food and nutraceutical, and relevant references.

Term	Definition	Reference
Functional food	Foods that encompass potentially healthful products, including any modified foods or food ingredients that may provide a health benefit beyond the nutrients it contains	Thomas and Earl (1994)
	Product which is shown in a satisfactory manner that, in addition to adequate nutritional effects, induces beneficial effects on one or more target functions of the organism, significantly improving the health status and welfare or reducing the risk of disease	Diplock et al. (1999)
	Nutrient consumed as part of a normal diet but delivering one or more active ingredients (that have physiological effects and may enhance health) within the food matrix	Zeisel (1999)
	Any food or ingredient that has a positive impact on an individual's health, physical performance, or state of mind, in addition to its nutritive value	Hardy (2000)
	Foods and food components that provide a health benefit beyond basic nutrition. These substances provide essential nutrients often beyond quantities necessary for normal maintenance, growth, and development, and/or other biologically active components that impact health benefits	IFT (2005)
	Foods that may provide a health benefit beyond basic nutrition	Day, Seymour, Pitts, Konczak, and Lundin (2009)
	Natural or processed foods that contain known or unknown biologically active compounds; which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic diseases	Martirosyan and Prasad (2009)
	Natural or processed foods that contain biologically active compounds; which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers for the prevention, management, or treatment of chronic disease or its symptoms	Gur et al. (2018)
Nutraceutical	Food or part of food that provides medical or health benefits, including the prevention and/or treatment of a disease	De Felice (1995)
	Any substance that is a food or a part of a food and is able to induce medical and health benefits, including the prevention and treatment of disease	Brower (1998)
	A diet supplement that delivers a concentrated form of a biologically active component of food in a nonfood matrix to enhance health	Zeisel (1999)
	A foodstuff (as a fortified food or dietary supplement) that provides health benefits in addition to its basic nutritional	Merriam-Webster Online Dictionary (2015)
	Nutritional products that provide health and medical benefits, including the prevention and treatment of disease	Santini et al. (2018)

relationships, disguising the observed effects, and leading to outcome misinterpretation.

2.2. Design: Approaches to deliver functional food

Although many proposals have been made for a common approach to deliver effective functional food, based on a rational design from the molecular to the macroscopic level (McClements, 2009), the lack of a defined target hinders their implementation (Gur et al., 2018).

The first step to develop a functional food is to identify a goal. This can be selected based on two opposite paths: one can be regarded as a top-down approach, deriving from a new idea to face food-related health issues. Although the innovative potential, this approach does not result in an adequate involvement of all the actors and might not fulfill consumer expectations. Thus, more favorably a bottom-up approach should be applied, to deliver effective solutions to food-related health issues, while guaranteeing consumer acceptability (Bigliardi & Galati, 2013; Bleiel, 2010; Gur et al., 2018; Jones & Jew, 2007; Siró, Kápolna, Kápolna, & Lugasi, 2008).

In industrialized countries, because of rising medical costs and increased life span, nutritional recommendations formulated by health professionals have motivated the food industry to provide products that help consumers to be in line with these recommendations (Kaur & Das, 2011). Considering the most incident health-related chronic diseases (*i.e.,* obesity, CVD, and diabetes), two are the major targets to be achieved through food design, *i.e.,* reducing the energy intake and introducing food with healthy properties (Table 2).

To reduce the energy intake, it is necessary decreasing the intake of macronutrients or slowing down their digestion thus maintaining constant their concentration in the bloodstream (Table 2). This, in turn, would contribute to increasing the satiety feeling, playing an indirect effect on the energy intake (Ruijschop, Burseg, Lambers, & Overduin, 2009). On the other hand, introducing food with healthy properties implies delivering micronutrients that play an active role in the prevention and management of diet-related chronic diseases.

These targets can be gathered through different tactics including simple dietary approaches, as well as technological interventions, intended as formulation or processing (Table 2).

2.2.1. Diet

The first crucial aspect to be considered when dealing with food functionality is the co-ingestion with other foods within a meal and/or with the drugs used to treat chronic diseases (Koziolek et al., 2019). Food-drug interactions are mostly examined from the side-effect viewpoint, instead of considering the possible beneficial outcomes. However, some studies highlighted the possibility to take advantage of these interactions. Table 3 reports some examples of positive food-drug interactions, considering the compounds under investigation, the food

Table 2
Target, strategy, and tactic to be implemented to design functional food.

Target	Strategy	Tactic
Reducing energy intake	• decreasing macronutrient intake • slowing down macronutrient digestion • increasing the satiety feeling	• using naturally low energy food • reducing conventional food portions • formulating low energy food • designing food structures able to slow down the digestion rate
Introducing food with healthy properties	• enhancing micronutrients intake and absorption	• using food naturally providing bioactive compounds • formulating food enriched/ fortified with bioactive compounds

Table 3
Examples of different approaches towards non-communicable diseases prevention and/or management, food matrix and treatment, bioactive compounds involved, effect on physiological functions (↑: increased/improved; ↓: decreased), and relevant references.

Approach	Food matrices/treatments	Interactions/Compounds	Effect on physiological functions	References
Diet: food-drug interaction	Green tea	Catechins – antihypertensives (diltazem, nicardipine, verapamil) Catechins – cardiovascular drugs (verapamil, nadolol) Catechins – anti-hypercholesterolemic drugs (simvastatin) Catechins – chemotherapics (tamoxifen, 5-fluoro-uracil, sunitinib) Catechins - antipsychotics (quetiapine, clozapine)	↑ Cardiovascular functionality ↓ Cancer cell proliferation ↑ Psychiatric condition	Albassam and Markowitz (2017)
	Coffee	Caffeine – cardiovascular drugs (lidocaine, mexiletine, propafenone, propranolol, triamterene, verapamil, warfarin) Caffeine – anti-inflammatory drugs (methotrexate) Caffeine – antipsychotics (clozapine, haloperidol, olanzapine) Caffeine – antidepressants (amitriptyline, clomipramine, fluvoxamine, mianserin, imipramine) Chlorogenic acids – antidiabetic drugs (acarbose)	↑ Cardiovascular functionality ↓ Inflammatory state ↑ Psychiatric condition ↓ Glycemic response	Belayneh and Molla (2020) Alongi and Anese (2018)
	Apple juice	Phenolic acids – antidiabetic drugs (acarbose) Flavonoids – anti-inflammatory drugs (midazolam, fexofenadine)	↓ Glycemic response ↓ Inflammatory state	Alongi et al. (2018) Khuda et al. (2019)
	Turmeric	Curcuminoids – antidepressants (buspirone, fluoxetine) Curcuminoids – cardiovascular drugs (losartan, talinolol, celiprolol, nifedipine, rosuvastatin) Curcuminoids – antihystamines (loratadine) Curcuminoids – chemotherapics (paclitaxel, docetaxel, etoposide, tamoxifen, everolimus, phosphosulindac) Curcuminoids – cardiovascular drugs (warfarin, clopidogrel) Curcuminoids – anti-inflammatory drugs (flurbiprofen, paracetamol) Curcuminoids – antibiotics (norfloxacin)	↑ Cardiovascular functionality ↑ Psychiatric condition ↓ Inflammatory state ↓ Cancer cell proliferation ↓ Infections	Adiwidjaja, McLachlan, and Boddy (2017) Bahramsoltani, Rahimi, and Farzaei (2017)
	Black currant and rowanberry	Polyphenols – antidiabetic drugs (acarbose)	↓ Glycemic response	Boath et al. (2012)
Diet: food-food interaction	Apple juice, apple cider	Polyphenols – carbohydrates	↓ Glycemic response ↑ Intestinal microbiota activity	Alongi, Verardo, Gorassini, Sillani, and Anese (2020) Renard et al. (2017)
	Green tea and milk	Polyphenols – lipids, proteins	↓ Cancer cell proliferation	Von Staszewski et al. (2012)
	Extra virgin olive oil	Polyphenols – lipids	↓ Oxidative status ↓ Cancer cell proliferation	Alu`Datt et al. (2014)
Formulation	Short dough biscuits enriched with apple pomace	Polyphenols, dietary fiber	↓ Glycemic response	Alongi, Melchior, and Anese (2019)
	Short dough biscuits enriched with spent coffee grounds	Polyphenols, dietary fiber, indigestible carbohydrates	↓ Glycemic response ↓ Oxidative status	Martinez-Saez et al. (2017)
	Cereal bars enriched with unripe banana flour	Resistant starch	↓ Glycemic response	Utrilla-Coello, Agama-Acevedo, Osorio-Diaz, Reynoso-Camacho, and Bello-Perez (2013)
	Bean paste enriched with onion skin	Polyphenols	↓ Glycemic response	Sęczyk et al. (2015)
	Bean paste enriched with onion skin	Polyphenols	↑ Protein digestibility ↑ Phenolic bioaccessibility	Sęczyk et al. (2015)
	Coffee added with milk	Polyphenols	↑ Phenolic bioaccessibility	Alongi, Calligaris, and Anese (2019)
	Sunflower oil enriched with turmeric extract	Curcuminoids	↑ Curcuminoid bioaccessibility	Calligaris et al. (2020)
Processing	Apple juice/pasteurization	Polyphenols	↓ Glycemic response	Alongi et al. (2018)
	Apple juice/ultrasonication	Polyphenols	↓ Glycemic response ↑ Serum transport	Alongi et al. (2019)
	Blackcurrant juice/enzymatic treatment and reverse osmosis	Anthocyanins, flavonols	↓ Glycemic response ↓ Oxidative status ↑ Cardiovascular functionality	Castro-Acosta et al. (2016) Pap et al. (2010)
	Coffee/roasting	Polyphenols, Maillard reaction products	↓ Glycemic response ↑ Phenolic bioaccessibility ↓ Oxidative status ↓ Cancer cell proliferation	Alongi and Anese (2018) Budryn et al. (2017)

matrices in which such compounds are contained, and the physiological functions affected by the interaction. It can be noticed that a plethora of physiological functions, mostly related to the onset of chronic non-communicable diseases, is influenced by food-drug interactions. However, most of the studies available in the literature refer to model systems and especially to bioactive compound extracts (Boath, Stewart, & McDougall, 2012; Ni, Hu, Gong, & Zhang, 2020), whereas only few examples deal with the whole food matrix (Table 3). This is because studying food-drug interaction is hindered by the food matrix complexity, which complicates the comprehension of interactions at the molecular level (Koziolek et al., 2019).

As a result, even if the development of improved drug delivery technologies is increasing, there is still a lack of understanding of the effect of food co-ingestion (O'Shea, Holm, O'Driscoll, & Griffin, 2019). In this regard, we recently tried to get an insight into the interaction between apple juice, *i.e.,* a whole food matrix, and acarbose, which is a drug used to treat type 2 diabetes. Acquired results showed that properly combining food with a conventional drug may produce synergies towards α-glucosidase inhibition *in vitro*, paving the way for drug dose reduction and side effects restraint (Alongi, Verardo, Gorassini, & Anese, 2018). Even so, this is still a very early topic and no authorized instructions to modify drug dose depending on the food consumed exist yet (Koziolek et al., 2019).

Besides food-drug interactions, also those among food components and between different foods could represent a promising dietary approach to be exploited for increasing food functionality. Even so, little information is available about the interactions among micronutrients and between these and the macronutrients (Alu'datt et al., 2019). Moreover, also in this case, only a few studies consider these interactions within the actual food matrices, whereas most studies deal with simplified systems containing pure compounds (Bungau et al., 2019). Nonetheless, food-food interactions have been demonstrated to affect several physiological functions. In particular, the few studies available on this topic highlighted the crucial role of phenolic compounds towards carbohydrate and lipid digestion, indicating that a proper dietary intake of these compounds can help to modulate macronutrient bioavailability and thus managing related diseases, such as cardiovascular ones and type 2 diabetes. In this regard, we demonstrated that administering short dough biscuits with apple juice, instead of a soft drink having the same sugar composition as the juice, allowed modulating the glycemic response (Alongi, Verardo, et al., 2020). This outcome was attributed to the bioactive compounds delivered by the juice, such as phenolic ones and soluble dietary fiber, which are known to exert an antidiabetic effect by inhibiting carbohydrate digestive enzymes and by modifying the intestinal transit rate, respectively (Boyer & Liu, 2004; Weickert & Pfeiffer, 2018). Similarly, as reviewed by Renard, Watrelot, and Le Bourvellec (2017) the intake of apple cider improved the intestinal microbiota activity thanks to the presence of proanthocyanidins which affect the production of colonic metabolites. Still, the mechanisms behind food-food interactions were only partially disclosed and further research is required to achieve an understanding deep enough to steer dietary interventions towards an effective health benefit.

2.2.2. Formulation

From the technological viewpoint, the first step to deliver health benefits through food is to modify their formulation in a tailor-made manner. Different tactics can be applied to accomplish the targets reported in Table 2. In particular, formulation can be directed to removing/replacing certain ingredients or adding bioactive compounds, thus obtaining:

- light food, in which the concentration of an undesired component is reduced (*e.g.*, "low fat", "low sugar"); it derives from the increase in the non-caloric fraction or the removal (and replacement) of undesired components (McClements et al., 2015);
- enriched or fortified food, in which a bioactive compound has been added (*e.g.*, prebiotics and probiotics, vitamins A, D, $B_{12,}$ and calcium in vegetable beverages) or its presence has been increased (*e.g.*, dietary fiber in bakery products, vitamins in fruit juices), respectively; these can be obtained by bolstering the delivery of naturally present bioactive compounds, by adding them to the product, or by inducing their formation upon processing (McClements, 2009);
- enhanced food, in which the content of a bioactive compound has been improved by specific agricultural (*e.g.*, selenium in potatoes), genetic (*e.g.*, vitamin A in rice), and breeding (*e.g.*, ω-3 in eggs) practices.

Regarding ingredient removal/replacement, one of the major issues concerns the excessive consumption of sugar, which is negatively associated with many health outcomes. Several ingredients are currently available and applied in the food industry to overcome this issue, such as low-calorie carbohydrates (*e.g.,* oligofructose, maltodextrin, and polydextrose), non-nutritive sweeteners (*e.g.,* acesulfame-K, sucralose, aspartame), as well as their combination (Luo, Arcot, Gill, Louie, & Rangan, 2019).

In the last years, there has been a growing interest also in fat mimetics to reduce caloric intake and/or to modulate lipid digestion (Guo, Ye, Bellissimo, Singh, & Rousseau, 2017; Martins, Vicente, Cunha, & Cerqueira, 2018). The most promising solutions are represented by emulsions and organogels. Besides replacing fat, in recent years these ingredients have been under investigation also for their capacity to address the second target of formulation interventions, *i.e.,* the delivery of bioactive compounds (Mao, Lu, Cui, Miao, & Gao, 2019; McClements & Li, 2010). In fact, these structured systems are able to protect lipophilic bioactives, such as curcuminoids and carotenoids (Calligaris, Alongi, Lucci, & Anese, 2020; Salvia-Trujillo et al., 2017), during the gastrointestinal transit and to increase their delivery, which is known to be critical otherwise. As reported in Table 3, studies regarding the addition of bioactive compounds mainly concern phenolic-rich ingredients for the control of the glycemic response, as in the case of bakery products formulated with spent coffee grounds, onion skin, and apple pomace (Alongi, Melchior, et al., 2019; Martinez-Saez et al., 2017; Sęczyk, Swieca, & Gawlik-Dziki, 2015).

Although several formulation strategies are available to steer food functionality, a major hindrance in the implementation of newly developed products at the industrial level lies in the lack of knowledge about the food matrix complexity (Parada & Aguilera, 2007). In fact, most studies do not take into account the interactions among food components upon formulation, resulting in the development of functional ingredients that are effective when assessed alone but behave unpredictably when used within a food formulation, due to antagonist, additive, or synergistic effects among components. In particular, synergies allow enhancing the bioactive effect (Jacobs, Tapsell, & Temple, 2011), representing a tool to increase functionality by taking advantage of food matrix complexity (Parada & Aguilera, 2007). In this regard, McClements et al. (2015) introduced the concept of excipient food, namely food that may have no bioactivity itself but boosts the efficacy of another bioactive agent. This can be regarded as an indirect approach to enrich food with bioactive compounds and has been trialed in polyphenol-containing beverages, such as fruit juices (Rodríguez-Roque, Rojas-Graü, Elez-Martínez, & Martín-Belloso, 2014), coffee (Alongi, Calligaris, et al., 2019), and tea (Lamothe, Azimy, Bazinet, Couillard, & Britten, 2014), by adding dairy products as excipient ingredients.

2.2.3. Processing

Together with diet and formulation, another key feature affecting food functionality is processing. The general belief is that it increases macronutrient digestibility and depletes micronutrients, thus reducing the overall nutritional value (Prochaska, Nguyen, Donat, & Piekutowski, 2000) and representing a drawback towards one of the major drivers for functional food design, *i.e.,* enhancing micronutrient intake and absorption (Table 2). Although it is well known to substantially affect matrix composition and interactions, only a few studies considered the effect of conventional and, even more so, unconventional processing on food functionality (Fig. 1b and Table 3). Indeed, the processing approach towards the prevention of non-communicable diseases deserves further investigation. As an example, we observed that roasting modified coffee phenolic profile, boosting its antidiabetic potential (Alongi & Anese, 2018). Such changes depended on the intensity of the applied process, suggesting that processing interventions can concur to modulate food functionality in a tailor-made manner, by finely tuning their parameters. Similarly, the effect of conventional pasteurization was demonstrated to increase the phenolic content and the bioactivity of apple juice thanks to the thermal inactivation of polyphenoloxidase (Alongi et al., 2018), whereas an unconventional pasteurization process based on ultrasounds further increased the phenolic content of apple juice, due to the combination of cavitation with heat that promoted the release of phenolic compounds from the vegetable matrix (Alongi, Verardo, et al., 2019). This evidence confirmed that processing can positively affect food functionality, and thus its effects need to be thoroughly investigated to understand the reasons behind this influence.

2.3. Evaluation: After all, does it work?

Indeed, further research is required to assess the actual impact of technological interventions, considering both formulation and processing, as well as the co-ingestion with other food and/or drugs, on the fate of bioactive compounds contained in real food matrices. In fact, to authorize the commercialization and to claim the bioactivity of functional food, it is necessary first to demonstrate its efficacy (Reg. (EU) n. 1924/2006).

Ascertaining the disease prevention capacity of a newly developed functional food requires understanding the factors governing the release of bioactive compounds from food, the extent of absorption, and their fate in the organism, considering all the steps along the journey from the food matrix to the target tissue or organ. These include consumption, gastrointestinal events, absorption, and distribution (Motilva, Serra, & Rubio, 2015), and their key indicators are (Stahl et al., 2002):

- Bioaccessibility: the fraction of ingested compound released from the food matrix and available for intestinal absorption (Ferruzzi, 2010). It depends not only on the liberation from the food matrix but also on the solubility in the gastrointestinal fluids and on the interactions with other constituents in the gastrointestinal tract.
- Transformation: bioactive compounds may incur chemical (*e.g.,* oxidation/reduction, hydrolysis) or biochemical (*e.g.,* enzymatic metabolism) transformations within the gastrointestinal tract, which may alter their molecular structure (McClements et al., 2015).
- Absorption: referring to the passage of bioactive compounds across the mucus layer, through the epithelium cells, and into the systemic circulation, mainly depending on the permeability of the gut wall and the transport mechanism (*i.e.,* active, passive, tight junction) (McClements et al., 2015; Rein et al., 2012).
- Biodistribution: that accounts for the temporal and spatial distribution of the bioactive compounds to different tissue compartments after intestinal absorption (Motilva et al., 2015), which mostly depends on their affinity for blood transport proteins.
- Bioavailability: representing the fraction of ingested bioactive compounds that end up in the systemic circulation reaching the active site in an active form (Stahl et al., 2002).

Evidence can be collected by applying the same approach as that used for orally ingested drugs, such as *in-vitro* mechanistic analyses, including simulated digestion and cell culture models, followed by *in vivo* studies, including animal experiments and human clinical trials (Fig. 2). However, the behavior of a food matrix is different as compared to that of drugs: even if they follow the same metabolic pathway, applying the pharmacokinetic concepts to food is challenging. Drugs contain one or few pure components targeting a specific action site, whereas, as already pointed out (Table 3), food contains a plethora of micronutrients potentially interacting one with each other, thus resulting in a modified outcome (Motilva et al., 2015). In addition, these compounds are present in a complex matrix, mainly consisting of macronutrients (*i.e.,* carbohydrates, proteins, and lipids), which affects the functionality indicators (Parada & Aguilera, 2007). Nonetheless, the digestion process and the presence of a complex intestinal microbiota can modify the micronutrients, affecting their bioactivity (Rein et al., 2012). As a result, unraveling the efficacy of functional food is challenging and pieces of information regarding the effects of food matrix on the bioactivity of some nutrients are still conflicting.

Although *in vitro* standardized models to simulate digestion are available in the pharmaceutical field (United States Pharmacopeia methods), they are unsuitable for complex food matrices. As several different methods have been applied in the food sector making a comparison impossible, the international INFOGEST network harmonized the conditions for a static simulation of food digestion (Brodkorb et al., 2019; Minekus et al., 2014) and more recently a semi-dynamic

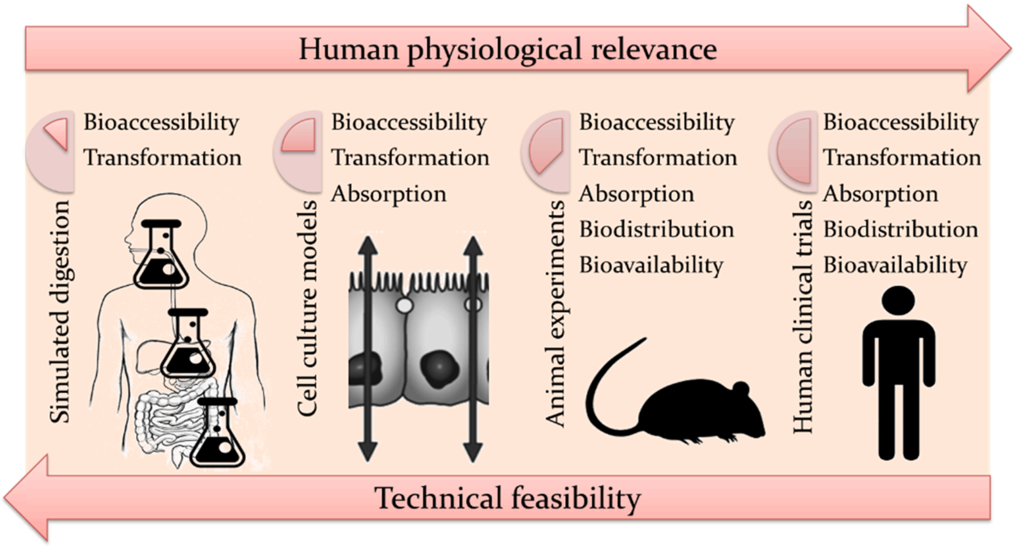

Fig. 2. Methodologies that can be applied to assess food functionality and relevant indicators.

standardized method has also been proposed (Mulet-Cabero et al., 2020). Indeed, the increase in precision and reproducibility guaranteed by standardized methods makes them a useful tool for sample screening, to get indications relevant to bioaccessibility and transformation.

In some cases, cell culture models (*e.g.,* Caco-2 cell line) are used after digestion simulation (Fig. 2) to investigate the mechanism and extent of absorption of bioactive components from food (Hur, Lim, Decker, & McClements, 2011), as well as to study the metabolic reactions occurring in the gut lumen or within the enterocyte, and leading to compound transformation (Konishi & Kobayashi, 2004).

After the preliminary *in vitro* screening, it is necessary to switch to *in vivo* models to understand the actual physiological response to specific foods, including information regarding biodistribution and bioavailability (Fig. 2). Animal models are generally applied first. However, although they allow getting close to physiological human conditions, they have been questioned both in reliability and ethical terms (Brodkorb et al., 2019). In addition, *in vitro* and animal experiments are only accepted as supporting data, whereas human clinical trials are compulsorily required (Reg. (EU) n. 353/2008) for the authorization of a health claim.

Even if human interventions represent the gold standard, they bring about further management and ethical issues (Brodkorb et al., 2019). Furthermore, both animal and human trials can only provide indications about the functional efficacy but do not give insights into the mechanism underlying it. They can thus only represent the final validation step (Dupont et al., 2018), while it is essential to get as much information as possible from the *in vitro* screening. In fact, details about the molecules carrying bioactivity and the mechanism behind it are essential to steer technological interventions towards functionality (Rein et al., 2012). In other words, *in vitro* trials represent a crucial tool to pre-qualify the technological interventions most promising in boosting food functionality before *in vivo* validation.

Once the functionality indicators have been assessed, the last key step to assess food functionality is measuring the targeted bioactivity, which represents the physiological effect carried out by a bioactive compound once it has reached its active site (Stahl et al., 2002). Both *in vitro* and *in vivo* trials are carried out to get an output that can be related to the physiological effect of the ingested functional food. Food functionality has been generally attributed to bioactive compounds having antioxidant, anticarcinogenic, and antidiabetic capacities. These properties can be tested by applying several techniques, most of which are based on *in vitro* tests. As already pointed out, these are easy, cheap, and fast. However, they do not consider the complexity of biochemical conditions occurring in the human body. In fact, for most bioactive compounds the metabolic pathway has not been fully characterized yet. This represents an essential step to understand which are the compounds responsible for the functionality of food and in which form they carry out the health-promoting effect (Rein et al., 2012). In addition, *in vitro* testing represents a simplification and does not take into account the actual physiological response. It is, therefore, crucial to measure the biological activity *in vivo*, by monitoring the parameters of interest relevant to a specific disease, through direct and dynamic measurements (Heaney, 2001). For instance, the antidiabetic efficacy can be assessed by measuring the glycemic response during the time after food consumption (Wolever, Jenkins, Jenkins, & Josse, 1991). Similarly, triglyceride blood levels are informative about interventions aimed at reducing lipid absorption (Tan, Wan-Yi Peh, Marangoni, & Henry, 2017). Still these tests are not revealing about the mechanisms underlying the observed effect.

Due to the need to understand both the efficacy under physiological conditions as well as the mechanism behind food functionality, there is an increasing interest in converging disciplines dealing with monitoring, modeling, and analysis of complex biological systems. The development of wearable devices, which has started in early 2000, has actually experienced a steep increase in the last 5 years, accounting for more than 5,000 published patent applications (Mück, Ünal, Butt, & Yetisen, 2019). Wearable devices, including smartwatches (*e.g.*, Apple Watch), glasses (*e.g.*, Google Glass), fitness bands (*e.g.*, FitBit), connected apparel (*e.g.*, Sensoria), are becoming particularly popular to monitor continuously the health status (Piwek, Ellis, Andrews, & Joinson, 2016). The presence of biosensors embedded in electronic tattoos, patches, prosthetics, textiles, wristbands, and contact lenses give direct access to personal analytics, including physical activity and posture, calorific expenditure, skin/core temperature, heart rate, respiratory parameters, oxygen consumption, electrocardiography (ECG), and sleep duration and quality (Yetisen, Martinez-Hurtado, Ünal, Khademhosseini, & Butt, 2018). This information can facilitate preventive care and aid in the management of non-communicable diseases. For chronic food-related diseases, wearables could be applied as a novel tool to assess food functionality *in vivo* through real-time detailed data (Piwek et al., 2016). In particular, some of these systems can be inserted in the oral cavity to measure food intake for controlling the eating behavior and provide data directly related to chronic diseases (Lee et al., 2018). In this way, patient progress could be monitored to assess the efficacy of applied interventions, which in turn can be personalized, thanks to the emerging scientific field of nutrigenomics (German, Zivkovic, Dallas, & Smilowitz, 2011). Indeed, when dealing with functional food development, personalized nutrition is hardly achievable in the narrower sense, *i.e.*, counting on individual characteristics to produce a dedicated output, as the cycle could not be applied to single cases. However, personalized nutrition can also be referred to the delivery of products to consumer categories having specific dietary requirements (Chaudharya et al., 2021).

In this terms, personalized nutrition could be exploited to categorize the population based on individual requirements, thus identifying consumer clusters to be addressed while developing functional foods.

Although several studies have attempted automating dietary monitoring using wearable devices, several issues remain opened (Prioleau, Ii, Member, & Paper, 2017). Few studies are available on the reliability of acquired data, as the major hindrance lies in the interference of signals. In addition, the output interpretation depends on the understanding of the analyzed biological system, requiring a deep knowledge of the mechanisms underlying targeted functionality.

2.4. *Market delivery: Last but not least, the consumer response*

The successful delivery of a newly developed functional food on the market is affected not only by the carried health benefit but strictly depends on several other factors. Besides the typical quality markers (*e. g.,* taste, convenience, price), these include market positioning and functionality communication (Kaur & Das, 2011).

Settling the most effective communication strategy should consider many determinants affecting the decision to accept or reject a new food (Giordano, Clodoveo, De Gennaro, & Corbo, 2018).

These include not only the product features, but also and most importantly the individual characteristics.

Product features represent primary factors leading consumption decisions and can be distinguished into intrinsic, *e.g.,* presence of health-promoting compounds, and extrinsic attributes, *e.g.,* package, brand, label claims (Bimbo et al., 2017). As product development is mostly focused on the intrinsic ones, a mismatch between the functional food features and consumer expectations may thus occur (Van Kleef, Van Trijp, & Luning, 2005), bringing about a high risk of product failure (Research and Markets, 2015). In fact, also the extrinsic attributes, among which labelled information, and especially nutritional and health claims, is the most crucial, may substantially contribute to the success of new functional food (Siegrist, Stampfli, & Kastenholz, 2008). However, these are often formulated in complicated terms, being less effective, as consumers cannot recognize the benefits nor their importance (Siegrist et al., 2008).

Individual characteristics represent another group of primary factors driving consumption intention. These are represented not only by demographic characteristics, such as gender and age, but when dealing with functional food include the knowledge about the health-diet relationship and the interest for maintaining a health status. In this regard, only a niche of the targeted consumer is aware of health-related benefits, making necessary further efforts to also reach the other consumers (Giordano et al., 2018). The psychological factors must also be included among individual characteristics. In fact, the consumption intention is based on two coexisting and opposite tendencies: the curiosity about novelty, called *neophilia*, and the prudence towards new and potentially dangerous products, namely *neophobia* (Fischler, 1988). Communication should thus find the optimal strategy to induce curiosity while preventing fear (Giordano et al., 2018), keeping an eye not only on the rational aspects, but also on the emotional perspective.

Pushing consumption intention becomes even more complicated when the primary factors must be matched with the secondary ones. These include risk perception, subjective norms, and cost/benefit balance.

A deep knowledge of the factors determining consumption decision is crucial to successfully drive the development of new products. To this purpose, consumer research must be applied by means of different tools (Van Kleef et al., 2005). These include qualitative methods (*e.g.*, focus group), which are indicated during the definition of labeled information, and quantitative ones (*e.g.*, conjoint analysis), suited to test the efficacy of claims (Van Kleef et al., 2005).

Although the availability of many tools, the literature reports contradictory results. According to some authors (Bimbo et al., 2017; Van Kleef et al., 2005), consumers prefer specific health claims, dealing with the prevention or risk reduction of a disease (*e.g.*, heart failure) more than general nutritional ones dealing with wellbeing (*e.g.*, energy-boosting). On the contrary, Schnettler et al. (2019) found consumers to be more interested in generic nutritional labeling (*e.g.*, source of fiber). Contradictory results may depend on the different decision patterns applied to different product categories (Bimbo et al., 2017), suggesting the need for a tailor-made product assessment. This would provide an essential tool to implement an approach to innovation that is not just product-driven but consumer-oriented instead (Van Kleef et al., 2005). In fact, consumers are currently only involved in the prototyping and launching phases, but they could potentially play a crucial role in the previous ones, namely idea generation and concept design (Busse & Siebert, 2018).

3. The “functional food development cycle”

Like other innovation systems, functional food development is a non-linear, multiple-actor process (Freeman, 1987). It involves several stakeholders, including food technologists, nutritionists, clinicians, marketing experts, as well as consumers, with different interests, perspectives, and skills that can hardly be matched. An attempt to provide a multidisciplinary tool for food design was presented by Sijtsema, Fogliano, and Hageman (2020), *i.e.*, the Circular Food Design. Such an approach is particularly focused on consumer, pointing out the importance of her/his involvement at all stages of food design from opportunity identification to market delivery.

Besides consumers, also the other actors taking part to functional food development should be directly or indirectly involved in all the required steps. Yet, merging all these different viewpoints probably represents the hardest task for manufacturers dealing with functional food development (Moors, 2012). Still, an integrated outcome is essential to successfully deliver a new functional food on the market. This principle actually lays the foundation for the circular and iterative approach here proposed as the “Functional Food Development Cycle”, consisting of sequential and interconnected steps (Fig. 3).

The preliminary step is called definition and implies selecting the disease to be addressed by the functional food, as well as choosing the most suitable food matrix and bioactive ingredient. As highlighted by Sijtsema et al. (2020), already during opportunity identification the

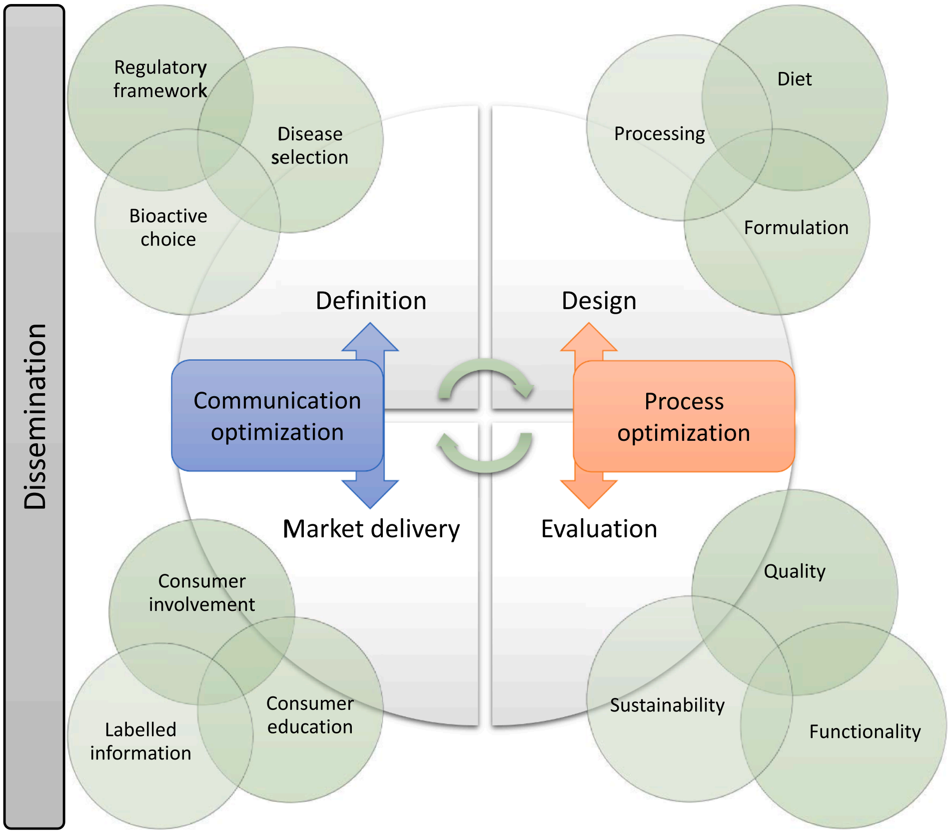

Fig. 3. Functional Food Development Cycle.

consumer must be involved. When dealing with the definition step of functional food development it is thus necessary to have clear in mind the group of consumers to be targeted and their requirements, paying attention to perceptions, barriers, needs and wishes.

All these activities should fit in a regulatory framework, including functional food definition, delineated by the legislator, which outlines and implements policies to influence the innovation process and guarantee the operability of the functional food market (Moors, 2012). To lay down definitions and rules for health claims, the legislator collects technical information from food technologists, clinicians, and nutritionists. Besides a general univocal definition of functional food is required, also more specific operative definitions could be descended from it, based on stakeholder requirements and taking into account the perspective of each involved discipline, to make clear and usable the concept for all the actors involved, ultimately making functional food development effective.

Once the target is known, it is possible to manage the second step, *i.e.,* functional food design. This represents the technological core of functional food development and requires selecting the most appropriate intervention, including dietary approaches, as well as processing and formulation. Food technologists play a crucial role in functional food design due to their technical skills, *i.e.,* knowledge of food matrix and technological interventions (Bigliardi & Galati, 2013; Granato, Nunes, & Barba, 2017). During functional food design, not only the targeted disease but also the targeted consumer group and its requirements, including the sensory ones but also habits and preferences, must be taken into account to develop successful products (Sijtsema et al., 2020).

The third step, *i.e.,* evaluation, is then crucial to assess the efficacy of technological interventions towards functionality, while guaranteeing the accomplishment of quality requirements, which are assessed by the food technologist. On the other hand, the efficacy evaluation is commonly a task of clinicians and nutritionists, particularly when dealing with *in vivo* trials (Granato et al., 2017).

Indeed, product design that is carried out by food technologists, and efficacy evaluation, which relies on the activity of nutritionists and clinicians, represent the key technological steps in functional food development and merging them is essential. However, this is not straightforward as it is difficult to find a common language among the actors involved. In fact, when the technological viewpoint prevails, the physiological effect (*i.e.,* digestion) is barely considered, and the targeted bioactivity is evaluated considering the undigested food matrix. Conversely, when the nutritional viewpoint prevails, the effect of digestion on bioactive compounds is assessed mostly on simplified model systems, thus not considering the technological history of food. This approach seems disjoint as it does not consider the complexity of the food matrix, the potential interactions occurring among food components, the effect of technological interventions, nor the actual bioactivity upon digestion, resulting in a gap between the technological and the nutritional viewpoints. Indeed, such a compartmentalized approach leads to misinterpretations. For instance, dealing with apple juice pasteurization, we observed a significant increase in the phenolic content when an unconventional process (*i.e.,* ultrasound-assisted) was applied instead of the conventional (*i.e.,* thermal) one. Even so, when digestion was simulated, differences induced by the technological intervention were flattened (Alongi, Verardo, et al., 2019). Analogous results were obtained in the case of coffee roasted to different intensities (Alongi, Frías Celayeta, et al., 2020). To bridge the gap between the technological and the nutritional viewpoints, an integrated approach to design and evaluate functional food should be considered (Fig. 4). Based on this approach, the effect of technological interventions, including dietary approaches, formulation and processing, should first be assessed in terms of safety and quality (*i.e.,* physical, chemical, and sensory properties). Technological interventions should be carried out to concomitantly boost food functionality while maintaining or improving product quality, as consumers are not willing to compromise the taste on behalf of health benefits (Lähteenmäki, 2013). Once quality requirements are satisfied, the impact on functionality should be assessed. Merging these outcomes in a process optimization perspective is then pivotal to develop effective functional foods.

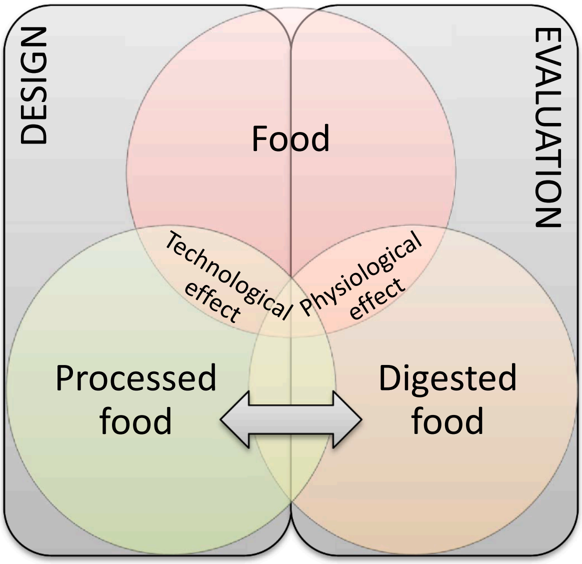

Fig. 4. Insight into the integrated approach to the key technological steps, *i.e.*, design and evaluation, of the Functional Food Development Cycle.

Nonetheless, market delivery is essential for the success of the newly developed functional food, and requires a fourth step, in which consumer education and labelled information play a pivotal role. To this purpose, the marketing expert collects information on consumer attitude and acceptability towards functional foods through marketing surveys. This information should be merged with social and cultural aspects by an anthropological approach, with special attention to food *neophilia* and *neophobia* (Van Kleef et al., 2005). Although during this step consumers mainly represent the observation subject (Van Kleef et al., 2005), communication strategies should be optimized, and besides accomplishing claim regulation (Siró et al., 2008), should help collecting information about consumer needs. This would represent an input for regulatory bodies to selectively drive the development of functional food within a virtuous cycle, including a deeper involvement of consumers in functional food development to lead the innovation process through a consumer need-driven approach (Busse & Siebert, 2018).

Being the approach here proposed (Fig. 3) an iterative cycle, consumer inputs (*i.e.*, requirements) drive consumer outputs (*i.e.*, attitude). In other words, the consumer requirements that are considered during definition and design are deduced from the output of market delivery, *i.e.*, consumer attitude. The latter in turn results from the consumer reaction to a functional food deriving from the previous cycle round, which has been developed based on previously outlined requirements, as in subsequent upward turns of a spiral.

Indeed, being functional food consumption associated with health-related benefits, also clinicians, together with nutritionists, are key actors dealing with consumers (Bigliardi & Galati, 2013). Besides defining nutritional needs, they should clearly outline to consumers the benefits deriving from the consumption of functional food, ultimately driving consumer choices.

As outlined by describing each step, functional food development requires a collaborative cross-network among stakeholders at all stages (Busse & Siebert, 2018). In light of this, functional food development cannot be referred to as a linear process starting from definition, going through design and evaluation, finally ending with market delivery. On the contrary, a circular approach, considering during all steps the contribution and the viewpoints from the other ones back and forward becomes crucial, particularly when dealing with health.

To this purpose, dissemination is a cross-cutting activity essential to merge each step of the cycle, thus guaranteeing its effective functioning (Fig. 3). In fact, dissemination represents the process of making available knowledge to stakeholders and the widest audience and can be therefore decoupled into two aspects. First, it is intended as informing and educating the public about the functional food issue. Overall, consumers demonstrate a high awareness, but a low level of actual knowledge, leading to high levels of concern that hinders the acceptance of functional foods especially when obtained by applying emerging technologies (Giordano et al., 2018). Educating consumers is crucial to increase the actual knowledge about newly developed functional food and the benefits associated with their consumption (Bech-Larsen & Scholderer, 2007). In fact, it is essential to carry out dedicated actions because, unlike sensory traits, consumers cannot directly perceive the benefits of the product (Siró et al., 2008). These actions may include educational activities in the schools, awareness-raising campaigns in public places, but could also take advantage of labeled information (Lähteenmäki, 2013). This should be intelligible by the average consumers, making them correctly understanding the information behind claims. The other dissemination task consists of raising stakeholder awareness. It relies on the exchange of information about the ongoing research and current development in the functional food field among professionals, such as scientists and researchers, health professionals, nutritionists, food technologists, and marketing experts (Gur et al., 2018). Dissemination can be carried out in conventional ways, such as conferences, workshops, and scientific publications, but also through emerging channels, including the social network (Cooper, 2014). The required effort is to find a common language among the experts involved in the cycle, to draw an exhaustive picture of the state of the art, and to identify the most effective strategy to be followed for functional food development. To do this, it is crucial to identify the factors influencing the communication among the actors involved in the development of new products. Generally, industries mostly focus on the internal communication between marketing and technology functions, but Jacobsen et al. (2014) highlighted the importance of filling the communication gap with external partners as well. In the context of functional food development, these include the legislator, nutritionists and clinicians, as well as the consumer.

Besides being an object of dissemination, during market delivery, the consumer can also play an active role in that. In fact, even though generally consumers are only involved in the prototyping and launching phases, they could potentially play a crucial role in the idea generation and concept design (Busse & Siebert, 2018). Indeed, a deeper involvement of consumers in functional food development would help the other stakeholders in developing customized and effective communication strategies.

4. Healthy and sustainable: The future of “functionable” food

During the last years, the need to redefine the boundaries of food production has come to light. We are currently dealing with major and opposite issues. On one hand, the exponential increase in worldwide population is posing at risk food security (Godfray et al., 2010). On the other hand, we are facing a dramatic increase in non-communicable diseases, caused by excessive food intake or unbalanced diets (WHO, 2014). To handle these trends, it is necessary to look in a more integrated way at the current food production (De Vries, Axelos, Sarni-Manchado, & O’Donohue, 2018). In other words, it is necessary to think in terms of *food system*. This is defined as a framework considering all the elements (*i.e.,* environment, people, inputs, outputs, processes, infrastructures, institutions) and activities related to primary production, processing, distribution, preparation, and consumption of food, also considering the socio-economic and environmental outcomes of these activities (Perrot et al., 2016). Thus, developing healthy products requires food product design to operate within environmental and health-related boundaries, to deliver on the market healthy and at the same time sustainable food (Willett et al., 2019).

To this purpose, it is essential to establish some limits. First, avoiding the unnecessary exploitation of resources, which is possible by applying different strategies, including consuming low density-high satiating food, and replacing traditional protein sources (*i.e.*, dairy products, conventional meat, eggs) with more sustainable ones, including vegetables, *e.g.*, legumes and algae (Bessada, Barreira, & Oliveira, 2019; Bleakley & Hayes, 2017), fungi, *e.g.*, Quorn® (Schweiggert-Weisz, Eisner, Bader-Mittermaier, & Osen, 2020) and animal sources, *e.g.*, insects and cultivated meat (Baiano, 2020; Tomiyama et al., 2020). Second, efficiently transform and use resources, that is feasible through targeted and eco-efficient processes. Lastly, valorizing processing discards, by applying the food waste pyramid (Manzocco, Alongi, Sillani, & Nicoli, 2016; Plazzotta, Manzocco, & Nicoli, 2017).

In other words, the functional food development cycle here proposed needs be framed in a wider background looking at its overall feasibility, which includes evaluating its sustainability (Fig. 3). Such an approach is in line with the Agenda 2030 of the European Union, in which the Sustainable Development Goals, and in particular the “Good health and well-being” and the “Zero hunger” goals, highlight the importance of a sustainable diet not only from a nutritional viewpoint but also for planet health (European Commission, 2019). Indeed, these requirements should match also economic objectives. These were recently demonstrated to be possibly maximized concomitantly with the environmental ones, by applying innovative valorization strategies such as the production of a functional flour from lettuce waste (Plazzotta, Cottes, Simeoni, & Manzocco, 2020). Ultimately, research urgently needs to focus on the application of conventional and unconventional processes, and on the exploitation of processing wastes as bioactive ingredients to increase the environmental and economic sustainability of food production, while enhancing its functionality (Van Der Goot et al., 2016), to obtain what can be called a “functionable” food.

5. Research on “functionable” food: what’s next?

Based on previous considerations, moving a step forward into implementing the functional food development cycle through a holistic approach appears crucial. Accomplishing this comprehensive aim requires pursuing specific ones, such as:

- Filling the gap between the key technological steps of functional food development, *i.e.,* design and functionality evaluation: merging these viewpoints, concomitantly considering the technological history of a food product and the changes induced by the physiological mechanisms upon its ingestion, is essential to avoid result misinterpretation and represents the foundation on which strong and reliable knowledge about food functionality can be built.
- Studying the complex matrix instead of bioactive extracts: exploring the functional properties of the whole food leads to different results as compared to those available in the literature on simplified model systems that generally consider bioactive compound extracts. The whole matrix plays a crucial role due to interactions occurring among the different components.
- Identifying bioactivity indicators, understanding the mechanisms behind functionality, and defining the targeted bioactivity: indicators of food functionality should be considered in the light of overall available data to prevent misinterpretation. For instance, the bioaccessibility of a bioactive compound is often regarded as the main indicator, but it provides only partial information. On the contrary, identifying its mechanism and defining the desired concentration at the intestinal level, as well as in the target organs and tissues, would help develop the proper technological intervention to drive functionality through food design by a customized approach.
- Understanding the mechanisms underlying food-drug interactions: in a real-life setting, patients take oral drugs with food. However, no

detailed information about the interactions occurring between food and drug is available, nor the knowledge of the mechanisms behind it. Indeed, pharmacodynamics and pharmacokinetic data regarding food-drug interactions could pave the way for adjusting drug dosage accordingly to the co-ingested food, possibly exploiting the bioactivity of compounds contained in functional food.
- Increasing the sustainability of functional food development, by using vegetable processing wastes, as well as alternatives to traditional protein sources, as innovative functional ingredients.
- Investigating consumer attitude towards the consumption of functional food formulated with vegetable processing waste: marketing and anthropological methodologies should be applied to define the most effective strategies to drive consumer choices.

6. Implications of "functionable" food: what's beyond?

Once the functional food development cycle has been implemented within the new boundaries in which the food system is required to operate, "functionable" food, able to prevent specific diseases while increasing the sustainability of food production, will be obtained. Besides the direct outcome, several impacts are expected in different fields, by affecting all the stakeholders involved in "functionable" food development and consumption:

- Research and education: improving the knowledge about the interconnection among food properties, biological functions, sustainability, and consumer perception will increase the awareness of the importance of producing and consuming functional food that is also sustainable. Understanding the interplay among food design, functionality, and sustainability will increase scientific knowledge regarding the formulation and processing of functional and concomitantly sustainable food. Studying consumer behavior and attitude will help to develop adequate strategies to communicate product innovation correctly and effectively, through health and sustainability claims, facilitating consumers to select food that fits into a healthy and sustainable diet.
- Economics: optimizing functional food development will incite producers to manufacture high-quality, healthier, and sustainable food that fulfills consumer and market expectations, increasing the innovative potential and competitiveness of the food industry. In addition, the opportunity to valorize industrial waste as a functional ingredient will help reducing waste management costs while benefiting from the generation of value-added output, representing an always available, cheap, and bioactive-compound-rich ingredient.
- Public health: once food functionality has been improved, considering its consumption in a real-life setting and bearing in mind the eventual food-drug interactions, health workers will be advocated to promote among patients healthy eating habits as the first tool to face non-communicable chronic diseases. This will not only improve population wellbeing but also reduce the healthcare costs required to manage non-communicable chronic diseases, by reducing the need for pharmacological interventions. This approach should be favored by a revision and an update of the current health and food policies, possibly implementing a dedicated regulatory framework for functional food.
- Environment: promoting the valorization of industrial waste will reduce the amount of food wasted upon industrial processes. The current waste management routes should be redefined by integrating waste valorization strategies, *e.g.,* implementing an industrial park-oriented view approach to minimize waste transport. Also in this case, the policy regarding waste treatment and disposal should be revised and updated, by implementing a dedicated regulatory framework for the reuse of discards as functional ingredients. On the other hand, the use of alternative protein sources would reduce the environmental impact associated with the consumption of conventional protein sources, such as the threaten to biodiversity, the excessive soil exploitation, and the production of greenhouse gases.

Author contributions

MA and MA contributed to the conceptualization and design of the proposed approach and the writing of the manuscript.

Ethics statement

The present research did not include any human subjects and animal experiments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Adiwidjaja, J., McLachlan, A. J., & Boddy, A. V. (2017). Curcumin as a clinically-promising anti-cancer agent: Pharmacokinetics and drug interactions. *Expert Opinion on Drug Metabolism & Toxicology, 13*, 953–972.

Albassam, A. A., & Markowitz, J. S. (2017). An appraisal of drug-drug interactions with green tea (*Camellia sinensis*). *Planta Medica, 83*, 496–508.

Alongi, M., & Anese, M. (2018). Effect of coffee roasting on *in vitro* α-glucosidase activity: Inhibition and mechanism of action. *Food Research International, 111*, 480–487.

Alongi, M., Calligaris, S., & Anese, M. (2019). Fat concentration and high-pressure homogenization affect chlorogenic acid bioaccessibility and α-glucosidase inhibitory capacity of milk-based coffee beverages. *Journal of Functional Foods, 58*, 130–137.

Alongi, M., Frías Celayeta, J. M., Vriz, R., Kinsella, G. K., Rulikowska, A., & Anese, M. (2020). *In vitro* digestion nullified the differences triggered by roasting in phenolic composition and α-glucosidase inhibitory capacity of coffee. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2020.128289.

Alongi, M., Melchior, S., & Anese, M. (2019). Reducing the glycemic index of short dough biscuits by using apple pomace as a functional ingredient. *LWT - Food Science and Technology, 100*, 300–305.

Alongi, M., Verardo, G., Gorassini, A., & Anese, M. (2018). Effect of pasteurization on *in vitro* α-glucosidase inhibitory activity of apple juice. *LWT - Food Science and Technology, 98*, 366–371.

Alongi, M., Verardo, G., Gorassini, A., Lemos, M. A., Hungerford, G., Cortella, G., & Anese, M. (2019). Phenolic content and potential bioactivity of apple juice as affected by thermal and ultrasound pasteurization. *Food & Function, 10*, 7366–7378.

Alongi, M., Verardo, G., Gorassini, A., Sillani, S., & Anese, M. (2020). Reformulation and food combination as strategies to modulate glycaemia: The case of apple pomace containing biscuits administered with apple juice to healthy rats. *International Journal of Food Sciences and Nutrition, 28*, 1–10.

Alu'Datt, M. H., Rababah, T., Alhamad, M. N., Al-Rabadi, G. J., Tranchant, C. C., Almajwal, A., & Alli, I. (2019). Occurrence, types, properties and interactions of phenolic compounds with other food constituents in oil-bearing plants. *Critical Reviews in Food Science and Nutrition, 58*, 3209–3218.

Alu'Datt, M. H., Rababah, T., Ereifej, K., Gammoh, S., Alhamad, M. N., Mhaidat, N., & Alnaiemi, O. J. (2014). Investigation of natural lipid-phenolic interactions on biological properties of virgin olive oil. *Journal of Agricultural and Food Chemistry, 62*, 11967–11975.

Bahramsoltani, R., Rahimi, R., & Farzaei, M. H. (2017). Pharmacokinetic interactions of curcuminoids with conventional drugs: A review. *Journal of Ethnopharmacology, 209*, 1–12.

Baiano, A. (2020). Edible insects: An overview on nutritional characteristics, safety, farming, production technologies, regulatory framework, and socio-economic and ethical implications. *Trends in Food Science and Technology, 100*, 35–50.

Bech-Larsen, T., & Scholderer, J. (2007). Functional foods in Europe: Consumer research, market experiences and regulatory aspects. *Trends in Food Science and Technology, 18*, 231–234.

Belayneh, A., & Molla, F. (2020). The effect of coffee on pharmacokinetic properties of drugs: A review. *BioMed Research International*. https://doi.org/10.1155/2020/7909703.

Bessada, S. M. F., Barreira, J. C. M., & Oliveira, M. B. P. P. (2019). Pulses and food security: Dietary protein, digestibility, bioactive and functional properties. *Trends in Food Science and Technology, 93*, 53–68.

Bigliardi, B., & Galati, F. (2013). Innovation trends in the food industry: The case of functional foods. *Trends in Food Science and Technology, 31*, 118–129.

Bimbo, F., Bonanno, A., Nocella, G., Viscecchia, R., Nardone, G., De Devitiis, B., & Carlucci, D. (2017). Consumers' acceptance and preferences for nutrition-modified and functional dairy products: A systematic review. *Appetite, 113*, 141–154.

Bleakley, S., & Hayes, M. (2017). Algal proteins: Extraction, application, and challenges concerning production. *Foods, 6*, 33–67.

Bleiel, J. (2010). Functional foods from the perspective of the consumer: How to make it a success? *International Dairy Journal, 20*, 303–306.

Boath, A. S., Stewart, D., & McDougall, G. J. (2012). Berry components inhibit α-glucosidase *in vitro*: Synergies between acarbose and polyphenols from black currant and rowanberry. *Food Chemistry, 135*, 929–936.

Boyer, J., & Liu, R. H. (2004). Apple phytochemicals and their health benefits. *Nutrition Journal, 3*, 1–15.

Brodkorb, A., Egger, L., Alminger, M., Alvito, P., Assunção, R., Ballance, S., … Carrière, F. (2019). *INFOGEST static in vitro simulation of gastrointestinal food digestion, 14*, 991–1014.

Brower, V. (1998). Nutraceuticals: Poisoned for a healthy slice of the healthcare market? *Nature Biotechnology, 16*, 728–731.

Budryn, G., Zakłos-Szyda, M., Zaczyńska, D., Żyżelewicz, D., Grzelczyk, J., Zduńczyk, Z., & Juśkiewicz, J. (2017). Green and roasted coffee extracts as antioxidants in βTC3 cells with induced oxidative stress and lipid accumulation inhibitors in 3T3L1 cells, and their bioactivity in rats fed high fat diet. *European Food Research and Technology, 243*, 1323–1334.

Bungau, S., Abdel-Daim, M. M., Tit, D. M., Ghanem, E., Sato, S., Maruyama-Inoue, M., … Kadonosono, K. (2019). Health benefits of polyphenols and carotenoids in age-related eye diseases. *Oxidative Medicine and Cellular Longevity*. https://doi.org/10.1155/2019/9783429.

Busse, M., & Siebert, R. (2018). The role of consumers in food innovation processes. *European Journal of Innovation Management, 21*, 20–43.

Calligaris, S., Alongi, M., Lucci, P., & Anese, M. (2020). Effect of different oleogelators on lipolysis and curcuminoid bioaccessibility upon *in vitro* digestion of sunflower oil oleogels. *Food Chemistry, 314*, 126–146.

Castro-Acosta, M. L., Smith, L., Miller, R. J., McCarthy, D. I., Farrimond, J. A., & Hall, W. L. (2016). Drinks containing anthocyanin-rich blackcurrant extract decrease postprandial blood glucose, insulin and incretin concentrations. *Journal of Nutritional Biochemistry, 38*, 154–161.

Chaudharya, N., Kumarb, V., Sangwanc, P., Pantd, N. C., Saxenae, A., Joshif, S., & Yadav, A. N. (2021). Personalized nutrition and -omics. *Comprehensive Foodomics, 3*, 495–507.

Cooper, A. (2014). The use of online strategies and social media for research dissemination in education. *Education Policy Analysis Archives, 22*, 2–27.

Day, L., Seymour, R. B., Pitts, K. F., Konczak, I., & Lundin, L. (2009). Incorporation of functional ingredients into foods. *Trends in Food Science and Technology, 20*, 388–395.

De Felice, S. (1995). The nutraceutical revolution: Its impact on food industry R&D. *Trends in Food Science and Technology, 1*, 59–61.

De Vries, H., Axelos, M. A. V., Sarni-Manchado, P., & O'Donohue, M. (2018). Meeting new challenges in food science technology: The development of complex systems approach for food and biobased research. *Innovative Food Science and Emerging Technologies, 46*, 1–6.

Diplock, A. T., Aggett, P. J., Ashwel, M., Bornet, F., Fern, E. B., & Roberfroid, M. B. (1999). Scientific concepts of functional foods in Europe: Consensus document. *British Journal of Nutrition, 81*, 13–14.

Dupont, D., Alric, M., Bornhorst, G., Cueva, C., Deglaire, A., Denis, S., … Deglaire, A. (2018). Can dynamic *in vitro* digestion systems mimic the physiological reality? *Critical Reviews in Food Science and Nutrition, 8398*, 1–17.

European Commission. (2019). Reflection paper towards a sustainable Europe by 2030.

Ferruzzi, M. G. (2010). The influence of beverage composition on delivery of phenolic compounds from coffee and tea. *Physiology & Behavior, 100*, 33–41.

Fischler, C. (1988). Food, self and identity. *Social Science Information, 27*, 275–292.

Freeman, C. (1987). *Technology policy and economic performance*. London, UK: Pinter.

German, J. B., Zivkovic, A. M., Dallas, D. C., & Smilowitz, J. T. (2011). Nutrigenomics and personalized diets: What will they mean for food? *Annual Review of Food Science and Technology, 2*, 97–123.

Giordano, S., Clodoveo, M. L., De Gennaro, B., & Corbo, F. (2018). Factors determining neophobia and neophilia with regard to new technologies applied to the food sector: A systematic review. *International Journal of Gastronomy and Food Science, 11*, 1–19.

Godfray, H. C. J., Beddington, J. R., Crute, I. R., Haddad, L., Lawrence, D., Muir, J. F., … Toulmin, C. (2010). Food security: The challenge of feeding 9 billion people. *Science, 327*, 812–818.

Granato, D., Nunes, D. S., & Barba, F. J. (2017). An integrated strategy between food chemistry, biology, nutrition, pharmacology, and statistics in the development of functional foods: A proposal. *Trends in Food Science and Technology, 62*, 13–22.

Grand View Research. (2019a). Functional foods market size, share & trends - Analysis report by ingredient, by product, by application, and segment forecasts, 2019-2025. https://www.grandviewresearch.com/industry-analysis/functional-food-market.

Grand View Research. (2019b). Functional foods market worth $275.7 billion by 2025. https://www.grandviewresearch.com/press-release/global-functional-foods-market.

Guo, Q., Ye, A., Bellissimo, N., Singh, H., & Rousseau, D. (2017). Modulating fat digestion through food structure design. *Progress in Lipid Research, 68*, 109–118.

Gur, J., Mawuntu, M., & Martirosyan, D. M. (2018). FFC's advancement of functional food definition. *Functional Foods in Health and Disease, 8*, 385–397.

Hardy, G. (2000). Nutraceuticals and functional foods: Introduction and meaning. *Nutrition, 16*, 688–689.

Heaney, R. P. (2001). Factors influencing the measurement of bioavailability, taking calcium as a model. *The Journal of Nutrition, 131*, 1344–1348.

Hur, S. J., Lim, B. O., Decker, E. A., & McClements, D. J. (2011). *In vitro* human digestion models for food applications. *Food Chemistry, 125*, 1–12.

IFT. (2005). Functional foods: Opportunities and challenges.

Jacobs, D. R., Tapsell, L. C., & Temple, N. J. (2011). Food synergy: The key to balancing the nutrition effort. *Public Health Reviews, 33*, 507–529.

Jacobsen, L. F., Grunert, K. G., Søndergaard, H. A., Steenbekkers, B., Dekker, M., & Lähteenmäki, L. (2014). Improving internal communication between marketing and technology functions for successful new food product development. *Trends in Food Science and Technology, 37*, 106–114.

Jones, P. J., & Jew, S. (2007). Functional food development: Concept to reality. *Trends in Food Science and Technology, 18*, 387–390.

Kaur, S., & Das, M. (2011). Functional foods: An overview. *Food Science and Biotechnology, 20*, 861–875.

Khuda, F., Ovais, M., Zakiullah, Khan, A., Ali, G., Ullah, S., … Qadar, N. A. (2019). Drug-food interactions of commonly available juices of Pakistan. *Pakistan Journal of Pharmaceutical Sciences, 32*, 2189–2196.

Konishi, Y., & Kobayashi, S. (2004). Transepithelial transport of chlorogenic acid, caffeic acid, and their colonic metabolites in intestinal Caco-2 cell monolayers. *Journal of Agricultural and Food Chemistry, 52*, 2518–2526.

Koziolek, M., Alcaro, S., Augustijns, P., Basit, A. W., Grimm, M., Hens, B., … Corsetti, M. (2019). The mechanisms of pharmacokinetic food-drug interactions – A perspective from the UNGAP group. *European Journal of Pharmaceutical Sciences, 134*, 31–59.

Lähteenmäki, L. (2013). Claiming health in food products. *Food Quality and Preference, 27*, 196–201.

Lamothe, S., Azimy, N., Bazinet, L., Couillard, C., & Britten, M. (2014). Interaction of green tea polyphenols with dairy matrices in a simulated gastrointestinal environment. *Food and Function, 5*, 2621–2631.

Lee, Y., Howe, C., Mishra, S., Sup, D., Mahmood, M., Piper, M., & Kim, Y. (2018). Wireless, intraoral hybrid electronics for real-time quantification of sodium intake toward hypertension management. *Proceedings of the National Academy of Sciences, 115*, 5377–5382.

Luo, X., Arcot, J., Gill, T., Louie, J. C. Y., & Rangan, A. (2019). A review of food reformulation of baked products to reduce added sugar intake. *Trends in Food Science and Technology, 86*, 412–425.

Manzocco, L., Alongi, M., Sillani, S., & Nicoli, M. C. (2016). Technological and consumer strategies to tackle food wasting. *Food Engineering Reviews, 8*, 457–467.

Mao, L., Lu, Y., Cui, M., Miao, S., & Gao, Y. (2019). Design of gel structures in water and oil phases for improved delivery of bioactive food ingredients. *Critical Reviews in Food Science and Nutrition*. https://doi.org/10.1080/10408398.2019.1587737.

Martinez-Saez, N., Tamargo, A., Domínguez, I., Rebollo-hernanz, M., Mesías, M., Morales, F. J., … del Castillo, D. M. (2017). Use of spent coffee grounds as food ingredient in bakery products. *Food Chemistry, 216*, 114–122.

Martins, A. J., Vicente, A. A., Cunha, R. L., & Cerqueira, M. A. (2018). Edible oleogels: An opportunity for fat replacement in foods. *Food and Function, 9*, 758–773.

Martirosyan, D. M., & Prasad, C. (2009). Functional foods for chronic diseases: Diabetes and related diseases. *In The 6th International Conference proceedings*.

Martirosyan, D. M., & Singh, J. (2015). A new definition of functional food by FFC: What makes a new definition of functional food unique? *Functional Foods in Health and Disease, 5*, 209–223.

McClements, D. J. (2009). Structural design principles for improved food performance: nanolaminated biopolymer structures in foods. In American Chemical Society (Ed.), Micro/Nanoencapsulation of Active Food Ingredients (Vol. 1007, pp. 3–34). Washington, DC.

McClements, D. J., & Li, Y. (2010). Structured emulsion-based delivery systems: Controlling the digestion and release of lipophilic food components. *Advances in Colloid and Interface Science, 159*, 213–228.

McClements, D. J., Zou, L., Zhang, R., Salvia-Trujillo, L., Kumosani, T., & Xiao, H. (2015). Enhancing nutraceutical performance using excipient foods: Designing food structures and compositions to increase bioavailability. *Comprehensive Reviews in Food Science and Food Safety, 14*, 824–847.

Merriam-Webster Online Dictionary. (2015). https://www.merriam-webster.com/.

Minekus, M., Alminger, M., Alvito, P., Ballance, S., Bohn, T., Bourlieu, C., … Brodkorb, A. (2014). A standardised static *in vitro* digestion method suitable for food – An international consensus. *Food & Function, 5*, 1113–1124.

Moors, E. H. M. (2012). Functional foods: Regulation and innovations in the EU. *Innovation - The European Journal of Social Science Research, 25*, 424–440.

Motilva, M.-J., Serra, A., & Rubio, L. (2015). Nutrikinetic studies of food bioactive compounds: From *in vitro* to *in vivo* approaches. *International Journal of Food Science and Nutrition, 66*, S41–S52.

Mück, J. E., Ünal, B., Butt, H., & Yetisen, A. K. (2019). Market and patent analyses of wearables in medicine. *Trends in Biotechnology, 37*, 563–566.

Mulet-Cabero, A. I., Egger, L., Portmann, R., Ménard, O., Marze, S., Minekus, M., … Mackie, A. (2020). A standardised semi-dynamic: *In vitro* digestion method suitable for food – An international consensus. *Food and Function, 11*, 1702–1720.

Ni, M., Hu, X., Gong, D., & Zhang, G. (2020). Inhibitory mechanism of vitexin on α-glucosidase and its synergy with acarbose. *Food Hydrocolloids, 105*, Article 105824.

O'Shea, J. P., Holm, R., O'Driscoll, C. M., & Griffin, B. T. (2019). Food for thought: Formulating away the food effect – a PEARRL review. *Journal of Pharmacy and Pharmacology, 71*, 510–535.

Pap, N., Pongrácz, E., Jaakkola, M., Tolonen, T., Virtanen, V., Turkki, A., … Keiski, R. L. (2010). The effect of pre-treatment on the anthocyanin and flavonol content of black currant juice (*Ribes nigrum L.*) in concentration by reverse osmosis. *Journal of Food Engineering, 98*, 429–436.

Parada, J., & Aguilera, J. M. (2007). Food microstructure affects the bioavailability of several nutrients. *Journal of Food Science, 72*, 21–32.

Perrot, N., De Vries, H., Lutton, E., van Mil, H. G. J., Donner, M., Tonda, A., … Axelos, M. A. V. (2016). Some remarks on computational approaches towards sustainable complex agri-food systems. *Trends in Food Science and Technology, 48*, 88–101.

Piwek, L., Ellis, D. A., Andrews, S., & Joinson, A. (2016). The rise of consumer health wearables: Promises and barriers. *PLoS Medicine, 13*, 1–9.

Plazzotta, S., Cottes, M., Simeoni, P., & Manzocco, L. (2020). Evaluating the environmental and economic impact of fruit and vegetable waste valorisation: The lettuce waste study-case. *Journal of Cleaner Production, 262*, Article 121435.

Plazzotta, S., Manzocco, L., & Nicoli, M. C. (2017). Fruit and vegetable waste management and the challenge of fresh-cut salad. *Trends in Food Science and Technology, 63*, 51–59.

Prioleau, T., Ii, E. M., Member, S., & Paper, R. (2017). Unobtrusive and wearable systems for automatic dietary monitoring. *IEEE Transactions on Biomedical Engineering, 64*, 2075–2089.

Prochaska, L. J., Nguyen, X. T., Donat, N., & Piekutowski, W. V. (2000). Effects of food processing on the thermodynamic and nutritive value of foods: Literature and database survey. *Medical Hypotheses, 54*, 254–262.

Rein, M. J., Renouf, M., Cruz-hernandez, C., Actis-Goretta, L., Thakkar, S. K., Pinto, S., & da Silva Pinto, M. (2012). Bioavailability of bioactive food compounds: A challenging journey to bioefficacy. *British Journal of Clinical Pharmacology, 75*, 588–602.

Renard, C. M. G. C., Watrelot, A. A., & Le Bourvellec, C. (2017). Interactions between polyphenols and polysaccharides: Mechanisms and consequences in food processing and digestion. *Trends in Food Science and Technology, 60*, 43–51.

Research and Markets. (2015). Global functional food and nutraceuticals market 2014-2020: benefits, origin & ingredients. http://www.Researchandmarkets.Com/Research/33gvv3/Global_functional.

Rodríguez-Roque, M. J., Rojas-Graü, M. A., Elez-Martínez, P., & Martín-Belloso, O. (2014). *In vitro* bioaccessibility of health-related compounds as affected by the formulation of fruit juice- and milk-based beverages. *Food Research International, 62*, 771–778.

Ruijschop, R. M. A. J., Burseg, K. M. M., Lambers, T. T., & Overduin, J. (2009). Designing foods to induce satiation: A flavour perspective. In *Designing functional foods* (pp. 623–646). Woodhead Publishing Limited.

Salvia-Trujillo, L., Verkempinck, S. H. E., Sun, L., Van Loey, A. M., Grauwet, T., & Hendrickx, M. E. (2017). Lipid digestion, micelle formation and carotenoid bioaccessibility kinetics: Influence of emulsion droplet size. *Food Chemistry, 229*, 653–662.

Santini, A., Cammarata, S. M., Capone, G., Ianaro, A., Tenore, G. C., Pani, L., & Novellino, E. (2018). Nutraceuticals: Opening the debate for a regulatory framework. *British Journal of Clinical Pharmacology, 84*, 659–672.

Schnettler, B., Ares, G., Sepúlveda, N., Bravo, S., Villalobos, B., Hueche, C., & Adasme-Berríos, C. (2019). How do consumers perceive reformulated foods after the implementation of nutritional warnings? Case study with frankfurters in Chile. *Food Quality and Preference, 74*, 179–188.

Schweiggert-Weisz, U., Eisner, P., Bader-Mittermaier, S., & Osen, R. (2020). Food proteins from plants and fungi. *Current Opinion in Food Science, 32*, 156–162.

Sęczyk, L., Swieca, M., & Gawlik-Dziki, U. (2015). Nutritional and health-promoting properties of bean paste fortified with onion skin in the light of phenolic-food matrix interactions. *Food and Function, 6*, 3560–3566.

Siegrist, M., Stampfli, N., & Kastenholz, H. (2008). Consumers' willingness to buy functional foods. The influence of carrier, benefit and trust. *Appetite, 51*, 526–529.

Sijtsema, S. J., Fogliano, V., & Hageman, M. (2020). Tool to support citizen participation and multidisciplinarity in food innovation: Circular food design. *Frontiers in Sustainable Food Systems, 4*, Article 582193.

Siró, I., Kápolna, E., Kápolna, B., & Lugasi, A. (2008). Functional food. Product development, marketing and consumer acceptance - A review. *Appetite, 51*, 456–467.

Stahl, W., Van Den Berg, H., Arthur, J., Bast, A., Dainty, J., Faulks, R. M., … Astley, S. B. (2002). Bioavailability and metabolism. *Molecular Aspects of Medicine, 23*, 39–100.

Tan, S.-Y., Wan-Yi Peh, E., Marangoni, A. G., & Henry, C. J. (2017). Effects of liquid oil vs. oleogel co-ingested with a carbohydrate-rich meal on human blood triglycerides, glucose, insulin and appetite. *Food & Function, 8*, 241–249.

Thomas, P. R., & Earl, R. (1994). Opportunities in the nutrition and food sciences: research challenges and the next generation of investigators. (Institute of Medicine's Food and Nutrition Board (IOM/NAS), Ed.) (National A). Washington, DC.

Tomiyama, A. J., Kawecki, N. S., Rosenfeld, D. L., Jay, J. A., Rajagopal, D., & Rowat, A. C. (2020). Bridging the gap between the science of cultured meat and public perceptions. *Trends in Food Science and Technology, 104*, 144–152.

Utrilla-Coello, R. G., Agama-Acevedo, E., Osorio-Diaz, P., Reynoso-Camacho, R., & Bello-Perez, L. A. (2013). Glycemic response in healthy rats fed with composite cereal bars. *Starch - Stärke, 65*, 354–359.

Van Der Goot, A. J., Pelgrom, P. J. M., Berghout, J. A. M., Geerts, M. E. J., Jankowiak, L., Hardt, N. A., … Boom, R. M. (2016). Concepts for further sustainable production of foods. *Journal of Food Engineering, 168*, 42–51.

Van Kleef, E., Van Trijp, H. C. M., & Luning, P. (2005). Consumer research in the early stages of new product development: A critical review of methods and techniques. *Food Quality and Preference, 16*, 181–201.

Von Staszewski, M., Jara, F. L., Ruiz, A. L. T. G., Jagus, R. J., Carvalho, J. E., & Pilosof, A. M. R. (2012). Nanocomplex formation between β-lactoglobulin or caseinomacropeptide and green tea polyphenols: Impact on protein gelation and polyphenols antiproliferative activity. *Journal of Functional Foods, 4*, 800–809.

Weickert, M. O., & Pfeiffer, A. F. (2018). Impact of dietary fiber consumption on insulin resistance and the prevention of type 2 diabetes. *The Journal of Nutrition, 148*, 7–12.

WHO. (2014). *Global status report on noncommunicable diseases*. World Health Organization.

Willett, W., Rockström, J., Loken, B., Springmann, M., Lang, T., Vermeulen, S., … Murray, C. J. L. (2019). Food in the anthropocene: The EAT–lancet commission on healthy diets from sustainable food systems. *The Lancet, 393*, 447–492.

Wolever, T. M., Jenkins, D. J., Jenkins, A. L., & Josse, R. G. (1991). The glycemic index: Methodology and clinical implications. *The American Journal of Clinical Nutrition, 54*, 846–854.

Yetisen, A. K., Martinez-Hurtado, J. L., Ünal, B., Khademhosseini, A., & Butt, H. (2018). Wearables in medicine. *Advanced Materials, 30*, 1706910.

Zeisel, S. (1999). Regulation of "Nutraceuticals". *Science, 285*, 1853–1855.