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Health, science and innovation for the future of food system

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Editorial: Health, science and innovation for the future of food system

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Editorial on the Research Topic
Health, science and innovation for the future of food system

The International Master Michele Ferrero 9th edition program (2022/23) integrated cutting-edge advances in Food Science, Food Technology (FS&T), Nutrition Science, health, innovation and digital proliferation. The curriculum featured novel pedagogical approaches and new product development, emphasizing healthy aging, innovation, adaptability, and sustainability. This program was a collaboration between the Ferrero Foundation, Soremartec, Turin University, and Catholic University of the Sacred Heart, Milan.

This Research Topic is one of the program outcomes, comprises nine papers derived from three seminars and two virtual webinars featuring sixteen globally renowned experts. It focuses on the complex aspects of food allergies and on protein needs, as well as on other recent breakthroughs in FS&T and healthy aging, furnishing most recent insights to augment scientific understanding and possible applications.

- *Food allergies around the world* (Wong):

This review explores the relationship between economic development, urbanization, and the increasing incidence of allergic conditions, with a specific focus on food allergy in infants and young children. In developed countries, one in three children suffer from at least one allergic disorder, including food allergies, eczema, allergic rhinitis, and asthma. Egg, milk, fish, wheat, peanuts and tree nuts are by far the most represented allergens. Identifying environmental and lifestyle factors associated with the notable difference of asthma incidence between urban and rural areas is crucial for developing effective primary prevention measures, particularly in vulnerable populations.

- *Food allergy issues among consumers: a comprehensive review* (Sansweet et al.):

This minireview highlights the multifaceted impact of food allergies (FA) on consumers, underlining its significant influence on social, psychological, and economic aspects of life. It emphasizes the need for increased awareness and education to improve quality of life (QoL) for individuals affected by (FA). The review advocates for collaboration among all stakeholders, including medical professionals, researchers, advocacy groups, and policymakers, to address these challenges. It underscores the importance of ensuring affordable and accessible care for all, highlighting potential solutions to alleviate the burdens faced by those with FA.

- *The future of cow's milk allergy – milk ladders in IgE-mediated food allergy* (Hicks et al.):

The perspective centers on the future management and treatment of cow's milk allergy (CMA), particularly focusing on the use of milk ladders (i.e., a stepwise progression from extensively heated *to less heated food*) in IgE-mediated food allergy. Some of its highlights include: consideration of various management approaches for CMA, including alternative milk sources. Discussion on the potential of milk ladders in CMA management. And emphasis on the need for ongoing research to enhance treatment options.

- *Dietary proteins: from evolution to engineering* (Daniel):

This review delves into the significance of dietary proteins in human nutrition, tracing their role from evolution to current consumption patterns, and future production prospects.. Main points include the importance of dietary proteins, which contain indispensable amino acids, playing a crucial role in human evolution and proper growth and body maintenance. Evolution of hominins in diverse food ecosystems highlighting the centrality of proteins in human nutrition. Future prospects for protein production delving on sustainability and meeting the increasing food demand are also reviewed. The review stresses the need for new protein sources that not only provide essential amino acids but also serve functional roles in food production, considering human physiology and metabolism from an evolutionary perspective.

- *The nutritional support to prevent sarcopenia in the elderly* (Giacosa et al.):

Sarcopenia is a condition characterized by muscle loss with significant health consequences. This review delves into its epidemiology, pathophysiology, and methods for early detection, with a focus on treatment through physical activity and nutritional support. Specific foods designed for sarcopenia management have shown promising results. Combining these interventions with physical activity enhances muscle protein synthesis and strength. Long-term efficacy and tolerability of these interventions require further investigation. Muscle-targeted nutritional supplementation combined with resistance exercise appears to be an effective strategy in preventing sarcopenia in high-risk elderly populations.

- *A review on nutritional quality of animal and plant-based milk alternatives: a focus on protein* (Karoui and Bouaicha):

The report highlights the growing consumer demand for protein-rich products and the nutritional differences between dairy foods and plant-based milk alternatives. Dairy products are recognized for their high-quality proteins, while plant proteins typically have lower essential amino acid content. This fact underscores the importance of ongoing research in improving the nutritional quality of plant-based milk alternatives, mainly by removing the anti-nutritional factors present in plant-based proteins and enhancing the protein content and amino acid composition of these alternatives, potentially by blending different plant proteins.

- *Possible interactions between selected food processing and medications* (Poli et al.):

This novel review highlights possible interactions between selected food processing technologies and medications by exploring both potential benefits and risks. The review delves into examination of thermal processing technologies' effects on drug absorption and metabolism. Innovative food processing technologies for enhanced bioavailability are described. It calls for multidisciplinary intensified scientific research and comprehensive investigations into possible interactions and their underlying mechanisms that are indispensable for ensuring food and medication safety and efficacy. It points to the integration between food processing and drug production underscoring the need for a unified approach for their future development.

- *The taste for health: the role of taste receptors and their ligands in the complex food/health relationship* (Morini):

The relationship between taste, food choices, and health goes beyond pleasure. G protein-coupled receptors (GPCRs) in the gastrointestinal tract detect sweet, umami, and bitter flavors, playing critical roles in nutrient sensing, hormonal regulation, microbiota balance, immune response, and gut-brain communication. These gut-based taste receptors regulate microbiota composition and immune activity. Their discovery has led to potential drug targets and therapeutic interventions. Integrating scientific advancements will enhance food design, support sustainable food production, and drive progress in functional foods tailored to health needs, fostering a holistic approach to nutrition and wellness.

- *ONE QUALITY concept: a narrative perspective to unravel nutritional challenges, controversies, and the imperative need of transforming our food systems* (Menta et al.):

The ONE QUALITY concept perspective advocates for a transformative approach to global nutrition, emphasizing culturally sensitive, evidence-based guidelines. It underscores the need for healthy and sustainable diets tailored to diverse cultural contexts and the importance of food safety policies that engage all stakeholders. The perspective moves away from demonizing specific dietary components like saturated fats and embraces a comprehensive view of diet, including plant-based foods. It highlights the role of international agencies and regulatory bodies in promoting evidence-based practices and addressing environmental constraints on food systems. The perspective also emphasizes the need for a comprehensive data bank to develop a global, science-based approach.

Author contributions

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Dietary proteins: from evolution to engineering

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Because of the indispensable amino acids dietary proteins are the most important macronutrients. Proper growth and body maintenance depends on the quantity and quality of protein intake and proteins have thus been most crucial throughout evolution with hominins living in quite diverse food ecosystems. Developments in agriculture and food science have increased availability and diversity of food including protein for a rapidly growing world population while nutrient deficiencies resulting in stunting in children for example have been reduced. Nevertheless, the developing world and growing population needs more protein of high quality – with around 400 million tons *per annum* estimated for 2050. In contrary, protein consumption in all developed countries exceeds meanwhile the recommended intakes considerably with consequences for health and the environment. There is a growing interest in dietary proteins driven by the quest for more sustainable diets and the increasing food demand for a growing world population. This brings new and novel sources such as algae, yeast, insects or bacteria into play in delivering the biomass but also new technologies such as precision fermentation or *in vitro* meat/fish or dairy. What needs to be considered when such new protein sources are explored is that proteins need to provide not only the required amino acids but also functionality in the food produced thereof. This review considers human physiology and metabolism in the context of protein intake from an evolutionary perspective and prospects on future protein production.

KEYWORDS

diet, new proteins, physiology, food biotechnology, evolution

Introduction

Whereas carbohydrates and lipids received over time enormous public interest (sugar tax, low carb, low fat etc.), only recently have proteins experienced a similar public perception. This is fostered by popular press referring to higher protein intakes to help weight loss but also by the wide use of protein supplements in the fitness and bodybuilding scene that often suggest that just eating more protein provides a proper body shape. Markets have seen the emergence of products in almost all food categories with added protein to satisfy this protein-hype. With the high consumption rate of animal-based products and a large array of food items with higher protein contents, the daily protein intake exceeds already the recommended intake levels in all developed countries substantially.

With the awareness of an increasing food demand for the growing world population on background of climate change and expected reductions in agricultural yields and available land area, the interest in proteins from new sources increased drastically. The quest for more sustainable diets in which meat and animal-based food items are replaced has fostered the academic interest in "new proteins" and many research activities have been launched in recent years. These are often embedded into national strategic initiatives to make food systems more resilient and less dependent on imports. While the agri-food sector currently focuses on protein-plants, improved yields and better climate-adopted plant varieties, the biotech sector provides new avenues for food production with renewable energy used to generate hydrogen, acetate or methanol that can serve as energy substrates for biomass production (1, 2). Novel organisms such as chemolithotrophic bacteria have already proven to provide sufficient biomass for protein production by using hydrogen as energy source and by trapping CO_2 from air (3). Cell culture techniques with stem cells as starters are in development to preplace conventional meat and fish products while "precision fermentation" with recombinant expression of target proteins in production strains of bacteria or yeast is used to provide for example dairy products based on bovine caseins or whey proteins by heterologous expression.

With the framing of "alternative proteins" we are thus exposed to a huge spectrum of approaches and numerous novel technologies that require the assessment of the safety and the nutritional and environmental quality of the new food items. It is the intension of the present review to provide a thoughtful reflection on the role of dietary proteins in human nutrition by taking an evolutionary perspective and by considering the new protein sources as part of future diets.

Proteins in the evolution of hominins

There can be no doubt that amongst the macronutrients, proteins with the essential amino acids are most crucial diet components in mammalian development. Whereas carbohydrates do not provide any essential entities, lipids have two fatty acids categorized as essential while there are 9 indispensable amino acids. Growth and development require these amino acids but their concentration in food items does not *per se* provide the best spectrum and in particular many plant proteins have individual amino acids in limited quantities. Therefore, combining plant foods to complement the amino acid profiles in the contained proteins is a principle and is realized in many kitchens all over the planet in which a few staple foods are available. This ensures that even with low overall protein contents in the diet optimal conditions for growth and development are realized. In contrast to plants, most animal food sources have amino acid patterns close to those of humans and thus those proteins have played an important role in human development. Although there is a long-lasting discussion on whether hominins evolved as carnivores or vegetarians or even frugivores, it has become obvious that depending on time and geographical location and climate, our ancestors have been consuming whatever the ecosystem provided and that was usually a mix of plant and animal-based products. In this respect it is misleading when argued that there is something as a "paleo-diet." A new interest in diets of hunters and gatherers emerged in recent years in the biomedical scene when microbiome profiling of stools samples of isolated populations or even of paleosamples revealed that the diversity of gut microbial species was much higher than that found in samples from individuals living in industrialized countries. This is frequently explained with more diverse diets than those of modern times. However, stool analysis of paleosamples (4) but also stool samples collected from people living in rural areas in central Africa (5) showed a high density of parasites and this even correlated with microbiome diversity. This adaptation of bacterial diversity to parasites seems to be a more common phenomenon also in other species (6).

In the Hazda hunter and gatherer society careful analysis of diets – that vary considerably by season – revealed that they have periods in which up to half of their caloric intake comes from honey whereas in other month´ and season up to 65% of daily calorie consumption derives from animal products (7). Such diet patterns we usually consider as most unhealthy but strikingly, Hazda people show low incidence of non-communicable diseases such as cardiovascular diseases (8). But these modern hunter and gatherer groups also provide a good example of how variable human diets have been and can be and how much those depend on the ecosystem setting.

As a more general finding it has been observed that the percentage of animal products as part of diets increases with a more northern latitude (7). For central and northern Europe that also applies to diets in early hominins. In remains of neanderthal species (age around 40.000 years) and other palaeolithic humans living in Europe, isotope analysis of ^{15}N in bone collagen revealed a signature that was even higher than that of pure carnivore species of the same regions suggesting that early humans had a very high rate of animal protein in the respective diets (9). The migration from a rather warm savanna ecosystem into a cold tundra-like landscape in northern Europe and Asia (see Figure 1) was likely associated with a marked change in diet and a high animal protein and fat consumption. The high protein quality of meat was clearly beneficial for development and that was even further enhanced when fire was introduced for food processing estimated as to happened about a million years ago. Raw diets consumed by humans are known to provide insufficient energy and nutrients leading to impairments in the female cycle or even loss of reproductive function (10). Heat treatment of food increases significantly the energy that can be absorbed from the small intestine (11, 12) and this is thought to have changed the anatomy and morphology of the gastrointestinal tract with markedly reduced mass relative to total body mass – leaving more nutrients and energy for brain development and overall body size. With the neolithic revolution and a more constant food supply by farming and animal husbandry, diets may have shifted to a higher proportion of plants while animals still delivered a considerable fraction of protein and fat. Domestication brought new protein sources such as bovine milk into the diet that was driving the adaptaion of humans to intestinal lactase persistance.

Most strikingly, daily protein intake across the world correlates strongly with average male and female body height and even with the phenotype frequency of lactose tolerance (13) suggesting that the high biological quality of dairy protein introduced in the neolithic period also promotes extra growth. Taken together, diets of hominins throughout evolution varied considerably by time, geography, season and ecosystem. Protein supply as well was highly variable but with the indispensable amino acids their contribution of the development of *Homo sapiens sapiens* has been most important for growth and development and similarly, food processing techniques that improved supply and digestibility as well shaped human physiology.

Proteins in the diet-health relationship

The quantity and quality of dietary proteins has been a key determinant in human development over millennia. Whereas a low protein supply is still a large problem in many low-income countries, daily protein intakes in developed countries exceed meanwhile

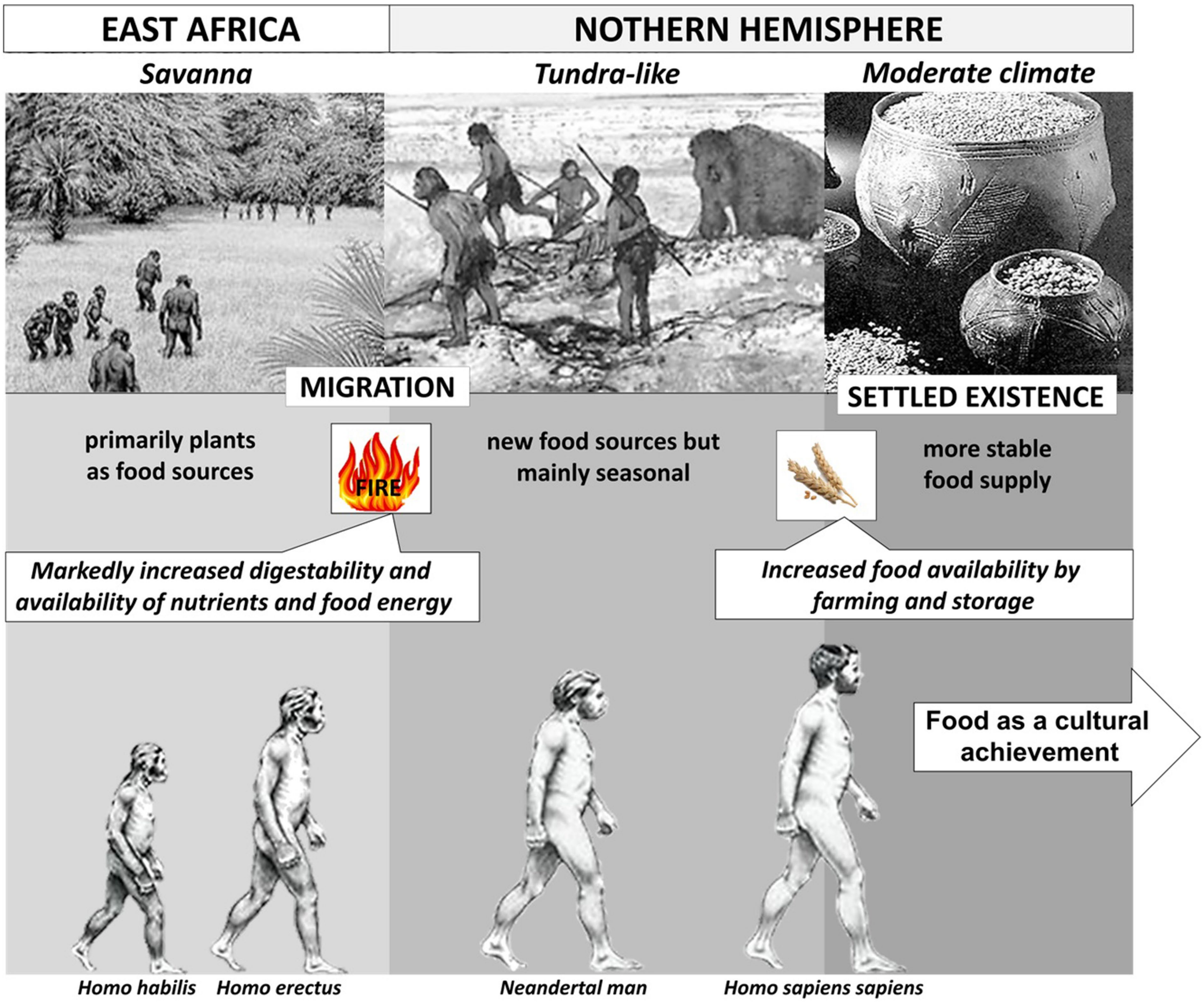

FIGURE 1
Milestones in the evolution of hominins and the role of diet as derived from different ecosystems.

significantly the recommended intakes (14). In addition, protein quality is no more a critical factor as food availability is unrestricted and with the enormous number of food items – available around the year – and with a high percentage of animal-based product this high protein supply status is just a measure of wealth without a need. Protein intakes are around 90 to 100 g per day in man and around 70 to 75 g per day in woman (14). Required minimum protein intakes when providing high quality proteins to maintain an equilibrium in humans have been estimated to range between 0.3 and 0.5 g/kg body weight/day with the medium requirement defined as 0.66 g leading to a recommended intake of 0.8 or 0.83 g/kg/day as safe population intake in adults and of 1.05 g/kg/day for senior citizens (15). Total protein synthesis in an adult is around 300 g per day with muscle, liver and renewal of circulating blood cells accounting for most of the newly synthesized protein quantities. There is a constant protein breakdown leading to release of free amino acids into a pool in which dietary amino acids enter as well with this pool serving as the resource for *de novo* protein synthesis (see Figure 2). When amino acid intake exceeds the needs, amino acids need to be used as energy substrates leaving nitrogen and sulphur for excretion – mainly via urine.

High protein intakes in high income countries that exceed recommended intake by around 20 to 40 g per individual and day, require that amino acids are immediately oxidised as the capacity for storage of a surplus of amino acids is very limited. Amino acid oxidation leaves nitrogen and sulphur for detoxification which also results in a substantial flux of these entities through the large intestine with effects on the microbiome and not yet adequately defined health consequences (16, 17). Moreover, the surplus of protein with the excess of nitrogen that needs to be excreted has been identified as a problem for the environment (18).

Recently markets have seen a real “protein hype” with many products enriched with an extra portion of protein which further increases total daily protein intake above needed and recommended quantities. This trend is mainly based on the concept that high protein diets reduce caloric intake by a higher satiety signal and thus promote weight loss (19). Indeed, in randomised controlled trials (RCTs) with energy-restricted diets, high protein intake (27–35% of energy intake) provided a greater weight loss (of around 0.8 to 1.2 kg over 1-to-3-month periods) than low protein diets (20). But, meta-analysis of similar RCTs not always confirm such an effect (21) and it seems that as longer the study lasts, as smaller the effects of the high protein diets

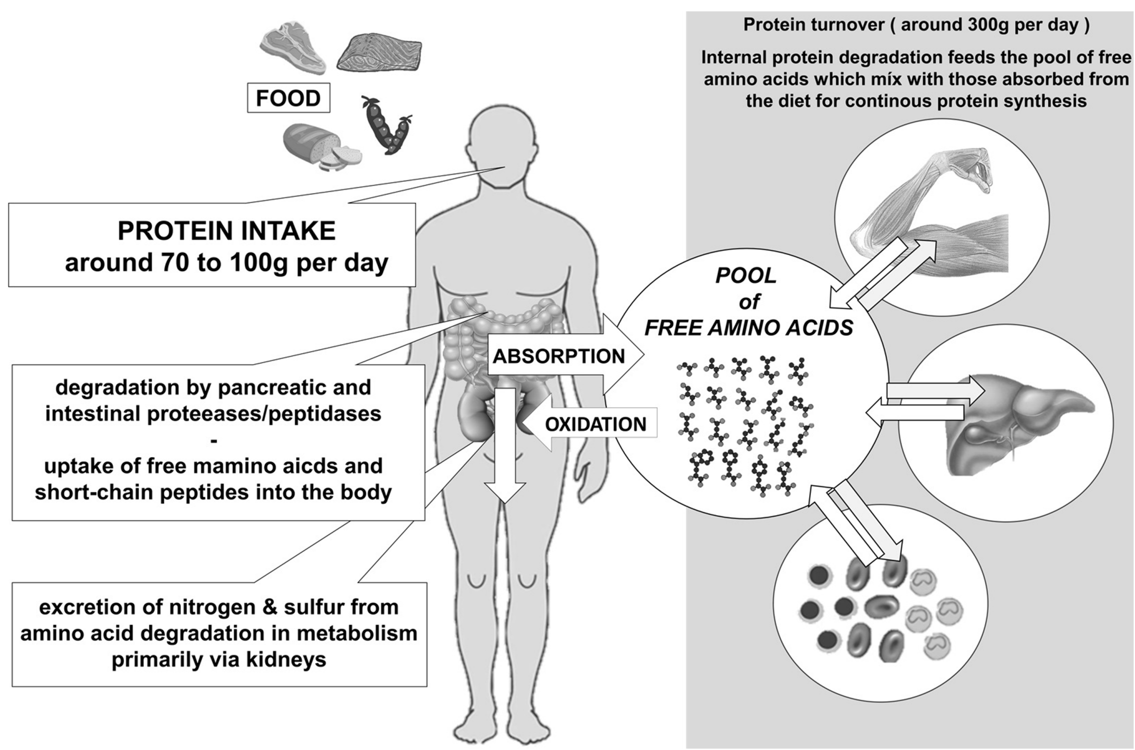

FIGURE 2
Fate of dietary proteins and turnover of body protein and utilisation of amino acids (per day) in adult humans.

become (22). In RCTs with non-energy-restricted diets effects on body weight were even smaller with 0.36 kg in >1 month study periods as an example (23) In addition to weight-loss as an endpoint, meta-analysis of many RCTs employing high protein diets could not demonstrate any (21) or only very small beneficial metabolic effects – except for modest reductions in blood triglyceride levels (20, 23). Taken together, long-term effects of high protein diets for improved weight management are scarce and small (19). Benefits of high protein products and diets claimed in the public domain thus often overstate the effect sizes.

Like never before has health become the most crucial criterion in assessing the impact of diets, individual nutrients or even individual food items or any ingredient. In view of the association of protein quantity and protein origin (plant-based or animal product-based) with various disease end-points and all-cause mortality as derived from observational studies it may be concluded that daily protein intakes in the range of up to 30% of energy intake are save with no significant risks for diseases such as cancers or cardiovascular disease (24). If specifically assessed for plant-based or animal-based proteins, it becomes obvious that a high intake of animal protein (up to 20% of energy intake) is associated with a modest increase in disease risks and increased all-cause mortality. This is mainly driven by red meat and processed red meat for which disease-associations have been demonstrated to be dose-dependent (25, 26). Plant-proteins on the contrary appear to have protective effects for most disease endpoints (26).

High protein consumption has for a long time been linked to negative effects on bone-health based on a high production of sulfuric acid when sulphur-containing amino acids are oxidised in metabolism (27, 28). However, recent meta-analysis and umbrella reviews conclude that even with protein intake rates exceeding 1.5 g/kg body weight per day bone mineral density or osteoporosis risk are not impaired – neither in younger nor in older individuals (29). That provides a safe basis for recommendations towards higher protein intakes in senior citizens to prevent or fight sarcopenia (29). Taken together, there is a large body of evidence that higher protein intakes (up to 30% of energy) are safe with some evidence that intake of red meat and processed red meat but not of other meat varieties nor plant proteins increase disease risk (for diabetes, certain cancers, CVD) and all-cause mortality (30).

When we assess environmental footprints of diets or of individual food items, we have an issue with protein intake rates exceeding those recommended. When amino acid intake exceeds the quantity needed for body protein synthesis, amino acids are immediately oxidised and that leaves large quantities of nitrogen for excretion. Urea and ammonia as end-products of this energetic utilisation of the surplus of amino acids are excreted in urine and faeces and this is a burden for the environment. A recent analysis of this nitrogen flow resulting form high protein diets exceeding recommended intake rates estimated for the US (18) a contribution of 28% of all N-emissions into the environment and mainly into the surface water. According to the FAO Statistical Year Book (31) the mean protein supply per day in the US and Europe is similar and N-emissions derived from the surplus of protein intake should therefore be very similar.

New proteins with new technologies

There can be no doubt that the growing world population needs more protein and that is frequently used as the key argument for initiatives to isolate proteins from any source and with new biomass production approaches employing novel organisms and technologies.

But the growing number of humans also need calories and even more so essential micronutrients such as vitamins and trace elements. Based on a model analysis it was concluded that the world produces already enough protein to satisfy the needs of 10 billion people by 2050 – when protein could be distributed evenly (32) whereas micronutrient supply will remain as most critical for billions of people. Iron-deficiency in particular is currently the most important individual nutrient deficiency leading to anaemia in around 500 million woman (31) and providing sufficient dietary iron will remain as one of the key problems in feeding the growing population.

Although there are many new sources for proteins such as micro-and macroalgae like spirulina, chlorella or kelp, mycoproteins, various insect species or new legume varieties (32), none of those sources deliver all essential nutrients that humans need (33). And when used as protein isolates or concentrates, they usually contain also some anti-nutritive compounds such as phytates, protease inhibitors, lectins or other unwanted compounds. Plant-based diets are known to reduce mineral and trace-element bioavailability and that has recently also been raised as concern for the so called "planetary health diet" as a model for future diets with minimal effects on environment but maximal effects on health (34). Moreover, plant-based protein blends (35) or burger patty substitutes (36) were shown to generate lower plasma levels of essential amino acids (EAAS) in postprandial states when provided in identical quantities as the animal-based reference protein. Although human studies in young healthy volunteers ingesting plant-based proteins or protein blends also revealed lower plasma levels of EAAS, differences in post-prandial protein synthesis could not be observed (37). However, in elderly in which postprandial protein synthesis is most important, a lower synthesis rate based on plant-protein rich food may be a problem (35, 38).

That means that when those protein sources are used in food production – mainly for replacing meat or dairy products – essential nutrients such as vitamins, minerals and trace elements need to be added to new food items created. That brings new products into the categories of so called ultraprocessed food (39). The growing consumer demands for plant-based replacers of meat, meat products and dairy has initiated a wide range of activities that go from protein isolation from side-streams or utilisation of new sources such as gras or hemp, to insects, mushroom-mycelium or novel production organisms such as chemo-lithotrophic bacteria.

What is not often considered is the functionality of the protein-concentrates and-isolates (PCIs) when used in production of new food items. Proteins provide many features required in food technology such as solubility, coagulation, emulsification, binding, foaming, gelation or whipping. And most importantly, products based on PCIs need to provide good taste or at least should not bring in off-flavours. Functionality of the various protein preparations is key for market success and that fosters studies that take plant PCIs and test their functional features.

An alternative route could be the synthesis of proteins with a defined functionality via biotechnology. With a better understanding of how amino acid sequence and structure of individual proteins translate into functionality, these proteins can be produced in large scale via expression in yeast – favourably via the methylotrophic yeast *Pichia pastoris* (40). Currently such proteins are produced as modular structures with known functionalities that mimic natural proteins such as collagen. They display interesting technological features such as undergoing temperature-or pH-dependent transitions between liquid and gel states (40). Other examples may be antifreeze-proteins that are employed in certain food categories such as ice-cream (41) or sweet-tasting proteins such as Thaumatin, Brazzein or Monellin (42).

Life science has generated over the last decades functional proteins as tools in cell biology that allow life cell-imaging for example or deliver/capture ligands upon activation by exposure to a defined wavelength of light. Such "protein cages" (43) could as well (given their safety) find numerous applications in food technology but are currently a science fiction domain. However, with the rapid development in artificial intelligence (AI) tools that predict 3D-protein structures from any given sequence and forecasting functional properties, the generation of *in silico* amino acid sequences for *de novo* synthesis of such novel proteins of a defined function may also become an option for food biotech applications of tomorrow.

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The future of cow's milk allergy – milk ladders in IgE-mediated food allergy

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Cow's milk allergy (CMA) is one of the most common and complex presentations of allergy in early childhood. CMA can present as IgE and non-IgE mediated forms of food allergy. Non-IgE mediated CMA includes food protein-induced enterocolitis syndrome (FPIES), eosinophilic gastrointestinal disorders (EGIDs), and food protein-induced proctocolitis (FPIAP). There are recent guidelines addressing CMA diagnosis, management, and treatment. Each of these guidelines have their own strengths and limitations. To best manage CMA, individualized avoidance advice should be given. Cow's milk (CM) can be replaced in the diet by using hypoallergenic formulas or plant-based milk, depending on factors such as the child's age and their current food intake. Oral and epicutaneous immunotherapy is used to increase tolerance in children with CMA but is not without risk, and the long-term outcome of sustained unresponsiveness is still unclear. The allergenicity of CM proteins are affected differently by different forms of heating, leading to the use of baked milk or milk ladders in the management of CMA, most likely the most promising option for future management and treatment of CMA. Future management of children with CMA will also include discussion around the immunomodulatory potential of the child's dietary intake.

KEYWORDS

food allergy, cow's milk allergy, nutrition, food ladders, pediatric

Introduction

Cow's milk allergy (CMA) is among the most common food allergies in children, with, for example, a prevalence of 1.8% in children aged 1 to 5 in the United States (1). CMA is divided into IgE mediated and non-IgE mediated CMA, although the European Academy of Asthma, Allergy and Clinical Immunology (EAACI) has recently suggested a more complex nomenclature, focusing on the underlying immunology (2). Diagnosis of CMA includes taking a clinical history, deciding on appropriate testing, followed by an oral food challenge (OFC) for IgE-mediated CMA or a period of avoidance followed by reintroduction/OFC for non-IgE mediated cow's milk allergies (FPIES, Eosinophilic Esophagitis [EoE], FPIAP). According to the recent EAACI guidelines "A medically supervised oral food challenge (OFC) is recommended to confirm or exclude food allergy in patients with an unclear diagnosis despite IgE-sensitization tests (high certainty of evidence)" (3). Current management strategies include individualized avoidance of foods containing cow's milk (CM), and precautionary advisory labelling. Depending on age, a hypoallergenic formula or plant-based substitute is recommended (4). For IgE-mediated CMA, emergency medications including epinephrine are used to treat anaphylaxis to CM. For IgE-mediated CMA, oral and epicutaneous immunotherapy can be used to increase tolerance in children but is not without risk, and the long-term outcome of sustained unresponsiveness is still unclear (5) (Waserman et al., 2023, Submitted)[1]. Many guidelines have recently been published to improve the diagnosis, management, and treatment of CMA (3, 6–7) (See footnote 1).

Prognosis is favorable for all types of CMA. For IgE-mediated CMA, approximately 80% of children outgrow their allergy by age 6 (8). It has been known for some time that children with CMA can often tolerate baked forms of the food, especially when combined with a flour matrix (9, 10) while still demonstrating symptoms to unbaked forms, with some studies reporting as much as 70% of CMA children tolerating BM (11–15).

At this time it remains a standard recommendation to offer an observed OFC to baked milk (BM) followed by continued home ingestion of similar products (16–18). However, even after tolerance of BM in an OFC setting, a significant number of patients continue to avoid BM. Dunlop et al. reported 28% of patients sent home with a plan for BM ingestion were avoiding CM in all forms 2 to 7 years later (19). Hicks et al. have recently conducted an international survey of children who had successfully passed a BM challenge and were instructed to introduce BM at home. It was indicated that 88% of participants were instructed to eat any BM-containing food or suitable commercial option. Still, only 27% were given suitable recipes, and the majority received only 1–2 recipes, demonstrating first-hand the need for improved, standardized guidance for families regarding the home introduction of BM (20). For non-IgE mediated CMA, the use of BM in the management of FPIES and EoE have been poorly studied, with two studies indicating that BM foods may be suitable in these patient populations (21, 22). An alternative approach is an at-home food “ladder” approach, used safely in milder forms of non-IgE mediated CMA such as FPIAP (23).

One of the most impactful findings in the management of IgE-mediated CMA is the recent finding from Ireland indicating that BM can be introduced at home in infants using a milk ladder approach (7, 9). One study indicated that 65% of children safely consumed CM 12 months post randomization using a milk ladder approach, and 86% were safely consuming baked foods at 6 months post randomization (7). This review offers recommendations on facilitating safe use of milk ladders for clinical use in IgE-mediated CMA to improve future management of CMA.

Reviewing the basis for ladders

CM contains a range of proteins of which 80% are casein proteins and 20% whey proteins. The allergenicity of these proteins are affected differently by different forms of heating, leading to the use of BM or milk ladders in the management of CMA. For example Bos d5 (beta-lactoglobulin) is found to be reduced by 99% with baking, whereas Bos d11 (b-casein) is reduced only by 30% (4, 24).

A food ladder is a stepwise progression from extensively heated to less heated food. Heating decreases the allergenicity of food proteins in egg and milk by degrading (altering) conformational epitopes so that the immune system has a reduced ability to recognize them (25). Heating has some but a limited effect on linear epitopes (25). Thus, it is assumed that progressing from extensively baked to less heated foods offers a progression from a less-allergenic to a more-allergenic form of the food protein. Food ladders also consider the amount of allergenic protein in each step of the ladder, which progressively increases as the ladder advances.

The first published ladder was created in 2013 for non-IgE mediated CMA (26) in the United Kingdom (UK) by Venter et al. This ladder initially contained 12 steps focusing on common British foods and was updated to a shortened ladder in 2017 that was more internationally focused regarding foods recommended (23). This ladder has been widely adopted for non-IgE-mediated CMA (27). Although initially created for non-IgE-mediated allergies, many providers also use ladders for progressive induction of tolerance at home for IgE-mediated allergies, especially to egg and CM (28). For example, one international survey found that as many as 60% of healthcare professionals responding to the survey used CM ladders for IgE-mediated food allergies (27).

There is evidence, although limited, demonstrating the development of tolerance via ladders. There have been recent publications regarding the use of home egg and CM ladders in Ireland, where pediatric allergy resources are limited, showing the safe use of a multi-step ladder. A significant number of participants achieved tolerance of egg or CM in all forms at the end of the study, even within the first year of life (28, 29). These studies were not controlled trials and included small sample sizes, limiting their generalizability.

Given that food ladders entail offering a child a known food allergen in the home, they come with inherent risk. Prior small-scale, non-randomized controlled trials (RCT) studies have reported their safe use, but the true risk of home-use of a food ladder has not been characterized (28), nor has it been described who may tolerate a ladder and who may not.

Additionally, home preparation of a ladder is not without risk, with the possibility that the amount of the allergenic protein differs from batch to batch of the same recipe or commercial food product. Further, the allergenic protein can even vary within a single serving, with the middle portion of the food being at higher risk for underbaking. Hindley et al. noted that in a BM muffin used in OFCs for CMA, baking partially denatured Bos d 11 (casein) at the periphery and had little effect on Bos d 11 in the remainder of the muffin. Bos d 5 (b-lactoglobulin) was more effectively denatured throughout the muffin (24). Thus, a ladder that could be safely used in IgE-mediated CMA would ideally have clear, simple instructions and have undergone some standardization in regard to the amount of food protein from batch to batch.

A published rostrum by Venter et al. (30) reviewed the current scientific basis for food ladders, their benefits and risks, and recommendations for the future. Possible benefits to using a ladder approach for IgE-mediated food allergy include (1) hastening of resolution of a food allergy (18), (2) increased diet diversity (31), (3) less healthcare utilization, (4) decreased cost, and (5) decreased patient burden (30). The rostrum also recommended standardization of food ladders regarding the allergenic protein content and cooking instructions for recipes, consideration of nutritional and health value of foods, acceptance of the food by a pediatric patient, and consideration of local/cultural eating practices. A review of the pros and cons of the use of ladders in IgE-mediated CMA is reviewed in Table 1.

Assessing ladders

When considering the various currently available CM ladders, which are examined individually in the following section, it is

1 Waserman S, Bahna SL, Arasi S, Canani RB, Dupont C, Shamir R, et al. World allergy organization (WAO) diagnosis and rationale for action against Cow's Milk allergy (DRACMA) guidelines update – IV clinical presentations: IgE-mediated & non IgE-mediated. *World Allergy Organ J.* (2023) Submitted.

TABLE 1 Pros/cons of milk ladders in IgE-mediated CMA and patient selection factors.

Milk ladders in IgE-mediated CMA	
Pros	**Cons**
A majority of CMA patients tolerate baked CM	Risk of anaphylaxis remains
Home-use decreases need for OFCs	Labor and resource intensive
Expansion of available foods in diet	Dependent on child's acceptance of offered foods

Patient/family factors	
Good fit	**Barriers**
Tolerance of baked milk	History of anaphylaxis to baked milk
Motivated family	Uncontrolled co-morbid conditions, i.e., asthma
Family comfort managing allergic reactions in the home	Socioeconomic barriers, i.e., language barrier, limited financial resources
Young age	Older age

important to consider aspects related to the ladder itself; the patient/family in question; the healthcare system in which the patient exists; and the ladders impact on the patient's nutrition, outside of allergen exposure.

Ladder design

For use in clinical practice for IgE-mediated allergy, a ladder must offer a stepwise progression of CM protein content, with decreased denaturing as the ladder progresses, to serve the desired effect. The initial dose of CM protein must balance safety and efficiency, not adding unnecessary steps but being a low enough starting dose to be safely initiated in a majority of patients. Subsequent steps of the ladder should again follow reasonable increases in protein content. The most effective starting dose as well as the rate at which the dose should increase is an area that needs further exploration.

Foods in a single step should also contain a similar amount of CM protein (23, 26, 32, 33), which is often not the case in some currently available ladders (34, 35), which can have significant variability in the food choices on a single ladder step.

Given that the ladder is intended for home use, ladders should also provide clear, simple recipes for families to follow, given the significant variability in milk protein content in different variations of a food type, such as a muffin (23, 26, 32, 33). Unfortunately, some of the currently available ladders do not offer recipes but only list food types to be offered, i.e., muffins or pancakes (34, 35).

Ideally, as part of the design process of the ladder, the calculated milk protein content should be verified via lab quantification (32, 33). This has not been the case in many of the currently available ladders. The ladders that have taken this step demonstrate the need, as there is often discrepancies between the calculated and tested milk protein content. Further, the total milk protein content can differ compared to the milk component content, meaning the foods could be arranged in a different order depending on if total milk protein vs. a milk protein component progression is used as the goal (32).

Another consideration in ladder selection is nutritional content as well as palatability. Given that ladders are primarily intended for use in infants, toddlers and young children, the nutritional content is of supreme importance but also has to be balanced with the sometimes-limited palate of this age group. Ladders should strive to limit additions of "less-nutritious" ingredients, including refined sugar and provide nutrient-dense ingredients, such as fiber, as able (23, 33). However, they must also be palatable to be useful, given if the child refuses to eat the food regularly, it will not be able to offer its desired effect. Cultural appropriateness of the food items are also important, as well as the ease in which families can acquire the needed ingredients (32).

Patient selection

Beyond the components of the ladder, consideration of patient-specific factors is also paramount for safe and successful use of a food ladder. Safety considerations are of highest importance, and it can be difficult to predict who may develop severe symptoms while stepping up a ladder. Prior reaction history to an allergenic food is not a strong indicator of future reactions (36). Further, modifying factors, such as illness, fatigue, exercise, or other poorly controlled atopic diseases (i.e., asthma), can lower a child's tolerance and make day-to-day consumption of a food allergen at home not without continual risk (37). A recent pediatric death, partially attributed to an unstandardized approach to BM intake, highlights the need for more investigation of the safety and effectiveness of a food ladder for IgE-mediated food allergy (38).

Outside of the patient's tolerance to the food allergen, family factors such as willingness and ability to procure and prepare the ladder foods must be considered. A myriad of socio-economic factors can make proper use of a ladder difficult, including but not limited to food costs, limited time, and language barriers.

The provider should also assess the family's ability to respond to any allergic reaction that occurs and consider their ability to access emergency services, should that be required.

Healthcare system

The healthcare system the patient resides in may alter the usability of a ladder, outside the availability of emergency medical services. Healthcare systems with limited subspecialty access, including pediatric allergists, may find ladders as a helpful alternative to observed OFCs to BM, which are resource and time intensive. As

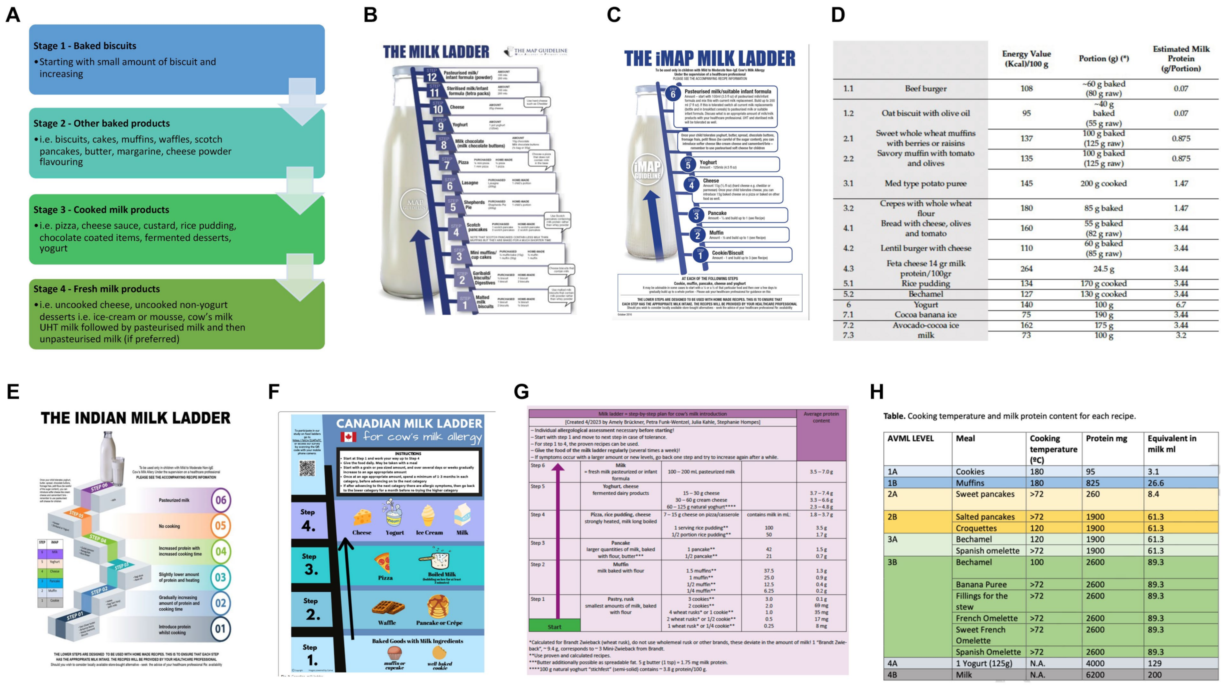

FIGURE 1
Current milk ladders **(A)** BSACI **(B)** MAP **(C)** iMAP **(D)** Mediterranean **(E)** Indian **(F)** Canadian **(G)** German **(H)** Spanish.

referenced above, there have been recent publications regarding the use of home egg and CM ladders in Ireland, where pediatric allergy resources are limited, showing the safe use of a multi-step ladder (28, 29). Limited healthcare resources also raises the question of who can safely prescribe use of a ladder. Prior work by our team has reported country-specific differences in the availability of allied health professionals (AHPs) such as Registered Dietitians (RDs), with some countries such as the UK having far more RDs available per patient and education regarding food avoidance and introduction often coming from these AHPs vs. a medical provider (20). There may be concern for the recommendation of ladders without direct consultation of a medical provider specialized in Allergy, but resource limitations in some regions of the world may necessitate relying on AHPs to administer ladders.

The healthcare cost of using a ladder should also be considered. It would likely cost less than an OFC to BM, but still requires subspeciality care with routine follow-up as well as coverage of emergency medications including epinephrine auto-injectors to be available at all times for patients utilizing a ladder approach.

The healthcare system and environment may also impact a provider's comfort of prescribing use of a ladder, given there is inherent risk, and providers in countries with more litigious medicolegal environments may be hesitant to extensively recommend use of home ladders.

Nutrition

Providers can also consider the impacts on nutrition and quality of life outside of allergen exposure when considering utilizing a ladder. It would be assumed that use of a ladder would broaden the foods available for a child to ingest, which would have a positive impact on their diet diversity as well as likely the quality of life of the child and their family given the decrease in dietary restrictions (31). This could also possibly result in improved growth parameters, as many food-allergic children having sub-optimal nutrient intake and growth due to their dietary restrictions (39). Many of these factors require further study to prove that such positive impacts truly do occur with use of a food ladder.

Comparison of current milk ladders

Multiple food ladders are currently available for use. Though many factors have been discussed above relating the safe use ladders, ultimately the safety of ladders depend on whether the steps are planned on calculated sequential increase of allergenicity, and ideally, if the allergenicity of the different steps have been tested (see Figure 1; Table 2).

Discussion

Ladders offer unique aspects that make them a desirable method of allergen introduction in some children with CMA. However, ladders are not without risk and dependent on the particular patient and ladder in use. We offer the following recommendations for the favorable use of ladders.

Patient selection is of utmost importance in the safe use of ladders. Ladders can be readily utilized in children with non-IgE mediated allergy, excluding FPIES, for a gradual introduction of a previously avoided food (35). In the setting of IgE-mediated allergy, the patient

TABLE 2 Comparison of currently available milk ladders.

# Steps	# Foods/ step	Recipes included	Dose escalation	Starting/ Ending dose	Measured Protein Content	Nutritional soundness	Culturally appropriate	Other Comments
BSACI (35)								
4	Multiple	No	Starts small but quickly escalated CM protein	Not listed	No	X	For British population	Foods in a single step are dissimilar in allergenicity
MAP (26)								
12	1	Yes	Moderate jump in steps (some steps subdivided into multiple steps)	35 mg/7.2 g	No	X	UK diet specific	Complex recipes
iMAP (23)								
6	1	Yes	Large jumps in steps (some steps subdivided into multiple steps)	95 mg/6.9 g	No	Yes	International	Simple recipes
Mediterranean milk ladder (33)								
7	1	Yes	Moderate jump in steps	70 mg/3.2 g	Yes – total protein, casein and beta-lactoglobulin	X	Mediterranean	Calculated and measured CM protein not always similar
Indian milk ladder (32)								
6	2–4	Yes	Moderate jump in steps	50 mg/8.68 g	Yes – total protein	High in sugar and fat – though recipes were adjusted to reduce sugar & fat content as able	Culturally relevant to India	Calculated and measured CM protein not always similar
Canadian milk ladder (34)								
4	2–4	No	Discrepancies in protein content in single steps	Not listed	No	X	Canadian foods	Simple
German milk ladder (40)								
6	1–3	Yes	Moderate jump in steps (each step is subdivided into multiple steps)	8 mg/7 g	No	X (some recipes adapted to contain less sugar)	German	Each step with progressive serving increases of the same food
Spanish milk ladder (41)								
4	1–6	Yes (not published currently)	Large jumps in some steps (each step is subdivided into multiple steps)	95 mg/6.2 g	No	Yes	Spanish	

ideally will have a history of prior mild reactions to CM and a higher prior tolerance level, although again prior reactions are not clear indications of any future reactions. The patient's comorbid conditions including asthma must be well managed to prevent more severe potential reactions. No language or comprehension barriers should exist, and families should have the time and resources needed to use the ladder. Families should also have education on reaction management, should have emergency medications in the home and should have ready access to emergency services. Lastly, a younger age may be preferred as older patients may be prone to persistence of allergy (30).

Aspects of the ladder design also must be considered for successful use. Ladders should offer clear information on food allergen content. This should include calculation and ideally measurement of the allergenic protein content. The ladder should include similar items in terms of allergenic protein content in each step, with clear recipes specifying time and temperature of heating. The health and nutritional value of the food as part of the patient's diet should be considered as well as the taste and acceptance of the food. Culturally appropriate ladders should be provided, and commercial options can be offered as able. There should also be clear guidance to families on how to offer each step and for how long prior to progressing, as well as instructions for safe dosing, i.e., when the child is in their normal state of health, in the home with a parent/guardian and access to emergency medications.

Benefits beyond allergen introduction

There are benefits outside allergen introduction in the use of food ladders for IgE-mediated CMA. This includes nutritional aspects such as increased food introduction and potential expanded diet diversity and increased fiber intake.

For families utilizing a ladder, they may appreciate the decreased need for label reading and less concern about precautionary advisory labeling (31). There may be a subsequent reduction in food related anxiety (31). The expansion of the diet may also improve socialization and expand/normalize the child's diet. There may be a financial benefit in a decreased need for observed OFCs, if the family would be expected to shoulder some of the financial cost of these challenges.

With the thought that ladders, with their gradual introduction of allergen, may promote tolerance, as well as their benefits outside of allergen introduction, they are a useful tool for providers to utilize in a carefully selected patient. Further studies both working on the creation of a ladder that meets all recommendations for safe use are needed, as well as studies that demonstrate their effectiveness in tolerance induction and their positive benefits outside of allergen introduction. However, while we await further investigation, ladders can be used judiciously in the properly selected patient with positive results. Future management of children with CMA may also include discussion around the immunomodulatory potential of the child's dietary intake, which includes factors considered in the ladder such as sugar, fat and fiber intake.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AH: Writing – original draft, Writing – review & editing. DF: Data curation, Writing – review & editing. CV: Writing – original draft, Writing – review & editing.

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Food allergy issues among consumers: a comprehensive review

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Food Allergy (FA) is a growing global public health concern. In the United States alone, 8% of children and 11% of adults have a convincing FA (symptoms consistent with an IgE-mediated reaction to a specific allergen). Given the significant prevalence of this condition, the objective of this mini-review is to illustrate the many dimensions of life that are impacted among those with FA. Summarizing findings from a breadth of current literature, we present how FA affects social, psychological, and economic-related quality of life. With this informative review, we endeavor to bring increased awareness to these issues and help cultivate a better future for individuals with FA.

KEYWORDS
food allergy, quality of life, psychosocial burden, public health, social determinants of health

1 Introduction

Food allergy (FA) is a significant public health concern, impacting about 8% of children and 11% of adults in the United States (1, 2). Although you can be allergic to any food, the top nine food allergens are peanuts, milk, shellfish, tree nuts, eggs, finfish, wheat, soy, and sesame. Every allergic reaction is unique to the individual and the situation, with 42% of children experiencing severe reactions reporting at least one lifetime visit to the Emergency Department (ED) (1). Although FA can develop at any age, certain allergens may be more prevalent at certain stages of life. In early life, milk is the most common allergen, impacting 53% of children <1 year old; in adolescence, peanuts are the most common impacting 29.5% of children >14 years old; and once individuals reach adulthood, shellfish is the most common, impacting 2.9% of adults (1). Children with FA are also significantly more likely to have atopic comorbidities, including asthma, atopic dermatitis, eosinophilic esophagitis (EoE), and allergic rhinitis. When comparing prevalence for all children to those with FA, the following were shown: for asthma, 12.2 to 32.6%; for atopic dermatitis, 5.9 to 14.9%; for EoE, 0.2 to 0.7%; for allergic rhinitis, 12.8 to 30.4% (1). Throughout this mini-review, we will explore the psychosocial and economic impacts on FA-related quality of life (QoL).

2 Daily quality of life with food allergy

The CDC defines health-related QoL as "an individual's or group's self-perception of their physical and mental health over time" (CDC-HRQOL) (3). Living with FA impacts both of these aspects and although there are many emerging treatments that may help mitigate the severity and reduce the burden, there is no cure. Food allergic individuals and their families must adapt and learn how to navigate the world with a potentially life-threatening food condition. One study assessing the psychosocial burden of FA among US adults found that multiple FA, severe reactions, a current epinephrine auto-injector prescription, a history of epinephrine use for FA treatment, and a FA-related ED visit in the last 12 months are all factors indicative of a higher Food Allergy Independent Measure (FAIM) score (4). The FAIM score assesses an individual's "perceived risk of accidental allergen exposure and the severity of the anticipated outcome" (4). Therefore, a higher FAIM score indicates a greater impact on QoL. The daily burden of FA management can increase stress and anxiety surrounding the fear of having a reaction, the ability to treat said reaction, and even the possibility of FA-related bullying. This need for hypervigilance can lead to avoidance, social isolation, and decreased QoL (5, 6). Areas of life where QoL impacts may be most abundant include the school setting, social interactions, family relationships, finances, allergen labeling on packaged foods, shopping for safe foods, dining out, and traveling.

2.1 School-related impacts

School is a place for children to learn and grow academically and socially. In early childcare settings, it is important to recognize that since children often cannot advocate for themselves, parents place their trust in the school to protect them and respond appropriately to a FA emergency. A survey of early childcare professionals reported 38% felt unprepared to administer epinephrine if a severe allergic reaction were to occur, more than 25% were unfamiliar with an Emergency Action Plan (EAP; outlines the steps to take when a specific child is having an allergic reaction), and less than half of respondents reported being comfortable identifying allergy-friendly food labels (7). Increasing efforts must be made to better prepare early childcare professionals to communicate with nonverbal children, recognize the signs of an allergic reaction in a young child, and know how to respond effectively.

About 18% of children with FA have had an allergic reaction at school and 25% experienced an anaphylactic reaction for the first time at school (8). In elementary and middle school, children may experience new stressors among their peers. Children without FA often do not understand their severity and how dangerous they can be. As a result, there is an opportunity for bullying to occur. One study found that 57% of participants reported they were either touched with their allergen, it was thrown at them, or their food was purposefully contaminated with the allergen (9). These interactions can further exacerbate the fear and anxiety associated with food allergies for the child and their caregiver. The child may feel unsafe attending school and caregivers may fear for their child's safety. Additional consequences to QoL could include the child missing school due to a visit to the ED, fear and anxiety leading to increased isolation (i.e., sitting separately from peers at lunch and, feeling different from one's peers) and the child's caregiver missing work.

As a child moves into adolescence and young adulthood, FA can lead to increased stress and risk-taking behaviors. An important indicator of engagement in risk-taking behaviors is the individual's support system. With less support, individuals are less likely to carry an epinephrine auto-injector, speak up at a restaurant, discuss their FA in social settings, and check food labels when trying foods (10). Adolescence and young adulthood is a time for individuals to discover themselves and find where they fit in, which can be difficult when they feel different from their peers. FA management requires hypervigilance and preparedness to avoid an emergency. While others may not think twice about going to a restaurant, for example, it can be isolating to be the odd one out, who may opt not to eat the food or not go in the first place.

The transition to college can be a daunting process for students with FA as they leave the support system they have built at home and independently manage their FA for the first time. One study gathered insight from college students and their parent's experiences, and many expressed concerns for their safety regularly and the detrimental toll it takes on their mental health. These concerns stemmed from dining halls being ill-prepared to safely prepare and label food correctly, roommates being careless with allergens, the fear of kissing someone who had previously eaten the allergen, and the fear of having a reaction and having to miss school which can negatively impact their studies (11). It is increasingly important to educate everyone on the severity of FA, implore them to take FA seriously, and implement safeguards and policies that will protect students and create an environment that allows for peace of mind and the ability to focus on academics without fear.

2.2 Work-related impacts

There is very limited research formally investigating the impacts of managing FA in the workplace, but there are countless articles, blogs, and podcasts of firsthand experiences and advice available. One article through the *Harvard Business Review* explored workplace inclusivity regarding FA, stating that "one in three people with FA report feeling uncomfortable or unsafe at work, and 60% of millennials with FA report experiencing anxiety at work because of their condition" (12). This is consistent with previous research concluding that FA adults' QoL is often impaired, and they may experience increased stress and anxiety (4, 13). It can be challenging to navigate the workplace as a FA adult due to concerns over being a burden, fear of cross-contact if proper precautions are not taken, and feeling isolated as most work events involve food (12). There is also the concern of FA bullying which persists through adulthood. Michele Payn's book and subsequent podcast on food bullying recounts an anonymous account of bullying in the workplace. The individual described coworkers intentionally leaving out open bowls of peanuts during meetings and at cubicles, while being aware of their severe peanut allergy (14). The burden of FA persists through adulthood and can greatly impact work life. Fortunately, FA is covered under The Americans with Disabilities Act of 1990 (ADA), therefore there are legal protections in place to combat FA-related discrimination (15). FA adults can advocate for change and bring awareness to employers and co-workers by talking with management, suggesting social events are non-food related, and sharing educational resources on food allergies, such as Food Allergy Research and Education's (FARE) series on food allergies in the workplace (16).

Abbreviations: FA, Food Allergy; QoL, Quality of Life; ED, Emergency Department; PAL, Precautionary Allergen Labeling; EAP, Emergency Action Plan.

2.3 Social interactions and relationships

As humans, our QoL is deeply tied to social interactions and relationships. One significant way people connect is through food, which is a major part of our identity and culture. Food allergies can put a strain on many people and relationships as their impacts are ingrained in our everyday lives. We have food at almost every social gathering, i.e., parties, sporting events, dining out, work conferences, etc. Research has found that many families with a FA child will often eat at the same restaurants they know are safe, avoid eating out completely, and limit travel and vacations if they must fly or stay overnight (17). In addition, the added burden has been found to cause strain on marriages, limit the child's ability to play at a friend's house or participate in parties, sports, and camps, and even cause caregivers to adjust their work schedules or stop working altogether to homeschool their children (5). One study exploring personality traits and FA experiences found that extroverted FA adults report more social challenges attributed to their FA, "such as people being unkind toward them and feeling anxious or stressed in social occasions and lack of understanding from others (18). Food allergies can be managed, but the burden can often be overwhelming when people do not feel they have adequate support to ensure their safety in food-related situations.

2.4 Food labeling practices

Navigating food labels and shopping for allergen-safe foods can be a daunting task. There is little regulation on food labels, specifically when it comes to precautionary allergen labeling (PAL) such as "may contain" or "manufactured on shared equipment" statements. Shoppers should always check ingredient labels in case of ingredient changes, or the addition of new allergens. Fortunately, the Food Allergen Labeling and Consumer Protection Act (FALCPA) requires labeling major allergens on packaged foods (19). According to a study assessing people's understanding of PALs, over half of those surveyed reported current labeling practices interfering with their daily lives and expressed interest in more information on the meaning behind PALs. In addition, 27% of respondents reported themselves or a family member having an allergic reaction after eating a food item with a PAL statement (20). Clear policies must be implemented to ensure clarity and consistency of PALs and the safety of FA consumers.

2.5 Economic impact and disparities

The financial burden of food allergy is another significant factor that can impact people's lives. The overall economic cost of FA is 24.8 billion, with 4.8 billion attributed to direct medical costs and 20.5 billion to family costs (21). In a cross-sectional survey given to 1,643 caregivers of children with current food allergies, the most frequent and common costs were hospitalizations, ED visits, special diets and allergen-free food, changes in childcare, special summer camps, changing schools due to FA, and missed work or job loss among caregivers (21). Unfortunately, managing FA and providing safe experiences comparable to those without FA can be incredibly expensive.

In addition, socioeconomic disparities that can increase the financial burden and negatively impact one's QoL must be considered. Research has found that historically underrepresented population groups using Medicaid often utilize the ED more frequently and are less likely to be diagnosed with a FA due to difficulty accessing specialized care through an allergist (22). Ensuring all FA patients have access to affordable specialty care, such as an allergist or primary care physician must be prioritized. Other factors to consider may include living in a food desert (areas with limited access to affordable and nutritious food) or food swamp (areas where fast food and junk food are more prevalent than healthier options) and experiencing food insecurity, which can further limit the availability and affordability of allergen-safe foods and negatively impact the nutritional quality of the individual's diet if the less nutritious option is deemed safer, more convenient, and more affordable (23, 24). These added burdens and lack of needed resources can further increase the stress and anxiety associated with managing a FA. Therefore, systems must be in place to support these individuals and families, such as routine food insecurity screening among FA patients (25).

3 Discussion

Managing FA is more complex than simply avoiding the allergen (s). The burden of the disease is on the individual and their entire support system, including family, friends, and the surrounding community, and can impact all aspects of life. In a study examining mothers' experiences of raising a child with FA, participants reported encountering skepticism about the severity of their child's allergy, judgment about their management approach, and expressed concerns about balancing politeness with ensuring their child's safety during food-related situations (26). It is easy to dismiss the severity of this burden if you are not directly affected, but by bringing awareness to the QoL impacts we can create safe, inclusive, and supportive communities for those struggling to manage FA.

There are several possible solutions to increasing awareness and positively impacting QoL, as outlined in Table 1. The first is to be intentional about creating a supportive community, which could look different for each person. One study found that 62% of early childcare professionals did not understand the terminology often used in an EAP (7). A helpful way to support your child would be through outlining an EAP with your child and their doctor and taking the time to sit down with their teachers and explain all the needed steps. It is also important for parents to empower their children and help them see the positives associated with their FA. Adolescents and young adults have reported that living with their FA has made them feel more responsible and helped them to better advocate for themselves and others (10). Parents should also seek counseling and/or support groups for themselves and their child to help manage and navigate the added stress and anxiety and share experiences with families in similar situations (5).

Food allergy education is vital to increasing community awareness and preparedness in case of a FA emergency. A review by Sansweet et al. (27) suggests that many negative QoL impacts of FA may stem from a lack of knowledge and awareness. This review highlights the importance of prioritizing community-based education initiatives on reaching high risk communities with limited access to resources. Public health workers should encourage schools, workplaces, and restaurants to provide regular education and training on FA. Education is a simple and effective way to increase awareness and improve knowledge and perceptions of FA. Teachers are often ill-equipped to

TABLE 1 Summary of food allergy-related impacts on consumers and proposed solutions.

Quality of life impacts	Proposed solutions
School-related • Safety, fear, anxiety, bullying, isolation, missed school/work • Lack of teacher preparedness (i.e., food labels, epinephrine autoinjector administration) • Risk-taking behaviors in adolescence and young adulthood *See *School-Related Impacts & Discussion* Sections	• Education and training o Teachers, nurses, staff, and students ■ Epinephrine use, signs and symptoms, cross-contact, safe-cleaning practices, reading food labels • Emergency Action Plan • Support system • Advocate for self and/or child
Work-related • Safety, fear, anxiety, bullying, isolation, missed work • Lack of knowledge and awareness among co-workers/employer • Work events (i.e., dinners, conferences) *See *Work-Related Impacts* Section	• Education and training o All staff ■ Sharing resources ■ Epinephrine use, signs and symptoms, cross-contact, safe-cleaning practices, reading food labels • Advocate for self o FA is protected under the ADA
Social Interactions & Relationships • Food is a part of daily life (parties, restaurants, traveling, playdates, camps, etc.) • Marriage strain on caregivers of FA child • Lack of awareness and understanding *See *Social Interactions and Relationships & Discussion* Sections	• Peer and family education o Sharing resources • Support system o Counseling, support groups o Peer support • Advocating for self/child • Safe dating practices
Allergen Labeling • Minimal regulation on PALs • Vigilance in checking labels in case of changes *See *Food Labeling Practices & Discussion* Sections	• Advocate for policy changes o FALCPA (19) o FASTER Act
Economic Burden and Health Disparities • $24.8 billion overall o $4.8 billion in direct medical costs o $20.5 billion in family costs ■ Hospitalizations, ED visits, special diets and allergen-free food, changes in childcare, special summer camps, changing schools due to FA, and missed work or job loss among caregivers • Financial burden • Food insecurity • Lack of access to care *See *Economic Burden and Health Disparities & Discussion* Sections	• Expanding insurance coverage • Volunteer allergists at clinics • Advocate for stock-epinephrine in schools and public places • Build a more diverse workforce more likely to advocate for change

manage a FA emergency even though they are often the first line of defense for students having a reaction. Training has been shown to increase awareness and teacher's confidence and ability to respond effectively in a FA emergency (28). The implementation of frequent and recurrent training can aid in increasing teachers' ability to correctly manage using epinephrine autoinjectors. In addition, students can also benefit from receiving FA education as their lack of knowledge can often lead to bullying situations that can become dangerous and life-threatening. Discussions should be encouraged at school and at home. Helpful education resources for all ages can be found on the Center for Food Allergy and Asthma Research website to help facilitate conversation (29).

Advocacy can be an effective tool for affecting policy change and has already proven useful at the federal level. Advocates have worked to regulate PALs across the US for many years. The Food Allergen Labeling and Consumer Protection Act (FALCPA) (19) became law in 2004, and that was the last time any changes were made since 2021 when the Food Allergy Safety, Treatment, Education, and Research (FASTER) Act was implemented. This law requires the addition of sesame along with the other previous top allergens to be labeled on packaged foods sold in the US and went into effect on January 1st, 2023 (30). This is an exciting and welcome addition that will help create peace of mind for shoppers allergic to sesame.

Lastly, medical professionals, researchers, advocacy groups, and policy makers must work together to mitigate the financial burden placed on families and reduce health disparities. There is not just one solution, but many systems that need to work together to ensure affordable and accessible care for everyone. This may include expanding insurance coverage, having allergists volunteer their time at clinics in underserved communities, or advocating for stock epinephrine in schools and public spaces. In addition, building a more diverse workforce of healthcare professionals who are more likely to advocate for change can build trust among patients of similar backgrounds and cultivate a more welcoming and accessible healthcare experience (31).

The public health burden of FA is complex and multifaceted. We must look at the issue from a holistic lens and ensure we capture the entire experience and acknowledge the toll it can take on one's physical and mental health. Hypervigilance is needed to ensure one's safety. In addition, the fear and anxiety of a potential reaction are often compounded by the social and financial pressures of being able to advocate for oneself among peers and afford safe foods and needed treatment. Increasing awareness of both the severity and QoL impacts of living with and managing the daily stressors associated with having a FA are imperative for creating a community of understanding and support.

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Possible interactions between selected food processing and medications

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The impact of food processing on drug absorption, metabolism, and subsequent pharmacological activity is a pressing yet insufficiently explored area of research. Overlooking food-processing-drug interactions can significantly disrupt optimal clinical patient management. The challenges extend beyond merely considering the type and timing of food ingestion as to drug uptake; the specific food processing methods applied play a pivotal role. This study delves into both selected thermal and non-thermal food processing techniques, investigating their potential interference with the established pharmacokinetics of medications. Within the realm of thermal processing, conventional methods like deep fat frying, grilling, or barbecuing not only reduce the enteric absorption of drugs but also may give rise to side-products such as acrylamide, aldehydes, oxysterols, and oxyphytosterols. When produced in elevated quantities, these compounds exhibit enterotoxic and pro-inflammatory effects, potentially impacting the metabolism of various medications. Of note, a variety of thermal processing is frequently adopted during the preparation of diverse traditional herbal medicines. Conversely, circumventing high heat through innovative approaches (e.g., high-pressure processing, pulsed electric fields, plasma technology), opens new avenues to improve food quality, efficiency, bioavailability, and sustainability. However, it is crucial to exercise caution to prevent the excessive uptake of active compounds in specific patient categories. The potential interactions between food processing methods and their consequences, whether beneficial or adverse, on drug interactions can pose health hazards in certain cases. Recognizing this knowledge gap underscores the urgency for intensified and targeted scientific inquiry into the multitude of conceivable interactions among food composition, processing methods, and pharmaceutical agents. A thorough investigation into the underlying mechanisms is imperative. The complexity of this field requires substantial scrutiny and collaborative efforts across diverse domains, including medicine, pharmacology, nutrition, food science, food technology, and food engineering.

KEYWORDS

food processing, thermal processing, non-thermal processing, food-drug interaction, membrane transporters, cytochrome P450, drug bioavailability

Introduction

The health effects of bioactive substances in the human body are affected by several factors, including food composition and processing conditions, storage conditions, light and heat, among others. These factors greatly limit the stability and bioavailability of bioactive substances (1).

Adverse food-drug interactions can be serious and, in extreme cases, may result in severe health consequences, including death. In children and older adults, undetected disadvantageous food-drug interactions may lead to serious morbidity and mortality and be misdiagnosed as chronic disease progression (2). For instance, recent recognition of the effects of certain foods on many drugs metabolized by CYP450 families or drugs susceptible to chelation and absorption have increased awareness for prevention of food-drug negative interactions (2–4).

However, the possible impact on health by the processes utilized in producing the various foodstuffs and their possible interactions with medications have not been adequately covered. A recent Google Scholar search (Dec. 4, 2023) yielded (for "effect of food on drug" and "effect of food processing on drug," or medication) 606 and 0 hits, respectively. As new technologies and novel drugs emerge, interactions between food processing and drugs can occur through various mechanisms (e.g., drug absorption, metabolism, effectiveness, chemical changes). Few selected possible aspects are summarized below, with the overall aim to raising awareness and incentivize future research on the possible pharmacological interactions between food processing and drugs and their health ramifications.

A recent review on the health-promoting features of food bioactive compounds including polyphenols, carotenoids, vitamins, glucosinolates, triterpenes, phytosterols, alkaloids, capsaicinoids, polysaccharides, polyunsaturated fatty acids and bioactive peptides, concluded that there are several factors that may affect the content and bioavailability of these compounds. Indeed, one of the factors that has a significant influence on bioactive compounds is the effect of food processing (5). Some selected types of food processing and their possible interaction with drugs are listed below.

Thermal processing

Among the traditional technologies of food processing, such as drying, addition of preservatives like salt, heating is certainly the most common one. Among many types of thermal processing deep fat frying, grilling or barbecuing are utilized both for home cooking, food service and industrial manufacturing. This unique unit operation requires high heat and the product undergoes texture changes, while a considerable amount of oil is often absorbed.

Reduction of the enteric absorption of drugs

Fried foods, typically prepared with high-fat cooking methods, can delay gastric emptying and influence the enteric absorption of certain drugs, particularly those that are lipophilic. Traditional fried food is made by immersing it in hot oil at a typical temperature of 150–200°C. Worldwide fast-food companies supply fried foods, such as French fries, fried chicken, fried pork chops, fried sweet potatoes, fried banana chips, to count only a few. Fried foods are widely popular due to their unique taste and flavor, golden color, crisp texture and other for the consumers appealing attributes. However, some fried foods absorb a large amount of oil during the traditional frying process, and the final oil uptake can reach in extreme cases up to 50% of the total weight (6). In many fried foods, oil uptake is above 20% of the total weight. For instance, in case of potato chips, it is 34.6%, corn chips, 33.4%, tortilla chips, 26.2%, doughnuts, 22.9% of the total weight (7).

Reduction of oil uptake is possible by applying a plethora of processing techniques. The frying process, product characteristics and oil quality are key factors affecting oil absorption. At higher frying temperatures, oil absorption is usually reduced, as the process is shorter and the enhanced crust formation acts as a physical barrier for oil imbibition. For instance, potato crisps fried at 120°C have higher oil content compared with their counterparts fried at 180°C (7). Various innovative frying processes have been developed to reduce oil uptake, like vacuum frying (VF), microwave frying (MF), microwave-assisted vacuum frying (MVF), ultrasound combined microwave vacuum frying (UMVF), air frying, and radiant frying (8). Baking is also utilized and could reduce oil uptake significantly (9).

Notably, in addition to oil uptake, frying produces volatile/non-volatile compounds which darken the food's color, generate aromas, and develop unique crust and textures (10, 11).

The high oil content of the fried foods could interact with the drug enteric coating. Some medications have enteric coatings to protect them from stomach acid and improve absorption in the intestines (e.g., erythromycin, pancrelipase, proton pump inhibitors, budesonide). Hence, different processing methods of the same food product, such as deep fat frying or baking may considerably and differently affect the dissolution of enteric coatings, by this way potentially altering the drug's release profile.

Generation of pleiotropic and harmful aldehydes

To properly and comprehensively analyze the frequent interference of food frying with the enteric absorption of various medicines, one must take into account also that the high temperature of the oil may induce harmful chemicals, above all it enhances the oxidation of oil lipids, of course via non enzymatic pathways, and it also induces the formation of several other potentially harmful compounds, like acrylamide (due to a Maillard reaction), polycyclic aromatic hydrocarbons and heterocyclic amines. Several strategies to reduce acrylamide formation during food processing (e.g., frying, baking) were recently reviewed (12, 13).

Extensively studied since many decades is the oxidation of polyunsaturated fatty acids (PUFAs) at the level of the carbon–carbon double bond(s), a free radical chain reaction called lipid peroxidation, which is leading to alkoxy-, peroxy-, lipid radicals and lipid hydroperoxides; the latter molecules are highly unstable, so easily break down generating various still reactive but much more diffusible end-products, of which the most studied are aldehydes, since provided with different toxicological properties (14–16).

Of the several aldehydes stemming from PUFAs, the quantitatively and qualitatively more important are malonaldehyde, generated from both ω-3 and ω-6 PUFAs, 4-hydroxyhexenal (HHE) from ω-3 PUFAs and 4-hydroxynonenal (HNE) from ω-6 PUFAs (16). These carbonyl compounds, in particular HHE and HNE, readily form stable adducts with proteins and lipids by this way deranging their structure and function, for example at the level of the intestinal epithelial layer, and also exerting strong pro-inflammatory stimuli (16, 17).

Indeed, the generation of these toxic aldehydes by high fat frying has been shown for four different vegetable oils, all containing both ω-3 (linolenic acid) and ω-6 (linoleic acid) PUFAs namely soybean oil, sunflower oil, rapeseed oil and corn oil (18). In the food cooked with any of these four vegetable oils the production of relevant amounts of HNE was demonstrated (19). Previously, the same harmful aldehyde was consistently detected in relatively high concentration in French fried potatoes obtained from six different fast food restaurants (20). HNE is most likely the most toxic aldehyde produced during lipid peroxidation (16), a biochemical process which in the thermal processing of food is driven and sustained by the reactive oxygen species generated in high amount by heat (21).

As regards HNE, a very important observation was recently made that points to an additional mechanism of interference by this aldehyde with the pharmacological effect of orally taken drugs. In fact, in a screening study actually simulating a clinical worst case scenario, bags for endogenous saline infusion, catheters and disposable syringes, all made with plastic polymers, were shown to leach HNE in their medicinal contents (22). Based on the recognized readiness of this reactive and diffusible carbonyl to form protein and lipid adducts, a direct addition of HNE and maybe other reactive aldehydes to active pharmacological principles (API) appears a quite likely event.

Indeed, deep fat fried food by-products are at present considered as a significant dietary contributor to the most common chronic diseases especially affecting the elderly, including atherosclerosis, cancer and hypertension (23). Hence, a spectrum of alternative types of food processing should be taken into consideration (e.g., baking, air frying).

Methylglyoxal, glyoxal and AGEs, as potentially dangerous products of Maillard reaction

Methylglyoxal (MG) and glyoxal (G) are two alpha-ketoaldehydes (dicarbonyls) that may derive from autoxidation of polyunsaturated fatty acids and glucose, and are consistently present in foodstuff rich in these nutrients, in which they are mainly formed via the Maillard reaction. The two reactive dicarbonyls form adducts with proteins, by this way being potentially cytotoxic, in the case of food potentially enterotoxic, and, in addition, they readily lead to a quantitatively considerable formation of advanced glycation end products (AGEs), chemical species with strong pro-oxidant, pro-inflammatory and cytotoxic properties (24, 25). In fact, following the binding of AGEs to the membrane receptors for advanced glycation end products (RAGEs), a redox signaling is generated that activates the inflammatory reaction and induces an oxidative burst (25, 26).

An excessive production of MG and G, as it could occur especially at very high temperatures and long time exposures, would contribute to bring in the gut a mixture of reactive species, with likely derangement of enteric structure and function (24, 27). An indirect, while quite effective, mechanism of malabsorption not only of nutrients but also of medications. But, by far more important as regards food processing interaction with drug pharmacokinetics, is the demonstrated reaction of dicarbonyls and AGEs with membrane transporters like ABCA1 (ATP binding cassette sub-family A member 1), considerably expressed on the surface of the intestinal epithelial barrier. Indeed, in the gut, one of the largest groups of membrane transporters, namely the ABC family, allows the intracellular uptake of a great variety of molecules including many drugs, mainly lipophilic ones. Years ago, glyoxal, but not methylglyoxal, was shown to destabilize the activity of ABCA1, in cultured human skin fibroblasts and murine macrophages, even if the protein synthesis of the transporter was not affected (28). Much more recently, using murine macrophages, the same group demonstrated this time that the advanced glycation of human albumin (AGE-albumin) was able to markedly inhibit the synthesis of the membrane transporter ABCA1. Moreover, those authors elucidated the mechanisms of such an effect of AGE-albumin, namely a net enhancement of ABCA1 ubiquitination and consequent proteasome degradation (29). Thus, based on these findings, one should most likely expect a significant contribution also by a “dicarbonyl stress” to the potential interference of food thermal processing on the uptake of drugs.

Thermal oxidation of sterols: oxysterols and oxyphytosterols

The high temperatures that could be reached in the industrial food processing, and during frying, grilling or barbecuing of a large variety of foodstuffs, generate another wide class of potentially harmful compounds, namely stemming from the heat-dependent oxidation of sterols, quantitatively well represented in foods both of animal and vegetable origin. By far more investigated and characterized is the family of oxysterols, 27-carbon atoms compounds derived from the oxidation of cholesterol, while the oxyphytosterols, i.e., the oxidation products of phytosterols, still need further characterization as regards their possible detrimental effects on health.

The thermal processing of food of animal origin has clearly been demonstrated to induce the non-enzymatic formation of a large variety of oxysterols (30, 31) the most dangerous of which are certainly 7β-hydroxycholesterol (7βOHC) and 7-ketocholesterol (7KC), since provided with highly cytotoxic and pro-inflammatory properties (32–35). An indirect interference with the gut absorption of medicines is that affordable by a mixture of oxysterols like that present in the gut of people fed a Western type of diet, because it contributes to damage the intestinal epithelial layer, in particular by deranging both tight and adherens junctions (36, 37). The impairment of the intercellular adhesion molecules should then mainly affect the paracellular absorption of drugs, i.e., the main mechanism of intestinal uptake of hydrophilic drugs (38).

On the other hand, hydrophobic drugs are absorbed via a transcellular route, taken up by active transporters (38), hence the high oxysterols’ intake due to thermal processed food might represent an obstacle for the physiological action of the numerous multidrug protein transporters selectively expressed along the gastro-intestinal tract (39). In principle, oxysterols could readily oxidize these transporters through the up-regulation of reactive oxygen species production, and, in addition, two of them, namely 5α,6α-epoxycholesterol and 5β,6β-epoxycholesterol, were even shown to form protein adducts by reacting with the ε-amino group of lysine (protein sterylation) (40). However, the suggested addition reaction of defined oxysterols with drug protein transporters is at present just a speculation, since no specific literature is available yet. The same lack of specific literature (addition reaction with membrane transporters) applies for HNE and other aldehydes, any way shown to readily undergo addition reaction with proteins.

In the food of vegetable origin, steroids are largely represented and are named phytosterols, compounds having a structure similar to cholesterol (41), and like cholesterol being prone to autoxidation, leading to the generation of quite a number of oxyphytosterols. As in the case of oxysterols, the quantitatively more relevant oxyphytosterols are 7K- and 7OH- derivatives of sitosterol and campesterol, but also the epoxy derivatives may reach elevated concentrations in the diet (41, 42).

A clear example of heat-induced oxidation of phytosterols, was provided by a careful and detailed analysis of the oxyphytosterol content of refined rapeseed oil, really one of the most used edible oils worldwide, before and after thermal treatment. Two different temperatures were considered, 60°C and 180°C, and various heating times. The total oxyphytosterol content detected in the rapeseed oil heated at 180°C for 15 min resulted to be four times as higher as that quantified in the 60°C heated oil (43). Even in this study, actually in line with a much earlier report (44), 7K- and 7OH- and epoxide derivatives of sitosterol and campesterol represented the major oxyphytosterols detected (45).

While systematic analysis and characterization of these compounds are still missing, oxyphytosterols were already recognized to exert cytotoxicity when present in relatively high amounts in the diet (42, 45). Consequently, they in principle could affect the enteric absorption of those medicines that are taken up by the intestinal epithelial layer, if some cells of this layer are irreversibly damaged by phytosterol oxides. Further, one should expect that oxyphytosterol-epoxides, like oxysterol-epoxides could lead to stable sterylation of proteins, possibly including multidrug transporters. Indeed, protein sterylation by oxysterols and oxyphytosterols appears to be a very interesting emerging issue that deserves to be elucidated soon.

As regards the possible toxicity of oxysterols and oxyphytosterols stemming from thermal processing of food, the actual extent of it might be modulated by the adopted diet. For instance, many representative compounds of the Mediterranean diet, like tocopherols, fatty acids, polyphenols, argan and olive oils, different cytotoxic effects of 7βOHC and 7KC result to be quenched (46, 47).

Heat-induced production of recognized cytochrome P450 isoenzymes inducers: acrylamide, heterocyclic amines and polycyclic aromatic hydrocarbons

Not only deep-fat frying, but also, while in a relatively less amount, air frying, barbecuing and grilling give rise to other harmful compounds, in particular acrylamide, polyciclic hydrocarbons, namely benzo[a]pyrene, benzo[a]anthracene, benzo[b]fluoranthene, chrysene, and heterocyclic amines (48, 49). Notably, all these compounds are metabolized by various hemoproteins of the cytochrome P450 (CYP) superfamily, and induce their own metabolism, as they are potent inducers of CYP enzymes (50, 51). Since several components of the CYP superfamily are involved in the metabolism and biotransformation of a great number of drugs, a possible interference by the aforementioned classes of side-products of thermal processing of food appears very likely, even if specific proofs are not available yet in the literature.

Figure 1 depicts the various mechanisms by which thermal processing of food may interact and affect the pharmaceutical action of several drugs, that is interfering with their intestinal uptake, both directly, by inhibition of or competition with the gut multidrug transporters and indirectly, by damaging the epithelial cells and the intercellular junction molecules of the intestinal barrier, and by affecting drug metabolism.

The heat-mediated oxidation of food may produce elevated amounts of electrophilic compounds, such as aldehydes and epoxides, ready to make irreversible adducts with nucleophilic, i.e., polar drugs, like some antibiotics and antiviral active compounds, by this way most likely altering their pharmacokinetics. On the other hand, the intestinal absorption of the numerous electrophilic drugs is mainly regulated by uptake transporters and export proteins expressed on the plasma membranes of the gut epithelial lining (52), susceptible to the attack by aldehydes and epoxides stemming from heat processed food. Not least of all, several harmful byproducts that could arise from heated food may quench the pharmacological effects of drugs metabolized by CYP enzymes.

Thermal processing of medicinal herbs

Thermal processing (e.g., boiling, drying, heating, steaming) are frequently reported during the preparation of various traditional herbal medicines (53). Before their medical use, thermal processing methods are frequently utilized to treat the traditional Chinese medicine (TCM) and herbal materials to improve their efficacy and/or reduce their side effects. In some cases, the thermal processing seems to alter the herbal chemical components (53).

Understanding the temperature-dependent chemical reactions of herbal materials is necessary to explore the underlying mechanisms and optimize the procedures of thermal processing. Numerous cases have been reported on how thermal processing could influence the phytochemical contents, and sometimes could alter the bioactivities of these plant-derived foods. In some cases, the formation of new phytochemical conjugates was occurring.

Thermal-induced molecular conjugates are utilized for their antioxidant, anti-cancer, anti-diabetic, and anti- inflammatory activities. It is believed that the energy derived from such thermal processing helps to overcome the energy barriers and hence facilitates the phytochemical transformations. Frequently, the observed thermal-induced change in phytochemical contents could be attributed to the Maillard reaction. However, in other cases, chemical reactions such as degradation, transglycosylation, deglycosylation, dehydration, and oxidation were proposed. Yet, the reaction mechanism remains to be elucidated (53).

A typical example is Fritillaria *thunbergii* Miq. (*F. thunbergii*, family Liliaceae), the underground bulbs officially listed in the Chinese Pharmacopoeia as "Zhebeimu," that has been considered an important antitussive, expectorant, and antihypertensive agent in TCM for thousands of years. The major active components of the *F. thunbergii* are steroidal alkaloids, including peimine, peiminine, zhebeinine, zheberine, and zhebeinone, among others (54, 55). Sun-drying method, when compared with microwave drying, yielded significantly lower peimine and peiminine total content, protein, soluble amylose, resistant starch (RS), solubility, swelling power, and

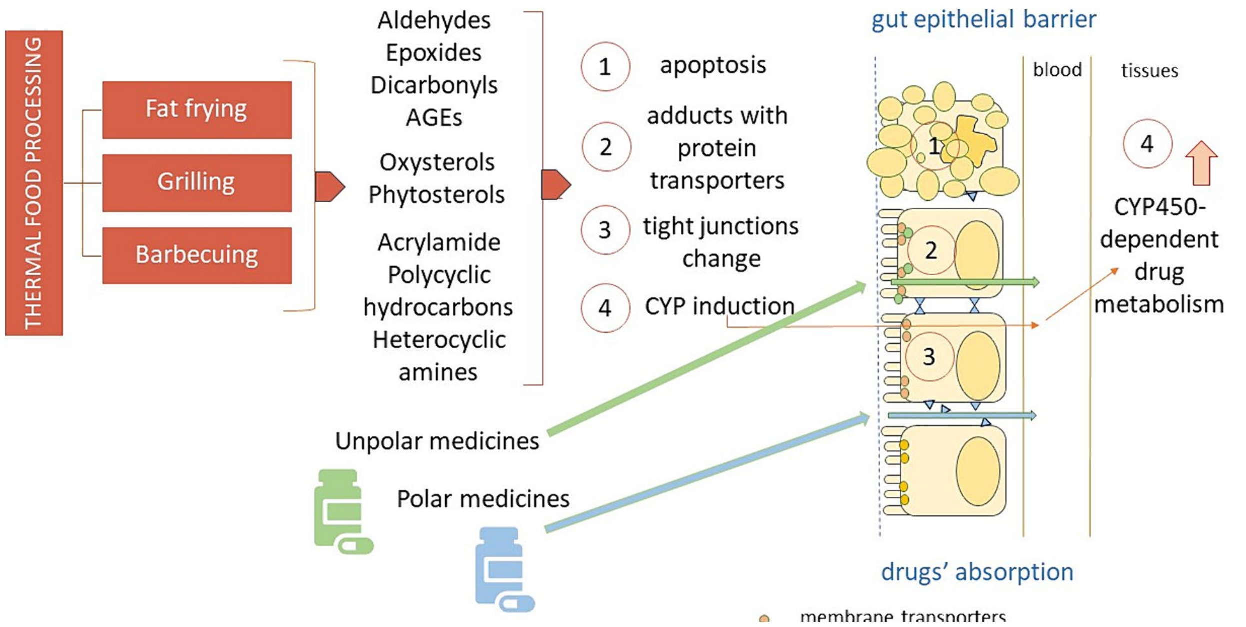

FIGURE 1
The different mechanisms by which thermal processing of food may interact and affect the pharmaceutical action of orally administered drugs. AGEs: advanced glycation end-products; CYP450: cytochrome P450.

relative crystallinity, while increased the insoluble amylose content and the water-binding capacity. Microwave-dried sample showed significant changes in starch content. Low levels of rapidly digestible starch and glucose and high RS levels were found in the hot air-dried and freeze-dried samples. It was concluded that *F. thunbergii* flour can be used as medicinal excipient and health product, especially when subjected to chemical or physical treatment (50).

Another example of a popular TCM is *Polygonum multiflorum* (Heshouwu), used for rejuvenate purposes. Steaming involved in the processing of *P. multiflorum* root extract leads to a new chromatographic peak in HPLC analysis. Its intensity increased with steaming times ranging from 8 to 48 h (53). It was shown that 2,3-dihydro-3,5-dihydroxy-6- methyl-4(H)-pyran-4-one and 5-hydroxymethyl furfural were confirmed (56). Likewise, in a subsequent study using steamed *P. multiflorum* extract, eleven new compounds were identified (4-furanones, 2-furans, 2-nitrogen compounds, 1-pyran, 1-alcohol and 1-sulphur compound) (57). Among these 11 newly formed products following steaming, 5-hydroxymethyl-furfural was further tested and demonstrated to have potent radical scavenging properties (57). In both studies, the Maillard reaction was believed to be involved in the formation of these new conjugates.

Panax ginseng is a further traditional medicinal herb treasured as health promoting tonic. Traditionally, *P. ginseng* could be processed into white ginseng (sun-dried ginseng) or red ginseng (steaming fresh ginseng at 95–100°C for a certain time duration), depending on the presence of this steaming step (53, 58). Previously, numerous studies reported on *P. ginseng* rich phytochemical contents (53, 59, 60). Panaxydol, a member of the class of polyacetylenes, is a phytochemical isolated from the root of *P. ginseng*. The steamed red ginseng was reported to contain higher panaxydol amount, compared to the un-steamed white ginseng sample (58). This finding bears medicinal significance, as this small molecule was shown to exert a net apoptotic effect in an anticancer study (61). One suggested possible route for the formation of panaxydol is via the oxidation of panaxytriol, another polyacetylene, following the thermal processing (53, 58).

In TCM, it is common to include the use of herb pair or herbal formula for treating diseases. Two or more different medicinal herbs could be combined in different ratios and processed into a single decoction (53, 62). It is believed that the combined herbs in an herbal formula could work synergistically and enhance the medicinal values. During the preparation of decoction from herbal formula, heating and boiling are usually involved. Some of these new phytochemical conjugates derived from herbal formula were not detected in any of the single herb (53). More recently it was shown that the primary structure of some ginsenosides can be modified to produce secondary ginsenosides through natural microbiota, or by various processes during the preparation of the phytotherapeutic product, such as heating or drying. Different species of genus *Panax* contain numerous compounds with diverse and important biological properties such as immunomodulatory, anti-inflammatory, and anti-cancer properties (63).

Nonthermal processing

Nonthermal processing refers to minimally processed food techniques to preserve foods without the use of high heat, allowing processors to improve quality, nutritional aspects, efficiency and superior consumer products. Some nonthermal processing include: 1. High-pressure processing (HPP), which is a non-thermal food and beverage preservation method that guarantees food and drink safety and achieves an increased shelf life, while maintaining the high organoleptic and nutritional attributes of fresh products. 2.

High-pressure homogenization (HPH), which is based on the same principles as homogenization process used in the dairy industry to reduce the size of fat globules, but it works at much higher pressures (100–400 MPa). 3. Pulsed electric fields (PEF) processing, which applies high voltage pulses (20–80 kV/cm) with a duration of milliseconds to microseconds to treat foods placed between two electrodes. For solid foods, due to the large gap required between the electrodes of the treatment chamber, and the power limit of the pulse generator, typical lower voltage pulses are applied (1–8 kV/cm).

The aforementioned nonthermal processing technologies offer what could be defined as "cold pasteurization" (64), a quite advanced application for PEF and HPP. Other processing technologies such as ozone and hydrogen peroxide treatments, are used in limited cases such as sanitization of dairy supply chain (65) and water (66). Gamma irradiation is yet another non-thermal process, but, due to consumer issues, its utilization is very limited (e.g., for spices) (67). Plasma technology is a further very promising minimally food processing technology. The use of plasma offers favorable potential owing to its different attributes including non-thermal food processing, enzyme inactivation, removal of pesticides toxin, less damage to food, low nutritional losses, and high quality of the final products (68). This technology is still under development and could become a very promising non thermal alternative in the near future.

High-pressure processing

A typical example of the effect of nonthermal minimally processed food is highlighted when comparing the *in vitro* bioavailability of isoflavones from soymilk-based beverages, high-pressure processing (HPP) (400–600 MPa, holding times from 1.5 to 6 min), pulsed electric field (PEF) (35 kV cm^{-1}) and typical regular thermal treatment (TT) (90°C for 1 min). The isoflavones concentration was found to be higher in HPP-treated samples (38.5%) whereas, in TT and PEF products, the range was significantly lower (25–26%) (69). These data highlight that processing plays a pivotal role in the bioavailability of isoflavones as well as many other active compounds.

It is known that flavonoids contained in grapefruit juice, such as naringinin and hesperidin, are responsible for the inhibition of transmembrane transporters, which play a role in the passage of several drugs from the intestinal lumen within the bloodstream (3). Thus, it clearly indicates that processing could have a significant potential interaction with drugs. As HPP orange and grapefruit juice are becoming quite popular currently, consumers are exposed to various levels of active compounds, such as relatively high concentrations of certain flavonoids. For instance, it was reported that the coadministration of drugs such as acebutolol, celiprolol or fexofenadine with grapefruit juice, or atenolol, ciprofloxacin, and fexofenadine with orange juice, decrease the oral bioavailability of antihypertensive, antibiotic and anti-histaminergic drugs (3, 70). In particular, the grapefruit juice can block the action of intestinal CYP3A4, the amount of which varies from person to person in the small intestine, so grapefruit juice may affect people differently even when they take the same drug. Besides the possible interference with drug metabolism, grapefruit juice can affect drug transporters proteins and the final result is that less drug enters the blood.

Besides grapefruit juice, *Ginkgo biloba*, an important herbal compound and a dietary supplement, has actually been proven to interfere with the effectiveness of some medications (71). *Ginkgo biloba* is used to improve brain performance and reduce fatigue (3). It is also commonly utilized by people experiencing cognitive decline; healthy adults seeking to improve performance or prevent a decline; and elite performers seeking to optimize their cognitive performance (72). The substances contained in the *Ginkgo biloba* that have pharmacological properties are flavonoids and triterpene lactones (gingkoloids and bilobalids). As a result, *Gingko biloba* is able to reduce platelet aggregation, and acts on the CPY2C9 and CYP3A4 isoenzymes, inhibiting the microsomal metabolism of warfarin (3). Therefore, herbal preparations containing *Ginkgo biloba* should be avoided in patients treated with antiplatelet or anticoagulant drugs (73). It should be also noted that products that are HPP-treated and contain ginkgo seed protein (GSP) showed markedly improved heat stability and emulsifying properties compared to the untreated GSP (74) and consequently may interfere with the effectiveness of some medications as aforementioned.

High-pressure homogenization and microfluidization

Another common nonthermal processing is high-pressure homogenization (HPH), that combines, in addition to high pressure action, some other physical effects (e.g., cavitation, shear stress, turbulence). Like HPH, microfluidization (MF) is a method used for production of micro and nanoscale size materials. It is commonly used both in pharmaceutical and food industry to make liposomal products, emulsion and to produce dairy products. Both processes could affect bioavailability of some active food compounds. For instance, HPH and MF processes were utilized in the emulsification of krill oil. Emulsions produced through MF exhibited several noteworthy advantages over those generated by HPH. Most prominently, MF-prepared emulsions featured smaller and more uniformly distributed particles, in stark contrast to the less uniform particles generated by HPH. Moreover, MF-based emulsions demonstrated significantly enhanced oxidative stability during storage. Astaxanthin degradation occurred at a substantially lower rate (38.1 and 89.4% for HPH and MF, respectively) (75). In *in vitro* simulated digestion, MF formulations exhibited superior stability and markedly higher bioaccessibility of food active components in comparison to their HPH counterparts. Significant increase in the release of free fatty acids was observed during the intestinal phase of digestion in MF emulsions, indicating an improved lipid digestion process (75). These findings highlight significant differences for ω-3 fatty acids, that can interact with blood thinning drugs and could have possible adverse effects, or determine therapeutic failure.

Pulsed electric fields

PEF deserves a closer look due to its unique capabilities as highlighted in the study of clinical applications and immunological aspects of electroporation-based therapies, food and medicine (76, 77). Consequently, PEF treatment is considered to be a promising technology that has in the last years received considerable attention in food and biotechnology related applications (78).

PEF impact causes membrane permeabilization, a process termed as electroporation (EP), and leads to an increased permeability of the membrane to ions and molecules (79). Depending on the intensity of the treatment applied (e.g., external electric field, single pulse duration, treatment time) and the cell characteristics (e.g., size, shape, orientation in the electric field), the viability of the electroporated cell can be preserved by recovering the membrane integrity (reversable permeability, REP). Conversely, EP can permanently lead to cell death (irreversible permeability, IRP). REP is a procedure commonly used in molecular biology and clinical biotechnological applications *in vivo* to gain access to the cell cytoplasm in order to introduce or deliver drugs (e.g., oligonucleotides, antibodies, plasmids) (78, 80). Most of food and biotechnology related applications of PEF are based on irreversible permeabilization of the cell membranes and mainly include "cold" pasteurization of liquid foods and disinfection of wastewater by means of microbial inactivation (78).

Typical applications of PEF technology in food processing include extended shelf life (81): 1. Apple juice; 2. Orange juice; 3. Milk; 4. Liquid egg processing (in combination with adopting a hurdle strategy); 5. Processing of green pea soup. Other applications include: Beer (inactivation and sublethal impairment of *Lactobacillus plantarum* a microorganism that can spoil beer). Most recent utilization of PEF includes (82): 1, Pineapple juice and coconut milk mixture; 2. Red wine; 3. Milk; and 4. Human milk (i.e., processing conditions were optimized to reduce bacterial counts in donor human milk, and to evaluate its effect on the bioactive proteins). Extraction of bioactive compounds in food using PEF processing is also a very common approach.

Nanosecond PEF (nsPEF) processed milk retaining over 60% of lysozyme, lactoperoxidase and lactoferrin, and 100% retention of xanthine oxidase and immunoglobulin A was reported. Additionally, the loss of milk proteins was smaller for samples treated with nsPEF (e.g., high voltage, high intensity pulses are used, with durations of 10–300 ns and electric fields of ~10 kV/cm to 300 kV/cm) in comparison with typical regular pasteurization process. These data indicated that nsPEF is a promising novel pasteurization method (83). However, the application of PEF to solid foods is much more difficult, mainly because microbial inactivation in this case is relatively unrealistic (82).

Despite many scientific studies on the principles and applications of PEF technology published to date, and the fact that PEF was introduced into the food industry many years ago, this technology is still considered as an emerging one. In the European Union there is no special legislation on food processed with PEF. In general, the use of this technique is coordinated by the Novel Food Regulation (EU) 2015/2283,[1] but implementation of PEF into production does not automatically mean that the food becomes "novel" (84). Novel food acknowledgement should be closely considered and evaluated when a new technology is to be implemented.

Although electroporation (EP) and electropermeabilization (EPP) are frequently used as synonyms, EP is related strictly to the aqueous pores formed in the lipid membranes of the cells, while EPP is related to all the events involved in the membrane permeabilization process, including modulation of membrane channels, cellular biophysical and biochemical changes (77). In medicine, EP is a platform technology for drug and gene delivery. When applied to cell *in vitro* or tissues *in vivo*, it leads to an increase in membrane permeability for molecules which otherwise cannot enter the cell (e.g., siRNA, plasmid DNA, and some chemotherapeutic drugs) (85). In oncology, reversible electropermeabilization (REPP) is applied for the intracellular transport of chemotherapeutic drugs as well as the delivery of genetic material in gene therapies and vaccinations. The physical changes of the membrane and the immunological aspects involved in electrochemotherapy and gene electrotransfer, were recently reviewed for two important EP-based cancer therapies in human and veterinary oncology (77). The two widely used chemotherapeutic drugs are bleomycin, a chemotherapy agent employed to treat various malignancies, including head and neck malignancy, lymphoma, and testicular tumors, among others,[2] and cisplatin, a chemotherapy drug used to treat testicular, ovarian, bladder, head and neck, lung and cervical cancer, among others.[3]

Possible increased absorption of nutrients related to non-communicable diseases due to food processing

As schematically reported in Figure 2, non-thermal processing often allows a better bioaccessibility and bioavailability of the active components present in the so processed foodstuff. Even if this fact appears positive *per se*, maximal attention must be given to the possible interference of an excessive intake of certain ions and biochemical compounds in the people under pharmacological treatment for non-communicable diseases (NCDs), mainly cardiovascular, respiratory, gastrointestinal, obesity, type-2 diabetes and other metabolic diseases. Typical examples are the deleterious interfering effects of a potential excessive uptake of potassium and phosphorus on the drug treatment of hyperkalemia and hyperphosphatemia, two main metabolic alterations in chronic kidney insufficiency (86), or that of sodium during treatment of the high blood pressure (87).

NCDs were connected to what is known as ultra processed foods (UPFs) as described by the NOVA classification system (88). UPFs is based on food processing classification. In essence, the classification is rather based on formulation focusing mainly on added fat, carbohydrates and other processing ingredients such as flavor. The topic is very controversial among experts (89, 90) and will not be discussed herewith. Nevertheless, in the public domain UPFs are perceived as hazardous (91).

Of note, the possible hindrance of a correct pharmacological treatment of NCDs by UPFs, due to an enhanced bioaccessibility of defined active principles, is dependent on the alteration of the correct metabolic contest necessary, e.g., for hypertensive drugs to exert their pharmacological action, with the consequent risk of drug's lower effect

1 https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32015R2283

2 https://go.drugbank.com/drugs/DB00290

3 https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/cisplatin

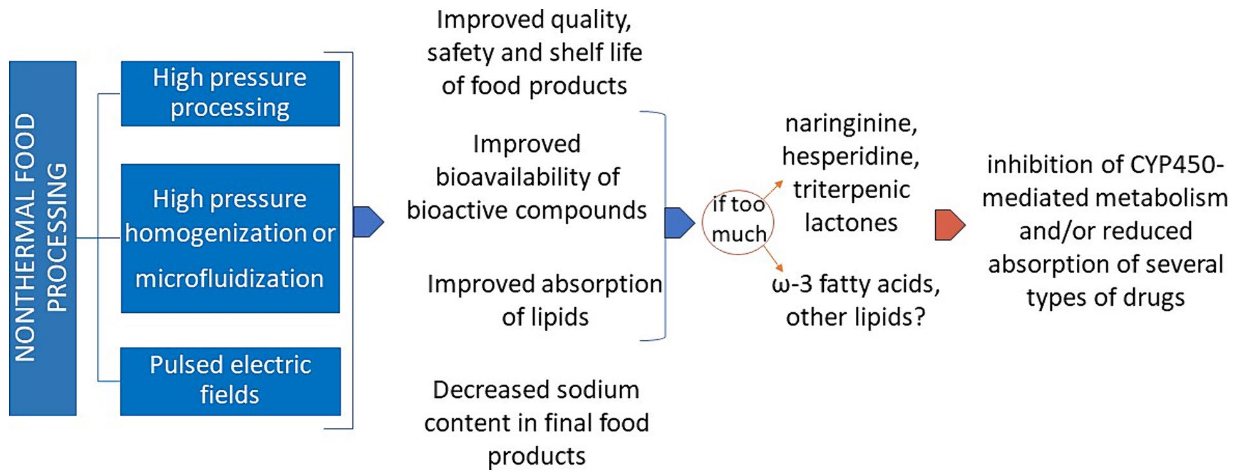

FIGURE 2
Various advantages and some possible drawbacks of non-thermal food processing. CYP450: cytochrome P450.

and possibly consequent overdosing with related complications. A scenario far from being uncommon, since NCDs incidence significantly increase from +55 years adults onwards, with the most occurrence and prevalence in elderly.

The Pan-American Health Organization Nutrient Profile Model (PAHO NPM) identified a variety of processed and ultra processed foods with a critical content of nutrients pathogenetically correlated with NCDs, including saturated fat, total fats, and sodium, having as a reference their recommended amounts by World Health Organization (92). It came out, for instance, that the majority of Australian people eat daily from three to five processed or UPFs containing those critical nutrients (93). In a large cohort of adults from Northern Italy, namely Emilia Romagna, renowned for ham and parmesan cheese, the mean sodium intake has been found as significantly higher than the recommended one, while that of potassium resulted to be just slightly lower to the recommended intake (94).

One should consider the fundamental physiological role of sodium and potassium. Age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol (mEq) per day. Hypertension is observed mainly in populations in which people consume more than 100 mmol (mEq) of sodium chloride per day (95). Although individual sodium intake in most populations throughout the world exceeds 100 mmol (mEq) per day, most people remain normotensive. It appears, then, that sodium intake that exceeds 50 to 100 mmol (mEq) per day is necessary but not sufficient for the development of primary hypertension.

In the Dietary Approaches to Stop Hypertension (DASH) sodium study, a reduction in sodium intake caused stepwise decreases in blood pressure. Isolated populations that eat natural foods have an individual potassium intake that exceeds 150 mmol (mEq) per day and a sodium intake of only 20 to 40 mmol (mEq) per day (the ratio of dietary potassium to sodium is >3 and usually closer to 10) (96). By contrast, people in industrialized nations eat many processed foods and thereby ingest 30 to 70 mmol (mEq) of potassium per day and as much as 100 to 400 mmol (mEq) of sodium per day (the usual dietary potassium/sodium ratio is <0.4) (97).

Food processing drastically changes the cationic content of natural foods, increasing sodium and decreasing potassium. Only approximately 12% of dietary sodium chloride originates naturally in foods, whereas approximately 80% is the result of food processing, the remainder being discretionary (added during cooking or at the table) (98).

The results and conclusions of this rather old while still highly cited report, that was pointing to a certainly minor contribution of the optional salt (NaCl) added by the consumer to the total sodium content of foodstuffs, were confirmed by a quite recent study, the size and features of which were more comprehensive (99). These authors recruited 450 adults from three different US regions, 50/50% M/F, of four races, and estimated, through already standardized procedures, the amount of sodium from the various sources, i.e., that inherent to food or deriving from food processing or added at home. The findings obtained were clearly consistent with those reported previously (98), a study was carried out only on white, mainly female, adults, from a single US region. In fact, the sodium deriving from processed food resulted to be 71% of the total, of course with some significant variations among the examined groups, being the sodium inherent to food 14%, the remaining percent amount added at home (99).

Apart from educating the public, an agreement by the food industry to limit the deviation of sodium content of processed foods from their natural counterparts appears essential. Indeed, an excessive intake of sodium with food would favor an increase of blood pressure, certainly not recommendable for +55 people. Even more important, such an overload could considerably interfere with the clinically expected effect of a given anti-hypertensive medication, a correct dosing of which could become complicated.

Besides the possible hindrance of a high sodium diet to a correct dosing of a given medication, proofs are available that support a direct alteration of the pharmacokinetics (PK) of different cardiovascular drugs. In fact, a marked impairment of the PK of the commonest antiarrhythmic drug quinidine when administered orally versus that administered intravenously was observed in healthy adult volunteers of both sexes fed a high-salt (400 mEq/day) for ten days then receiving 600 mg of the drug (100). No changes in the PK of the drug administered i.v. The reported marked drop in the bioavailability of quinidine given *per os* was occuring early after its oral administration, suggesting a pre-hepatic, most likely intestinal, impairment of the drug's absorption operated by the dietary salt excess (100). The significantly decrease in bioavailability of quinidine, when orally given, as induced by a high dietary salt concentration was considered as mainly due to an altered metabolism or a deranged transport of the antiarrhithmic drug (or both) at the intestinal level (101).

Further studies by the same group found a similar lowering effect of high dietary salt on the bioavailabilty of verapamil, another common antiarrhithmic and antihypertensive medication. Once again, the interaction between a high sodium dietary intake and the absorption of verapamil appeared to take place at the level of the epithelial intestinal layer, most likely involving the CYP3A-dependent drug metabolism and/or the intraepithelial uptake of the drug through the action of ATP-binding cassette sub-family B member 1 (ABCB1) (102).

Another more recent investigation was performed on male adults under a dietary sodium excess, to whom a single oral dose of an angiotensin-converting enzyme inhibitor (ramipril) or one of two different angiotensin II receptor blockers (candesartan cilexetil and valsartan) or the β1-adrenergic blocker atenolol was administered. A net impairment of the PK of candesartan and atenolol was observed in the healthy volunteers fed a high sodium diet, as to that occurring in volunteers under a low sodium diet who received the same oral dose of such drugs. Conversely, the PK of valsartan and ramipril remained unchanged (103). The authors reached the same conclusion drawn by Darbar and colleagues several years before, i.e., the high sodium dietary regimen may likely affect the intestinal absorption and metabolism of various medications.

Even if a conclusive mechanistic elucidation of the interaction between high sodium in the diet and the absorption and metabolism of the above reported drugs has not been obtained yet, it certainly develops at a pre-hepatic level (first-pass drug metabolism) and it most likely involves changes of the sympatetic gut function, beyond CYP-dependent metabolism and membrane transporters (103).

From a culinary standpoint, salt boasts numerous desirable qualities that enhance the positive sensory attributes of foods and plays also a role in ensuring product safety. However, escalating worries about the adverse effects of excessive sodium chloride (NaCl) consumption have propelled research into reducing NaCl content while maintaining quality and safety. Various cutting-edge technologies for NaCl reduction (e.g., others chloride salts, non-chloride salts, vacuum curing, ultrasound drying, microwave vacuum drying, infrared radiation drying, flavor enhancers) have been explored in meat curing (104). One promising approach involves replacing NaCl with up to 70% potassium chloride salt (KCl).

In an attempt to encourage this shift, the Food and Drug Administration (FDA) has issued an advisory document, advocating for the incorporation of potassium chloride as an alternative to NaCl in food.[4]

It is essential to note that this transition from NaCl to KCl may introduce potential deleterious effects, particularly concerning an excessive uptake of potassium. This may pose challenges to drug treatments for hyperkalemia and hyperphosphatemia, two prevalent metabolic alterations in chronic kidney insufficiency (86). This calls for better communication between food professionals and physicians. Additionally, the aforementioned concerns about possible salt-drug interference provide a supplementary impetus for the exploration and expansion of food processing methods capable of delivering salt-reduced products without the additional of other salts that may have a negative impact. The subsequent section reviews selected examples of salt-reducing food processing techniques in light of these considerations.

Positive effects of food processing on drug delivery, stability and health safety

Delivery of drugs due to their inherent attributes (e.g., sensitivity to heat and oxygen, hydrophobicity, bitter after-taste, poor dissolubility, low bioavailability, instability to gastric conditions, possible adverse effects in the gastrointestinal tract, toxicity) is quite challenging.

To overcome some of these obstacles, encapsulation, nanoparticles and other food processing were utilized (105, 106). Few examples are listed below.

Polymers-mediated drug delivery

Delivery of therapeutics using synthetic polymers is challenging due to toxicity, immunogenicity and impaired bioavailability following administration of the latter compounds. However, natural polymers are being explored as safe for their use as a substitute for synthetic polymers. Derivatization of starches has the potential to achieve desired properties (e.g., improved solubility, stability, bioavailability) of an incorporated drug and lower-down induced toxicities. Starch structure and chemical modification methods integrating aspects of its use in developing drug delivery devices like tablets, hydrogel, and patches were described and may be applied as a reference for future chemically modified starch as excipient in drug carrier studies (107).

Carotenoids' bioavailability

The consumption of specific carotenoids has been associated with reduced risks of contracting a number of chronic conditions. Extrinsic factors affecting carotenoid bioavailability include food-based factors, such as co-consumed lipid, food processing, and molecular structure, as well as environmental factors, such as interactions with prescription drugs, smoking, or alcohol consumption (108). Carotenoid bioavailability varies with different food cooking and processing procedures as well as with the amounts of dietary fat, fiber, and competing compounds present in the meal (109). Upon ingestion, carotenoids are released from the food matrix and are emulsified with fat and incorporated into lipid micelles in the small intestine for absorption by intestinal enterocytes. Once thought to be taken up strictly via passive diffusion, carotenoid absorption is facilitated via membrane proteins (109). Cooking, heating, or mechanical or

4 https://www.fda.gov/food/cfsan-constituent-updates/fda-issues-draft-guidance-regarding-use-alternative-name-potassium-chloride-food-labeling

enzymatic processing may also increase carotenoids accessibility by softening the tissue matrix (110). Another example is pasteurization shown to increase bioavailability of processed juice compared with its fresh counterpart (111).

Nanoparticles – biomimetics

Nanoparticles have unique biological properties which can be used for detection, prevention, and treatment of diseases, such as cancer, pulmonary diseases, etc. and for drug delivery and gene therapy as well (112–114). Nanomaterials can be created in one (nanoscale), two (nanowires and nanotubes), or three dimensions (nanoparticles) (115). Nanoparticles are a particular type of nanomaterial that can occur naturally, be created using unintentionally, or indeed be engineered on purpose (112). Numerous processing technique could be utilized to produce typical nanoparticles that could include liposomes polymer-drug conjugates, etc. To date, the utilization of food processing for the creation of nanoparticles faces some key issues and hurdles such as the need to use economical processing techniques to make edible delivery systems while also ensuring that they are safe and palatable for human consumption (116).

Whilst nanotechnology applications have been planned for a variety of benefits in the agri/food/feed chain, the use of materials that contain nanoscale particles has also raised concerns over their potential adverse effects on consumers' health (117). Therefore, safety is of primary concern and should be carefully considered before nanoparticles could be used in foods.

A recent review focused the attention on the recent new interest in developing biomimetic plant foods (BPFs), considering the likely disassembly that plant food structures undergo during processing first, then during digestion in the human gastrointestinal tract (GI) (118). A deep insight into these modifications of the original plant food structure is needed in a way to properly design future nature-inspired food structures that could indeed safely contribute to health and well-being (118).

A recent and typical example of biomimetic is represented by the naringenin-loaded macrophage membrane-coated liposome-based nanoparticles. They are provided with distinct physicochemical compositions and biological attributes to improve the bioavailability of the carried drug specifically at the target site. The developed biomimetic nanoparticle (BNP) has shown good biocompatibility, stability, satisfactory particle size, pH-responsive drug (naringenin) release kinetics, and higher cellular uptake *in vitro* (119). Yet another study showed that oral supplementation of vegan collagen biomimetic has beneficial effects on human skin physiology (120). Biomimetics will most likely have a pivotal interaction with delivery of food components and drugs.

Non-thermal processing for salt reduction: a crucial support to anti-hypertensive drug therapy

A reduced intake of sodium is often recommended for therapeutic reasons, especially in elderly, as mentioned before, but to deliver reduced-salt products through a process that would not affect their physicochemical and sensory and hedonic attributes, as it often happens with NaCl salt replacers, indeed represents a big challenge for food industry (121). In relation to this task, it is noteworthy to mention some successful results achieved through the adoption of defined procedures of non-thermal processing. For instance, the fruitful application of PEF in reducing NaCl content in the preparation of jerky beef has been very recently described. PEF treatment (0.52 kV/cm, 10 kV, 20 Hz, 20 μs) applied to jerky beef test samples allowed to diminish the product's sodium content by 34% as to untreated identical meat samples, fully preserving the main characteristics and the overall acceptability of the controls (122).

At present, more reports are available as far as the HPP of food is concerned, experimentally shown to be both a direct salt reducing procedure and a technology able to enhance the safety of sodium reduced meat products. HPP (treatment at 150 MPa for 5 min) of pork meat before manufacturing breakfast sausages with a reduced salt concentration, was shown to allow salt lowering up to 1.5% without affecting the main quality features of the sausages themselves but actually minimizing the typical cooking loss of the non-HPP treated products (123). A marked prevention of cooking loss was observed in the production of ready-to-eat chicken breasts undergoing a partial substitution of NaCl with KCl, when HPP was applied for 5 min after tumbling (300 MPa) and for 3 min to the final product (600 MPa). Moreover, such a treatment allowed to maintain the physicochemical features and the sensory attributes of the food product and even improved its microbiological quality in comparison to identically processed but HPP untreated chicken breasts. Notably, while the affordable NaCl reduction with the standard non-HPP procedure was of about 25%, that achieved by HPP treatment was 50% (124).

A similar result was reported for a further type of food, namely cooked fish batter, in which a reduction by 25% of NaCl concentration was achieved through the application of HPP (300 MPa for 5 min at 25°C) (125). Just one more example that pointed out the possible adoption of this non-thermal processing to downsize sodium amount in meat, a food in which this chemical element is anyway essential to guarantee texture, microbiological safety and suitable shelf-life [see for a specific review (126)].

Iodination

A clear example of food processing that in some way facilitates a clinically effective intake of drugs is represented by the iodization of salt as the best method of hypothyroidism prophylaxis. Iodine is necessary for thyroid hormone production and its deficiency causes mental retardation, short stature, goiter and an increased risk of death in childhood in developing countries (e.g., iodization of salt increased the survival and birthweight in some African countries). In developed countries iodine sufficiency is attained by iodization of salt and by the introduction of iodine in food processing (e.g., the use of iodine as a bread stabilizer). In regions where iodine deficiency is prevalent, iodine supplementation or iodized salt is often used to prevent hypothyroidism (127).

However, in areas with sufficient iodine in the diet, excessive iodine intake can also be a concern and may contribute to thyroid dysfunction. Patients who are taking drugs like levothyroxine to treat hypothyroidism, or propylthiouracil and methimazole to treat hyperthyroidism, or undertaking radioactive iodine therapy, must be warned of the potential drugs' side effects due to the presence of iodine in foods.

Forward looking

The food processing is currently facing a profound transformation, often referred to as the 'fourth industrial revolution'. This evolution encompasses cutting-edge technologies such as precision fermentation, pervasive digitalization, gene editing, and molecular technologies (128), as well as artificial intelligence (AI), internet of things (IoT), sensors, big data, cloud computing., etc. Some argue that these advancements hold the potential to revolutionize food systems (129).

Recent strides in food biotechnology and precision fermentation (130), along with parallel developments in plant molecular farming focused on generating therapeutic proteins (131), underscore the remarkable progress occurring at the intersection of science, technology, and innovation. This progress is blurring traditional distinctions between food processing and drug production.

Various synthesis systems, ranging from wild-type to modified mammalian cells, plants, insects, yeast, fungi, or bacteria, exemplify the diversity of approaches (132). Consequently, it is reasonable to anticipate a future in which the boundaries between certain food processing methods and drug manufacturing become increasingly blurred. This paradigm shift is prompting the need for a unified and simultaneous approach to address the future development of both sectors. A notable quote from Hippocrates, "Let food be your medicine and medicine be your food," reinforces the intrinsic connection between these domains, advocating for an integrative and synergistic approach. In essence, the evolving landscape suggests that the realms of food processing and drug development will likely converge, driven by shared scientific principles and technologies.

Conclusion

The preceding data underscore the dearth of elucidation on explicit interactions between food processing and their potential beneficial or adverse drug interaction consequences, which may precipitate in some cases in health hazards. Noteworthy are the plausible alterations in herb new molecular conjugates, drug absorption and efficacy, thereby instigating health implications and possible negative ramifications. Consequently, this discernible gap necessitates intensified and targeted scientific inquiry into the myriad conceivable interactions among food composition, food processing, and pharmaceutical agents, alongside a comprehensive investigation of the underlying mechanisms at play. It would be also interesting to determine if new molecular phytochemical conjugates may possess other therapeutic potentials undiscovered yet. The nebulous nature of this field demands substantial scrutiny and collaborative efforts across diverse domains, encompassing medicine, pharmacology, nutrition, food science, food technology and food engineering.

Author contributions

GP: Conceptualization, Writing – original draft, Writing – review & editing. EB: Supervision, Writing – review & editing. IS: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

GP and IS have scientific consultancy contracts with Soremartec Italia Srl. EB is employed by the Fondazione Ferrero, Alba, Italy.

Publisher's note

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ONE QUALITY concept: a narrative perspective to unravel nutritional challenges, controversies, and the imperative need of transforming our food systems

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Ensuring a healthy and sustainable diet for all should be a global priority, and to achieve this goal the food system requires substantial changes. Adopting a one-size-fits-all approach is not feasible, and we need to consider the cultural particularities of each geography and not try to export models that work in one place but may be unsustainable in others. Our discussion will center on two key aspects within this overarching process: (a) the combination of a rigorous evidence-based approach with existing or proposed Nutritional Guidelines and policies required to realize the "ONE HEALTH" and "ONE QUALITY" concepts. Examining the Mediterranean diet and the latest findings on saturated fats will aid us in comprehending the necessary paradigm shift required to formulate new guidelines with substantial impact in preventing the rising prevalence of Non-Communicable Diseases worldwide; (b) the adequacy and scope of the data bank necessary to develop a global, science-based approach.

KEYWORDS

ONE QUALITY, database, Med Diet, SFA, plant-based, food system, NCDS

1 Introduction

A perfect storm is currently brewing within the global food system. Not only diet has an effect on health; factors such as population growth, climate change, inequalities among different regions and individuals, urbanization, and evolving cultural values regarding food understanding and use have created a complex and multifaceted reality that affects us all (1–3). Sustainable and healthy diets have become the guiding principles of prominent institutions like the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) (4). The role of food in determining health outcomes is gaining importance at the citizen level, leading to the emergence of new dietary habits. The intricacies and interrelationships among the various components of the food system do not permit definitive and conclusive solutions. The growing significance of exposome research (5) represents one of the few holistic approaches currently embraced. For instance, we consider whether urbanization plays a more or less critical role than physical activity levels and how these factors impact the ultimate outcomes. Furthermore, the role of gender has been significantly underestimated, and evidence of its influence is poised to unveil new perspectives in nutrition research and policy (6). However, in light of the growing awareness aimed at resolving these challenges, it is high time to initiate an inclusive and comprehensive debate. Assuming that a Healthy Diet is, and will remain, a fundamental prerequisite, we will begin by defining this essential aspect of human heritage and basic need.

2 Healthy diet: an expanding pillar inside food system

There are numerous definitions of a healthy diet. In this discussion, we will adopt and expound upon the definition recently provided by Neufeld et al. (7) that states, "*A healthy diet is health-promoting and disease-preventing. It provides adequacy, without excess, of nutrients and health-promoting substances from nutritious foods and avoids the consumption of health-harming substances…*"

Therefore, the concept of a "healthy diet" is inherently linked to food safety. Once food security and food safety are assured, along with food availability, we can work toward achieving the goal of consistent food quality for everyone. While this concept may appear self-evident, there remains a considerable journey ahead to achieve it on a global scale. Despite acknowledging that food safety is a collective responsibility involving various stakeholders, the persistence of unsafe foods and the inadequate handling of food safety incidents hinders its global assurance (8). The ONE QUALITY concept is prevalent in several ongoing projects at the level of major UN agencies such as WHO and FAO. It is increasingly recognized as a strategic approach to promoting a healthy diet for all.

With these principles in mind, let us explore a few examples of the uncertainties that arise in real-life situations, such as the Mediterranean Diet (Med Diet) and fat controversy and their ripple effects on diet, nutritional health, and the entire food system.

The Med Diet has evolved into a kind of "panacea" and a model for a healthy diet. Ancel Keys' renowned "Seven Countries Study" (9) introduced a somewhat vague concept based on a self-approved synthesis of observational data. This was during a period when the economic situation in the Mediterranean region was quite poor, and the collected data were somewhat arbitrarily selected. The tremendous popularity that followed the publication of Keys' work elevated the Med Diet to the status of a global paradigm.

The understanding and adoption of the Seven Countries Study concept regarding diet composition revolved around the idea that saturated fats promote an increase in blood cholesterol levels, which in turn leads to cardiovascular diseases (CVDs). However, this interpretation was not exactly what A. Keys himself proposed. He argued that despite the significant and fundamental role of diet, it was not the sole factor at play. Keys (9) emphasized the importance of factors such as physical activity, strong family ties, and a relaxed way of life as primary components and determinants of better health. In essence, A. Keys anticipated the concept of lifestyle and believed it was responsible for the lower incidence of CVDs.

Over time, the positive effects of the Med Diet have been attributed to various factors, including olive oil (OO - Extra virgin: EVOO), low meat protein consumption, and, more recently, the content of polyphenols (10).

Now, let us consider a hypothetical scenario where the Med Diet is adopted as a universal approach. Several critical and unrealistic points become evident:

OO, and even less so EVOO, cannot serve as the universal oil. The annual production of 2–3 million tons of olive oil represents approximately 1% or less of the total oils and fats needed globally (11). Simply put, there is insufficient olive oil and olives to meet the demands of more than a few countries. Therefore, alternative oils should be identified.

The preference for low meat and relatively high fish intake should align with the accepted data that sea-based protein sources constitute only about 6% of the world's protein needs. While aquaculture may increase fish protein availability in the future, there are several sustainability concerns associated with this practice that require thorough evaluation.

More recently, "polyphenols" have been suggested to have protective effects and promote healthier dietary and metabolic habits. However, complete information on the metabolism, absorption, and long-term effects of polyphenols is lacking in the scientific literature, with only a few exceptions. The Phenol-Explorer, for example, cites data on a total of 458 foods and 501 different polyphenols (12). There are several million, if not billions, of food items, while polyphenols constitute a family of phytochemicals with more than twenty thousand identified molecules (13). Furthermore, data on polyphenol metabolism are sparse and not systematically explored (14). With such limited information available, it becomes challenging to make any general inferences about the effects of this important dietary component in a science-based approach.

While the Mediterranean Diet promotes low meat protein consumption, comparing it with the Indian diet—the largest vegetarian diet worldwide—yields compelling evidence for a more robust comparison. There are various models of vegetarian diets globally, and the Indian diet stands out as one of the most frequently cited and recognized. When we account for the impact of scarcity and poverty, specifically addressing inadequate nutrient and calorie intake, the positive health effects of the traditional Indian diet become evident (15). However, these statements require careful evaluation due to several confounding factors, including economic, geographic, and cultural influences.

- Vegetable oil: The Indian diet utilizes groundnut and mustard oil instead of olive oil (16).
- Fish is not a standard or significant component of the Indian diet, while legumes are the preferred and more relevant source of proteins.
- Omega-3 fatty acids (ω3) in the Med diet primarily come from fish, whereas in the Indian diet, they come from vegetable oils.

These differences raise the question: Can both diets be compared, given their different sources of macronutrients and completely different chemical compositions? Even if we accept this premise -which may not necessarily be the case- where does the scientific evidence stand when we compare the nutrients of these diets?

On top of that, it is well-known that there is significant variability in the fatty acid components of several vegetable oils (17). For instance, in OO the concentration of palmitic acid can range from 7.5 to 20%, and the oleic acid concentration can vary from 55 to 83% (18).

Additional insights can be gleaned from the "Blue Zones" (Figure 1). There are several points of overlap between some Blue Zone diets and the Med Diet, but there are also significant differences. For example, in the Sardinia Blue Zone diet, the primary source of

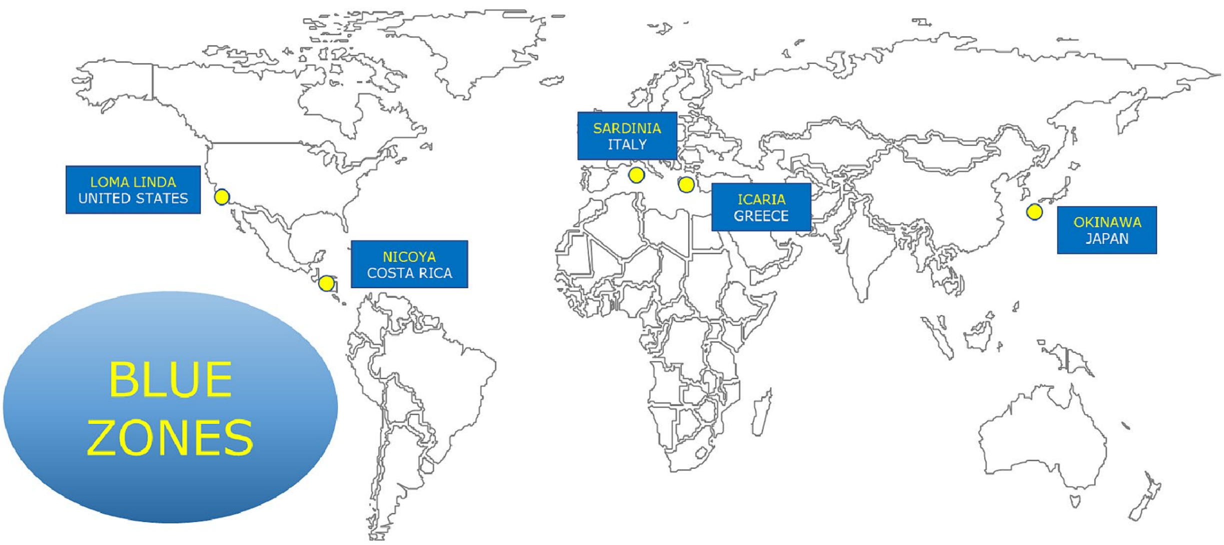

FIGURE 1
Blue zones are regions where a higher than usual number of people live much longer than average. There are five blue zones areas in the world.

TABLE 1 It presents evidence highlighting three main differences between the average diet of Americans and that of Ikaria: daily calorie intake, the percentage of energy derived from carbohydrates, and the percentage of energy derived from fats (20, 21).

	Total Energy	Carbohydrate % of daily calories	Protein % of daily calories	Fat % of daily calories	Alcohol % of daily calories	Fiber grams/day
Average American adult	2,270	43%	16%	36.5%	4.5%	14 g
USDA ideal American adult	2,240	53%	16%	27%	4%	32 g
Ikaria, Greece	1800*	32%	13%	50.5%	4.5%	24 g

*Amount adjusted for age and sex of average population.

animal protein is sheep, while the Med Diet emphasizes fish protein. The Okinawa Blue Zone diet includes a substantial portion of pig components. Calorie restriction cannot be considered a universal factor among these Blue Zone diets, as the caloric intake varies significantly, ranging from 1,500 kcal/day in Ikaria, Greece, to 2,392 kcal/day in Nicoya, Costa Rica (19).

When we compare the Ikaria's diet to the Western-style diet in the United States, it's easy to appreciate the significant differences, particularly in the amount of fat as an energy source (see Table 1).

If we compare the amount of fat recommended by dietary guidelines, we can see that the Ikaria Blue Diet provides approximately 100 grams of fat per day, while the average intake in the United States is around 90 grams per day. Furthermore, when we analyze the Sardinia Blue Zone diet, we find that the predominant source of dietary fat is of animal origin, and a significant portion of it is saturated. This pattern holds true for other Blue Zones as well (22).

Available data suggest different and very plausible interpretations. The calorie amount might be part of the explanation for the positive effects of the Med Diet recorded in the Seven Countries Study. However, the primary role of saturated fatty acid (SFA) is being challenged by new epidemiological analyses and meta-analyses, including valuable contributions like the Cochrane reviews. Notably, the hypothesis of a positive role, without the biological identification of related mechanisms, remains lacking.

A fresh start in analyzing and interpreting the available data seems imperative, as well as the development of new dietary guidelines that should be rigorously evidence-based.

3 Fat controversy, the role of saturated fatty acids

The discussion surrounding the role of SFA in dietary guidelines has been ongoing. In 2010, a meta-analysis (23) challenged the link between SFA intake and NCDs. P.W. Parodi's study (24), synthesizing data from major population-based studies, revealed a weak positive correlation, contradicting the notion of a negative relationship between SFA intake and daily energy intake.

Randomized controlled trials (RCTs), considered the gold standard in nutritional research, were pivotal in understanding SFA's role. D. Mozaffarian's seminal paper initiated the scientific discourse (25), but the Cochrane group critically evaluated it, identifying biases in data treatment, particularly regarding industrially trans-fatty acids (iTFA) and psychoactive drugs (26). Their findings questioned the efficacy of replacing SFA with polyunsaturated fatty acids (PUFA), highlighting confounding factors from iTFA (27).

The "fat controversy" today stems from varied interpretations of cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). The perspective presented emphasizes two fundamental principles: first, the consideration of evolution, and second, the recognition that human metabolism, rooted in biochemistry, offers more robust and evidence-based insights than mere epidemiological associations, keeping in mind that this kind of studies are the starting point to find causal links between diet and health.

Exist extensive discussions on the role and level of evidence from epidemiological studies, cohort studies, and RCTs in defining dietary guidelines, particularly regarding saturated fats (28, 29). The focus shifts to the biochemical evidence, guided by Bill Lands' understanding of fat metabolism through the Lands' cycle framework (30). Emphasizing the significance of plasma LDL, the paper suggests that the causal role of LDL in inflammation is debatable, with excess energy intake being the primary driver. Metabolism adaptations, assessed through β-hydroxybutyrate levels, are considered in the context of evidence.

The fatty acid composition of any tissue is highly variable, this highlights the role of Highly Unsaturated Fatty Acids (HUFA) and the causative role of oxidized fats in chronic low-grade inflammation, leading to cardiovascular diseases (CVDs) (31). Acknowledging contradictory data, we believe that a good starting point would be that unbalanced PUFA intake may trigger inflammation due to competition in metabolic cascades between Omega-3 (Ω3) and Omega-6 (Ω6), favoring an excess of Ω6, causing metabolic imbalance.

A key convergence point is that SFA intake is not the direct cause of atherosclerosis and related NCDs. Longevity, as demonstrated by Blue Zones, suggests diverse approaches. We advocate a shift from a nutrient-focused to a holistic dietary concept, considering the entire diet's effects.

In the context of ongoing climate change affecting food composition, there's a call for adaptable food systems. Regulatory bodies are urged to adopt a flexible approach, acknowledging data limitations and being open to updating dietary guidelines. Saturated fats, in particular, are highlighted as an example, with prominent scientists advocating for changes in dietary guidelines, especially regarding the role of saturated fats (32).

4 The database used for food composition by policymakers and operators is far from being readily available

The role of the scientific database is crucial for defining the best possible Dietary Guidelines. Currently, they are weak and inconsistent. We align with those who support the idea that "something – limited evidence: authors' comment – is not better than nothing" (33). While this statement pertains to energy intake, it can be extended to other biological entities.

Considering the complexity of the evolving Food System and the crucial role of Dietary Guidelines, there is unanimous agreement that the starting point, i.e., the food composition database, should be complete and up-to-date. Are the current food databases of the required and expected quality? Furthermore, do the levels of detail provided in these databases align with the latest knowledge in the field of nutritional research and policies? In a perspective of Aleta et al. (34) emphasize the critical step of characterizing exposure to the food system in the context of sustainable and healthy nutrition research. The primary challenge identified is obtaining comprehensive compositional data that encompass various aspects such as nutrient content, bioactive compounds, energy density, bio-accessibility and bioavailability of nutrients, together with sensory attributes, processing methods, socio-economic and environmental impacts. Despite efforts by initiatives like EuroFIR, USDA, and INFOODS, existing data are often heterogeneous, noisy, and incomplete.

Using olive oil as an example, the paper (34) illustrates the challenges related to data quantity and quality in nutritional studies. Olive oil composition, impacted by genetic, environmental, and technological factors, varies widely. Data incompleteness, leading to misleading results or unsubstantiated correlations, hampers progress. Traditional nutritional approaches focusing on main components neglect non-trivial interactions and chemical components not in the database, influencing results. It is highlighted the need for increased quality and availability of food chemical composition data, emphasizing the difficulty in establishing meaningful causal associations without comprehensive information. Variability associated with intake estimations is considered multidimensional, involving economic capacity, cultural factors, and social influences. Defining relations between nutrition, health status, and the production system requires a system-wide analysis, posing a pressing challenge for providing global dietary recommendations that consider cultural and behavioral covariates.

Scientifically speaking, derivatives that inform nutritional guidelines cannot be supported if they focus only on macronutrients. Despite our conviction of their absolute necessity for dietary guidelines, we can collectively agree that the available data are at least very unsatisfactory. In other words, while we all agree on the concept of a "Healthy Diet," the definition of quality requires the inclusion of new available biomarkers and, even more, new hypotheses and theories.

Today, a strong trend supports a shift from our westernized diet to a more, or substantially more, plant-based diet (35). Increasing the amount of vegetable protein at the expense of fats and carbohydrates, mainly reducing simple carbohydrates, is universally accepted for better health and a less or not relevant impact on the environment. If we follow this trend, it is time to search for the best possible treatment of plant-based food to achieve both goals of better health and a safer planet.

5 Discussion

Globally, the primary determinants of food choice are taste and price. While the food industry can now offer products that closely align with dietary recommendations, their success varies significantly. Taste, however, remains a critical factor. Interestingly, taste preferences can be modulated or evolve with age.

The challenge for our food system is to create products that are in line with current scientific knowledge, while also considering the effort required to achieve the same sensory excellence using alternative and environmentally friendly ingredients. Balancing risk and communication to consumers is crucial relying on low or very low levels of evidence may breed skepticism, while demanding large investments with high risks may not yield the desired results.

We all need to join efforts, ideas, investments, and thoughts to change the food system. Our proposal is to (re)start from a common shared level: evidence-based practices. Governments must show leadership in adopting and implementing food safety policies that ensures that every stakeholder knows and properly plays its role, from prevention to response otherwise, access to safe food for all will remain an elusive goal. Plant-based foods are and will be a major component of the human diet. We should learn from the unsuccessful approaches adopted in the past, avoiding dogmatic positions such as the one related to SFAs, which are no longer sustainable as the major responsible for CVDs. As the most authoritative scientists have claimed for many years, the drivers are and will be international agencies such as WHO, FAO, and regulatory bodies. They should define the need to demonstrate and promote the advantages of shifting from today's "normality" to the future constraints that environmental degradation imposes on all of us.

We have the concrete chance to write a new chapter in food development, the food market, but the only possible way is to define a shared concept of ONE QUALITY for all, everywhere, as the basis for any further discussion.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

RM: Conceptualization, Writing – original draft. GR: Writing – review & editing. FC: Writing – review & editing, Visualization.

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The nutritional support to prevent sarcopenia in the elderly

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Sarcopenia has been described as a muscle disease, with multiple adverse consequences on human health. Recommendations aimed at supporting awareness, prevention, early detection and treatment of this disease are needed. This review focuses on the epidemiology, pathophysiology and early detection of elderly sarcopenia. As far as treatment is concerned, physical activity and nutritional support are specifically evaluated. An individually tailored resistance exercise training program appears to be crucial for a positive outcome of the sarcopenia prevention and treatment. The nutritional intervention is mostly based on the supplementation with high-quality proteins (i.e., whey protein) in order to increase the intake of essential amino acids and in particular of leucine. In addition, of relevant importance appears to be the supplementation with vitamin D, with omega-3 fatty acids and probiotics. This review evaluates the results of the most qualified studies on the nutritional supplementation of sarcopenic elderly subjects and shows that promising results have been achieved in community elderly subjects, or subjects followed in rehabilitation centers and in nursing homes, with additional resistance exercise programs.

KEYWORDS

elderly sarcopenia, leucine, muscle mass, muscle protein synthesis, muscle strength, omega-3 fatty acids, vitamin D, whey protein

1 Introduction

Sarcopenia is a muscle disease, (1) characterized by a progressive and generalized alteration of skeletal muscles, with a reduction in muscle mass and muscle strength. Sarcopenia is associated with physical disability, poor quality of life and increased mortality (2).

The prevalence of sarcopenia is high in the elderly population of both sexes. The epidemiological data show a high percentage of sarcopenia either among aging communities (5–10%) (3–5) or among elderly residents living in care homes (15–30%) (3, 5), or hospitalized in acute care wards (37%) (3, 6). For elderly patients followed in a rehabilitation setting the rate of sarcopenia goes up to 76% (7). Additionally, sarcopenia may coexist with obesity in the form of sarcopenic obesity, due to the frequent sedentary lifestyle in adult and elderly population (8). Sarcopenia is tightly related to aging, malnutrition, sedentary lifestyle, low physical activity and chronic diseases (9). It is associated with negative physical conditions because it favors clinical frailty (10, 11) and it increases falls (12) mortality, disability and institutionalization (13–15).

Although the negative effects of sarcopenia on human health and on social and healthcare costs have been widely demonstrated (16–19), this clinical problem is often under considered and undertreated, (7) (Figure 1).

Many recent studies evaluated the nutritional approach to treat sarcopenia in the elderly (20–23).

The objective of this review is to focus on a recommended muscle-targeted intervention—namely a whey protein, leucine, vitamin-D, Omega-3-fatty acid and probiotic supplementation—for the prevention or treatment of sarcopenia (9, 24, 25).

2 Pathophysiology of sarcopenia

Aging is physiologically associated with a decrease in muscle mass that represents a physiological process. This reduction is roughly 8% every ten years after the age of 40 and 15% after 70 years (3). The increase of inflammation and of anabolic resistance as well as a reduction of the protein intake and of physical activity are the main causes of this pathophysiological event (9, 24, 26, 27). The increased amino acids (AAs) splanchnic extraction represents an additional reason of their reduced availability in aging (25). In addition, after short term hospitalization or bed rest, the synthesis of muscle proteins is reduced by 30% in elderly subjects, with a loss of 1 kg of muscle mass in 3 days; whereas, after four weeks in similar conditions, young adults show a muscle loss of 0.5 kg (28).

Various new substances that could improve the muscle anabolism with modulation of androgen receptors or of the myostatin–activin process are being studied (27). Myostatin and activin are negative regulators of muscle growth and are now used as markers of loss of muscle mass, that is of sarcopenia (29). In any case, it must be emphasized that the adequate nutritional intake is the fundamental requirement to ensure the optimization of the muscle mass and of its function in the elderly. The scientific evidence available today indicates that an appropriate intake of proteins, an adequate physical exercise and vitamin D supplementation when it is deficient, are the fundamental nutritional requirements to achieve this goal (9, 24, 25). For people older than 65 years it is recommended a daily intake of 1–1.2 g/kg of proteins every day, with a higher amount of proteins (1.2–1.5 g/kg/day) when an inflammatory pathology is present. Proteins should mostly be of high quality, such as whey proteins, with high content of essential amino acids (EAAs) and rich in leucine (24, 25). At each meal, the intake of proteins of high quality should vary from 25 to 30 grams, with a leucine intake ranging from 2.8 to 3 grams and this should be provided at least twice a day (24, 30, 31). The minimum daily intake of leucine should be of 78.5 mg/kg (24, 30, 31). The high presence of EAAs and the fast digestion process of whey protein ensure that this protein source guarantees a marked anabolic efficacy (32) leucine has proven to be particularly effective in favorably modulating protein turnover and anabolism (30, 33).

Specific foods for special medical purposes (FSMP) should be provided when the food intake is inadequate. Various studies showed that oral supplementation with whey protein rich FSMP is followed by the greatest post prandial concentration of plasma AAs and by the greatest muscle protein synthesis, when compared with any other protein source (34, 35). This effect is demonstrated either with additional supplementation of leucine or not, either with additional increase of the energy supply or not and either with additional physical exercise or not (34, 35).

Beta-hydroxy beta-methylbutyrate (HMB), is a metabolite of leucine and it has been shown to be useful in the attenuation of the muscular mass loss, muscle strength and muscle function (36). The pharmacokinetics of leucine are characterized by a fast absorption and distribution, while HMB shows a slow metabolism with longer promotion of muscle protein synthesis (MPS) and lower breakdown rates (36).

The supplementation with essential amino acids also appears of great interest since these amino acids are rapidly assimilated by the digestive system without consumption of energy, that is of adenosine triphosphate (ATP), according to the blood /cell cytoplasm gradient. The more rapid the increase in concentration in the blood, the faster EAAS enter the cell. Finally, the intake of essential amino acids in free form is a more efficient anabolic stimulus than the intake of an equal quantity in the form of proteins (37).

Vitamin D has been demonstrated to be effective in various ways on muscle recovery and MPS (38) and its synergic effect with leucine in stimulating protein anabolism has been well described (39). Therefore, by virtue of the frequent finding of vitamin D deficiency in elderly subjects, a supplementation of at least 800–1,000 IU every day of vitamin D should be provided in sarcopenic elderly subjects (40–42). Also, omega-3 fatty acids can reduce muscle loss and favor muscle synthesis (43) on muscle mass has been shown in various animal models and *in vitro* (44–46) as well as in human experiments, regardless of the anti-inflammatory action (47).

Recently, a gut-muscle correlation has been described (48). Gut microbiota could mediate the correlation between nutrition and aging

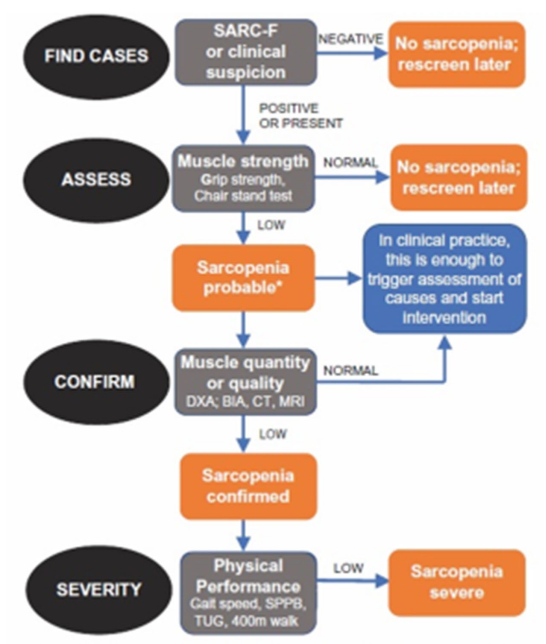

FIGURE 1
Diagnostic algorithm of sarcopenia produced by the European Working Group on Sarcopenia in Older People (7).

Abbreviations: AA, amino acids; EAA, essential amino acids; FSMP, foods for special medical purposes; HMB, beta-hydroxy beta-methylbutyrate; MPS, muscle protein synthesis; ATP, adenosine triphosphate; SPPB, short performance physical battery; MT-FSMP, muscle targeted foods for special medical purposes; CRP, C-reactive protein; TUG, timed up and go test; SPPB, short physical performance battery; ADL, activity daily living; QoL, quality of life.

by regulating the host's immune function, metabolism, insulin activity and gene expression (49, 50), and gut microbiota has been correlated with physical performance of elderly subjects (51, 52). Various studies have shown a correlation between gut microbiota composition and physical performance in the older population (51, 52). Aged rats supplemented with *Lactobacillus paracasei* PS23 showed a reduced muscle loss (53) and reduced cognitive decline (54). Therefore, a probiotic supplementation could be useful to favorably influence gut microbiota in elderly subjects with sarcopenia.

3 Efficacy trials

Among the numerous studies on the efficacy of FSMP useful for muscular mass synthesis, the most qualified clinical trials, with randomized and controlled study protocols and high number of recruited patients, are here reported.

In the PROVIDE study, malnourished older patients with sarcopenia living independently were randomized to vitamin D and leucine-enriched whey protein nutritional supplement or to an isocaloric control product, given twice daily for 13 weeks. Although the trial did not reach a significant between group difference in SPPB (Short Performance Physical Battery) and grip strength, the chair stand test as well as the appendicular muscle mass showed a significant improvement in patients supplemented with the muscle targeted food for special medical purposes (MT-FSMP) (55).

In the randomized study performed by Chanet et al. to evaluate the effect of a standardized breakfast supplemented with vitamin D and leucine enriched whey protein or a non-caloric placebo in healthy older men, a significant benefit towards appendicular lean mass was observed only in the test group at the end of a 6 week intervention (56).

In another controlled study, 130 sarcopenic elderly subjects were randomly supplemented with one serving per day containing 22 grams of whey protein, 10.9 grams of essential amino acids (including 4 grams of leucine), 100 IU of vitamin D or an isocaloric quantity of maltodextrin for 90 days. A personalized program of moderate-intensity physical activity was planned at the same time for all subjects. The intervention group showed a significantly higher increase in muscle mass, handgrip strength and physical performance, when compared with the control group (57). In addition, the intervention group showed lower CRP values and improved quality of life scores.

The IRIS randomized study evaluated the efficacy of a whey protein-based nutritional formula, enriched with leucine and vitamin D, twice daily, in addition to a standard hospital diet and a physical exercise rehabilitation program, in older in-patients with sarcopenia and compared it with an isocaloric control formula supplemented for 8 weeks (57). The four meters gait speed as well as the chair stand test, the TUG (timed up and go test), the SPPB (short physical performance battery), the Barthel index, the handgrip strength, the ADL (activity daily living), the QoL (quality of life) and appendicular muscle mass were significantly improved only in the intervention group. Moreover, CRP levels, healthcare resource consumption, and length of stay in hospital were lowered only in the intervention group (58).

Sarcopenia associated with obesity (8) is an interesting topic because weight loss is beneficial in overweight older subjects, but it may be associated with loss of skeletal muscle mass and sarcopenia. Verreijen et al. showed that a 13 week weight loss program was followed by a similar weight loss and fat mass loss in older obese subjects supplemented with whey protein, leucine and vitamin D as compared to the control group; but the intervention group showed an increase in appendicular muscle mass, whereas the control group evidenced a decrease in the same variable (59).

The effect on muscle mass of a two-month randomized intervention in sarcopenic elderly subjects with a MT-FSMP composed of 500 mg of omega-3 fatty acids, 2.5 g of leucine and probiotic *Lactobacillus paracasei* PS23 (30 billion, freeze dried), versus a placebo control group, has been evaluated by Rondanelli et al. (60). The obtained data showed a significant increase of appendicular lean mass, of the Tinetti scale, of the SPPB total score and of the handgrip strength in the intervention group, while the control group did not show any difference. Moreover, the comparison between the two studied groups demonstrated a significant decrease of the visceral adipose tissue and a significant increase of valine, leucine, isoleucine, and total amino acids only in the test group (60).

4 Discussion and conclusion

Several studies have been conducted with different muscle targeted foods for special medical purposes in older subjects with sarcopenia. The obtained results demonstrate that the intervention with these products, possibly in combination with a physical exercise program, promotes muscle protein synthesis and promotes the increase of muscle mass and muscle strength, and improves the physical performance of elderly sarcopenic subjects (Table 1). In addition, multiple studies show that these interventions prevent the muscle mass loss in subjects at high risk of becoming sarcopenic (Table 1).

The efficacy of MT-FSMP is higher in association with physical activity and in particular with resistance exercise programs (57–59,

TABLE 1 Nutritional and physical interventions to treat or prevent elderly sarcopenia.

Critical Factor	Intervention	References
Low protein intake	Increased protein intake (1–1.5 g/Kg/day) "Fast" proteins (Whey protein): 25 g each meal at least twice a day	(24, 25)
Low muscular protein synthesis	Increased leucine supply 2.5–2.8 g/meal at least twice a day	(34, 35)
Low serum vitamin D	Increased vitamin D ≥800 IU/day	(38–42)
Low intake of omega-3 fatty acids	Increased omega 3 fatty acids ≥500 mg/day	(43–46, 61–63)
Microbiota unbalance	Probiotic supplementation *Lactobacillus paracasei* PS23	(51–53, 60)
Sedentarism	Increased physical activity ≥30 min/day	(24, 25)

64, 65) have also been shown in subjects who do not increase physical activity (65–67). This is a great advantage for individuals who, for various reasons, have difficulty in carrying out rehabilitative physical activity programs. The same muscular benefits have been demonstrated in elderly obese individuals who need to implement nutritional measures aimed at reducing body weight (59, 68, 69). The efficacy of MT-FSMP has been shown in heterogeneous patient populations, (70, 71) and these nutritional interventions showed to reduce healthcare resource consumption in rehabilitation (58). To detect the recovery of muscle mass, the minimum duration treatment should be 4–8 weeks. Future research should evaluate the efficacy of long-term supplementation. Data on its tolerability up to 6 months have been provided (65, 72, 73). Moreover, this nutritional intervention could prevent the oxidation of dietary proteins as a source of energy (74). The effect of combined, multifactorial interventions (MT-FSMP and physical activity) would be desirable due to their synergistic effects. It has to be stated that, according to the triage theory of Bruce Ames, it could be advisable to supplement all the population with clinical signs of sarcopenia (75).

In conclusion, available data indicate that a muscle-targeted oral nutritional supplementation constitutes an effective treatment of sarcopenia and should be offered as a first-line therapeutic intervention in these subjects. The positive outcome of the nutritional intervention may be additionally increased when a targeted resistance exercise program is added. This intervention appears useful also to prevent sarcopenia in high-risk elderly subjects.

Author contributions

AG: Conceptualization, Writing – original draft. GB: Writing – review & editing. FM: Writing – review & editing. MR: Writing – review & editing.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The taste for health: the role of taste receptors and their ligands in the complex food/health relationship

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Taste, food, and health are terms that have since always accompanied the act of eating, but the association was simple: taste serves to classify a food as good or bad and therefore influences food choices, which determine the nutritional status and therefore health. The identification of taste receptors, particularly, the G protein-coupled receptors that mediate sweet, umami, and bitter tastes, in the gastrointestinal tract has assigned them much more relevant tasks, from nutrient sensing and hormone release to microbiota composition and immune response and finally to a rationale for the gut–brain axis. Particularly interesting are bitter taste receptors since most of the times they do not mediate macronutrients (energy). The relevant roles of bitter taste receptors in the gut indicate that they could become new drug targets and their ligands new medications or components in nutraceutical formulations. Traditional knowledge from different cultures reported that bitterness intensity was an indicator for distinguishing plants used as food from those used as medicine, and many non-cultivated plants were used to control glucose level and treat diabetes, modulate hunger, and heal gastrointestinal disorders caused by pathogens and parasites. This concept represents a means for the scientific integration of ancient wisdom with advanced medicine, constituting a possible boost for more sustainable food and functional food innovation and design.

KEYWORDS

taste receptors, extra-oral, T2R, metabolism, microbiota, immunity

Introduction

The "food is medicine" concept and approach has been rooted in humans, as proven by the first cookbook published in print around 1,470 by Bartolomeo Platina, "De honesta voluptate et valetudine" ("On right pleasure and good health") (1). It is actually not just a cookbook but a systematic treatment of culinary arts, dietetics, warnings about the nature of foods, and their nutritional and healing power, with indications and contraindications of different items and preparations and much more that authors of previous centuries had illustrated on the matter. The crucial role of food and food consumption patterns on health have been confirmed by scientific research, from earlier to contemporary times, with new timely discoveries that go hand in hand with an increasingly complex vision (2). If the initial studies concerned a few nutrients and their balance and were addressed to all people, currently there are available databases like FooDB that record the presence of more than 70,000 distinct biochemicals in food (3). Molecular and personalized nutrition are attempting to unravel every organism's responses to nutrients at a molecular level. Moreover, in the recent decades, diet has been recognized as one of the key factors for the selection and development of trillions of microorganisms that constitute our microbiota, and growing evidence suggests that the relationship between an individual and its microbiota may underlie broad effects of diet on human health and disease (4).

The involvement of taste in this scenario has been, for a long time, limited to its participation in the control of motivational processes that guide eating behavior and food choices, allowing the recognition of nutrients, while avoiding potential toxic compounds (5, 6). The identification of taste receptors, particularly the G protein-coupled receptors (GPCRs) that mediate sweet, umami, and bitter tastes, in the gastrointestinal (GI) tract [as well as in many other locations, not the subject of this article, (7)] has revealed many more relevant tasks for them, from nutrient sensing and consequent hormone release to microbiota composition and immune response (8–10).

Taste receptors

In humans, taste is mediated in the buccal cavity by two types of specific transmembrane receptors grafted at the apex of the taste receptor cells (TRCs): ion channels, which mediate sour and salty tastes, and GPCRs, for sweet, umami, and bitter tastes (11). The epithelial sodium channel ENaC is a possible receptor for salty taste (sensitive to Na^+), but still there is no consensus as to whether it is the only one (12). Quite recently, there has been an agreement on the proton-selective ion channel Otop1 as the detector of acidic stimuli (13), as well as of alkali and ions able to modify the pH (14, 15).

Sweetness and umaminess are sensed mainly by two heterodimeric receptors: taste receptor type 1 member 2 (T1R2) and member 3 (T1R3) for the sweet taste receptor, while T1R1 and T1R3 constitute the principal umami receptor (16). T1Rs present a long extracellular N-terminal domain, the so-called Venus flytrap module (VFM), forming the main binding site of the receptor (for sugars, aspartame and sucralose among sweet compounds, and for glutamate and nucleotides among umami ones). The recognition of other tastants and taste modulators occurs in different domains, like the seven transmembrane domain (TMD) and the cysteine-rich domain (CRS) (17–19).

More articulated is the system to perceive bitter taste. To date, over 1,300 bitter compounds have been isolated and tested on human bitter receptors [bitterDB, (20)], approximately 250 of which are of natural origin (21), but it is estimated that there may be up to tens of thousands of them. For a comparison, the known sweet compounds are in the order of the hundreds [SweetenersDB; (22)]. For this reason, vertebrates are equipped with a great number of bitter taste receptors, and their number correlates with the fraction of plants in their diet (23, 24). In humans, 26 active receptors dedicated to bitter compounds, taste receptor type 2 (T2Rs), have been identified, one of them being active in some populations only (25, 26). Some of these receptors are relatively "specialized," i.e., capable of responding to a limited number of bitter compounds, others, called "promiscuous," are generalist, i.e., capable of recognizing a larger number of even very chemically different compounds (24). However, others are "monogamous" and hyper-specialized, recognizing only one class of compounds. To date, two are still "orphans" T2Rs, which means that they are not activated by any bitter compound tested so far. T2Rs are more conserved in structure than in sequence, and thus, they are not easy to classify, although they are often considered class A GPCRs, presenting a short N-terminal extracellular domain (25). Moreover, some compounds act as agonists for certain T2Rs and as antagonists for others (27), making structure–bitterness relationship studies almost non-feasible. When comparing bitter taste receptors from different species, for most of them, no one-to-one orthologs are identified as they are organized in species-specific gene expansion groups (28, 29), and therefore, it is not straightforward to draw conclusions about their functionality in humans from animal studies. In addition, the interpretation of bitter taste as a means of rejecting potentially toxic compounds is certainly too simplistic since bitter compounds are not necessarily toxic, nor all toxic compounds taste bitter (30). Indeed, many bitter compounds, which include phenolics, terpenoids, alkaloids, and glucosinolates, have proven to have beneficial health effects (31, 32), and diets including higher amounts of bitter-tasting plants or phytochemicals have been associated with better health (33, 34).

Taste receptors and nutrient sensing in the GI tract

Most of the nutrients perceived as taste stimuli (particularly the macronutrients) are also under homeostatic control, and therefore, their introduction has to be detected to start and regulate their uptake. Not surprisingly, the GI tract is the largest hormone-producing organ in the body, with enteroendocrine cells (EECs) representing only 1% of the intestinal epithelium, yet capable of producing more than 20 hormones (35). These cells, scattered from the stomach to the rectum, make direct contact with what is present in the GI tract—food (both nutrient and non-nutrient compounds), its digestion products and residues, molecules produced by the microbiota, etc.—and release gut hormonal responses able to convey nutrient-related information to the brain, where they are integrated with other endocrine and neural inputs, generating responses that ultimately control feeding behavior and energy homeostasis through efferent outputs (gut–brain axis) (36).

Among the sensors that account for the ECCs capability to respond to the variety of nutrient stimuli, sweet umami and bitter taste receptors have been identified (37–39): upon activation, these taste receptors trigger the release, among others, of cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1). CCK has a central effect via the vagal afferents, slowing gastric emptying and therefore reducing food intake, and a GI effect, increasing pancreatic enzymes secretion and gallbladder contraction (35). GLP-1 has its target in pancreatic β-cells, indicating a directly promoted insulin secretion (and inhibition of glucagon) with a relevant effect on glucose control. GLP-1 is the main hormone with "incretin effect" (the increased insulin response after oral ingestion of glucose, compared to that observed when the same glucose load is administered parenterally). With the incretin effect accounting for 50–70% of insulin secreted in response to oral glucose, GLP-1 and its analogs became an effective therapeutic strategy to treat type 2 diabetes (35, 40). GLP-1 receptors are also expressed in the ganglion of the vagus nerve, suggesting a potential gut–vagus–pancreatic islet neural loop. Its release is also followed by slower gastric emptying.

While the contribution of sweet and umami receptors to the regulation of glucose blood level and feeding control could be intuitive since they respond to nutrients, it is surprising that this effect is also mediated by bitter taste receptors due to the fact that, most of the times, the ligands of these receptors are not macronutrients and, therefore, do not provide energy to the body.

The metabolic roles of bitter taste receptors

Over the centuries, various bitter medicinal plants (most of them non-cultivated) have been used in traditional medicines and bitterness intensity as a food/medicine watershed (41). In particular, for plants used in different folk medicines worldwide to treat diabetes, the bitter connection is obvious. In recent years, for many of them, the glucose control activity has been explained at the molecular level through bitter taste receptor activation by some of their components and subsequent GLP-1 release (42–47).

The alkaloid berberine, produced by several plants growing in different continents and used in traditional medicines to treat diabetes (in the midst of other diseases), has been proven to release GLP-1 (also) through bitter taste receptor pathways (48). Bitter melon (*Momordica charantia L.*) is a food/medicine widely consumed throughout sub-tropical countries (China, India, Thailand, East Africa, and Central and South America), particularly in the management of diabetes. It is a hallmark of Okinawa diet, with goya champuru being Okinawa's signature dish. It is very likely that its activity in glycemic control is due to several mechanisms, with the release of GLP-1 via bitter taste receptor activation being one of them (49). In the context of glycemic control via nutrition, particular interest should be given to steviosides, secondary metabolites sharing the common aglycone steviol (ent-13-hydroxykaur-16-en-18-oic acid) but different in the number and types of sugar residues, extracted from the leaves of the *Stevia rebaudiana Bertoni*. This plant is native to Paraguay, where it has a long history of use for its sweetness and to treat several diseases, with diabetes being one of the most relevant (50). Currently, steviosides are widely used as intensive sweeteners and still the only ones of natural origin allowed in Europe. A recent study (51) demonstrated that their activity on glucose control is due to GLP-1 release triggered by the activation of bitter taste receptors (T2R4 in particular) while excluding any participation by sweet taste receptors in the process. Another reason why steviosides are of particular interest is that they enhance pancreatic β-cell function by potentiation of TRPM5 channel activity (52). As TRPM5 is also expressed in EEC cells, the activity of steviosides as modulators of GLP-1 also through this route has not been excluded (51).

Another specific example of traditional use of plants in metabolic control, explained at molecular level via a bitter taste receptor expressed in the gut (T2R14), is the anti-hunger activity of *Hoodia gordonii*, an indigenous plant of South Africa, Botswana, and Namibia (53).

Bile acids (BAs) are produced in the liver during the catabolism of cholesterol and then conjugated with glycine or taurine to make them amphipathic and therefore able to work as emulsifiers, exerting a key role in intestinal absorption and transport of dietary lipids. Through multiple and complex pathways, only partially unraveled, they have a role also in incretin secretion, glucose and energy metabolism, endoplasmic reticulum stress, and GI microbiota composition (55). The activation of several human bitter taste receptors by physiological concentrations of bile acids has been proven (54), and it has been hypothesized that this activation might contribute to the role of BA in glucose control (55, 54). Moreover, this finding indicates the role of bitter taste receptors as chemosensors for endogenous ligands, thus opening new fields of discoveries.

The activation of T2Rs and their involvement in digestion and satiety has also been shown at gastric level. Caffeine, which is able to activate five bitter taste receptors in humans, induces gastric acid secretion, known to have a role in satiation, as well as an important signal to initiate gastric protein digestion (56). Interestingly, a similar effect was proven for bitter amino acids (57) and peptides produced during the gastric digestion of caseins (58), demonstrating the participation of bitter taste receptors in the well-known satiety properties of proteins and amino acids.

Bitter taste receptors in innate immunity and in shaping the microbiota

One of the first, and apparently less logical to explain, location in which extra-oral bitter receptors were identified were the airways. In fact, while their expression in the digestive apparatus can still be inherent to food and its components, this is not at all the case for the respiratory tract. However, since the first evidences of their presence in solitary chemosensory cells in the nasal epithelium it was first brilliantly intuited and then proven their function to respond to acyl-177 homoserine lactones (AHLs) produced by Gram-negative bacteria as quorum-sensing signals (59). This intuition was absolutely endorsed by the following studies, proving that bitter taste receptor activation by AHLs triggers the release of nitric oxide (NO), a toxic defense molecule against pathogens, and increases ciliary beating (60). Similar cells in the gut, tuft cells, detect parasite and bacterial homeostatic dysregulation and initiate a type II immune response, therefore having a role in microbiota composition and, finally, in maintaining gut barrier integrity (61). It has been demonstrated that they monitor intestinal contents using succinate (the main microorganisms and helminths parasite metabolite) as well as sweet and bitter taste receptors (62, 63). In particular, bitter taste receptors activation has been related with their role in repairing gut barrier integrity compromised by obesity and dysbiosis (64).

The effect on T2R38 bitter taste receptor-mediated immunity of the bitter agonist allyl isothiocyanate (AITC), one of the most abundant phytochemicals in plants of the genus Brassica (produced from the precursors glucosinolates in a degradation reaction catalyzed by myrosinase), has also been proven at the systemic level using human peripheral blood, demonstrating that a single intake of an AITC-containing food product resulted in its concentration at plasma levels able to trigger bitter taste receptor-dependent immune cell responses (65).

With microbiota emerging as one of the key components in health status and in the genesis of many diseases, including cancer (in particular colorectal cancer), the modulation of bitter receptors in the GI could also be exploited to develop targeted microbial therapies or as chemopreventive agents though the diet, to promote overall health and against tumorigenesis (66, 67).

To underline their role in monitoring endogenous compounds and microbiota metabolites, it is noteworthy that bitter taste receptors are the only chemosensory receptors from intronless genes, usually associated with rapidly changing expression levels in response to stress (68).

Conclusion

Taste receptors, given their broad extra-oral expression, have relevant and extensive chemoreception roles, and are much more than simply gatekeepers of food ingestion and data providers for perception. For this reason, some authors even suggested addressing them with a different name rather than simply "taste receptors" (68, 69). Indeed, the discovery of extra-oral taste receptors and their functions gave them the role of ecological sensors in inter-kingdom communication, working at the interface between us and the outside world and also between us and our inner world. In particular, bitter taste receptors in the GI tract, which have been proven to be involved in metabolic responses to food molecules, their metabolites, and endogenous compounds, as well as in immunological response and in microbiota composition, became an important factor in shaping the health and unraveling the complex diet/health relationship, as well as in the gut–brain axis, emerging as potential new drug targets (and their ligands new medications).

During the revision process of this perspective, a nutraceutical formulation based on *Cinchona* bark, *chicory*, and *Gentian* roots has been presented in an open article after having being patented (70), with indications for appetite and weight management. Interestingly, the combination of plants has been appropriately designed to simultaneously target and stimulate several different T2Rs, proving the validity of the proposed approach in this perspective.

The information about the most advanced knowledge on bitter taste receptors and the function of their ligands should be spread to food producers: the growing demand in dietary proteins, especially plant protein ingredients and their derived final products, coincides with the problem of undesirable sensory properties, among which bitterness is often reported. Attention should be paid to debittering through bitter taste receptor inhibition since this action could affect the described metabolic roles and the microbiota composition. In addition, the knowledge on bitter taste receptors should be spread to consumers so that they can realize, or better to say, regain, the value of taste as a tool of knowledge (a form of intelligence) to identify bioactive compounds in food, and this understanding could contribute to their sensory acceptability.

Finally, due to the recent discoveries and the rooted role of bitterness in the food–medicine continuum in traditional knowledge, bitter taste receptors and their ligands could represent a tool for the scientific integration of ancient wisdom with conventional and advanced medicine, constituting a boost also for sustainable and functional food innovation and design.

Data availability statement

The original contributions presented in the study are included in the article further, inquiries can be directed to the corresponding author.

Author contributions

GM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Food allergies around the world

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The increase in the prevalence of food allergy has been considered as the second wave in the allergy epidemic following the first wave of increase in asthma and allergic rhinitis. It is well known that the prevalence of allergic conditions would follow economic development and urbanization in many countries or regions. In developed countries, one in three children suffered from at least one allergic disorder and these conditions include food allergy, eczema, allergic rhinitis and asthma. Food allergy is very often the first allergic manifestation affecting infants and young children. The exact etiologies are not known. The clinical manifestations ranged from a simple rash or an itch around the mouth, to the more severe manifestations of angioedema and potentially fatal anaphylaxis. Among all cases of childhood anaphylaxis, food is the most common cause. The common allergens resulting in food allergies in developed countries include egg, milk, fish, wheat, peanuts and tree nuts. However, there are marked variations in the patterns of food allergens in developing countries. In line with the epidemiology of asthma, food allergy is also much less common in rural areas. Clear understanding of reasons explaining the disparity of food allergies between urban and rural population would pave the way to the development of effective primary prevention for food allergy.

KEYWORDS

food allergy, risk factor, anaphylaxis, epidemiology, global

Introduction

The first wave of the allergy epidemic began more than 50 years ago with the increase in the prevalence of asthma and allergic rhinitis. Food allergy has been considered as the second wave of the allergy epidemic started about 20 years ago. Similar to the epidemiology of asthma, countries with high prevalence rates of asthma were also found to have higher prevalence of food allergy (1, 2). Although there have been many epidemiology studies of food allergies around the world, accurate determination of the true prevalence of food allergies is very difficult. Most published studies have only used questionnaires to ascertain possible allergic symptoms related to food allergies, and only a small proportion of studies included objective testing such as skin prick test, serum specific IgE measurements or food challenge (3). The lack of objective testing and use of different methodologies make comparison of the data from different published epidemiology studies very difficult. Nevertheless, the patterns of food allergies appeared to be different across the world (2). Early guidelines from many countries recommended dietary avoidance or delayed introduction of allergenic foods especially in high risk infants. However, there have been several prospective randomized trials showing that early introduction of allergenic foods may be beneficial in preventing food allergies (4, 5). Subsequently, guidelines from around the world now recommend early introduction rather than avoidance of allergenic foods in infancy (6, 7). The continuing changes in the environment including dietary changes will shape the epidemiology of food allergies around the world. Clear understanding of how these environmental factors interact with the immune system resulting in the manifestations of food allergies will lead to development of effective primary preventive strategies.

Epidemiology of food allergy

Food allergy is defined as an adverse health effect due to a specific immune response that reproducibly occurs upon exposure to a specific food. Such adverse effects can be sub-divided in to two major types, IgE-mediated or non-IgE-mediated. Over the past few decades, there have been many epidemiology studies of food allergy around the world, and most of these studies evaluated the IgE-mediated type of food allergy using non-standardized methodologies (3, 8). Due to the complexity of evaluation of serum IgE in large-scale population studies, most published studies have only used questionnaires to evaluate the symptoms of food allergy without objective testing. However, many other diseases may have symptoms mimicking those of true food allergies. Studies using only questionnaires frequently overestimated the true prevalence of food allergy. Furthermore, the lack of standardization of various studies made comparison of the results difficult, if not impossible. Nevertheless, the prevalence rates and the patterns of food allergens appeared to be widely different across the world (2, 9, 10).

The most common food allergens include cow's milk, wheat, egg, peanuts, shellfish, fish, soy, and tree nuts. In some parts of the world such as some Asian countries, other exotic allergens such as insects and bird's nest can also induce food allergies (2). A telephone survey conducted across 10 European countries revealed a wide variation in the prevalence of food allergy among children in these countries. In this study, parents or guardians were interviewed to ascertain possible symptoms of food allergies of their children (11). Finland was found to have the highest reported prevalence of 11.7% while Austria was lowest at 1.7%. Cow's milk, fruits, and egg were the top three most common offending foods. The European Community Respiratory Health Survey also revealed a wide variation of symptoms of adverse food reactions in European adults. The highest rate was reported in Melbourne, Australia, while it was lowest at 4.6% in Spain (12). A meta-analysis of 51 studies across the world revealed marked variations of the prevalence of food allergies ranging from 3 to 35% (3). However, the average prevalence rate of food allergy was only 3% if only studies with objective testing were included. These findings suggest marked over-estimation of the true prevalence by studies using questionnaires only. Food allergy has been reported to be common in the United States, affecting up to 8% of children and 10% adults. These studies were based on questionnaires only and might potentially overestimated the true prevalence (13, 14). The HealthNuts study from Melbourne, Australia used food challenge to document true food allergies. These Australian infants had a very high prevalence of food allergies (3% to peanuts, 8.9% to raw egg) (15).

In the past two decades, exposure to rural environments has been persistently documented to be a major protective factors against the development of allergies (16). Food allergy is no exception. A comparative study using both questionnaire and skin prick test were conducted in South Africa to evaluate the prevalence of allergic diseases in both urban and rural children (17). A total of 1,185 urban and 398 rural toddlers aged 12–36 months were recruited for this study. The prevalence of food allergy was 2.3% in the urban population while it was only 0.5% in the rural population. The recent EuorPrevall-INCO study evaluate a large sample of 35,549 school children from China, Russia, and India using standardized questionnaires along with skin prick test and serum specific IgE measurement demonstrated that children from the highly urbanized city of Hong Kong had a prevalence of food allergy 3 times higher than those of children from mainland China (10). Furthermore, among children recruited from Hong Kong, those born and raised in Hong Kong had a prevalence of food allergy three times higher than those children born in mainland China and subsequently migrated to Hong Kong. Given the same genetic background of these two groups of children, early life exposures most likely have affected the early development of the immune system leading to differences in the subsequent manifestations of food allergy. A recent comparative study also demonstrated that Asians born in Australia had markedly higher prevalence of food allergy when compared to Asians from Singapore (18, 19). Many factors may potentially be important in explaining the disparity, and the potential factors are summarized in Table 1. Further studies are needed to evaluate how various environmental exposures and dietary factors might influence the early maturation of the immune system resulting in protection against the development of food allergy.

Spectrum of food allergic reactions

The manifestations of food allergy vary widely from a very mild itch or redness on the skin, urticaria affecting a large area on the body, sneezing, itchy and watery eyes to the more severe symptoms such as difficulty with breathing and hypotension (19). Pollen-food allergy syndrome is a specific type of food allergy when the primary sensitizer is pollen such as birch pollen (20).

Due to similarity to other allergens found in fruits and vegetables, binding of the food allergens with the cross-reacting IgE would result in various symptoms of food allergy. The mildest form of pollen-food allergy syndrome typically associated with symptoms including itchy mouth, swelling of the lips and tongue. Such mild reaction is termed oral allergy syndrome, but more severe reactions including anaphylaxis can occur in patients with pollen-food allergy syndrome. Anaphylaxis is the most severe manifestation of food allergy, and appropriate treatment must be provided promptly to prevent mortality. Hospital admission data from across the world in the past 2 decades revealed significant increase in the number of food induced anaphylaxis admitted to hospitals in the United Kingdom, USA, Australia and Hong Kong (21–24). The increase was found to be highest in Australian children under 4 years of age. From 1998 to 2012, the Australian hospital admission rate due to food induced

TABLE 1 Potential factors associated with the development of food allergy.

Factors	Protection or risk factor for food allergy
Urban vs. rural	Rural environment may be associated with protection
Breast feeding	Protection: exclusive breast feeding for at least 6 months
Eczema	Risk: poorly control eczema associated with food sensitization through the inflamed skin
Introduction of solids	Protection: introduction of complementary foods at around 6 Months
Maternal diet	No evidence for food avoidance during pregnancy
Formula	Inconsistent evidence for the use of hydrolyzed formula for the prevention food allergy
Probiotics	Inconsistent results for the prevention of food allergy
Vitamin D	Inconsistent and requires further studies

anaphylaxis in children under 4 years has increased from 7.3 to 21.7 per 100,000 per year (21). Hospital admission data from Hong Kong also showed a doubling of anaphylaxis admission in 2019 when compared with data in 2009 (24). In order to optimize the clinical care of patients with food allergy, appropriate counseling of patients at risk for development of severe food allergic reactions is extremely important. However, there are no reliable features that can accurately predict the severity of food allergy. Many studies have showed that prior anaphylaxis was not a good predictor of the future risk. In fact, fatality associated with food induced anaphylaxis often occurred in patients with only prior mild reactions. Many co-factors are known to be associated with more severe reactions, such as concomitant poorly controlled asthma, medications (ACE inhibitor, beta-blockers), febrile illness, and menstruation (25, 26). Exercise is a well-known trigger typically associated with wheat allergy due to IgE sensitization to omega-5-gliadin (27). These patients usually can tolerate a small dose of wheat, but exercise would dramatically reduce the threshold and result in severe reactions. Due to the limitation of accurate prediction of severe reactions, all patients with food allergy should be educated to recognize and manage severe food allergic reactions. Although many different foods can result in food allergic reactions, they tend to differ in different regions of the world. In Europe, North America, and Australia, peanut, tree nuts, and cow's milk are the most common foods resulting in food induced anaphylaxis while shellfish and seafood are more common in Asia and Latin America (2, 25). The exact reasons explaining such differences in the pattern of food allergens are not clear. In Hong Kong, shrimp has been found to be the most common food resulting in anaphylaxis seen in the emergency department (28). However, variations of environmental factors and dietary exposures are likely important in causing some of the differences. In rural China, cockroach has been found to be a major cross-reactive allergen source in shrimp-sensitized children (29). Further studies are needed to clearly understand how environmental exposures may influence the manifestations of food allergy in different parts of the world.

Recent development and updates of food allergy guidelines

Allergen avoidance, whether during pregnancy or in early infancy, has been thought to be useful in reducing the risk of sensitization, and hence the risk of allergy. In the past, many guidelines from around the world recommended a variety of avoidance measures during pregnancy or in early infancy especially for high risk infants (30–32). For example, it was recommended that infants should avoid egg and milk for the first year of life, and peanuts, tree nuts, shellfish till 2–4 years of age. However, recent randomized controlled trials have documented that avoidance of food allergens during pregnancy could not reduce the risk of food allergy in their offspring. Furthermore, there have been several prospective randomized clinical trials testing whether food avoidance in early infancy was effective in preventing subsequent food allergies (4, 5). The Learning Early About Peanut (LEAP) trial recruited 640 high risk infants and randomized them to consume 6 g of peanut protein weekly or to avoid peanuts for the first 5 years of life (4). At 5 years of age, peanut allergy documented by food challenge in the avoidance group was 17.2% as compared with the 3.2% in the intervention group. In the Enquiry About Tolerance (EAT) study, more than 1,300 infants were recruited and randomized to introduction of six allergenic foods (peanut, egg, cow's milk, sesame, fish, and wheat) starting at 6 month of age (5). The children were followed up till 3 years of age for assessment of possible food allergy to the six allergenic foods. In the per-protocol analysis, the primary outcome was significantly lower in the early introduction group (2.4%) than in the standard-introduction group (7.3%), but the difference was not significantly different in the intention-to-treat analysis. Adherence to this challenging protocol was very low at 42.8% as many parents found it very difficult to feed so many different types of solid foods to their young infants. These clinical trials clearly demonstrated that early consumption rather than delayed introduction was likely more beneficial as primary preventive strategy. Since the publication of these clinical trials, guidelines from around the world have been updated to recommend early introduction of allergenic food at around 6 months of age, and maternal dietary restrictions during pregnancy are no longer recommended (6, 7).

The remaining question is how to translate these trial findings into the real world. A recent study from Australia has been conducted comparing the prevalence of peanut allergy in one-year-old infants before and 2 years after the guideline recommendation was changed (33). A total of 7,209 infants were recruited with 1933 in 2018–2019 and 5,276 in 2007–2011. Despite earlier introduction of peanut in the later cohort, there was no significant change in the prevalence of peanut allergy across this population. Further studies are needed to determine how to introduce allergenic foods early in infants in the community level, and evaluate other potential environmental factors which may affect the manifestation of food allergy. One should also note that the prevalence of peanut allergy is extremely rare in many Asian countries such as Thailand and China (10). A birth cohort from Singapore documented a very low prevalence of food allergy despite rather late introduction of allergenic foods (34). Therefore, a consensus statement from the Asia Pacific Academy of Pediatric Allergy, Respirology & Immunology recommends that it is not necessary to delay introduction of solids, but more studies are needed to determine the role of early introduction of various allergenic foods in populations with a very low background prevalence of food allergy (35).

Discussion

There is no doubt that food allergy is becoming a major problem especially in the developed countries such as United Kingdom, United States, and Australia in the past two decades. The exact reasons driving the increase in the prevalence are not clear. Evidence is building up that early consumption as opposed to delayed introduction may be a more effective approach to prevent the subsequent development of food allergy. On the other hand, there are potentially many lessons we can learn from countries where the background prevalence of food allergy is very low, and yet early introduction of allergenic foods in these countries is not the norm. Similar to the manifestations of other atopic conditions such as asthma or allergic rhinitis, the development of food allergy is the result of the complex interactions between environmental exposures and genetic influences. The disparity of food allergy in populations with the same genetic background brought up in different environments clearly illustrates the importance of environmental exposures which include dietary variations in shaping the development of food allergy. Clear understanding of the underlying reasons explaining the variations of food allergy epidemiology around the world will provide clues for developing effective primary preventive strategies.

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GW-KW: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing.

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A review on nutritional quality of animal and plant-based milk alternatives: a focus on protein

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In recent years, the demand of consumers for products rich in protein is of significant growth. Due to its structure in tissues, protein is considered an essential nutrient for maintenance and growth. It is well known that dairy foods differ from plant-based milk alternatives in their composition. In addition to protein content, nutrients in milk and plant-based beverages vary greatly in composition and content, such as: Calcium, fiber and fat. The nutritional quality of dairy protein sources depends on both their amino acid composition and bioavailability. Indeed, dairy products are considered to be excellent sources of proteins with high Digestible Indispensable Amino Acid Score (DIAAS) values varying from 100 to 120. However, plant proteins are considered to have generally lower essential amino acid contents and lower DIAAS values than dairy proteins. For example, pea and rice proteins are known to have medium and lower DIAAS with values of 62 and 47, respectively. The present review is dedicated to study the nutritional quality of animal and plant-based milk alternatives, where a focus on protein composition and amount are determined.

KEYWORDS
animal dairy products, plant-based milk alternatives, protein, nutritional, quality

1 Introduction

In recent years, consumers have increasingly opted for plant-based diets (1, 2). In fact, according to Battisti et al. (3), plant-based milk alternatives are one of the emerging areas in the food industry, as the consumption of plant-based milk alternatives has increased significantly and is rapidly gaining popularity, mainly due to its nutritional value and numerous positive effects and health benefits to humans (4). Given that approximately 65% of the world's population has reduced lactose digestibility and allergies, reliance on plant-based milk alternatives has emerged as an ideal alternative to meet the daily nutritional needs of these consumers.

In this context, both research and industry are interested in developing plant-based milk alternatives as an alternative to animal milk products. The market is expected to reach $66.9 billion by 2030, according to a new report from Grand View Research, Inc. as indicated in previous research studies (5, 6). As depicted by Pritulska et al. (6), plant-based milk alternatives could be produced from nuts (almond milk), grains (oat milk), legumes (soy milk), seeds (hemp milk) and so on.

Numerous research studies were conducted to determine the quality, functionality, and nutritional properties of plant-based milk alternatives. For example, Le Roux et al. (7) depicted that plant-based milk alternatives produced with pea and faba beans presented protein digestibility varying between 51–66 and 42–73% for static and dynamic digestion systems, respectively. In another approach, Khalesi and FitzGerald (8) blended soybean or pea protein at a level of 25% with animal milk protein and observed an amelioration in the digestibility level since soy and animal milk protein blend was found to be digested in the gastric phase, while pea and animal milk protein blend was mainly digested during the intestinal phase.

Despite the popularity of plant-based milk alternatives, these products sometimes presented some unpleasant sensory notes such as beany off-flavor, chalky or grainy mouthfeel, darker appearance, instability manifested by liquid separation (9, 10). To counteract these disadvantages and increase the acceptability of plant-based milk alternatives, flavorings and stabilizers are used in the formulation of plant-based milk alternatives (11). However, the use of additives in the formulation of plant-based milk alternatives may lead to concerns among consumers who are increasingly scrutinizing the nature of ingredient lists (12). To address this problem, recent research studies have been conducted by combining different plant proteins such as soy and almond milk blend, oat, and cashew blend, and flaxmilk and pea protein allowing to produce products with a high nutritional value (12). Therefore, this paper aims to provide a comprehensive review of the quality of plant-based milk alternatives compared to animal dairy products by focusing on protein.

2 Milk and milk analogs in terms of their composition in protein and digestibility

Dairy milk is considered to be a source of protein, fat, mineral especially calcium and phosphorus, and several other micronutrients (Table 1). For the production of plant-based milk alternatives, different ingredients such as: (i) vitamins A and D, minerals and so on (16); and (ii) sugars, flavors, are used to improve taste and texture, thus affecting the overall health profile.

Protein is fundamental to maintain human body function. The nutritional quality of proteins is affected by their amino acid composition and bioavailability. The protein level is calculated using the nitrogen conversion factor, depending on the protein's origin. Table 2 expressed the nitrogen to protein conversion factor for animal and plant protein, while Table 3 indicated the amino acid composition varied according to the plant-based milk alternatives (25–27).

The digestible indispensable amino acid score (DIAAS) of some plant-based milk alternatives has recently determined by Khamzaeva et al. (27) (Table 4). For cow's milk, all DIAAS were higher than 100% with the lowest one (117%) for tryptophan and the highest one (198%) for histidine. Lower DIAAS values were determined for individual amino acids for the other plant-based beverages. Indeed, for soy plant-based beverages, the lowest DIAAS values (111%) was noted for valine and tryptophan and the highest one (164%) for histidine. Again, all DIAAS values for soy beverages were higher than 100%. Regarding oat beverages, histidine and lysine presented, respectively, the highest (183%) and the lowest (73%) DIAAS values, respectively. For the oat almond beverages, lysine, threonine and tryptophan presented the lowest DIAAS values, respectively: 34, 93 and 94%. The highest DIAAS values was noted for Histidine with 187%.

2.1 Soybean milk

The production and consumption of soybean milk have increased significantly over the last two decades due to its nutritional value and health benefit (25, 26). For example, besides the absence of lactose and cholesterol in soy milk, its protein composition is quite similar to that of cow milk (27).

According to the United States Department of Agriculture Food Composition Databases, soybean milk contains a protein level of 3.65 g/100 g. In order to increase the bioavailability of bioactive compounds present in soybean milk, a fermentation process could be applied. Indeed, it has been reported that the fermentation process reduced anti-nutritional factors (proteinase- inhibitors, phytic acid, urease, oxalic acids) and increase the bioavailability of bioactive components (28). The authors explained this trend by the fact that during the fermentation process, micro-organisms break down complex organic substances into simpler molecules increasing the number of free isoflavones and peptides (28). In another approach, Sanjukta and Rai (29) fermented soybean with *B. subtilis MTCC5480* and observed a higher amount of free amino acids level due to the protein hydrolysis. The authors mentioned that *B. subtilis* increase the free radical scavenging property to an appreciable level and inhibits

TABLE 2 Nitrogen to protein conversion factor for animal and plant protein.

Protein type	Factor	Reference
Milk	6.38	(17)
Almond	5.18	(18)
Rice	5.95	(17)
Soybean	5.71	(17)
Coconut	5.31	(19)

TABLE 1 Composition of bovine milk compared to some plant-based milk alternatives.

	Macromolecules			Minerals		References
Milk type	Protein (%)	Fat (%)	Carbohydrates (%)	Ca (mg/100 g)	P (mg/100 g)	
Bovine milk	2.9–6	3.4–6.4	3.20–5.40	122–134	119–121	(13)
Almond milk	1.9–2.50	3.20–3.60	4.30–4.70	13.05–13.15	75.03–75.33	(14)
Soy milk	3.82–3.98	3.1–4.3	4.64–4.92	4–5.4	49–62.6	(14)
Rice milk	0.28–1.26	0.97–1.11	9.41–12.7	118–121.35	55.91–56.86	(15)
Coconut milk	0.59–2	4.12–6	3.75–9.41	176–178.1	240–256.35	(15)

TABLE 3 Comparative overview of some amino acid profile of bovine milk with commercially nondairy plant-based milk alternatives.

	Some amino acids (mg/100 g)							References
Milk type	Lysine	Methionine	phenylalanine	tryptophan	Leucine	Histidine	Valine	
Bovine milk	49–96	17–27	38–56	n.d.	90–108	15–26	33–53	(5, 20)
Soy bean milk	0.88–3.92	0.31–0.85	1.86–2.79	0.3–0.8	2.94–4.24	0.55–1.49	1.32–2.59	(5, 21)
Almond milk	36.2–57.4	27.1–27.95	50.9–50.55	13.9–13.98	83.2–83	21.8–25.7	38.3–73.6	(5)
Rice milk	118.4–179.4	155.6–168.9	393.3–448.5	n.d.	496.9–585.2	186.6–206.6	306.2–375.2	(5, 22)
Peanut milk	36.75–36.7	n.d.	n.d.	30.02–30.3	64.5–64.3	27.2–27.73	32.63–32.79	(5, 23)
Coconut milk	3.50–5.1	1.2–2.9	2.7–5.9	3.20–3.30	3.9–6.5	1.8–1.9	3.5–7.5	(5, 24)

n.d., not determined.

TABLE 4 Digestible indispensable amino acid score (DIAAS)[a] ratio for Histidine, Threonine, Valine, Isoleucine, Leucine, Lysine and Tryptophan in soy, oat, and almond plant-based beverages and cow's milk (27).

	DIAA reference ratio						
	Histidine	Threonine	Valine	Isoleucine	Leucine	Lysine	Tryptophan
Cow's milk	1.98	1.48	1.35	1.51	1.38	1.60	1.17
Soy beverage	1.64	1.39	1.11	1.47	1.14	1.24	1.11
Oat beverage	1.83	1.17	1.24	1.30	1.18	0.73	0.95
Almond beverage	1.87	0.93	1.08	1.26	1.10	0.34	0.94

[a]The DIAA reference ratio was calculated by dividing the content of the indispensable amino acid by the reference pattern of the respective amino acid (27).

angiotensin I-converting enzyme resulting in decreasing blood pressure level. Recently, Battisti et al. (3) analyzed 15 different commercial soy milk using a label-free quantitative proteomics approach and found different levels of essential amino acids and non-essential amino acids. The authors depicted a relative lower amount of histidine, methionine, tryptophan and cysteine in soy milk and recommended the necessity of fortifying commercial soy milk with these amino acids. The obtained results are confirmed, recently, by others who depicted the absence of tryptophan in soybean grain (27).

2.2 Almond milk

Almond is considered one of the "brain-foods" since it is considered to promote mental alertness, concentration, recall skills, memory and helps to get good sleep when taken at night (30). Patients who are suffering from lactose intolerance are advised to consume almond milk instead of soy milk (31). Recently, Ashkanani (32) compared the nutritional quality of almond and oat milk and found that the former was more effective to increase protein level among others. Ashkanani (32) depicted that the *in vitro* digestion of almond proteins by pepsin led to the destabilization and coalescence of almond oil bodies that did not significantly affect the rate of protein delivery to the small intestine.

In a different approach, Wang et al. (33) determined the DIAAS of almond milk compared to cow milk. It is well known that the higher the DIAAS score, the greater the quality of the protein material in the food. The authors depicted a DIAAS of 0.39 and 1.45 for almond and cow milk, respectively indicating the higher digestibility of the former milk. The same authors used another universal score called PDCAAS and again found that cow milk scored higher than almond milk (1 vs. 0.4, respectively). One of the main conclusions of their study was that almond milk is not a substitute for cow's milk because of its lower DIAAS value.

Almond is ranked as fourth among other tree nuts allergy that could be presented as mild such as simple oral allergy and complex as fatal anaphylaxis. Among allergy compounds, amandin is the major protein in almond, legumin, and pruning. The amandin allergen is highly resistant to heat treatments but sensitive to pepsin enzyme (34). As for soy bean milk, the application of mechanical and fermentation treatments removed easily allergen proteins allowing almond milk to make its position among other plant-based milk alternatives substitutes in the market.

2.3 Rice milk

Rice milk is made primarily from ground rice and water. It is easy to digest, and suitable for allergy sufferers. Like other plant-based beverages, rice milk presents a creamy texture that resembles dairy milk (35). Although rice contains a relatively high level of proteins (10%), it suffers from the absence of threonine and lysine. On the contrary, it contains significant amounts of ferulic acid, sinapic acid and p-coumaric acid. The most abundant amino acids in black rice milk are leucine, glutamic acid, serine, and aspartic acid (36). The low protein content in black rice milk contributed to the low number of amino acids in agreement with the findings of others (35).

It has been reported that soaking is effective in increasing the minerals and vitamins (B6 and B12), insoluble fiber and bioactive components in rice (37). As for soy and almond milk, fermentation with the use of lactic acid bacteria breaks down the anti-nutritional factors and enhances calcium, magnesium, and iron levels, and helps in the digestion and immunity of other internal organs (37).

2.4 Coconut milk

Coconut milk is prepared by a mechanical method that starts by shelling the nut and separating the meat, which is cleaned and grated. Mixing with warm water to extract oil, milk, and aromatic components (38). Different parameters such as grinding time and incubation time present a major impact on coconut milk yield production. Coconut milk contains protein, fat, carbohydrates, minerals (calcium, phosphorus, and potassium), and vitamins (vitamins B1, B3, B5, and B6, C, E) (39). Coconut protein presents a large number of essential amino acids, which are more easily digested and absorbed with a DIAAS value of 0.79 versus 1.45 for cow milk (40).

Thaiphanit and Anprung (41) produced yoghurt samples with different ratios of cow and coconut milk (100:0, 80:20, 60:40, 50:50, 40:60, 20:80, 0:100). The authors found that producing yoghurt with cow and coconut blends is more nutritious than the ordinary one and suggested more exploration of the use of coconut and cow blend milk for the production of yoghurt.

2.5 Oat milk

Oat presents nutritional components including phenolic compounds, saponin, sterol, phytic acid and other anti-oxidant components. Oat contains various fiber components such as polysaccharides, oligosaccharides, lignin. Plant-based beverages containing lentils and peas or just adding peas to oat drinks increase the concentration of amino acids (42). The authors found that the most ideal mixture to obtain a complete amino acid composition was obtained with: (i) a raw material containing 1.1% oat protein, 1.5% each pea and lentil protein; (ii) 1.1% oat protein, 2.9% pea protein; (iii) 0.8% oat protein, 1.1% pea protein, and 2.1% lentil protein. These mixtures were found to significantly increase the amounts of phenylalanine, leucine, and threonine, and to a lesser extent isoleucine, valine, methionine, histamine and lysine. One of the main conclusions of their study is that most plant-based beverages made from single-plant ingredients do not have an amino acid profile that meets human needs.

As observed for other plant-based milk alternatives, the fermentation process induces the formation of active ingredients improving thus the quality of plant-based milk alternatives, plant based dairy products (43). In this context, germinated oat beverages fermented with *Lactobacillus reuteri*, *Lactobacillus plantarum* B28, and *Streptococcus thermophilus* was found to present health benefits for consumers (44, 45).

3 Conclusion

Plant-based milk alternatives will continue to be an important research area in the new product development category of food science and technology by setting a more strategic direction for innovation and next-generation protein blends. Plant-based milk alternatives meet the changing consumer behavior toward novel plant-based milk alternatives, the scientific community expects continuous efforts to improve plant-based milk alternatives quality through R&D activities and technological interventions. It is noted that deep and continuous research studies should be realized in the next years to ameliorate the nutritional quality of plant -based milk, particularly in their composition in amino acids. This could be achieved by combining different plant proteins that induce an amelioration in the composition of amino acids of plant-based milk alternatives. In addition, research on plant-based milk alternatives should be deepened regarding the amelioration of their organoleptic properties and the prolongation of their shelf life. This can be achieved by inactivating plant enzymes using new process techniques such as high-pressure treatment, pulsed electric fields, ohmic heating and cold plasma.

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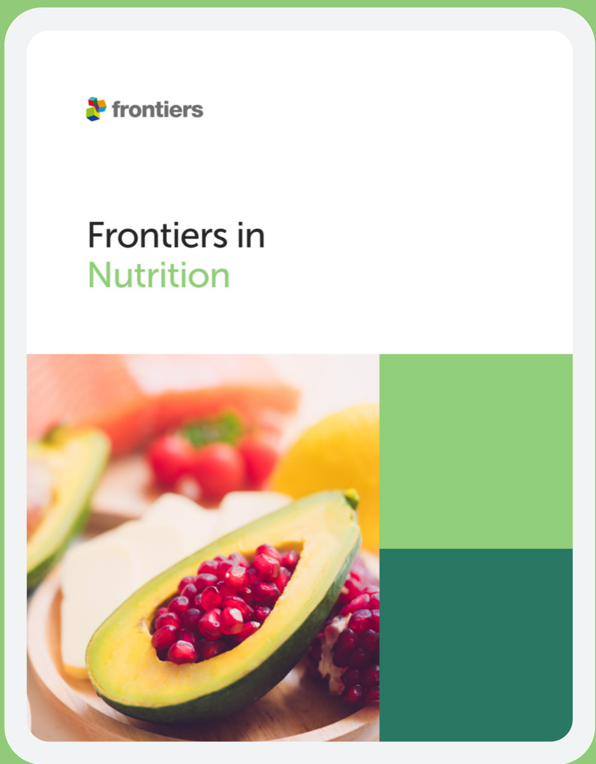

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