Food and Agriculture Organization of the United Nations

FOOD SAFETY
in personalized nutrition

A focus on food supplements and functional foods

Co-funded by the European Union

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Food and Agriculture Organization of the United Nations
Rome, 2025

Required citation:
Di Martino, M. 2025. *Food safety in personalized nutrition – A focus on food supplements and functional foods*. Rome, FAO. https://doi.org/10.4060/cd4280en

ISBN 978-92-5-139611-7

This publication has been produced with the assistance of the European Union. The contents of this publication are the sole responsibility of FAO and can in no way be taken to reflect the views of the European Union.

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ACKNOWLEDGEMENTS

The Food and Agriculture Organization of the United Nations (FAO) extends its sincere appreciation to the many individuals who provided valuable advice and guidance during the preparation of this document. The research and drafting of this publication were undertaken by Maura Di Martino, Food Safety Specialist in the Agrifood Systems and Food Safety Division at FAO, under the technical leadership and guidance of Markus Lipp, Senior Food Safety Officer and Vittorio Fattori, Food Safety Officer, both from the Agrifood Systems and Food Safety Division at FAO.

The peer review process benefited greatly from the insightful comments of various FAO staff and external experts, particularly Carmen Bullon (Development Law Office, FAO), Magdalena Niegowska Conforti (Agrifood Systems and Food Safety Division, FAO), Eleonora Dupouy (Agrifood Systems and Food Safety Division, FAO), Jane Feeney (Agrifood Systems and Food Safety Division, FAO), Masami Takeuchi (Agrifood Systems and Food Safety Division, FAO), Johanna Trieb (Agrifood Systems and Food Safety Division, FAO), the Food and Nutrition Division (FAO), William Hallman (Professor and Chair, Department of Human Ecology, School of Environmental and Biological Sciences, Rutgers Global Health Institute, the United States of America), Amie Steel (Associate Professor, Australian Research Consortium in Complementary and Integrative Medicine, School of Public Health, University of Technology Sydney, Australia) and Greg Wasinski (Head of Strategic Insights, Science Evidence and Research Division, Food Standards Agency, United Kingdom of Great Britain and Northern Ireland).

Experts from regional and national authorities who contributed to the review of the section on regulatory frameworks are gratefully recognized. Special acknowledgment is given to the Codex focal points of Argentina, Australia, Brazil, Canada, China, Egypt, Europe, India, Nigeria, Japan, the United Arab Emirates, and the United States of America. The document was technically edited by Christin Campbell, with graphic design provided by QUO.

ABBREVIATIONS

ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (National Administration of Drugs, Foods, and Medical Technology)
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (the French Agency for Food, Environmental and Occupational Health and Safety)
ANVISA	Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency of Brazil)
API	active pharmaceutical ingredient
ARTG	Australian Register of Therapeutic Goods
CAA	Consumer Affairs Agency
CAC	Codex Alimentarius Commission
CAM	complementary and alternative medicine
CFDA	China Food and Drug Administration
CFR	Code of Federal Regulations
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EC	European Commission
EFSA	European Food Safety Authority
EGCG	epigallocatechin gallate
EDA	Egyptian Drug Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FBO	food business operator
FDA	Food and Drug Administration
FDR	Food and Drug Regulations
FFC	functional food claims
FNFC	foods with nutrient function claims
FOSHU	foods for specified health uses
FSANZ	Food Standards Australia New Zealand
FSA	Food Standards Agency
FSSAI	Food Safety and Standards Authority of India
GACC	General Administration of Customs China
GACP	good agricultural and collection practices
GMP	good manufacturing practice

GRAS	generally recognized as safe
HACCP	Hazard Analysis and Critical Control Points
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JEMRA	Joint FAO/WHO Expert Meetings on microbiological risk assessment
LFN	Laws of the Federation of Nigeria
MRA	microbiological risk assessment
NAFDAC	National Agency for Food and Drug Administration and Control
NCI	National Cancer Institute
NDI	new dietary ingredient
NFSA	National Food Safety Authority
NHC	National Health Commission
NHFPC	National Health and Family Planning Commission
NHP	natural health product
NNHPD	natural and non-prescription health products directorate
RDI	recommended daily intake
RDC	Resolution of the Board of Directors
RNPA	Registro Nacional de Productos Alimenticios (National Register of Food Products)
SAHPRA	South African Health Products Regulatory Authority
SAMR	State Administration for Market Regulation
SFA	Singapore Food Agency
TGA	Therapeutic Goods Administration
TCM	traditional Chinese medicine
UL	upper limit
USP	United States Pharmacopeia
WHO	World Health Organization

EXECUTIVE SUMMARY

Over the past two decades, personalized nutrition has gained considerable traction among industry professionals, consumers and researchers. While still a niche practice, primarily among consumers in high-income countries, personalized nutrition reflects a growing recognition of the crucial role that food and nutrition play in health and well-being. Dietary recommendations have traditionally been aimed at large populations, but it is increasingly evident that physiological responses to food can vary between individuals. This realization has prompted a new approach to nutrition, encouraging a personalized method which aims to tailor dietary interventions to an individual's unique characteristics.

Food supplements and functional foods are key components of personalized nutrition plans, claiming to modulate physiological functions based on consumer needs. As the field of personalized nutrition continues to develop, it is important to consider the safety aspects associated with the use of products like food supplements and functional foods, particularly given their rising levels of consumption. While these products are generally perceived as safe, they may nonetheless pose potential food safety and nutritional challenges. Additionally, in some countries, the lack of clarity regarding regulatory requirements, definitions and terminology across different jurisdictions contributes to significant variation in how these products are regulated worldwide.

In this publication, the Food and Agriculture Organization of the United Nations (FAO), provides a comprehensive overview of potential safety concerns associated with food supplements and functional foods, including adulteration, drug interactions, overdose, and toxicity, supported by case studies from scientific literature and media reports. It also examines regulatory frameworks across various countries and regions, including Argentina, Australia, Brazil, Canada, China, Egypt, Europe, India, Japan, Nigeria, South Africa, the United Arab Emirates, and the United States of America. These frameworks cover key areas in the field of food supplements and functional foods such as classification, labelling, claims, composition, and registration, highlighting the differences in regulatory approaches.

The report also explores consumer perceptions of the safety of food supplements and functional foods, analysing the motivations behind their use and the impact of marketing on their adoption. As scientific understanding of the impact of food on the human body advances, more precisely tailored products are likely to emerge to address individual health needs. Regulatory frameworks may need to evolve to address these innovations and the associated food safety challenges. FAO will continue working with its members and relevant stakeholders to share up-to-date knowledge on food safety issues related to food supplements and functional foods, supporting competent authorities in protecting public health.

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1. INTRODUCTION

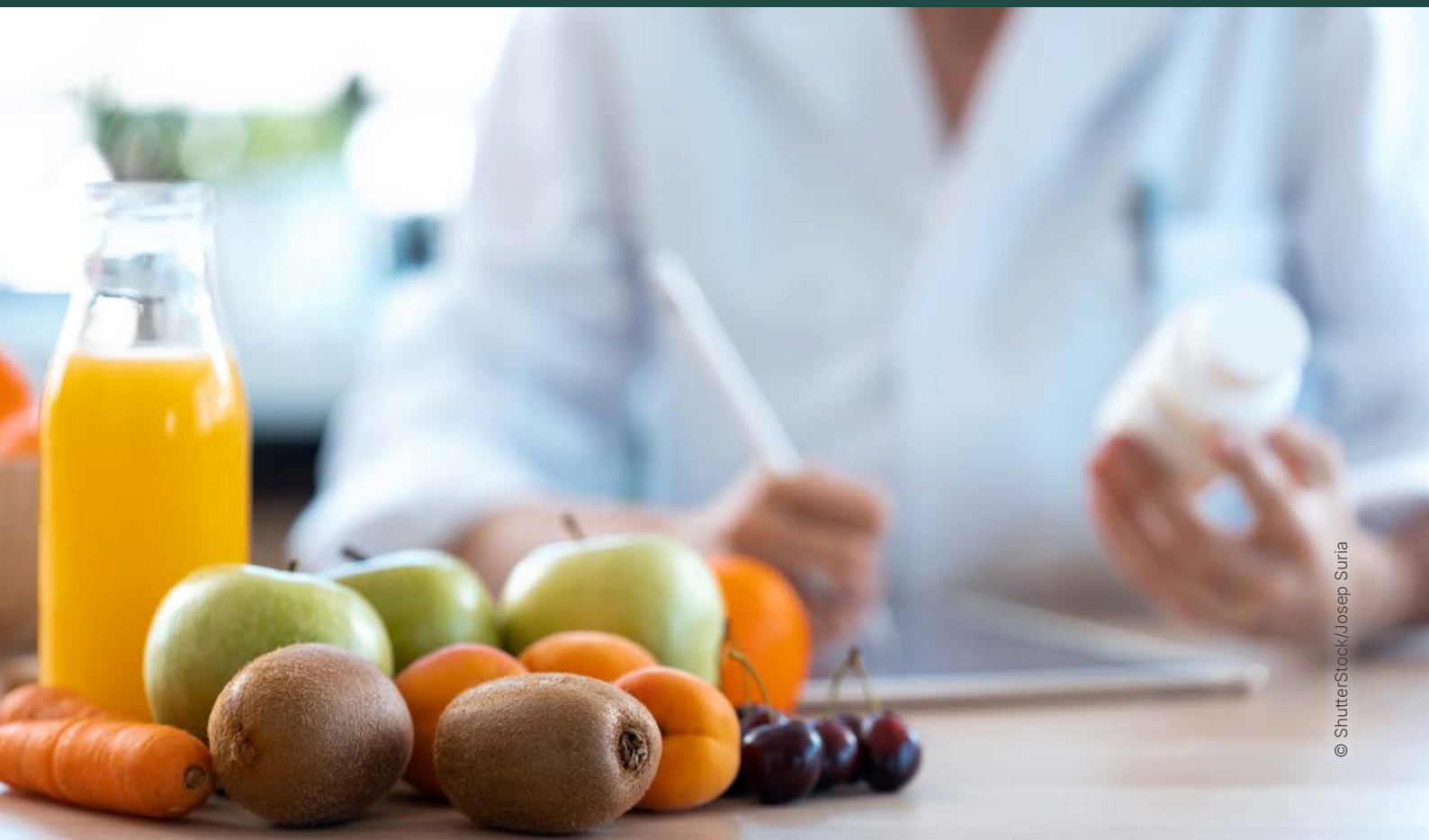
Emerging research in the field of personalized nutrition has increased the understanding of how food affects the body at a molecular level. Research has shown that specific nutrients can affect cellular functions, modulate cellular responses, and regulate numerous metabolic pathways through genomic interactions, thereby impacting health parameters (Sikalidis, 2019). This knowledge has invigorated the "food as medicine" concept, which integrates nutritional interventions into health care systems to treat and prevent chronic conditions, enhance health outcomes, and promote health equity (Mozaffarian *et al.*, 2024; Downer *et al.*, 2020).

The correlation between health and susceptibility to disease is intrinsically tied to the absorbance and functions of nutrients through consumption of food. This association has been the basis for dietary recommendations for centuries. Adequate nutrition is associated with more secure pregnancies and childbirth, improved maternal and child health, enhanced immune systems, and a decrease in the incidence of non-communicable diseases such as obesity and diabetes (Sikalidis, 2019).

It is also important to consider that physiological responses to foods can vary significantly among individuals. Therefore, to help individuals achieve optimal health outcomes, some literature suggests that the traditional "one-size-fits-all" approach to dietary recommendations is increasingly being complemented by personalized recommendations (Bland, 2019). Nonetheless, standard dietary guidelines continue to play a significant role. The personalized nutrition approaches consider many additional elements including the unique genetic makeup, gut microbiota, lifestyle factors, medical conditions, and phenotypic parameters of each person, to customize dietary interventions, thus offering a more effective strategy for optimizing health outcomes and preventing diseases (Adams *et al*., 2020; Röttger-wirtz and Alie, 2021; Strauss, Short and Lotfian, 2023; Selvi *et al*., 2022).

Although there is increasing global attention towards personalized approaches to health and wellness, they are not a new concept; they are deeply rooted in several traditional medicinal systems, including ayurvedic medicine, traditional Chinese medicine, and others (Banerjee, Debnath and Debnath, 2015; Capodice and Chubak, 2021). These approaches have long utilized detailed empirical knowledge about the health impacts of specific foods, a practice that has been studied and applied across numerous cultures for millennia. However, over the past two decades personalized nutrition has increasingly captured the interest of industry professionals, the public and researchers, regaining recognition and media attention. From a societal perspective, aspects such as an aging demographic, inactive lifestyles, and increasing health care costs have played a significant role in driving interest towards improving health outcomes through dietary interventions. The successful completion of the Human Genome Project in the early 2000s served as a major driver for the expansion of the commercial personalized nutrition sector. This milestone significantly advanced the fields of nutrigenetics and nutrigenomics (de Roos, 2013). Nutrigenetics explores how individual genetic variations affect a person's response to specific nutrients, explaining why certain diets may be more effective for some individuals than others. Nutrigenomics, on the other hand, investigates how nutrients and dietary components interact with genes, influencing gene expression and, consequently, overall health outcomes. Moreover, the reduction in cost of DNA sequencing, resulting from the progress in DNA sequencing methods, along with advancements in computational and software innovations within the domain of bioinformatics, have significantly contributed to the enlargement of personalized nutrition services.

A nutritionist prescribing a personalized dietary plan



Commercial personalized nutrition services provide advice based on data-driven insights into the relationships between physiological responses to food and individual phenotype data. These data are collected through various methods, including questionnaires, tracking devices, software applications, blood biomarkers, DNA tests, and metabolic parameter tracking. A significant part of this advice includes food supplements and functional foods, which play a key role in personalized nutrition as they promise to modulate physiological functions as desired by the customer.

In this report, we utilize the terms "food supplement" and "functional food" as working terminologies, consistent with previous documentation produced by the Food and Agriculture Organization of the United Nations (FAO) (please refer to Section 1.4 for additional information). "Food supplements" are characterized as products that comprise concentrated sources of nutrients that are intended to supplement an individual's dietary intake, whereas "functional foods" represent a classification of nourishment that provides a health advantage beyond fundamental nutrition. It is important to acknowledge that the scope of products encompassed by these terminologies is extensive, and these commodities are identified by diverse nomenclature across various jurisdictions.

Since the field of personalized nutrition continues to develop, ensuring the safety of the products used, including food supplements and functional foods, becomes increasingly important. These products are often seen as safe by consumers, but there are potential food safety challenges as with all other food items. Additionally, there is limited clarity regarding the regulatory requirements, definitions, and the terminology used to classify these products among different jurisdictions (Thakkar *et al.*, 2020; Durazzo *et al.*, 2022; Lam *et al.*, 2022). Food supplements and functional food regulations show considerable variation across different countries and are subject to oversight by diverse federal agencies and government regulations depending on the contexts in which these products are used.

As part of its Food Safety Foresight Programme[1] the Food and Agriculture Organization of the United Nations (FAO) offers with this report an analysis of the food safety and regulatory implications associated with the emerging topic of personalized nutrition, focusing on food supplements and functional foods.

1.1 Scope

This publication contains an overview of the potential food safety issues linked to the use of food supplements and functional foods and discusses the regulatory challenges they pose. While it also provides a snapshot of national and regional legislative frameworks worldwide, an exhaustive analysis of legislations governing the regulation of food supplements and functional foods across different jurisdictions is outside the scope of this publication.

This study's main aim is to identify the food safety implications associated with food supplements and functional foods which play a significant role in personalized nutrition. The identification of these implications is intended to aid decision-making processes and ensure the safety of such products.

Medical foods, defined by Codex as "foods for special medical purposes" (CXS 180-1991) (FAO and WHO, 1991), also play a role in personalized nutrition. These are foods specifically formulated for the dietary management of diseases with unique nutritional requirements and may be used only under medical supervision that cannot be fulfilled by a normal diet alone. However, this category is not within the scope of this report.

This publication does not intend to provide or assess information on the efficacy of food supplements and functional foods, nor does it aim to address all other aspects of personalized nutrition, such as testing services and nutritional advice.

[1] See FAO – Food Safety and Quality: Foresight, for more information: https://www.fao.org/food-safety/scientific-advice/foresight/en/

A person lifting weights in a gym. Athletes sometimes use supplements tailored for sports activities

1.2 Search strategy

The publications cited in this document were retrieved from open-access databases such as PubMed and Google Scholar, using keywords such as “personalized nutrition”; “food safety”; “food supplements”; “dietary supplements”; “natural health products”; “herbal supplements”; “herbal medicine”; “vitamins”; “minerals”; “probiotics”; “prebiotics”; “nutraceuticals”; “functional foods”; “regulatory challenges”; “regulatory science”; and “regulatory framework”.

Data and information pertaining to the food safety of the substances discussed were sourced from reports, scientific articles, news and the websites of national authorities, international organizations, and associations. The regulatory section (Section 4) was assembled for a selection of countries representing diverse geographic areas, based on pertinent local legislation and information provided by national authorities.

1.3 Working terminology

For clarity in this document, the term “food supplement” is employed as a working term, following the usage by the Codex Alimentarius Commission on the “Guidelines for vitamin and mineral food supplements (CAC/GL 55 – 2005)” (FAO and WHO, 2005). The term “functional food” is defined as a “foodstuff that provides a health benefit beyond basic nutrition, demonstrating specific health or medical benefits, including the prevention and treatment of disease” (FAO, n.d).

1.4 Structure of the report

This document is organized into six sections. Section 1 is the present introductory chapter. Section 2 delves into the key features of food supplements and functional foods, including trends, innovations, and product development. Section 3 provides a summary of the food safety issues associated with food supplements and functional foods. Section 4 offers an overview of the global regulatory frameworks pertaining to food supplements and functional foods. Section 5 explores consumer perceptions of safety in food supplements and functional foods and their cultural significance. Finally, Section 6 concludes the document by outlining a way forward.

2. DEVELOPMENT AND TRENDS IN FOOD SUPPLEMENTS AND FUNCTIONAL FOODS

The commercial landscape of food supplements and functional foods has seen a significant rise over the past decades (Djaoudene *et al.*, 2023; Boggia, Zunin and Turrini, 2020). The COVID-19 pandemic in early 2020 has since further accelerated the sale of food supplements and functional foods, leading to a significant increase in their demand worldwide (Farzana *et al.*, 2022). Current trends in the food industry indicate that these products are becoming more prevalent in the daily diets of many countries, presenting a profitable segment in food production (Barauskaite *et al.*, 2018). The market expansion is not only reflected in sales but also in the diversity of available food supplements and functional foods. This includes a broad selection of products, brands and formulations distributed through a wide array of marketing channels (Lam *et al.*, 2022). However, while both functional foods and food supplements aim to contribute to overall health improvement, they differ in form, usage and regulations, which can vary across different jurisdictions (see Section 4).

Food supplements provide a concentrated source of nutrients or other bioactive components claimed to have nutritional or physiological benefits, such as vitamins, minerals, herbal and botanical compounds, probiotics, prebiotics, amino acids, metabolites, and more. They are generally available in dosage forms like capsules, pastilles, soft gels, gelcaps, tablets, pills, powder sachets, and other systems intended to be consumed in small, measured quantities. They are not intended for use as a conventional food, meal or diet, but rather to supplement the diet in order to confer the alleged benefits from such substances (Brown *et al*., 2016; Wierzejska, 2021).

Functional foods are food items that provide health benefits beyond basic nutrition (FAO, 2001). They are specifically designed to have physiological benefits and/or reduce the risk of chronic diseases since they contain not only essential nutrients but also bioactive ingredients. Functional foods closely resemble traditional food items in appearance, and they are seamlessly integrated into a regular diet, thereby incorporating health benefits into daily eating habits. A variety of functional food and beverage preparations available on the market have been developed and studied to cater to diverse consumer needs (Dahiya *et al*., 2023). Examples include cereals enriched with soluble fibres claimed to aid digestion, orange juice fortified with calcium claimed to support bone health, and yoghurts supplemented with probiotics claimed to improve gut health.

Functional foods can be grouped into four categories based on the processes used: fortified products, enriched products, altered products, and enhanced commodities. Fortified products have an increased level of nutrients already present in the original item, such as fruit juices with added vitamin C. Enriched products include nutrients not typically found in the original food, like calcium in fruit juice. Altered products replace existing nutrients with others that offer additional health benefits, for instance, substituting saturated fats in milk with oleic acid. Enhanced commodities involve modifying the raw ingredients to boost their nutrient content, such as fruits cultivated or processed to have a higher vitamin concentration (Domínguez Díaz, Fernández-Ruiz and Cámara, 2020). In addition to these formulated products, there are also functional foods that are naturally rich in bioactive compounds such as vitamins, minerals, antioxidants, and fibre (Vlaicu *et al*., 2023). Despite their dissimilarities, the bioactive ingredients utilized in both food supplements and functional foods are similar and are obtained using the same methods (Table 1).

Bottles of probiotic yoghurt, a popular functional food

Table 1 Categories of bioactive ingredients commonly used in food supplements and functional foods and their source

Bioactive ingredient category	Examples	Source of the bioactive ingredients
Vitamins	Vitamin A, vitamin B, vitamin C, vitamin K, biotin, vitamin D, vitamin E, thiamin	They can be obtained from natural sources like fruits, vegetables, and animal products. However, they can also be synthesized in laboratories.
Minerals	Calcium, magnesium, iron, zinc, phosphorus, iodine	They are naturally occurring in various foods but can also be produced synthetically.
Botanicals[2]	*Echinacea*, ginger, *Ginkgo biloba*, *Curcuma longa*, *Aloe vera*, ashwagandha, ginseng, *Astragalus*, bilberry, bitter orange	They are sourced from their respective plants.
Botanical compounds[3]	Caffeine, curcumin, catechin	They are found naturally in various plants. However, they can also be synthesized in laboratories.
Amino acids	Tryptophan, glutamine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine	They can be obtained from natural sources like proteins in food. They can also be synthesized in laboratories.
Prebiotics	Inulin, fructo-oligosaccharides	They are present in many foods such as whole grains, bananas, greens, onions, garlic, soybeans, and artichokes. They can also be synthesized in laboratories.
Probiotics	*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*	Probiotic microorganisms are produced through fermentation.
Carotenoids	Beta-carotene, zeaxanthin, lycopene, lutein	They are naturally present in various fruits and vegetables. They can also be synthesized in laboratories.
Polyphenols	Resveratrol, isoflavones, anthocyanins	They can be obtained from natural sources like fruits and vegetables. They can also be synthesized in laboratories.
Phytosterols	Sterols and stanol	They are naturally present in plants. Some of them can also be synthesized in laboratories.
Polyunsaturated fatty acids	Omega-3 and Omega-6 fatty acids	They can be obtained from natural sources like fish, seeds and nuts.

Source: Author's own elaboration.

[2] It refers to a plant or a part of a plant.

[3] It is the distinct chemical active ingredient that originates from plants, although it can also be synthesized.

2.1 New technologies to boost bioavailability of bioactive ingredients and extend product shelf-life

Food supplements and functional foods employ bioactive ingredients which can derive from natural sources (e.g. plants, animals and minerals), generated through the fermentation of microorganisms or synthesized in laboratories (Table 1). Regardless of the source or the technique used, bioactive ingredients undergo a process of extraction, isolation and purification. Therefore, it is important to consider these variables during both the manufacturing process and the design of the product. For example, the extraction method is key in determining the yield, potential contamination, and the possible induction of desirable or undesirable chemical/biological transformations, playing a significant role in ensuring the safety and quality of the final product. The evaluation of the effectiveness of food supplements and functional foods is beyond the scope of this publication. Nevertheless, it is a priority to acknowledge the technologies utilized in the manufacturing of food supplements and functional foods as an important aspect in the safety assessment of these products (refer to Section 3).

Food supplements and functional foods often claim to have a physiological effect on an organism. However, for an active ingredient to exert its intended effect, it must be bioavailable, hence readily absorbed and utilized by the body (Yetley, 2007). Numerous studies have been carried out to find techniques for enhancing the solubility, durability and availability of bioactive ingredients. Therefore, effective vehicles are essential for the delivery of bioactive ingredients in food supplements and functional foods to retain the requisite benefits during their traversal through the gastrointestinal tract. Methods like microemulsion, nanoemulsion, solid-lipid nanoparticles, liposomes, microgel biopolymers, and electrospinning have proven to be effective in improving the bioavailability of bioactive ingredients in food supplements and functional foods (Bonat Celli and Abbaspourrad, 2018; Granato *et al*., 2020; Wezgowiec *et al*., 2021; Nikmaram *et al*., 2017; Tapia-Hernández *et al*., 2019; Wang *et al*., 2019).

Throughout the product formulation design, it is important to consider that the degradation process of the bioactive ingredient depends on its chemical and physical properties, which can degrade through a variety of mechanisms including photo-degradation, oxidation, interaction with storage materials, moisture, temperature, and pH (Ribeiro *et al*., 2011). For instance, specific conditions can affect the degradation rates of different vitamins or can alter the conformation of proteins (Ferguson *et al*., 2014).

Hence, to prevent degradation and microbiological contamination that could compromise the product, it is important to consider storage conditions. One of the issues that affects the product shelf-life is moisture absorption over time, which compromises the stability of the final products. Specific coatings can be applied to protect the finished products against moisture, reducing moisture uptake, thereby improving final product quality and safety and increasing in-use shelf-life (Lam *et al*., 2022). However, these technologies can potentially induce alterations in the ingredient's chemical structure, its interactions with other ingredients or drugs, and its effects on the human body.

Additionally, one of the most significant challenges lies in the controlled release of the bioactive ingredient from the food matrix to the gastrointestinal tract, in order to ensure that the ingredient is released in the body in a controlled manner and does not exceed safe levels retaining its bioactivities (Dahiya *et al*., 2023). An uncontrolled release could lead to an overdose of the bioactive ingredient, which could potentially have harmful effects (see Section 3). Consequently, it is of utmost importance to take into consideration the impact of the technologies implemented during the manufacturing process on the safety of the final product. While the development and application of these technologies hold great promise for improving the nutritional value of foods, their safety and efficacy must be rigorously evaluated, ensuring that the benefits of these bioactive ingredients can be safely and effectively harnessed.

2.2 Claims

Food supplements and functional foods often boast a variety of claims on their labels, which can pertain to health, nutrition, or disease risk prevention. As consumers are increasingly health-conscious and intrigued by the potential advantages of these products, it is important to guarantee the accuracy of the claimed benefits to avoid any misleading information. This could mislead the consumer as well as impact their health, particularly for members of vulnerable population groups.

For instance, maintaining proper nutrition is crucial for older adults, as dietary needs change with ageing in several ways, and this population often experiences nutritional deficiencies, leading them to depend frequently on nutritional supplements to meet their dietary needs (Haines *et al*., 2023). The complex nutritional needs of older adults stem from the physiological changes associated with ageing and the presence of comorbidities. Research suggests that about 20 percent of elderly individuals suffer from atrophic gastritis, a condition characterized by chronic inflammation that damages the acid-producing cells in the stomach (Russell, 2001). This reduction in stomach acid can hinder the absorption of essential nutrients like vitamin B12, calcium, iron, and magnesium. Another nutritional challenge that comes with aging is the reduced caloric requirement. Therefore, while older adults generally need fewer calories, their nutrient intake needs to remain high; hence, the consumption of nutrient-dense foods, including food supplements and functional foods, may provide a means to meet these nutritional demands without exceeding caloric requirements (Shimokata and Kuzuya, 1993; Elia, 2001). Research demonstrates that due to less efficient nutrient absorption, older adults' nutrient needs per body mass often increase, making a nutrient-rich diet critically important for supporting their health (Pillsbury *et al*., 2010).

If supplements and functional food products fail to contain the claimed bioactive ingredients in the right proportions for these individuals as their dietary intake might not meet their nutritional requirements, it can pose potential health risks. Therefore, it is essential to ensure the quality and efficacy of food supplements and functional foods, to safeguard the health of vulnerable population groups who rely on these products to meet their nutritional needs.

2.3 The multifaceted distribution channels of food supplements and functional foods

Food supplements and functional foods are distributed through various channels, including offline channels like pharmacies, drugstores, supermarkets, specialty stores, independent retailers, and other outlets that directly reach the consumer (Djaoudene *et al*., 2023). The offline sector has dominated the market with 81 percent of total sales (Morgovan *et al*., 2019) with supermarkets and hypermarkets, constituting 33.9 percent of all offline food supplement sales in 2021 (Djaoudene *et al*., 2023). However, the distribution channels have undergone changes due to the prevalent accessibility of the internet, mobile devices, and the emergence of social media.

These platforms have now become a new way of obtaining information, which consumers use to investigate and acquire knowledge about the food supplements and functional foods they plan to consume (Hamulka *et al*., 2020). Additionally, in recent years there has been a significant expansion of e-commerce platforms that offer a wide variety of supplement brands, making them conveniently accessible to consumers (Boggia, Zunin and Turrini, 2020). Considering these developments, it is crucial to incorporate these emerging distribution channels when ensuring the food safety of food supplements and functional foods.

A consumer reading a food supplement label in a supermarket

2.4 Safety assessment of bioactive ingredients: when should it be considered?

In the process of evaluating the safety of bioactive ingredients derived from natural sources, the degree of processing and modification they undergo plays a pivotal role (Vilas-Boas, Pintado and Oliveira, 2021; Samarasiri, Chai and Chen, 2023). As an example, turmeric (*Curcuma longa*) powder, a spice that is commonly used in food and undergoes minimal processing, is widely acknowledged as safe due to its extensive history of consumption. However, curcumin, the botanical compound derived from turmeric, may present different safety profiles and thus necessitate a separate safety assessment, as it is significantly modified or purified from its plant source. People may assume that curcumin provides the same effectiveness as whole turmeric without considering how extraction, concentration and purification can alter the levels of ancillary ingredients that may have synergistic or protective effects, ultimately affecting the safety and efficacy of the product (Sharma *et al.*, 2024).

Another example involves the catechins contained in green tea (*Camellia sinensis*) which when consumed as a traditional infusion are generally deemed safe due to their natural form and the long history of green tea consumption. However, green tea extracts may contain a highly concentrated amount of catechins that have a different consumption pattern compared to catechins from green tea infusions. As a result, to determine appropriate uses and safe exposure levels to these extracts a safety assessment could be considered due to their high concentration and absence of ancillary, synergistic factors, which could potentially alter their safety profile compared to the consumption of infused green tea leaves (Hu *et al.*, 2018; Isomura *et al.*, 2016; EFSA, 2018).

Therefore, the necessity for a safety assessment often arises when a substance undergoes purification since the more a substance is purified, the more it may diverge from its natural form,

potentially introducing safety concerns that are not present in the whole food with a history of safe use (Kennedy *et al*., 2018; SFA, 2023; Vettorazzi *et al*., 2020). Additionally, it is important to consider the consumption profile of a specific bioactive ingredient, as any deviations from traditional food consumption patterns, such as changes in quantity, frequency, or preparation method, could potentially introduce safety concerns. Consuming a bioactive substance frequently or in its concentrated form, as opposed to its natural form, could lead to higher exposure levels which might not have been a concern with traditional consumption patterns (Kennedy *et al*., 2018; Vilas-Boas, Pintado and Oliveira, 2021). Therefore, a comprehensive understanding of the consumption profile is essential in assessing the safety of bioactive ingredients derived from natural sources. Another aspect to consider in the safety assessment are the changes in the chemical structure of a bioactive ingredient during the manufacturing process, which might occur and could alter the toxicity profile of the substance (Vilas-Boas, Pintado and Oliveira, 2021). Furthermore, bioactive ingredients that could accumulate in the human body and potentially cause allergic reactions also require a careful safety assessment.

The threshold to decide when a safety assessment is necessary is not fixed and depends on several factors, as described above, including the extent of modification of the bioactive ingredient, its nature, and its intended use (SFA, 2023; Vettorazzi *et al*., 2020). Food competent authorities can potentially consider these aspects in order to establish guidelines and regulations to ensure that any potential risks associated with the consumption of these bioactive ingredients are thoroughly evaluated and mitigated. This approach would not only protect consumers but also help manufacturers and suppliers to preserve the safety of products containing these compounds.

Chinese Wulong tea

3. SAFETY ISSUES OF FOOD SUPPLEMENTS AND FUNCTIONAL FOODS

While consumers often perceive food supplements and functional foods as "safe" and less likely to cause health issues, it is important to recognize that these products can still pose potential safety risks (Siddiqui and Moghadasian, 2020). Since these products provide a concentrated source of nutrients and other substances with claimed physiological effects, there is a concern about potential adverse effects. This risk may be heightened by various factors, including overdosing, prolonged use, interactions with prescription medications, allergenic reactions, and the presence of contaminants (Costa *et al.*, 2019).

This section delves into the main safety concerns associated with food supplements and functional foods and examines the factors which can contribute to these risks. Additionally, a few illustrative examples are given to help clarify the types of hazards associated with the product/bioactive ingredients, which are intended to provide a clearer understanding of the safety concerns and to highlight the complexity and diversity of potential issues.

Spices sold in a local market. Spices are commonly used in both culinary dishes and food supplements. Morocco

3.1 Interaction between food and drugs

The absorption and metabolism of a drug can be significantly affected by the presence or absence of specific nutrients in the gastrointestinal tract and within the body's physiological systems (Zou, 2022). Drugs and foods have the potential to interact bidirectionally, as drugs could alter the nutritional status of the patient, body weight, and availability of nutrients, while foods can exert an impact on the effects and effectiveness of drugs (D'Alessandro *et al*., 2022). Hence, since the metabolism of medicines can be significantly influenced by diet composition, understanding the interaction between bioactive ingredients and medications is essential for optimizing drug efficacy and minimizing adverse effects (Boik *et al*., 2009; de Boer, Hunsel and Bast, 2015).

Given that these interactions can pose significant health risks for individuals already undergoing pharmacological therapy, it is essential to adopt a personalized approach that considers the complexity and interplay of various factors, including comorbidities and the number and types of allopathic medications taken alongside dietary choices. This is particularly important for those who consume food supplements without consulting a qualified health professional. Many individuals opt for these products with the intention of enhancing their health and well-being, as suggested on the label, in addition to receiving nutritional support (Marra and Bailey, 2018). The self-administration of food supplements and functional foods is widespread, largely due to their availability and the fact that they can be purchased without a prescription. Furthermore, food safety authorities in many jurisdictions around the world do not require warnings about potential drug interactions on the labels of these products, leading to their use without adequate awareness of the associated risks.

It has been reported that specific bioactive ingredients can interact with various medications, including cancer treatments, oral contraceptives, antidepressants, antidiabetic drugs and others, altering the effectiveness of these drugs or leading to adverse effects (Zou, 2022; Fagiolino *et al*., 2018;

Omachi *et al*., 2019; Briguglio *et al*., 2018; PDQ Integrative, 2020). Thus, it is of utmost importance that these interactions are managed and monitored by health care professionals, to ensure the patient's safety and the therapeutic effectiveness of the medication (Lopes *et al*., 2021).

The complexity of drug-supplement interactions often increases due to the presence of numerous diverse compounds among the bioactive ingredients (Gupta *et al*., 2017). For example, antioxidants like resveratrol and quercetin, when obtained from plant extracts, contain numerous other compounds resulting in a more complex interaction mechanism. Consequently, studies that focus exclusively on a single bioactive ingredient, like a specific compound, may not necessarily correlate with the results from studies that examine the same bioactive ingredient obtained from plant extracts (Choi and Chin, 2020; Lopes *et al*., 2023). The chemical composition of a plant extract can exhibit variations (see Section 3.3), even when sourced from different plants of the same species. Factors like the location of growth, cultivation conditions, time of harvest, conditions during transport and storage, and the extraction methodology employed influence chemical composition. Moreover, additional complexities in evaluating potential interactions between supplements and drugs can arise due to the presence of contaminants (see Section 3.2) (Choi and Chin, 2020; Waidyanatha *et al*., 2018).

It is important to note that interactions between food and drugs are not limited to food supplements alone, as research suggests that everyday food items can significantly influence drug effectiveness or absorption. In fact, the interaction mechanisms between drugs, and between drugs and bioactive ingredients contained in food, food supplements and functional foods are essentially identical. For example, certain tetracyclines and fluoroquinolones found in antibiotics can bind to products containing divalent cations (like calcium in dairy), leading to decreased drug absorption and potential therapeutic failure (Choi and Ko, 2017). Additionally, it has been reported that the flavonoids present in grapefruit juice inhibit transmembrane transporters, which play a crucial role in the transfer of drugs from the intestinal lumen to the bloodstream (Petric *et al*., 2020; D'Alessandro *et al*., 2022). Pineapple fruit juice has also been observed to exhibit inhibitory properties on cytochrome P450 (CYP) metabolizing enzymes due to its high bromelain content, consequently slowing down the drug metabolism (Petric *et al*., 2020). Moreover, foods high in fat can enhance drug absorption by improving the solubility of lipid-soluble drugs (Le Tiec *et al*., 2005) while fibre-rich meals may alter their absorption (D'Alessandro *et al*., 2022). However, the prediction of these interactions poses a challenge due to the uncertain quantity of a specific bioactive compound accountable for the interaction in a food, alongside the variability in drug metabolism among individuals.

A glass of milk, naturally containing minerals and proteins. Bangladesh

3.1.1 Food-drug interaction mechanisms

Food products can influence drug absorption by slowing gastric emptying, stimulating or increasing bile or splanchnic blood flow, changing gastrointestinal pH, or modifying gut microbiota through mechanical or physiological actions (D'Alessandro *et al*., 2022). Medications are frequently taken alongside meals, which can affect therapeutic outcomes, as the co-administration of food and drugs may lead to chemical or pharmacological interactions (Gupta *et al*., 2017). The possible interactions between drugs and bioactive ingredients in the body can be categorized into two main types: pharmacokinetics and pharmacodynamics. Pharmacokinetics investigates the journey of a drug through the body, encompassing processes such as absorption, distribution, metabolism, and excretion (ADME). Conversely, pharmacodynamics delves into the effects of a drug on the body including the biochemical, physiological, and molecular impacts of drugs, as well as the mechanisms of action. These interactions can influence the effectiveness of drugs, potentially leading to a decrease or increase in their action or an amplification of adverse reactions (Gupta *et al*., 2017). The outcomes of these interactions hinge on the nature of the drugs involved; in fact, certain bioactive ingredients can either induce or inhibit the enzymes involved in drug metabolism, thereby affecting the drug's efficacy and potential side effects.

It has been reported that approximately 80 percent of food supplements currently available globally are likely to interact with CYP in the human body (Zarowitz, 2010; Lam *et al*., 2022). The CYP system is a family of enzymes mainly found in the liver, which are involved in the metabolism of various substances. Hence, food supplements can interact with the CYP system in several ways, inducing the expression of certain CYP enzymes, thereby increasing the rate at which certain drugs are metabolized, leading to a reduced drug efficacy (Sasaki *et al*., 2017). On the other hand, some supplements may inhibit the activity of CYP enzymes, slowing down drug metabolism and leading to increased drug concentrations and potential toxicity (Sasaki *et al*., 2017).

P-glycoprotein (P-gp) is another important player in drug metabolism, playing a significant role in drug-supplement interactions (Elmeliegy *et al*., 2020). P-gp is an efflux transporter, widely distributed throughout the body, which restricts the cellular absorption and distribution of xenobiotics and harmful substances (Vimalavathini, Subhashri and Kavimani, 2018). It has been reported that pharmacokinetics of a drug can undergo changes when co-administered with compounds that either inhibit or induce P-gp (Murakami, Ishiguro and Oda, 2017). A multitude of compounds could modulate P-gp's expression and function, leading to interactions between P-gp and drug/bioactive ingredients, which could potentially alter the absorption and efficacy of medications (Dixon, 2017; Matura, Shea and Bankes, 2022).

A woman taking food supplements

Examples of drug-supplement interactions

Table 2 presented below gives some illustrative examples of the complex interactions that can occur between pharmaceutical drugs and the bioactive ingredients found in food, food supplements and functional foods (Lopes *et al.*, 2023). However, the field of drug-food interactions is vast and continually evolving; therefore, this section cannot provide a complete list of interactions. Furthermore, it is worth noting that some of these interactions have only been observed *in vitro*, and in most cases no clinical studies *in vivo* have been conducted to confirm them. These examples are intended to provide a deeper understanding of the potential complexities involved, emphasizing the importance of considering interactions when combining pharmaceutical drugs with food supplements and functional foods.

Table 2 Examples of interactions between drugs and bioactive ingredients contained in food, food supplements and functional foods

Bioactive ingredient	Potentially interact with...	Effects	Reference
Vitamins			
Vitamin A	• Anticoagulants • Antihyperlipidemic drugs • Analgesics • Antipyretics	• Increase bleeding risk • Hepatotoxicity	Berginc and Kreft, 2014; Rogovik, Vohra and Goldman, 2010
Vitamin B3	• Anticoagulants • Antiplatelet agents • Non-steroidal anti-inflammatory drugs • Antidiabetics • Statins	• Increase bleeding risk • Reduce the effectiveness of antidiabetic drugs • Increase risk of myopathies when used with statins	Rogovik, Vohra and Goldman, 2010
Vitamin D	• Anticoagulants • Antihypertensives • Cardiotonic and antiarrhythmic • Calcium metabolism modifiers	• Increase the risk of thrombosis when co-administrated with anticoagulants • Increased risk of hypermagnesemia • Increase of intestinal absorption of aluminium • Induce hypercalcemia • Increase the risk of cardiac arrhythmias • Increase the risk of hypoglycemia	Levy *et al.*, 2017; Rogovik, Vohra, and Goldman, 2010
Vitamin E	• Antiplatelet • Anticoagulants • Antidiabetic drugs • Non-steroidal anti-inflammatory drugs • Cardiotonic and antiarrhythmic • Antihyperlipidemic drugs	• Increase bleeding risk • Increase the risk of hypoglycemia • Increase the risk of cardiac arrhythmias	Pastori *et al.*, 2013; Rogovik, Vohra and Goldman, 2010
Vitamin K	• Anticoagulant	• Antagonistic effect on anticoagulants drugs	Rogovik, Vohra and Goldman, 2010

Bioactive ingredient	Potentially interact with...	Effects	Reference
Minerals			
Calcium	• Bisphosphonates • Penicillamine • Antibiotics • Cardiotonic and antiarrhythmic • Antirheumatic drugs	• Potentiate the development of antimicrobial resistance • Increase the risk of cardiac arrhythmias • Reduce the effectiveness of certain drugs • Hypercalcemia	Levy *et al.*, 2017; Mouly *et al.*, 2017
Iodine	• Thyroid drugs • Antibiotics	• Reduce the effectiveness of certain drugs	Levy *et al.*, 2017
Iron	• Thyroid drugs • Antibiotics • Bisphosphonates	• Reduce the absorption of drugs	Bordes *et al.*, 2020; Mouly *et al.*, 2017
Magnesium	• Thyroid drugs • Antibiotics • Antirheumatic drugs	• Reduce the effectiveness of certain drugs	Bordes *et al.*, 2020; Mouly *et al.*, 2017
Potassium	• Antibiotics • Immunosuppressants • Non-steroidal anti-inflammatory drugs • Corticosteroids	• Increased risk of hyperkaliemia • Increase the risk of hypokalemia	Karalliedde *et al.*, 2016
Amino acids			
Creatine	• Aminoglycoside antibiotics • Non-steroidal anti-inflammatory drugs • Anticancer drugs • Radiocontrast dye	• Potentiate kidney disfunction	Boccanegra *et al.*, 2020
Glutamine	• Antidiabetic drugs	• Additive hypoglycemic effect	Boccanegra *et al.*, 2020
L-Carnitine	• Anticoagulant	• Increase bleeding risk	Nauffal and Garibaldi, 2016
L-Lysine	• Antibiotics • Non-steroidal anti-inflammatory drugs • Anticancer drugs • Radiocontrast dye	• Potentiate kidney disfunction	Nauffal and Garibaldi, 2016
L-Tryptophan	• Aminoglycoside antibiotics • Non-steroidal anti-inflammatory drugs • Anticancer drugs • Radiocontrast dye	• Potentiate kidney disfunction	Mouly *et al.*, 2017
Taurine	• Antidiabetic drugs	• Additive hypoglycemic effect	Boccanegra *et al.*, 2020

Bioactive ingredient	Potentially interact with...	Effects	Reference
Fatty acids			
Evening primrose oil (from *Oenothera biennis L.*, seed)	• Antipsychotics • Anticoagulant	• Increase risk of seizure • Increase the risk of thrombocytopenia	Wang, Jiang and Batra, 2020
Fish oil/ Omega-3 fatty acids	• Anticoagulants • Non-steroidal anti-inflammatory drugs • Inhibitor of platelet aggregation	• Increase bleeding risk	Boccanegra *et al.*, 2020
Flaxseed oil (from *Linum usitatissimum L.*, seed)	• Anticoagulants • Non-steroidal anti-inflammatory drugs • Inhibitor of platelet aggregation	• Increase bleeding risk	Levy *et al.*, 2017
Polyphenolic compounds			
Caffeine	• Antihypertensive • Inhibitors of platelet aggregation • Non-steroidal anti-inflammatory drugs • Antimigraine • Antimalaria • Antibiotics • Antidepressants • Antipsychotic • Diuretic • Anticoagulant • Skeletal muscle relaxant • Anxiolytics • Thyroid drugs • Antipyretic drugs • Non-narcotic analgesic	• Interaction with CYP enzymes • Caffeine is a neurostimulator • Change in gastric pH • Caffeine is a vasopressor drug	Spanakis *et al.*, 2021; Bailey *et al.*, 2016
Catechins	• Antihyperlipidemic • Immunosuppressants • Inhibitors of platelet aggregation • Cardiotonic and antiarrhythmic drugs • Antihypertensive • Anticoagulant	• Increase/decrease the bioavailability of certain drugs • Increase bleeding risk • Antiplatelet aggregation action	Eagappan *et al.*, 2014; Ge, Zhang, and Zuo, 2014; Kim *et al.*, 2017; Xiao *et al.*, 2020
Quercetin	• Antihyperlipidemic • Immunosuppressants • Cardiotonic and antiarrhythmic drugs • Anxiolytic • Antihypertensive • Antibiotics • Non-steroidal anti-inflammatory drugs • Anticancer drugs • Radiocontrast dye	• Increase/decrease the bioavailability of certain drugs • Potentiate kidney disfunction	Williamson, Driver and Baxter, eds., 2009; Xiao, Sarker, and Asakawa, eds., 2020

Bioactive ingredient	Potentially interact with...	Effects	Reference
Resveratrol	• Anticoagulant • Inhibitors of platelet aggregation • Antibiotics • Non-steroidal anti-inflammatory drugs • Anticancer drugs • Radiocontrast dye	• Increase bleeding risk • Potentiate liver disfunction • May cause kidney damage	Williamson, Driver, and Baxter, eds., 2009; Xiao, Sarker and Asakawa, eds., 2020
Alkaloid compounds			
Melatonin	• Non-benzodiazepine hypnotics • Benzodiazepines • Antipsychotic • Antidepressants • Antiepileptic • Antihypertensive	• Increase cognitive function impairment • Possible additive effect • Affect calcium signalling	Boccanegra *et al.*, 2020; de Boer, Hunsel, and Bast, 2015
Piperine	• Antiepileptics • Antibiotic • Antihypertensive • Antiretroviral	• Increase the absorption of certain drugs	Williamson, Driver and Baxter, eds., 2009; Ulbricht *et al.*, 2008
Botanicals			
Allium sativum (Garlic)	• Non-steroidal anti-inflammatory medications • Anticoagulants • Salicylate drugs • Antiplatelet	• Increases bleeding risk	Zarowitz, 2010
Camellia sinensis (Green tea)	• Anticancer therapy • Anticoagulants • Blood pressure medicines • Statin	• Decrease drug absorption and bioavailability of the drug	Tsai *et al.*, 2013; Knop *et al.*, 2015
Ginkgo biloba	• Anticoagulants • Antiplatelet • Pain killers • Non-steroidal anti-inflammatory medications • Antiviral medicines • Salicylate drugs • Antihypertensive drugs • Antiepileptic medication	• Increases bleeding risk	Zarowitz, 2010; de Boer, Hunsel and Bast, 2015; Sprouse and Van Breeman, 2016
Glycyrrhiza glabra (Licorice)	• Antihypertensive drugs • Salicylate drugs • Antihistamines • Thyroid drugs • Analgesics drug • Benzodiazepines	• Increased arterial blood pressure • Increase hypokalemia	Kwon *et al.*, 2020; Makino *et al.*, 2012

Bioactive ingredient	Potentially interact with...	Effects	Reference
Hypericum perforatum (St John's wort)	• Antidepressants • Oral contraceptives • Pain killers	• Additive effects with antidepressants • Decrease the effectiveness of medications	Zarowitz, 2010; de Boer, Hunsel and Bast, 2015
Panax ginseng	• Anticoagulants • Antiplatelet • Pain killers • Non-steroidal anti-inflammatory medications • Salicylate drugs • Antihypertensive drugs	• Increases bleeding risk	de Boer, Hunsel and Bast, 2015; Sprouse and Van Breeman, 2016
Valeriana officinalis	• Antidepressants • Sedatives • Anticoagulants	• Additive effects	Zarowitz, 2010

Source: See References.

Boxes of "pastilles" made with gum arabic, formulated to relieve respiratory tract irritations. Senegal

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Case study 1
ANSES opinion on potential drug interaction of melatonin

The food competent authority in France, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES), conducted an assessment in 2018 on the potential health risks linked to the consumption of food supplements containing melatonin. The agency documented 90 cases of adverse effects following the intake of these supplements. The symptoms reported where melatonin was taken in combination with other products (particularly neuroleptic or antipsychotic drugs) were headaches, nausea, visual hallucinations, balance disorders, drowsiness, extrapyramidal syndrome, and arterial hypotension.

The agency's opinion emphasizes the existence of at-risk populations and situations where the consumption of melatonin in supplement form should be avoided or undertaken only with medical consultation. The report states that melatonin can alter the plasma concentration of drugs metabolized by the isoenzymes CYP1A1, CYP1A2, CYP1B1, or CYP2C19. It also suggests a possible pharmacodynamic interaction between melatonin and platelet inhibitors, anticoagulants, anti-inflammatory agents, and substances affecting the central nervous system, especially hypnotic and antiepileptic agents. Therefore, ANSES recommends that individuals with conditions such as epilepsy, asthma, mood, behaviour, or personality disorders, as well as inflammatory or autoimmune diseases, or those undergoing other drug therapies, consult a health professional prior to consuming food supplements containing melatonin. Moreover, due to identified risks associated with high doses, ANSES advises adhering to a specific daily dosage of melatonin.

Source: ANSES. 2018. *Opinion on the risks associated with the consumption of food supplements containing melatonin*. ANSES Opinion Request No 2016-SA-0209. Maisons-Alfort, France.
https://www.anses.fr/en/system/files/NUT2016SA0209EN.pdf

Case study 2
Potential interaction of *Hypericum perforatum* with various medications

The Therapeutic Goods Administration (TGA), the Australian government authority responsible for evaluating, assessing and monitoring products that are defined as therapeutic goods (see Section 4), published an information sheet to alert doctors and pharmacists and complementary health practitioners on the interactions of St John's wort (*Hypericum perforatum*) preparations with prescription medicines.

It has been reported that the active compound, hyperforin, can bind the nuclear receptor that controls the expression of intestinal CYP3A4 and P-glycoprotein. Hence, according to TGA, *Hypericum perforatum* has the potential to interact with several medications, leading to a reduction in their degradation and subsequently an increase in their levels and effects. These medications include immunosuppressants, anticancer drugs, oral contraceptives, cardiovascular drugs, antimicrobials, antidepressants, anxiolytics, anticonvulsants, oral hypoglycemic agents, anesthetics, respiratory and gastrointestinal agents, anti-migraine drugs, muscle relaxants, and medications utilized in drug abusers. Therefore, TGA recommends that individuals undergoing drug therapies should consult a health professional prior to consuming food supplements containing St John's wort.

Source: Australian Government. Department of Health. 2000. St John's Wort: information sheet for health care professionals. In: *TGA*. [Cited 20 September 2024].
https://www.tga.gov.au/news/safety-alerts/st-johns-wort-information-sheet-health-care-professionals

Case study 3

The use of antioxidants and cancer therapy could pose a potential risk

The National Cancer Institute (NCI), the leading federal agency for cancer research and training in the United States of America, has developed a document titled "Cancer Therapy Interactions with Foods and Dietary Supplements (PDQ®)" available online (National Cancer Institute, n.d.). This document, designed for both patients and health professionals, offers a comprehensive examination of the potential interactions between cancer treatments and various foods and food supplements, investigating how these combinations could potentially interact, leading to adverse effects. The document details various interactions, including those between drug therapies and antioxidants such as vitamin C, vitamin E, flavonoids (for instance, soy isoflavones and green tea catechins), beta-carotene, and glutathione.

According to the NCI, anticancer agents produce reactive oxygen species, which result in a reduction in antioxidant levels, damage to deoxyribonucleic acid (DNA), and the death of cancer cells. Consequently, cancer patients may opt to consume antioxidant food supplements without consulting a health professional, as these supplements are thought to protect and repair healthy cells that have been damaged by cancer therapy. However, the NCI states that there is insufficient data to determine the safety and efficacy of many specific antioxidant supplements as complementary therapies to standard cancer treatment.

Source: PDQ Integrative. 2020. Cancer therapy interactions with foods and dietary supplements (pdq®)–patient summaries. In: *National Cancer Institute (US)*. https://www.cancer.gov/about-cancer/treatment/cam/patient/dietary-interactions-pdq

3.2 The impact of bioactive ingredients in food supplements and functional foods on pre-existing medical conditions and lifestyle habits

In the realm of pre-existing medical conditions and individual lifestyle habits, it is crucial to recognize the potential impact of bioactive ingredients present in food supplements or functional foods which have the capacity to worsen symptoms or induce adverse effects, particularly when consumed without the guidance of a health professional (Mezza *et al*., 2020).

For example, in the context of cardiovascular health, it is crucial to consider the impact of bioactive compounds like omega-3 fatty acids, which are prevalent in many food supplements. While these compounds could potentially offer health benefits, excessive intake may lead to adverse effects, especially in individuals with blood clotting disorders (Li, Fu and Koonen, 2018).

On the other hand, in the context of thyroid issues, the consumption of supplements containing *Brassica oleracea* (broccoli), which contains compounds known as goitrogens, can be problematic. These compounds have the potential to modulate thyroid function, although the extent of their impact depends on the quantity of the bioactive ingredient consumed (Paśko *et al*., 2022).

Romanesco broccoli, naturally containing functional compounds. Italy

The supplementation of beta-carotene, a type of carotenoid that is converted into vitamin A in the body, could potentially increase the risk of lung cancer in smokers (Alsharairi, 2019). The exact reason for this increased risk is not fully understood, but it is assumed that high doses of beta-carotene might act as a pro-oxidant under certain conditions, leading to oxidative damage and potentially contributing to cancer development (Middha *et al.*, 2019).

Therefore, it is important to consider these factors in the context of a healthy and balanced diet, recognizing the potential risks associated with excessive or unsupervised consumption of food supplements and functional foods containing certain bioactive ingredients, especially for individuals with pre-existing health conditions.

3.3 Safety consideration of botanical extracts used in food supplements

In botanical extracts used in food supplements and functional foods, the extraction process may involve concentrating desired elements, reducing the presence of unwanted components or impurities, enhancing shelf-life, and ensuring uniform material. Depending on the botanical material type and extraction techniques, various pretreatments like cutting, grinding to minimize particle dimensions, optimizing surface area exposure, and defatting may precede extraction.

The chemical composition of botanical extracts from identical plants can significantly differ based on the extraction solvents utilized, the temperature and duration of extraction, and the drying methods employed. Other factors contributing to variability encompass the methods used for concentrating or eliminating targeted components or categories of components, as well as the compounds generated during extraction or subsequent processing stages.

Further discrepancies in the composition of botanical extracts derived from the same plant species may arise due to genetic variations, environmental factors, and farming practices.

During food safety assessment it is essential to consider all these factors, as they have a significant impact on the overall safety of the product. For example, the solvent used in the extraction process can influence the safety profile of the bioactive ingredient (Zhang *et al.*, 2018). Extraction processes that utilize water are considered safer than those that employ chemical solvents, because water is less likely to leave harmful residues in the final product (Popova and Bankova 2023). In addition to the type of solvent, the method of extraction itself should also be considered since different extraction methods can lead to varying levels of potential contaminants and can affect the concentration of the active ingredient (Chemat *et al.*, 2020). For example, kava

Fresh carrots, naturally containing beta-carotene. Bangladesh

(*Piper methysticum*), a traditional Pacific Island plant known for its anxiolytic properties, can pose risks when extracted using chemical solvents like ethanol or acetone, which have been associated with potential liver toxicity. In contrast, water extraction is considered a safer alternative, as it reduces the likelihood of harmful chemical residues and adverse health effects (Sarris, LaPorte and Schweitzer, 2010). Therefore, understanding the extraction method used can provide valuable insights into the safety of the ingredient (Koina, Sarigiannis and Hapeshi, 2023).

The management of inherent variations in source materials is a crucial factor in ensuring the safety and quality of the product. Therefore, the use of standardized extraction protocols is essential to produce extracts with consistent compositions (Monagas *et al*., 2022). The standardization process, which aims to reduce the inherent variability in the composition of natural products, is achieved by implementing quality assurance practices in both agricultural and manufacturing processes. This optimization results in a product that maintains consistency from one batch to another. However, achieving standardization of botanical raw materials can be a challenging task, and it is frequently reported to be low (Righetti *et al*., 2022).

An important aspect to consider in the food safety assessment of plant extracts is the final concentration of the bioactive ingredient. In some jurisdictions, substances with a high concentration of bioactive ingredients (exceeding 95 percent) may necessitate a comprehensive food safety assessment by food competent authorities. This is because these highly concentrated substances may exhibit different properties and effects compared to conventional food items with a history of safe consumption. For example, the bioactive compounds found in green tea (catechins), turmeric (curcumin), and ginger (gingerols) are typically regarded as safe when consumed as part of a regular diet. However, these substances, when ingested in concentrated forms such as in food supplements or functional foods, may present potential health risks (EFSA, 2018; EFSA 2021).

3.3.1 Plant to Extract ratios

Botanical extracts are often defined by the Plant to Extract ratio, which refers to the amount of raw plant material, or biomass, used to produce a unit of extract. For instance, a dehydrated extract with an extract ratio of 10:1 implies that approximately 10 grams of dried botanical material were used to produce 1 gram of extract. The yield of an extract depends on the extraction process and the amount of extractable material in the starting plant biomass (Monagas *et al*., 2022).

In some jurisdictions, high plant to extract ratios may necessitate a safety assessment of the extract by a competent food safety authority because the amount of initial biomass used may not be comparable to the consumption of conventional food. For instance,

an extract derived from 10 000 g of garlic biomass could pose food safety assessment challenges, as this quantity of garlic is not comparable to conventional consumption levels. However, the amount of starting biomass also depends on the part of the plant used. For example, the monograph for the United States Pharmacopeia Asian Ginseng Root and Rhizome outlines the quality criteria for the dried roots and rhizomes of Panax ginseng, specifying minimum concentrations of ginsenosides. In a batch of dried raw material of the same age, the proportional levels of ginsenosides show a notable increase in the fibrous root section compared to the rhizome, branch root, and main root. Thus, a higher Plant to Extract ratio would be needed when using main root and rhizome material to achieve the same levels of the marker ginsenosides compared to extracts of the branch and fibrous roots (Monagas *et al.*, 2022; Pan *et al.*, 2021).

Herbal pharmacopoeias

Herbal pharmacopoeias provide qualitative and therapeutic monographs on botanicals, defining a botanical drug and providing information that allows for its proper identification. These documents contain basic descriptions of the plant including nomenclature, part used, constituents, range of application, contraindications and side effects, incompatibilities with other medications, dosage, use, and action of the herb, representing essential reference documents.

Source: Alamgir, A.N.M. 2017. Pharmacopoeia and Herbal Monograph, the Aim and Use of WHO's Herbal Monograph, WHO's Guide Lines for Herbal Monograph, Pharmacognostical Research and Monographs of Organized, Unorganized Drugs and Drugs from Animal Sources. In: *Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1*. pp.295–353. Vol.73. Cham, Springer International Publishing. https://doi.org/10.1007/978-3-319-63862-1_7

3.4 Contaminants

When food supplements and functional foods are consumed, as with any other food, there is a risk of ingesting various other substances and potential toxic compounds. These compounds may originate from contaminated raw materials, or they can be natural constituents, such as plant toxins like pyrrolizidine alkaloids (see Box 1).

The Codex Alimentarius defines a contaminant as follows:

Any substance not intentionally added to food or feed for food producing animals, which is present in such food or feed as a result of the production (including operations carried out in crop husbandry, animal husbandry and veterinary medicine), manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food or feed, or as a result of environmental contamination. The term does not include insect fragments, rodent hairs, and other extraneous matter (FAO and WHO, 1995, p.5).

To reduce food contaminations, Codex Alimentarius has established limits for these chemical components in food in the "General standard for contaminants and toxins in food and feed CXS 193-1995" (FAO and WHO, 1995). The scope of this standard is to outline key principles for managing contaminants in food and feed. It specifies maximum levels, along with sampling plans for international trade commodities, particularly focusing on contaminants that can transfer to food and impact public health. Contaminants can include mycotoxins, heavy metals, pesticide residues, and environmental pollutants such as polychlorinated biphenyls (PCBs) and dioxins which can originate from the environment where the raw materials are sourced, or during their handling and transportation processes. Some of the contaminants have been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), an international scientific expert committee which evaluates the safety of food additives, contaminants, naturally occurring toxicants and residues of veterinary drugs in food.

Food supplements are also susceptible to microbial contamination. In this context, the Joint FAO/WHO Expert Committee on microbiological risk assessment (JEMRA), an international scientific expert group which evaluates various aspects of microbiological hazards in the food supply, promotes the microbiological risk assessment (MRA) framework to inform actions and decisions aimed at reducing foodborne disease and facilitating domestic and international food trade. The MRA framework is a tool to compare and evaluate different scenarios and identify the types of data necessary for estimating and optimizing mitigating interventions.

3.4.1 Unintentional contaminants in food supplements and functional foods

Despite rigorous quality control measures, the presence of unintentional contaminants in food supplements and functional foods can be inadvertent and unpredictable. For example, metal contamination has been identified in several types of raw materials used in food supplements and functional foods, which can occur due to a single factor or a combination of sources, depending on the type of supplement. For example, with plant-based supplements, various factors can lead to contamination, including the soil's chemical composition, the plant's characteristics and growing conditions, as well as factors related to the purity of extraction methods, formulation and manufacturing processes, transportation, and storage conditions (Costa *et al.*, 2019; Smichowski and Londonio, 2018).

In addition to these, the use of contaminated water for irrigation, the application of fertilizers or pesticides, and the proximity to industrial areas or polluted sites can also lead to contamination of raw materials used in food supplements and functional foods (FAO, 2024; Scutarașu and Trincă, 2023; Costa *et al.*, 2019).

Also, plant-based supplements can be unintentionally contaminated with unwanted plants, which is a concern during the harvesting process (Chan, 2017). This could occur when the plants used in food supplements and functional foods are mechanically harvested along with other non-target species growing in the same area. Some of these non-target species can be toxic plants, posing a risk to human health. Harvesting is often a manual process in many

Women collecting tea leaves. Sri Lanka

parts of the world, requiring a prominent level of expertise to accurately identify the plant of interest from other similar-looking species. However, due to a lack of adequate training or supervision, harvesters may unintentionally collect toxic plants along with the desired ones. To address this, the World Health Organization (WHO) has developed guidelines on good agricultural and collection practices (GACP) for medicinal plants (WHO, 2003). Post-harvest, these plants are typically dried and ground together, making it impossible to remove toxic contaminants and significantly more difficult to visually identify contaminant plants in the raw materials. Consequently, the consumption of these contaminated supplements can lead to a range of health issues, from mild allergic reactions to severe poisoning. Therefore, it is important to implement quality control measures during the harvesting process to prevent such contamination (Balekundri and Mannur, 2020).

While the individual contribution of food supplements and functional foods to overall contaminant exposure is typically minor (Gil, Hernández and Martín-Domingo, 2016), it is crucial to acknowledge the potential risks associated with prolonged or concurrent exposures. Even if exposure from a single product is low, the cumulative effect of consuming multiple products over an extended period can heighten the risk. This concern is particularly pertinent as these products are often integrated into daily routines, potentially leading to chronic exposure to contaminants (Costa *et al.*, 2019). Equally, concentrated plant extracts may further concentrate contaminants, increasing the potential for harmful exposure. On the other hand, food supplement products such as protein powder, which are consumed in larger quantities, may pose a bigger concern for contaminations. However, this risk is comparable to that of conventional food; hence, the same safety measures can be employed.

Box 1

Pyrrolizidine alkaloids

Pyrrolizidine alkaloids (PAs) are a group of naturally occurring compounds found in a wide range of plant species. They are synthesized by plants primarily as a defense mechanism against herbivores, insects and pathogens. However, PAs are known to be potent hepatotoxic and genotoxic compounds, meaning they can cause injury to the liver and damage to the genetic information within a cell, potentially causing mutations (Schramm, Köhler and Rozhon, 2019).

There are over 350 PAs found in over 6 000 plant species, about half of which are thought to have hepatotoxic properties. The levels of pyrrolizidine alkaloids present in plants can vary due to factors such as environmental conditions, climate, season, plant maturity, and plant part.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated PAs in 2015 (WHO, 2015).

> The Committee noted that most studies of toxicity, and of occurrence of PAs in food, were focused on the 1,2-unsaturated PAs. The Committee concluded that while the saturated PAs could not elicit toxicity via the same mechanism as 1,2-unsaturated PAs, their toxicity in humans could not be excluded, but there were insufficient studies for evaluation. The Committee therefore decided to focus the evaluation on the 1,2-unsaturated PAs. Exposure to 1,2-unsaturated PAs has been associated with a wide range of effects, with rats being the most sensitive species studied. *In vitro* studies on metabolic activation indicate that humans are also likely to be sensitive. Laboratory studies have identified the liver as the most sensitive organ in rats, following both short-term and long-term administration of a number of PAs. The 1,2-unsaturated PAs that have been tested form DNA adducts and are mutagenic. Based upon an understanding of their chemistry and metabolism, it is concluded that this property is common to all 1,2-unsaturated PAs, albeit with differing potencies, and that it is relevant to humans. PAs appear to be antimitotic in hepatocytes. A number of 1,2-unsaturated PAs have been shown to be carcinogenic in rodents, primarily causing haemangiosarcomas in the liver, i.e. originating in the endothelial cells rather than the

hepatocytes. Carcinogenicity has not been investigated in case studies of human poisoning with PAs. The Committee considered that derivation of a health-based guidance value for PAs was not appropriate in view of the genotoxic mode of action. From the carcinogenicity data in rats, a BMDL10 of 182 µg/kg bw per day for liver haemangiosarcoma in female rats.

Source: WHO. 2015. Pyrrolizidine alkaloids. In: *WHO*. Geneva, Switzerland. [Cited 22 October 2024]. https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/6301

Case study 4
Potential presence of puberulic acid in red yeast rice food supplements in Japan

In March 2024, Japan faced a major scandal involving health issues linked to a company's red yeast rice supplements. These products, intended to lower cholesterol, were found to cause serious health problems, including kidney disease, due to the presence of toxic substances. The toxic substance identified in the supplements was "puberulic acid," a metabolite from certain moulds, which is highly toxic despite its antibacterial properties.

The contamination affected a wide range of products, leading to a massive recall and severe financial and reputational damage to the company. The number of deaths potentially linked to the consumption of the supplements exceeded 100, with more than 400 people hospitalized. The crisis escalated when it was revealed that the company had been aware of the potential risks since January 2024 but delayed reporting the issue until March. This delay in addressing the health hazards contributed to significant public outrage. The exact cause of the illness is still under investigation.

Source: Nikkei Asia. 2024. Kobayashi Pharma to exit red yeast rice business amid health scandal. In: *Nikkei Asia*. [Cited 8 August 2024]. https://asia.nikkei.com/Business/Pharmaceuticals/Kobayashi-Pharma-to-exit-red-yeast-rice-business-amid-health-scandal

3.4.2 Adulteration

The high market value and widespread consumption of food supplements and functional foods have made these products attractive targets for economically driven adulteration, which is a common food fraud carrying a potentially serious safety risk. Adulteration of food supplements involves a mismatch between the product's label and its actual composition. A variety of methods are used to adulterate food supplements, including the incorporation of undisclosed substances, inaccurate representation of a compound or ingredient's concentration, introduction of unauthorized ingredients, or the use of lower quality plants or different plant parts in the case of plant-based supplements, such as using stems instead of flowers, or adding different plant species as fillers.

Some manufacturers may resort to these strategies to cope with shortages of botanical products or to boost profit margins (Wallace *et al*., 2018; Wallace *et al*., 2020). Botanical adulterations are common forms of fraud in plant-based supplements, generating potentially dangerous repercussions for consumers (see case study 5). Recent studies have explored various strategies and techniques for identifying botanical frauds in food supplements, providing detailed insights into this issue (Paiva *et al*., 2024; Geller *et al*., 2015).

A prevalent form of adulteration in food supplements is the incorporation of active pharmaceutical ingredients (APIs), also called "spiking". This method is used to substantiate the product's advertised

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A woman packing aromatic and medicinal plant powder. Tunisia

effects, misleading consumers into attributing the product's efficacy to the properties of the bioactive ingredients (Rocha, Amaral and Oliveira, 2016). The adulteration of supplements with APIs presents a significant public health concern since it could profoundly affect consumers' health, potentially triggering a wide array of adverse reactions that can vary from mild to severe. Further complicating this issue is the presence of slightly modified molecules, known as API analogues, which are designed to evade detection by regulatory authorities, thereby increasing the associated risks because the safety, toxicity, and efficacy data for most of these compounds are unknown (Tucker *et al*., 2018). Recent reports highlight an increasing trend of adulteration in plant-based supplements that are commonly used for maintaining or enhancing cognitive health. This involves the incorporation in the food supplements of pharmaceutical substances such as sedatives, hypnotics and nootropics, among others, which are added with the intention of enhancing the product's performance (Paiva *et al*., 2024).

Adulteration also aims to enhance the visual appeal of raw materials. An example is the global issue of lead adulteration in spices, which is a growing public health concern since it is becoming a widespread practice. This is evidenced by the well documented case of turmeric adulteration where lead chromate ($PbCrO_4$) is deliberately mixed with turmeric roots during the polishing process, to intensify the spice's yellow colour (Gleason *et al*., 2014; Forsyth *et al*., 2019a; Forsyth *et al*., 2019b) and contributing to an increase in the weight of spices (Cowell *et al*., 2017; Galvin-King, Haughey and Elliott, 2018). For instance, a study by Cowell *et al*. (2017) linked the ingestion of lead chromate-contaminated turmeric to cases of childhood lead poisoning in the United States of America. Another common adulterant found in turmeric, Metanil Yellow (a yellow azo dye), has raised concerns due to its neurotoxic effects (Dhakal *et al*., 2016; Ghosh *et al*., 2017).

In general, potential drug interactions (see Section 3.1) may arise when adulterated food supplements are consumed alongside prescribed medications. These interactions could go unrecognized, as neither the consumer nor the prescribing physician may be aware of the adulteration in the supplement. This lack of awareness can lead to unexpected side effects or alterations in the effectiveness of the prescribed medication, posing a risk to the consumer's health.

Case study 5
Adulteration in plant-based supplements: botanical substitutions

In 2000 the herb *Aristolochia fangchi* was replaced with Stephania tetrandra in a food supplement, resulting in severe kidney damage in over 100 patients, with additional 18 cases developing kidney or bladder cancer (Nortier *et al*., 2000). *Aristolochia fangchi* contains aristolochic acids, which are known to be nephrotoxic and carcinogenic. Despite being banned in the United States of America, a 2014 study revealed that 20 percent of *Stephania tetrandra* products available online still contained *Aristolochia fangchi*, underscoring the challenges in ensuring the safety and authenticity of plant-based supplements.

Source: Vaclavik, L., Krynitsky, A.J. and Rader, J.I. 2014. Quantification of aristolochic acids I and II in herbal dietary supplements by ultra-high-performance liquid chromatography–multistage fragmentation mass spectrometry. *Food Additives and Contaminants:* Part A, 31(5): 784–791. https://doi.org/10.1080/19440049.2014.892215

Case study 6
Food supplements used for weight reduction spiked with drugs to increase effectiveness

Food supplements used for weight loss are among the most adulterated products. They are often consumed by individuals aiming to prevent excessive fat accumulation. Adulterants in these products can include sibutramine, anorectics like amfepramone and fenproporex, antidepressants such as fluoxetine, anxiolytics like benzodiazepines, diuretics, and laxatives (Carvalho *et al*., 2010). A study of 164 weight loss supplements found sibutramine and phenolphthalein to be common adulterants, with some products containing a combination of these substances. The United States Food and Drug Administration (FDA) has reported similar findings, with sibutramine, its analogues, phenolphthalein, and fluoxetine being prevalent in adulterated weight loss supplements. Both sibutramine and phenolphthalein have been withdrawn from the US market due to health risks (Tucker *et al*., 2018).

Source: Hachem, R., Assemat, G., Martins, N., Balayssac, S., Gilard, V., Martino, R. and Malet-Martino, M. 2016. Proton NMR for detection, identification and quantification of adulterants in 160 herbal food supplements marketed for weight loss. *Journal of Pharmaceutical and Biomedical Analysis*, 124: 34–47. https://doi.org/10.1016/j.jpba.2016.02.022

Case study 7
Persistent market presence of food supplements containing prohibited substances

As reported by Cohen *et al*., (2022), the United States Food and Drug Administration (FDA) issued warning letters aimed at the detection of beta-methylphenethylamine (BMPEA), methylsynephrine, or dimethylhexylamine (DMHA) in 31 food supplement products. Among these 31 products, the manufacturer recalled one. Subsequently, 9 out of the 31 products were still accessible for online purchase, with an average duration of six years post the FDA's warning letters. Out of these nine products, four indicated the presence of at least one banned substance on their labels. One product specifically mentioned the same forbidden ingredient that led to the FDA's warning letter, while the other three products disclosed additional FDA-prohibited components. Upon conducting chemical examinations, it was discovered that five out of the nine products contained at least one FDA prohibited ingredient.

Source: Cohen, P. A., Avula, B., Katragunta, K. and Khan, I. 2022. Recalls, availability, and content of dietary supplements following FDA warning letters. *JAMA*, 328(4): 393–395. http//doi: 10.1001/jama.2022.9734

Case study 8

An analysis from the Netherlands Food and Consumer Product Safety Authority found pharmacologically active substances in food supplements

As reported in Biesterbos *et al.*, (2019), between October 2013 and October 2018, the Netherlands Food and Consumer Product Safety Authority conducted an analysis where a total of 416 supplements were examined, revealing that 264 of them contained pharmacological active substances. These substances comprised caffeine, synephrine, sildenafil, icariin, sibutramine, higenamine, hordenine, phenethylamine, methyl synephrine, dimethylamylamine, phenolphthalein, octopamine, and ephedrine. The daily doses of these substances in the supplements often exceeded safe levels, posing a potential risk to consumers who may be unaware of their presence.

Source: BBiesterbos, J. W., Sijm, D. T., van Dam, R. & Mol, H. G. 2019. A health risk for consumers: the presence of adulterated food supplements in the Netherlands. *Food Additives and Contaminants: Part A*, 36(9): 1273–1288. https://doi.org/10.1080/19440049.2019.1633020

3.5 Unexpected allergenic ingredients in food supplements

The presence of unexpected allergenic ingredients in food supplements and functional foods is a significant food safety concern. This issue often arises when supplements contain ingredients derived from known allergens. For instance, a person allergic to shellfish may unknowingly consume a claimed joint health supplement containing glucosamine, which can be derived from shellfish, leading to an allergic reaction. Similarly, isoflavones, found in supplements marketed for menopause relief or hormonal balance, are often sourced from soy; hence, individuals with soy allergies may experience adverse effects from supplements containing soy-derived isoflavones.

While consumers typically check food labels for allergens when purchasing groceries, they may not apply the same level of scrutiny to food supplements. This is partly due to a lack of awareness about the origins of the bioactive ingredients contained in these products. A food supplement might contain a compound derived from soy or dairy, which are known allergens, but if the compound is listed under a different name or if the consumer is unaware of its origin, the consumers might not realize the potential for an allergic reaction (see Case study 9).

Additionally, Reker *et al.*, (2019) reported that inactive ingredients, which are added to enhance the taste, appearance, shelf-life, absorption, and other attributes of pills and capsules, could potentially trigger allergic reactions. The study found that 92.8 percent of the analysed products contained at least one such inactive ingredient. Specifically, lactose was found in approximately 45 percent of the products, while food dye was found in around 33 percent of the products.

Moreover, some food supplements may contain novel ingredients or complex botanical extracts with unknown allergenic potential, underscoring the importance of allergenicity assessment of new ingredients before they are used in food supplements (Poms, Capelletti and Anklam, 2004). It is crucial for manufacturers to ensure accurate and comprehensive labelling of their products, highlighting the presence of potential allergens, especially when they are not obviously present in the product. Regulatory bodies also play a key role in monitoring these products and implementing labelling regulations (see Section 4) to protect consumer health (Gendel, 2012).

Case study 9

Adverse events reported in Singapore due to the consumption of food supplements containing glucosamine

In Singapore, a study revealed that among the 625 adverse event reports linked to food supplements, known as complementary health products, 517 (82.7 percent) were connected to products containing glucosamine and represented non-severe hypersensitivity responses. Of these incidents, 375 involved female individuals, 136 involved male individuals, and six did not specify the gender of the individuals. 329 cases associated with glucosamine, indicated that the adverse event was an allergic reaction, while 43 cases were determined to be non-allergic reactions. Uncertainty regarding whether the adverse event was an allergic reaction was noted in 140 cases, with five cases lacking the necessary information.

Source: Xu, Y., Patel, D.N., Ng, S.-L.P., Tan, S.-H., Toh, D., Poh, J., Lim, A.T. *et al.*, 2018. Retrospective study of reported adverse events due to complementary health products in Singapore from 2010 to 2016. *Frontiers in Medicine*, 5: 167. https://doi.org/10.3389/fmed.2018.00167

3.6 Suggested daily dose and the risk of overdose of certain bioactive ingredients

The overdose issue surrounding food supplements is a critical concern that demands attention and awareness. Typically, food supplements are accompanied by suggested daily dosages prominently displayed on their labels. These recommendations are established based on the nutrient requirements and on the upper-level intake levels set by food competent authorities at national, regional or international level (see Section 4). The primary objective behind these recommendations is to safeguard public health by ensuring the safe and appropriate consumption of these products.

Food supplements provide a range of micronutrients, from amounts less than the recommended intakes to significantly more, making them potential contributors to total nutrient intake. While these supplements can be beneficial in correcting micronutrient deficiencies or maintaining adequate intake, it is noteworthy that food supplements are often consumed by individuals who show no clinical signs or symptoms of deficiency (Zhang *et al.*, 2020). This practice could potentially lead to overconsumption of these products and, in some cases, overdoses which can result in adverse health effects, ranging from mild discomfort to severe toxicity and even long-term health complications. In certain circumstances, a health provider may recommend taking more than the recommended daily dose of certain nutrients to correct a deficiency. Therefore, it is important for consumers to adhere to the recommended dosages and consult health professionals before initiating any supplementation regimen, particularly if they have underlying health conditions or are taking other medications (see Sections 3.1 and 3.2).

For instance, vitamin supplements rank among the most used food supplements worldwide. However, an overdose of these supplements can lead to a condition known as hypervitaminosis which arises when an individual consumes an excessive amount of a specific vitamin, which is otherwise an essential nutrient required for maintaining optimal health under normal circumstances.

Overconsumption of minerals can be also harmful and lead to various health issues (Soni *et al.*, 2010). This is because minerals, much like vitamins, are needed by our bodies in specific amounts to function properly but when these levels are exceeded, it can result in a condition known as mineral toxicity. For instance, consuming excessive amounts of iron can lead to a condition known as hemochromatosis, which can cause damage to organs such as the heart and liver (Iglesias-Vázquez *et al.*, 2022; Omena *et al.*, 2021). Iron is an essential dietary mineral that plays a key role in transporting oxygen throughout the body. However, iron toxicity refers to the harmful effects of excess iron which

Oranges, naturally containing Vitamin C. Italy

may occur when people overdose on iron supplements, take high-dose supplements for too long or suffer from a chronic iron overload disorder (Bateman *et al*., 2018). Similarly, overconsumption of calcium can lead to hypercalcemia, which can result in kidney stones, confusion, abdominal pain, and depression (Xiao *et al*., 2013; Cormick *et al*., 2021; Fikri, 2023).

In addition, some nutrients compete for absorption, and as such, high levels of one mineral may cause depletion or deficiency of another. For example, excessive intake of zinc can impair copper absorption, leading to copper deficiency, while high calcium intake can interfere with magnesium absorption, potentially causing a deficiency in magnesium (King, Shames and Woodhouse, 2000; Bohn *et al*., 2004).

It is important to note that the risk of experiencing mineral or vitamin toxicity is low for most people who follow a balanced diet. When consumed naturally through food, these nutrients such as minerals and vitamins are unlikely to cause harm, even in copious amounts. However, when taken in concentrated doses as food supplements without healthcare guidance, there is a risk of overconsuming them, leading to adverse health outcomes.

3.6.1 Factors contributing to the issue of overdose consumption of food supplements

The issue of overdosing on food supplements is complex and dynamic, with numerous factors contributing to it. A primary driver is the evolving marketing strategies employed by companies to render their products more attractive and tastier. In recent years, there has been a noticeable surge in the use of vibrant colours and appealing flavours and shapes to enhance the attractiveness of food supplements.

For instance, gummy and chewable multivitamins adorned with popular cartoon or film characters to attract child consumption have proliferated in the market (Elliot, 2019). Child-friendly packaging and flavours can potentially foster overconsumption among young users, as parents could perceive these products as healthier alternatives to traditional candies. Another example illustrating this trend is the proliferation of spray food supplements designed to be sprayed directly onto the tongue. However, this method of application can inadvertently lead to overconsumption as consumers, particularly those who are not fully aware of the recommended dosage, may end up spraying more than necessary.

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Food supplements in gummy form

This is because controlling the amount of product dispensed through a spray can be challenging, especially for those not accustomed to this form of application.

It is important to emphasize that the target population is a significant factor in preventing the overdose of specific bioactive ingredients. For instance, products formulated for adults may not be appropriate for children due to the adjusted levels of vitamins and minerals for each category. The degree of toxicity is determined by body weight, which is why the recommended daily dosage is typically designed according to the target consumers; hence, a product for adults can be toxic for children due to the amount of bioactive ingredients.

Additionally, as outlined in Section 2, the excessive bioavailability of certain bioactive ingredients can potentially lead to side effects and toxicity. This is due to their rapid absorption into the bloodstream, which can result in high concentrations within the body. Such concentrations can overwhelm the body's metabolic and elimination processes, leading to adverse reactions (Rein *et al.*, 2013; Ali *et al.*, 2018). In this context, the use of plant mixtures in food supplements has been found to significantly increase the bioavailability of certain bioactive compounds, becoming a widespread practice in the manufacturing process of these products. For instance, research indicates that the combination of piperine, from black pepper, with curcumin, from turmeric, significantly enhances the absorption of curcumin, which is not easily absorbed by the body when consumed alone (Gupta, Patchva and Aggarwal, 2013; Bang *et al.*, 2009; Derosa, Maffioli and Sahebkar, 2016; Hewlings and Kalman, 2017). However, even if the combination of piperine and curcumin can enhance the bioavailability of curcumin, excessive bioavailability could also lead to health complications if not appropriately managed, potentially leading to negative health outcomes.

A significant aspect to consider is also the practice of using proprietary blends on food supplement labels, which is allowed in certain jurisdictions. This practice primarily serves to safeguard the intellectual property of manufacturers within the food supplement industry. However, it also results in the opacity of the precise quantities of each constituent ingredient within the blend. The use of proprietary blends carries various implications. On the one hand, it fosters an environment conducive to innovation by enabling manufacturers to shield their unique formulations from competitors, but it poses challenges for consumers and health practitioners seeking to discern the exact composition of these supplements. From a safety standpoint, the inability to ascertain the specific quantities of individual ingredients could raise concerns. This is especially pertinent for components that may elicit adverse effects when consumed in excessive amounts, or for individuals adhering to specific dietary restrictions.

Case study 10
A case of vitamin D overdose

British media reported the case of an 89-year-old man who died due to an "overdose" of vitamin D supplements, which failed to provide warnings about the potential risks of excessive consumption. The man was found to have dangerously high levels of vitamin D when he was admitted to the hospital. He was diagnosed with hypercalcemia, a condition characterized by an excess of calcium in the body, often linked to excessive vitamin D intake. It is reported that the man had been consuming the vitamin D supplement for at least nine months, which did not carry any warnings about the specific risks or side effects associated with excessive intake. In fact, currently the Food Standards Agency, the food competent authority in the in England, Wales and Northern Ireland, does not mandate the inclusion of these risks on labelling requirements nor the side effects on the packaging of food supplements containing vitamin D.

Source: BBC News. 2024. Surrey coroner calls for change after 89-year-old's fatal vitamin D overdose. In: *BBC News*. [Cited 29 February 2024] https://www.bbc.co.uk/news/uk-england-surrey-68436576.amp

3.7 Toxicity of plant-based supplements due to overconsumption or improper use

While many food supplements containing botanicals available in today's market are considered safe from a toxicological standpoint, there is an increasing concern regarding the rise in reported cases of liver injury associated with their use (Gurley, McGill and Koturbash, 2022).

Plant-based supplements have been documented to potentially pose risks due to the presence of toxic compounds which can lead to a variety of adverse effects, including hepatotoxicity, cardiovascular toxicity, digestive system toxicity, renal toxicity, reproductive toxicity, endocrine toxicity, and dermatological toxicity, which could pose a significant public health concern (Jităreanu *et al*., 2022).

Several case studies reported the toxic effects of plant-based bioactive ingredients. However, there is a scarcity of information regarding the precise minimum toxic doses in both animals and humans and much of the literature on this topic is based solely on *in vitro* models (Wang *et al*., 2021). Also, it is important to note that many studies report toxicity and adverse events resulting from food supplements containing botanicals only after consumption of doses significantly exceeding those recommended by the manufacturer. In fact, adverse events are typically linked to overdoses of certain bioactive ingredients, often with increased bioavailability also. As such, to minimize potential health risks, it is of utmost importance to strictly follow the recommended daily dosage indicated on the product label. Additionally, it is worth noting that some botanical supplements are derived from plants not typically consumed by humans. As a result, the safety and efficacy of these plants remain uncertain, as their long-term effects and overall effectiveness are yet to be fully understood (Gurley, McGill and Koturbash, 2022).

For example, green tea extract derived from leaves of the *Camellia sinensis* plant is currently the most acknowledged component frequently associated with hepatotoxicity (Oketch-Rabah *et al*., 2020). The consumption of green tea is widespread globally and while the safety profile of green tea as a beverage is known, the ingestion of a concentrated extract heightens exposure to the catechin polyphenols contained in it, particularly when one is in a fasted state (Gurley, McGill and Koturbash, 2022). And yet, example of liver damage from green tea as a beverage are exceedingly rare. Conversely, the surge in popularity of green tea extract and products containing green tea extract in the past two decades has been accompanied by numerous instances of liver injury that can be linked to the intake of these food supplements.

The precise causes and mechanisms underlying green tea extract-induced liver damage are not yet fully comprehended. However, it has been reported that the presence and concentration of specific catechins, particularly epigallocatechin gallate (EGCG), play a crucial role in hepatotoxicity (Mazzanti, Di Sotto and Vitalone, 2015; Patel, Thapa and Sharma, 2023). Additional factors may either contribute to or exacerbate hepatotoxicity induced by green tea extract. Notably, research involving animals and clinical trials have indicated that consuming green tea extract on an empty stomach leads to significantly higher plasma concentrations of catechins compared to consuming the extract in a fed state, thereby substantially enhancing EGCG induced liver damage (Paine *et al*., 2006; Schmidt *et al*., 2021). Moreover, the influence of genetic predisposition in green tea extract-induced liver injury is increasingly gaining recognition (Chalasani *et al*., 2014).

Another example is ashwagandha, a widely utilized botanical in the realm of Ayurvedic medicine, derived from the roots of *Withania somnifera*. While acknowledged as safe for consumption, instances of liver damage linked to its use, albeit rare, have been documented (Gurley, McGill and Koturbash, 2022). The first reported case of ashwagandha-related liver injury occurred in Japan in 2017 (see Case Study 11), followed by further instances reported worldwide (Björnsson *et al*., 2019).

In Australia, the Therapeutic Goods Administration (TGA) has raised safety concerns about *Withania somnifera* following reports of adverse effects. Consumers have reported acute symptoms such as nausea, vomiting, and diarrhea, sometimes occurring after a single dose and resulting in hospitalization in certain cases. In response, the TGA issued a safety advisory for products containing this plant (Australian Government, 2024). A safety investigation indicated an exceptionally rare risk of liver injury associated with the plant; however, the TGA is closely monitoring the situation and may consider actions. The TGA recommends that individuals with current or past liver conditions avoid products containing *Withania somnifera*. They also advise consumers to be alert for symptoms of gastrointestinal distress or liver injury and to seek medical advice if such symptoms arise (Australian Government, 2024).

Case study 11
Liver dysfunction in a 20-year-old man linked to ashwagandha use

In 2017 in Japan a 20-year-old man with social anxiety disorder was hospitalized with liver dysfunction characterized by significantly elevated bilirubin levels (hyperbilirubinemia) and prolonged intrahepatic cholestasis. He had been self-administering Ashwagandha, which he purchased online, alongside multiple prescribed anti-anxiety medications. Over the course of a month, he had exceeded the recommended dosage of Ashwagandha. Upon admission, he presented with symptoms of jaundice and abnormal liver function tests. Medical investigations included a comprehensive drug-induced liver injury (DILI) assessment, which highlighted Ashwagandha as a possible contributor to his liver injury.

Source: Inagaki, K., Mori, N., Honda, Y., Takaki, S., Tsuji, K., & Chayama, K. 2017. A case of drug-induced liver injury with prolonged severe intrahepatic cholestasis induced by Ashwagandha. *Kanzo*, 58(8), 448-454. https://doi.org/10.2957/kanzo.58.448

Case study 12
The impact of traditional herbs on liver fibrosis in sub-Saharan Africa

In a comprehensive research study carried out by Auerbach and his team in 2012, they found that the utilization of traditional herbal extracts is widespread in sub-Saharan Africa. Despite their popularity, there are escalating concerns about the potential harmful effects these herbs could have on liver health. However, the full extent of their impact remains unexplored.

The study was designed to investigate the possible link between the use of these traditional herbs and liver fibrosis, a condition characterized by the scarring of liver tissue. The research was conducted in rural Uganda and involved a sample size of 1 000 individuals, half of whom were living with HIV, while the other half were not. The study discovered that the use of herbal extracts, particularly those derived from the plant families *Asteraceae* and *Lamiaceae*, was associated with an increased likelihood of developing significant liver fibrosis regardless of HIV.

Source: Auerbach, B.J., Reynolds, S.J., Lamorde, M., Merry, C., Kukunda-Byobona, C., Ocama, P., Semeere, A.S. *et al.*, 2012. Traditional herbal medicine use associated with liver fibrosis in rural Rakai, Uganda. *PLoS ONE*, 7(11): e41737. https://doi.org/10.1371/journal.pone.0041737

Case study 13
Italian guidelines on the use of food supplements containing curcuma extracts

In 2019, the Italian Ministry of Health issued a circular (11889 of 24 December 2019) providing important guidelines on food supplements containing extracts and preparations of *Curcuma longa* plants. However, in 2022, following the evaluation of newly reported cases of hepatotoxicity, resulting from the intake of food supplements containing *Curcuma longa* extracts, the Ministry issued a new circular (0033749-03/08/2022-DGISAN-MDS-P) with updated guidelines.

Considering the persistence of hepatotoxicity cases, an interdisciplinary group of experts deemed it necessary to insert a specific warning for supplements containing ingredients derived from *Curcuma longa* saying:

> IMPORTANT WARNING: In case of alterations of liver function, biliary or gallstone disease, the use of the product is not recommended. Do not use it during pregnancy and breastfeeding. Do not use it for prolonged periods without consulting a doctor. If you are taking medication, it is advisable to hear the opinion of the doctor (Italian Ministry of Health, 2022).

The circular also states the duty of the food business operator (FBO) to verify that the ingredients used are NOT novel foods as per regulation (EU) 2015/2283, acquiring all the necessary documentation to prove it, and making it available to the competent authority for checks, if requested.

After the aforementioned circular, in May 2023, a new circular from the Ministry of Health (0018484-04/05/2023-DGISAN-MDS-P) stated that there was no demonstrated significant use in the food field for the extract of *Curcuma longa* rhizome, titled at 95 percent in curcumin. However, a substantial history of consumption was identified for food supplements. The Italian directive further stipulates that any process that enhances solubility or bioavailability could be subject to the regulations governing novel foods. Consequently, ingredients that contain *Curcuma longa* extract with a curcumin concentration equal to or exceeding 95 percent are considered novel foods in Italy. As such, food supplements containing these ingredients are not permitted for sale in the country.

Source: Italian Ministry of Health. 2022. *Circolare 0033749-03/08/2022-DGISAN-MDS-P: Linee guida aggiornate sugli integratori alimentari contenenti estratti di Curcuma longa*. Rome https://www.cna.it/wp-content/uploads/2022/08/01082022-cambio-decreto-curcuma-associazioni-rev-2.pdf

Case study 14
Liver injury and consumption of green tea extract

A 44-year-old woman from Canada was admitted to the intensive care unit due to a severe and rapidly progressing case of acute liver failure. Her medical history was unremarkable, with obesity being the only notable condition. Six months before being admitted, she had been following a weight-loss programme that encouraged increased physical activity and the consumption of food supplements containing green tea extract. Her social and family histories were not significant, and she denied any use of alcohol or illicit drugs. Upon initial examination, she was found to be jaundiced and exhibited signs of grade I encephalopathy. Tests for active hepatitis A, B, and C were negative, as were extensive toxicology screenings. Upon admission, she started on an intravenous infusion of acetylcysteine. However, her encephalopathy worsened after 24 hours. A percutaneous liver biopsy was performed, revealing more than 50 percent hepatocellular necrosis and a mixed inflammatory infiltration with a high number of eosinophils. Sixteen days after her initial presentation with acute liver failure, she underwent a cadaveric orthotopic liver transplant. Her postoperative recovery was marked by prolonged encephalopathy and severe muscular weakness, which eventually resolved.

Source: Molinari, M., Watt, K.D.S., Kruszyna, T., Nelson, R., Walsh, M., Huang, W.-Y., Nashan, B. and Peltekian, K. 2006. Acute liver failure induced by green tea extracts: Case report and review of the literature. *Liver Transplantation*, 12(12): 1892–1895. https://doi.org/10.1002/lt.21021

Case study 15
Adverse effects linked to a weight loss supplement

As reported by Lin and Tujios (2023), the United States Food and Drug Administration (FDA) banned food supplements containing ephedra in 2004 due to adverse effects on the cardiovascular, neurological, and hepatic systems. Two cases of acute hepatocellular injury, accompanied by jaundice, were associated with the consumption of a leading weight loss supplement brand in the United States of America. This product, introduced in 2002, contained ma huang *(Ephedra sinica)*, a botanical source of ephedra alkaloids. Despite the removal of ephedra, instances of liver injury linked to this brand persisted, with an additional nine cases documented. A recent report detailed 17 instances of severe liver damage connected to the same supplement brand. The affected group comprised of nine males and eight females, with an average age of 30 years. These patients exhibited symptoms of hepatocellular injury, characterized by transaminase levels exceeding 1 000 U/L, and jaundice that appeared approximately 6.4 weeks (about one and a half months) after starting the supplement regimen. Positive antinuclear antibodies were not uncommon, and histological analysis indicated either cholestatic hepatitis or extensive necrosis. All these individuals required hospitalization. Three underwent liver transplants, and one succumbed to the condition. The exact ingredient or combination of ingredients within the supplement responsible for the hepatotoxicity remains uncertain.

Source: Lin, J.K.-S. & Tujios, S.R. 2023. Hidden dangers: herbal and dietary supplement induced hepatotoxicity. *Livers*, 3(4): 618–636. https://doi.org/10.3390/livers3040041

3.8 Food supplements and new ingredients

In the dynamic global market, companies manufacturing food supplements and functional foods are perpetually seeking new ingredients that can confer physiological benefits. These ingredients, often without a prior history of being consumed as food, are considered novel in the realm of food supplements. This novelty necessitates a comprehensive and rigorous food safety assessment before these ingredients can be introduced into the market, evaluating any potential risks associated with their consumption to ensure that any potential hazards linked to the consumption of these new ingredients are identified and mitigated before they reach consumers. It is worth noting that regulatory systems are in place in numerous countries to oversee this process (refer to Section 4).

Packages of dried herbs. Türkiye

4. REGULATORY FRAMEWORKS FOR FOOD SUPPLEMENTS AND FUNCTIONAL FOODS

Food supplements and functional foods have been available to consumers globally for several decades. The usage context of these products varies widely from one country to another, leading to significant differences in the regulatory frameworks related to these products across various jurisdictions. Some countries classify such products as food items, while others categorize them as health products or pharmaceuticals (Low *et al.*, 2017). However, given the increasing number of individuals that use food supplements and functional foods (Djaoudene *et al.*, 2023; Boggia, Zunin and Turrini, 2020), ensuring their safety and quality has become a pressing concern for food competent authorities. Numerous governments worldwide have already instituted stringent and comprehensive regulations and standards on these products to ensure consumer safety, truthful labelling and fair-trade practices, but there is no harmonized approach to regulate the scope, requirements, or even the definitions or terminology used to classify these products from one country to another (Thakkar *et al.*, 2020; Dwyer *et al.*, 2018).

At the international level, the Codex Alimentarius Commission established guidelines in 1997 relating to the use of nutrition and health claims in food labelling, which include food supplements and functional foods (FAO and WHO, 1997). Additionally, in 2005 other guidelines specifically tailored for vitamin and mineral food supplements were established to offer direction on the composition of food supplements, including the criteria for setting minimum and maximum levels, as well as packaging and labelling (FAO and WHO, 2005).

This section aims to depict the regulatory landscape pertaining to food supplements and functional food in jurisdictions where these products have a long-standing presence, to help understand the complexities and nuances of the various regulatory frameworks in place in different countries.

The examples are grouped based on the Codex regions, namely Africa, Asia, Europe, Latin America and the Caribbean, the Near East, North America and the Southwest Pacific (FAO and WHO, n.d.). The quantity of examples from each region varies, based on the unique characteristics of a specific jurisdiction and on the information that is publicly accessible. The content has been prepared in consultation with the Codex focal point of each country to align with their specific regulatory requirements and practices. It is important to note that regulatory frameworks worldwide are continually evolving. Therefore, a complete analysis of legislations governing the regulation of food supplements and functional foods across different jurisdictions is not within the scope of these sections.

4.1 Regulatory challenges

There is no global consensus on how to categorize food supplements and functional foods, with each country not only using different terminology (see Section 4.1.1) but also having different dosage requirements for a product to be defined as a supplement or a drug. Certain products, classified as food supplements in some jurisdictions, may be considered medicinal products in others, being subjected to different regulations, and overseen by different agencies. For instance, vitamin D at 5 000 International Units would be classified as a drug in the European Union, while in the United States of America it would be considered a dietary supplement. Another example is represented by melatonin, which is regulated as a food supplement in the European Union and in the United States of America, but in Australia, it is considered a prescription medication (Dwyer *et al.*, 2018).

It is worth noting that food supplements are not typically regulated as a separate category in most countries, but they are instead often included as a subcategory within existing regulations. The overarching legislation frequently plays a crucial role in determining the kind of claims that can be made and the degree of scrutiny and oversight that will be applied. In numerous jurisdictions, food supplements are simply encompassed under the prevailing food or drug regulations. However, in some instances, specific regulations are formulated to manage these products. In such cases, distinct categories are established within a highly structured regulatory framework, especially in countries with a strong tradition of health and healing practices, such as traditional Chinese medicine in China, Ayurvedic medicine in India, and Kampo medicine in Japan.

4.1.1 Food supplements and functional foods: definition, terminology, and classification

As outlined in Section 1, food supplements are products that contain a concentrated source of nutrients, typically sold in dosage form, which have the purpose to complement one's diet. The terminology used to categorize these products varies significantly among different jurisdictions, as shown in Table 3. This difference in terminology can lead to a product being categorized differently, resulting in significant variations in regulatory decisions by country (Thakkar *et al.*, 2020).

Table 3 Terminology used by different countries to address food supplements products (as defined in Section 1 of this document)

Country	Terminology used	Regulatory agency
Argentina	Suplementos dietarios	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), decentralized organism of the Ministry of Health
Australia	Complementary medicine	Therapeutic Goods Administration (TGA)
Brazil	Suplementos alimentares	National Health Surveillance Agency (ANVISA)
Canada	Natural health product	Health Canada
China	Health food	China Food and Drug Administration (CFDA)
Egypt	Food supplements	National Food Safety Authority of Egypt
Europe	Food supplements	European Food Safety Authority (EFSA) and National competent authorities
India	Health supplements	Food Safety and Standards Authority of India (FSSAI)
Nigeria	Herbal medicine and related products	National Agency for Food and Drug Administration and Control (NAFDAC)
Japan	Food with health claims	Ministry of Health, Labour and Welfare (MHLW) for medicine
South Africa	Health supplements Complementary medicine	The South African Health Products Regulatory Authority (SAHPRA)
United Arab Emirates	Health supplements	Dubai Municipality
United States of America	Dietary supplements	Food and Drug Administration (FDA) through the Dietary Supplement Health and Education Act (DSHEA)

Source: Author's own elaboration.

Regarding functional foods, there is currently no statutory definition (Granato *et al.*, 2020). The term was first coined in Japan during the 1980s and presents a nuanced definition across countries. These products, which have nutritional value like conventional foods, are claimed to mitigate the risk of various diseases, but they do not have the capacity to heal, prevent, or cure diseases (Brown *et al.*, 2018; Cassidy, McSorley and Allsopp, 2018).

The classification of food supplements and functional foods varies across different jurisdictions. In some regions, both food supplements and functional foods fall under the same category and are governed by the same legislation. For instance, in Europe and in the United States of America both products are regulated under the general food law. However, in other jurisdictions, these two categories are considered separately. In Australia, for example, food supplements are classified as medicinal products and are therefore subject to different regulations compared to functional foods which follow the food regulation. In yet other jurisdictions, the classification is based on the health claims made on the product label. For example, in countries like Japan and China, both food supplements and functional foods are considered health products if they carry certain health claims on their labels. This diversity in classification and regulation underscores the complexity of the global food and health product market and the regulatory landscape. This section has the purpose of highlighting these differences among various regulatory systems.

A woman packaging hibiscus flower juice containing anthocyanins. The Gambia

4.1.2 Market entry requirements in different countries

In some countries, the introduction of functional foods and food supplements to the market requires adherence to specific notification or registration-based systems. These regulatory systems are crucial in ensuring product safety and quality while allowing for market innovation. As the global market for functional foods and food supplements grows, regulatory frameworks vary significantly between countries, ranging from minimal oversight to stringent, multistep approval processes. Understanding the distinction between notification-based and registration-based systems is essential for both manufacturers and regulators, as the choice of system directly impacts the speed of market entry, the level of scrutiny products undergo, and the responsibilities placed on both parties.

Product notification or product registration?

Although variations exist among nations, a notification-based system typically serves as a method for alerting regulatory bodies about a product's market entry. This system would not require an explicit positive response of the government before marketing. Notifications usually include details about the manufacturer, product type, formulation, and labelling and are usually subjected to minimal scrutiny by authorities. Products must contain ingredients from an approved list, if available, and their introduction to the market does not imply approval or authorization from regulators; however, regulators may retain the right to query or oppose a notification. This method requires minimal premarket resources for both industry and regulators, enabling them to concentrate their efforts on enforcing post-market surveillance. The European Union exemplifies a region that favours a notification-based approach (see Section 4.2.3).

On the other hand, the registration-based approaches demand more detailed information through a registration dossier, a rigorous review by regulators, and an extended evaluation period. This system gives a positive response from the regulatory authorities for the product to be commercialized. A typical registration dossier necessitates significantly more information compared to a notification, encompassing specifics about the final product, evidence supporting ingredient safety and effectiveness, stability tests, product labelling and more (Shao, 2017). While this approach may be slower and require substantial resources in countries where registration is mandatory, it offers a high level of scrutiny of the product. Argentina is an example of a country that employs this registration-based approach (see Section 4.2.4.1).

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A woman drinking passion fruit juice naturally containing functional compounds. Uganda

In contrast, in certain jurisdictions, there are no stringent requirements for the registration or notification of food supplements before they are introduced into the market. This means that manufacturers and distributors can freely sell these products without having to submit detailed information to regulatory bodies for review and approval. For example, in the United States of America the Food and Drug Administration (FDA) does not require dietary supplements to be registered or notified before they are marketed, unless they contain a new dietary ingredient (NDI) (see Section 4.2.6.3).

Post-market surveillance

Despite the variances in premarket protocols, a method for evaluating product safety is post-market surveillance, which involves monitoring product performance through the systematic collection, management, and investigation of consumer inquiries, complaints, and adverse reactions. Through this process, issues such as manufacturing errors, product contamination, and tampering can be discerned and addressed promptly (Shao, 2017). Food competent authorities typically do not weigh individual adverse event reports independently. Instead, they analyse all incidents comprehensively, contextualizing them to pinpoint potential issues (Shao, 2019).

In some countries, should manufacturers identify potential safety risks linked to their food products, they are obligated to carry out a thorough safety investigation and assessment. If the products are found to be unsafe, manufacturers are required to immediately cease production, initiate a product recall from the market, and inform relevant business partners and consumers. It is also mandatory for them to keep records of the recall and all related notifications. Similarly, food distributors and providers, including those operating online, are required to immediately halt the supply of products upon detecting any non-compliance with food safety standards.

Positive and negative ingredient lists

In many countries, regulatory authorities utilize formalized lists of ingredients, often referred to as positive or negative lists, to guide safety evaluations for food and food supplements. These lists serve to delineate which ingredients are considered safe for use in these products and which are not permitted.

Positive lists include ingredients that have been assessed and approved for use, while negative lists contain ingredients that are explicitly prohibited. In some instances, positive lists may also stipulate specific warnings that must be included on the product label when certain ingredients are used.

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A farm employee labels a bottle of tamarind drink for shipping. Nigeria

Definitions of nutrition and health claims

- **Nutrition claim** means any representation which states, suggests or implies that a food has particular nutritional properties including but not limited to the energy value and to the content of protein, fat and carbohydrates, as well as the content of vitamins and minerals. The following do not constitute nutrition claims: (a) the mention of substances in the list of ingredients; (b) the mention of nutrients as a mandatory part of nutrition labelling and; (c) quantitative or qualitative declaration of certain nutrients or ingredients on the label if required by national legislation.
- **Nutrient content claim** is a nutrition claim that describes the level of a nutrient contained in a food. (Examples: "source of calcium"; "high in fibre and low in fat".)
- **Nutrient comparative claim** is a claim that compares the nutrient levels and/or energy value of two or more foods. (Examples: "reduced"; "less than"; "fewer"; "increased"; "more than".)
- **Health claim** means any representation that states, suggests, or implies that a relationship exists between a food or a constituent of that food and health. Health claims include the following:
  - **Nutrient function claims** – These are claims that describe the physiological role of the nutrient in growth, development and normal functions of the body.
  - **Other function claims** – These claims concern specific beneficial effects of the consumption of foods or their constituents, in the context of the total diet on normal functions or biological activities of the body. Such claims relate to a positive contribution to health or to the improvement of a function or to modifying or preserving health.
  - **Reduction of disease risk claims** – These are claims relating the consumption of a food or food constituent, in the context of the total diet, to the reduced risk of developing a disease or health-related condition. Risk reduction means significantly altering a major risk factor(s) for a disease or health-related condition. Diseases have multiple risk factors and altering one of these risk factors may or may not have a beneficial effect. The presentation of risk reduction claims must ensure, for example, by use of appropriate language and reference to other risk factors, that consumers do not interpret them as prevention claims.

Source: FAO. 1997. *Guidelines for use of nutrition and health claims CAC/GL 23-1997*. Rome.
https://www.fao.org/ag/humannutrition/32443-04352e8311b857c57caf5ffc4c5c4a4cd.pdf

A variety of food supplements in different forms, including capsules, tablets and soft gels

The approach to these lists varies globally. Some countries rely solely on either a positive or negative list, while others employ a combination of both.

The criteria for the inclusion or exclusion of an ingredient or substance on these lists can differ significantly across different jurisdictions. These criteria may be based on factors such as scientific evidence of safety, historical use, and risk-benefit analysis.

4.2 Regulatory landscape

4.2.1 Regulatory landscape in Africa

4.2.1.1 Regulation of food supplements and functional foods in Nigeria

Classification

In Nigeria, it is important to distinguish between food supplements and functional foods, as they are regulated under different frameworks with the provisions of the National Agency for Food and Drug Administration and Control (NAFDC). Food supplements fall under the Herbal Medicine and Related Products Labelling Regulations of 2019 (NAFDC, 2019a), which govern products containing plant materials and those with therapeutic or prophylactic claims. These regulations do not apply to functional foods, which are instead regulated under the NAFDAC Food Safety and Applied Nutrition Directorate Guidelines and the NAFDAC Guidelines for Food Product Registration of 2019 (NAFDC, 2019b).

Labelling

The labelling of food supplements in Nigeria is regulated by the Herbal Medicine and Related Products Labelling Regulations of 2019 (NAFDC, 2019a). Mandatory labelling requirements, which must be in English, should include the brand name and the botanical, or common name, if any, the list of all ingredients in the product, the net content of the product in terms of weight, the name and address of the manufacturer, the directions for the safe use of the product including dosage, instructions, the lot number, the expiration dates, and the storage conditions. On the other hand, functional foods labelling falls under the NAFDAC Pre-packaged Food Labelling Regulations (NAFDC, 2019c).

Composition

Allowed ingredients used in food supplements in Nigeria include vitamins, minerals, enzymes, and amino acids. Products can be successfully registered if these ingredients are added in quantities that are not considered toxic.

Registration

Food supplements that are manufactured, imported, exported, advertised, sold, or distributed in Nigeria must be registered in accordance with the provisions of the NAFDAC Act, CAP N1 (LFN) 2004 (NAFDAC, 2004). Conversely, functional foods are classified and registered as regular food products under NAFDAC regulations (NAFDC, 2019d).

Claims

In Nigeria, both nutrition and health claims are subject to regulation. Under NAFDAC Pre-packaged Food Labelling Regulations (NAFDAC, 2019c) no claims regarding medicinal effects (preventive, alleviative, or curative) can be made. If a claim of effectiveness or therapeutic indication is made for any Herbal Medicine and Related Products, it must prominently display, near the claim, a statement asserting that such claim has not been evaluated by NAFDAC, unless the claim has been clinically validated and deemed satisfactory by the Agency.

An employee sets up the batch code machine for the finished products. Nigeria

4.2.1.2 Regulation of food supplements and functional food in South Africa

Classification

In South Africa, food supplements are a subcategory of complementary medicines, which are classified in the Medicines and Related Substances Act, 1965 (Act No.101 of 1965) as any substance, extract, or mixture of substances, sold in dosage forms used for restoring, or modifying any physical or mental state by complementing health, supplementing the diet, or a having a nutritional effect (SAHPRA, 1965).

A "complementary medicine" is a substance or combination of substances that 1) originates from a variety of natural sources such as plants, fungi, algae, seaweeds, lichens, minerals, animals, or any other substance as approved; 2) is used, claimed to be suitable for use or manufactured or sold to maintain, enhance or assist the physical or mental state; and 3) is used as a health supplement or in accordance with disciplines as approved by the Authority.

Labelling

Health supplements must adhere to the labelling regulations outlined by the Medicines and Related Substances Act, 1965. The label should include the Nutrient Reference Value (NRV), a clear indication if artificial sweeteners are used, the name of the food, the name and address of the manufacturer, importer, or seller, instructions for use, net contents, country of origin, list of ingredients, the batch identification number and a statement emphasizing that a varied diet is the most effective and safe way to achieve good nutrition, health, body composition, and mental and physical performance. Any pictorial representation must not be false, misleading, or deceptive, nor create an erroneous impression regarding product character, origin, composition, quality, nutritive value, nature, or other properties in any respect (SAHPRA, 2010).

Composition

Supplements are required to adhere to the guidelines set forth by the South African Health Products Regulatory Authority (SAHPRA, 2022). Health supplements can contain only low-risk substances and indications, which are intended for general health enhancement, health maintenance, or for alleviating minor symptoms not associated with any disease or disorder (SAPHRA, 2024).

The health supplements' guideline stipulates the minimum and maximum amount for various components. These include probiotics, prebiotics, vitamins, minerals, proteins and amino acids, animal extracts and derivatives, fats, oils and fatty acids, carotenoids, polyphenols (including bioflavonoids), and amino saccharides.

Registration

The South African Health Products Regulatory Authority (SAHPRA) manages the registration of health products. Since 2013, SAHPRA has mandated that complementary medicines are subject to registration (SAHPRA, 2022).

Claims

For products that are authorized by SAHPRA and regulated under the Medicines and Related Substances Act of 1965 (Act No.101 of 1965), it is prohibited to disseminate false claims or misleading information about the therapeutic efficacy of these products. Authorized health and nutrition claims are clearly defined in the Regulations Relating to the Labelling and Advertising of Foodstuffs R146 (SAHPRA, 2010). Each nutrient has established conditions for nutrient content claims, with specific wording required. If a claim necessitates more than one condition, all conditions must be satisfied for the claim to be considered valid. Claims of medicinal benefits, such as cures, are prohibited. Furthermore, it is not permissible to make disease risk reduction claims or indications that either explicitly or implicitly refer to the treatment or cure of specific diseases. These regulations are in place to ensure the accuracy and integrity of health-related information provided to the public.

4.2.2 Regulatory landscape in Asia

4.2.2.1 Regulation of food supplements and functional food in China

Classification

The Chinese Food Safety Law, established in 2015 (Standing Committee of the National People's Congress, 2015), classifies "health foods" as a special category of foods divided into two subcategories: 1) Nutrition Supplements, which are products designed primarily to supplement or replenish nutrients, such as vitamins and minerals to enhance the nutrient intake of the consumer; and 2) Functional Health Foods, which are products that possess properties similar to regular food items but claim to have specific health functions or physiological effects on the human body.

The concept of health food is defined in China (in the GB Standard for Natural and Health Foods GB16740-2014) as foods which claim to have specific health functions or can supplement certain vitamins and/or minerals and are suitable for certain people to help them improve body functions. They are not for the purpose of therapy, and they do not bring harm to the human body (National Health Commission, 2014).

Under the Chinese food safety law, herbal supplements are categorized either as "supplements" or as "medicine". Herbal supplements categorized as "supplements" are products regulated by the State Administration for Market Regulation (SAMR). On the other hand, herbal supplements classified as "medicine" fall under the purview of hospital care and are regulated by the National Health Commission (NHC). Products classified as medicine, particularly those falling under traditional Chinese medicine (TCM), have a significant presence in China. TCM encompasses products that have a long history of use among the Chinese population, deeply ingrained in the Chinese health care system, from manufacturing to hospital care. TCM is well regulated in China and its regulatory structure is well-established and streamlined (Standing Committee of the National People's Congress, 2015). Therefore, in China, health foods and TCM are both recognized for their health benefits, but they serve different purposes and are regulated differently. Health foods are generally used to supplement diet and improve physiological functions, while TCM is used for both preventive health care and disease treatment.

Labelling

In China, the Administrative Measures of Food Labelling governs the rules and regulations pertaining to food labelling. The information that should be present on food labels includes the name of the food, the name, address and contact information of the manufacturer, the production date, the expiration date, and the ingredient list. All information shown on product labels must be accurate, true and not misleading to the consumer (State Administration for Market Regulation, 2019).

Composition

All food products must also comply with compulsory national standards on food safety and related regulations. For example, the use of vitamins, minerals and other nutritive substances allowed in various food products is governed by the national standards, which provide comprehensive requirements on food additives and nutritional ingredients allowed in China, including the type, the maximum amount and their sources.

New food materials are defined as materials that are not traditionally consumed in China, including 1) animals, plants, and microorganisms; 2) their extracts; 3) food materials obtained by changing their structure; and 4) other newly developed food materials. New food materials must be approved by the NHC before they can be used in food products in China. If an imported food product contains food materials that are new in China, the materials must be approved as new food materials before the food product can be imported.

According to the Food Safety Law of the People's Republic of China, traditional Chinese medicine in the food and medicine continuum (abbreviated as *food and medicine continuum list*) can be added to food. The *food and medicine continuum list* shall be published by the health administrative department of the State Council in conjunction with the food safety supervision and management department of the State Council. In order to standardize the management of the *food and medicine continuum list*, the NHC has formulated the *Regulations on the Management of the Food and Medicine Continuum List*, which provides regulations on the definition of *food and medicine continuum list* and the revision procedures of the list (National Health Commission, 2021).

Registration

Under the Food Safety Law of the People's Republic of China, companies intending to introduce health food products to the Chinese market shall apply for and obtain the health food registration certificate or the filing certificate. For health foods manufactured domestically in China, the registration process is overseen by the State Administration for Market Regulation (SAMR, formerly known as CFDA). The filing process, on the other hand, is managed by the Provincial Administration for Market Regulation.

For health foods imported from overseas factories, both the registration and filing processes are handled by SAMR. Furthermore, foreign companies are required to establish a permanent representative office in China or appoint a Chinese agent to facilitate the registration or filing process and secure the necessary certificates. The requirements for either registration or filing are listed on the measure. Registration is requested for domestic health food of which raw materials are not listed in the health food raw material directory and which is imported to China for the first time. The registration process involves submitting detailed information about the product, including its ingredients, manufacturing process, and intended health benefits. The SAMR reviews this information to ensure the product meets the necessary safety and efficacy standards.

Filing is required for domestic health foods whose raw materials are entirely listed in the health food raw material directory. Additionally, health foods imported into China for the first time, with functions classified as nutrient supplementation (vitamins and minerals), also require filing. Furthermore, the General Administration of Customs (GACC) mandates that health food manufacturers register their establishments. This involves providing detailed information about the manufacturing facility, including its location, size, equipment, and sanitation practices (Standing Committee of the National People's Congress, 2015).

A man sells ginger at a market. Ginger is widely used as an ingredient in food supplements and functional foods. China

Claims

In China, the SAMR published the *Directory of Health Functions Available to be Claimed by Health Food – Non-nutrition Supplements* (2023 Version), which includes health food function evaluation methods. Conventional food products are regulated by SAMR according to food standards and are only permitted to make health claims that align with the GB 28050 standard, which provides an exclusive list of general health claims allowed for these products.

For the submission of a new claim, the draft guidelines stipulate that applicants must provide a methodology to evaluate and verify the new function. These evaluation and verification methods must be validated by local Chinese accredited laboratories. SAMR provides a comprehensive checklist of data requirements when applying for a new claim, including details on how the new claim is developed, its function in the human body, the method of evaluating the function, and how the claim is regulated in other countries. It is important to note that health foods are not intended for diagnosing, treating, curing, or preventing any disease; hence, any misleading or unproven health claims are strictly prohibited, to maintain the integrity of the health food market and protect consumers from potential harm (State Administration for Market Regulation, 2023).

4.2.2.2 Regulation of food supplements and functional food in India[4]

Classification

In India, the food supplements and functional foods are regulated by the Food Safety and Standards Authority of India (FSSAI). FSSAI has notified Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016, which came into effect upon their publication in the Official Gazette (Gazette of India, 2016).

The regulation covers eight categories, namely, health supplements, nutraceuticals, foods for special dietary use, foods for special medical purpose, specialty foods containing plant or botanical ingredients with safe history of usage, foods with added probiotic ingredients, foods with added prebiotics ingredients, and novel foods. These products are intended for persons above the age of two years and can be marketed in forms such as capsules, tablets, pills, sachets and in any other format as measured unit quantities except those formats that are meant for parenteral administration. The products falling under these regulations shall not include drugs as defined in the Drugs and Cosmetics Act, 1940, hormones or steroids or psychotropic ingredients (FSSAI, 2016).

Labelling

The Food Safety and Standards (Labelling and Display) Regulations, 2020 covers the labelling requirements of pre-packaged foods and display of essential information on premises where food is manufactured, processed, served and stored (FSSAI, 2020). The labelling, presentation and advertisement of products covered under Nutraceutical Regulations shall not claim that the product has the property of preventing, treating or curing a human disease, or refer to such properties. Further, the label of the product should include the category name such as health supplement, nutraceuticals, food for special dietary use and so on; the common name of the product; the declaration of the amount of the nutrients or substances with a nutritional or physiological effect present in the product and the quantity of nutrients along with a warning “not exceed the recommended daily usage”, “the product should be stored out of reach of children”, and “not for medical use” together with a warning or any other precautions to be taken, if any, while consuming the product (FSSAI, 2020).

Composition

Nutraceutical regulation contains a positive list for vitamins and minerals, amino acids, plant or botanicals ingredients, ingredients as nutraceuticals, probiotics, prebiotics and food additives.

As stated in Nutraceutical Regulations, novel food is a food that (a) may not have a history of human consumption; or (b) may have any ingredient used in it which or the source from which it is derived, may not have a history of human consumption; or (c) a food or ingredient obtained by new technology with innovative engineering process, where the process may give rise to significant change in the composition or structure or size of the food or food ingredients which may alter the nutritional value, metabolism or level of undesirable substances.

[4] These regulations are currently under revision, which may lead to potential changes in the requirements for food supplements and functional foods.

A woman choosing spices at the market. India

No novel food shall be manufactured or imported for commercial purposes without the prior approval of the Food Authority by filing an application along with all relevant documents and details as specified by the Food Authority from time to time (FSSAI, 2016).

Licensing

The process and requirements for licensing and registration are governed by the Food Safety and Standards (Licensing and Registration of Food Business) Regulations, 2011 (FSSAI, 2011).

In India, any entity operating as a food business operator must be licensed with the Food Safety and Standards Authority of India (FSSAI) to sell the product covered under Nutraceutical Regulations, 2016.

It is mandatory for anyone involved in the sale of products covered under Nutraceutical regulation to possess a valid FSSAI License. This also indicates that the food business is licensed with FSSAI, facilitating easier tracking of licenses and adherence to regulations such as safety audits, product testing, and recalls.

Furthermore, depending on the specific ingredients present in the product and the claims made on the label, it may be necessary to obtain approval from the Food Authority prior to marketing the product.

Claims

The Food Safety and Standards Regulations 2016 states that every food business operator may make nutritional or health claims relative to an article of food (FSSAI, 2016).

a. Nutritional claim shall consist of the "Ingredients (nutrient or nutritional) content" of an article of food which shall be subject to the nutritional supplement requirements specified in the schedules of Nutraceutical Regulations.

b. Health claim refers to any representation made about a food product that suggests or implies a relationship between a specific nutrient or nutritional component and health-related outcomes, including the prevention or management of diseases. Health claims typically consist of two main elements: 1) the nutrient or nutritional ingredient involved, and 2) the associated health benefits or disease-related conditions the nutrient may impact.

The health claim relative to an article of food may include the following types, but are not limited to: 1) ingredient (nutrient or nutritional) function claims; 2) enhanced function claims; 3) disease risk reduction claims; and 4) health maintenance claims.

Any other claims in an article of food that are not drug claims may be allowed subject to prior approval of the Food Authority. The product-led claims relative to an article of food shall be based on human studies with evidence-based data, and the food business operator shall notify the Food Authority before putting the article on the market, by submitting relevant documents along with a copy of the label. For health claims where scientific support does not exist, or if a novel ingredient is to be introduced, there shall be prior approval of the Authority, which shall be based on adequate scientific evidence.

4.2.2.3 Regulation of food supplements and functional food in Japan

Classification

The primary legislation overseeing the quality and safety of food in Japan is the Food Sanitation Act (FSA), which does not specify food supplements or functional food but regulates food in general (MHLW, 2020). Under the Food Labelling Act, the "Foods with Health Claims" category is divided into three distinct subcategories: 1) Food for Specified Health Uses (FOSHU); 2) Foods with Function Claims (FFC); and 3) Food with Nutrient Function Claims (FNFC). Each of these subcategories is regulated through different pathways by the Consumer Affairs Agency (CAA) (CAA, 2015).

Labelling

The regulation that comprehensively oversees the labelling of food is the Food Labelling Act, which regulates the labelling of food for sale. For processed food, the basic labelling requirements include the name, use-by date or best-before date, manufacturer's name and address, storage instructions, raw materials, quantity contained, additives, nutrient components, country of origin, and any additional specifications pertinent to food categories (CAA, 2020).

Composition

Food additives, including vitamins and minerals that serve a physiological purpose, must adhere to their respective usage standards. These standards stipulate maximum limits and conditions of use and must also comply with the Specifications and Standards of Food Additives (JSFA), which encompass monographs and manufacturing standards. Additionally, a "list of examples" also exists for flavourings derived from plant or animal sources, as well as for other substances used as food additives. They contain ingredients that have been evaluated and deemed safe for use in food products (MHLW, 2021).

Regarding the use or inclusion of additives, processing aids, vitamins, minerals, or nutritive substances in food products, stringent guidelines have been set. In line with the FSA's regulations, food products containing these ingredients are not allowed to be sold, or be produced, imported, processed, used, stored, or displayed for the purpose of sale unless they have been authorized by the CAA (MHLW, 2020).

Registration

Foods for Specified Health Uses (FOSHU) was established by the Ministry of Health, Labour and Welfare in 1991 and transferred to the CAA in 2009. FOSHU are scientifically recognized as helpful for maintaining and promoting health and are permitted to bear claims such as "Slows cholesterol absorption". In order to sell food as FOSHU, the assessment for the safety of the food and effectiveness of the functions for health is required, and the claim must be approved by the CAA. On the other hand, as to the category of FFC, government-conducted safety and efficacy assessments are not mandatory, and companies submit premarket notifications in accordance with Food Labelling Standards. This category of FNFC refers to foods that are labelled with specific nutrient function claims as specified by the CAA which are based on the nutritional functions of certain nutrients, such as vitamins and minerals. These foods can be freely manufactured and distributed without any permission from or notification to the national government if they meet the standards (CAA, 2015).

Claims

It is important to note that the claims used on the three categories of "Foods with Health Claims" are regulated differently.

FOSHU are recognized as helpful for maintaining and promoting health and are authorized to bear health claims. Applicants for FOSHU approval must submit their documentation to the Commissioner of

the CAA. FOSHU health claims are individually reviewed and approved based on scientific evidence. Once permission for marketing is granted, the food must carry the logo of approval by the Commissioner of the CAA on the package label. The criteria for FOSHU approval include clear evidence of effectiveness on the human body, absence of safety concerns, and establishment of quality control methods.

The safety and effectiveness of Foods with Function Claims (FFC) are not evaluated by the government. Operators must base appropriate function claims on scientific evidence, which must stem from clinical trials or systematic literature reviews, supporting the effectiveness of the claim. However, unlike FOSHU, individual product approval by the Commissioner of the CAA is not required.

Foods with Nutrient Function Claims (FNFC) refers to foods that can supplement or complement daily nutrient requirements. FNFC are all foods that are labelled with the nutrient function claims specified by the CAA. The standards for indication of nutritional function have been so far established for 20 nutrients (13 vitamins, 6 minerals, and n-3 fatty acid). If a product contains specific nutrients, such as vitamins or minerals, whose function is supported by scientific evidence, it can bear a nutrient function claim without government notification. These foods can be freely manufactured and distributed without any permission from or notification to the government if they meet the standards. The standards require that the amount of nutrient in the recommended daily intake of the product must be within a specified range (CAA, 2015).

Preparing herbal infusion tea

4.2.3 Regulatory landscape in Europe

4.2.3.1 Regulation of food supplements and functional foods to which vitamins, minerals and/or certain other substances have been added in the European Union

Classification

The regulatory framework for food supplements and foods to which vitamins, minerals and/or certain other substances have been added in Europe follows general food legislation, and their manufacturing processes are subjected to good manufacturing practice (GMP) and Hazard Analysis and Critical Control Point (HACCP) procedures. Specifically, the European Union regulates food supplements as a category of food products under the Directive 2002/46/EC, which defines them as:

> foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities (European Union, 2002, p. 51).

Labelling

The labelling of foods to which vitamins, minerals and/or certain other substances have been added shall not include any mention stating or implying that a balanced and varied diet cannot provide appropriate quantities of nutrients. The labelling of foods to which vitamins and minerals have been added shall not mislead or deceive the consumer as to the nutritional merit of a food that may result from the addition of these nutrients. Nutrition labelling of products to which vitamins and minerals have been added and which are covered by Regulation (EC) No.1925/2006 is compulsory and needs, apart from the nutrition declaration required for all foods, to include information about the total amounts of the vitamins and minerals present when added to the food.

The amount of nutrients or substances with a nutritional or physiological effect present in the product shall be declared on the labelling in numerical form. The amounts of the nutrients or other substances declared shall be those per portion of the product as recommended for daily consumption on the labelling. Information on vitamins and minerals shall also be expressed as a percentage of the reference values mentioned, as the case may be, in the Annex XIII to Regulation (EC) No.1169/2011.

Additionally, Directive 2002/46/EC established that food supplements' labels shall bear a cautionary warning against exceeding the recommended dose, a statement that food supplements should not be used as a substitute for a varied diet and advice for storing the product out of reach of young children. The Directive also explicitly prohibits the labelling, presentation, or advertisement of food supplements as capable of preventing, treating, or curing diseases.

Regulation (EC) No.1169/2011 indicates that labels must include the name of the food, the ingredient list, the allergen information, the quantity of certain ingredients, the best before/use by date, the country of origin, the name and address of the food business operator established in the European Union or importer, the net quantity, any special storage conditions and/or conditions of use, and the instructions for use if needed (European Union, 2011).

Composition

The Directive 2002/46/EC delineates a positive list in Annex I of vitamins and minerals permitted for food supplements, including their allowed sources listed in Annex II.

The Regulation (EC) No.1925/2006 harmonizes provisions which relate to the addition of vitamins and minerals and of certain other substances to foods in the European Union. This Regulation establishes a positive list in Annex I of vitamins and minerals that may be added to foods, including their allowed sources listed in Annex II. Article 8 of Regulation (EC) No.1925/2006 provides for a procedure whereby the addition to foods or the use in the manufacture of foods of a substance other than vitamins or minerals for which a harmful effect on health has been identified, or an ingredient containing that substance, can be prohibited, restricted or placed under Community scrutiny.

Annex III provides a list of those substances whose addition to foods or use in the manufacture of foods has been prohibited (part A), restricted (part B), or placed under Union scrutiny (part C). This list is applicable to all foods, including food supplements. Specific national rules setting out which substances other than vitamins and minerals may be used in foods and food supplements and their conditions of use may also exist. For botanicals, various Member States of the European Union have devised and consistently updated their positive or negative botanical ingredient lists.

A food, including if intended for use in food supplements and foods to which vitamins, minerals and/or certain other substances have been added is a "novel food" if it has not been consumed to a significant degree in the European Union before 15 May 1997, and falls under the Regulation (EC) No.2015/2283. This includes if a new production process has been used, or if it contains or is composed of engineered nanomaterials. Novel foods require authorization, following a safety assessment by the European Food Safety Authority (EFSA) in accordance with Regulation (EC) No.2015/2283 on novel food. A centralized list of novel foods authorized in the European Union can be found in the Regulation (EC) No.2017/2470, which is updated by the European Commission to add newly authorized novel foods, and it includes their conditions of use, labelling requirements, and their specifications.

Monitoring

To facilitate efficient monitoring of food supplements, the Directive 2002/46/EC stipulates that national authorities may require manufacturers or the person placing the product on the market in their territory to notify the competent authority of that placing on the market by forwarding it a model of the label used for the product.

Similarly, for foods to which vitamins and minerals have been added, and of foods containing substances listed in Annex III, Parts B and C of Regulation (EC) No.1925/2006, Member States of the European Union may require the manufacturer or the person placing such foods on the market in their territory to notify the competent authority of that placing on the market by providing a model of the label used for the product. In such cases, information on the withdrawal of the product from the market may also be required.

For foods bearing nutrition or health claims, Member States of the European Union may require the manufacturer or the person placing such foods on the market in their territory to notify the competent authority of that placing on the market by forwarding to it a model of the label used for the product.

Claims

In the European Union generally, nutritional claims and health claims are identified. Under Article 2 of Regulation (EC) No.1924/2006, a nutrition claim is described as any claim which states, suggests or implies that a food has particular beneficial nutritional properties due to the energy (calorific value) it provides at a reduced or increased rate; or does not provide; and/or the nutrients or other substances it contains in reduced or increased proportions; or does not contain. A positive list for nutrition claims is in the Annex, which also explains the condition of use. The Regulation, on the general principles to be respected for all claims, provides that the use of nutrition and health claims shall not: (a) be false, ambiguous or misleading; (b) give rise to doubt about the safety and/or the nutritional adequacy of other foods; (c) encourage or condone excess consumption of a food; (d) state, suggest or imply that a balanced and varied diet cannot provide appropriate quantities of nutrients in general (...); and (e) refer to changes in bodily functions which could give rise to or exploit fear in the consumer, either textually or through pictorial, graphic or symbolic representation. This Regulation shall apply to nutrition and health claims made in commercial communications, whether in the labelling, presentation or advertising of foods to be delivered as such to the final consumer.

Health claims, as defined by European regulations, refer to "any claim that states, suggests, or implies that a relationship exists between a food category, a food or one of its constituents and health." However, it is important to note that these claims must not suggest that the product can diagnose, prevent, treat, or cure diseases. Health claims are prohibited unless they are authorized and are only authorized for use in the European Union after a scientific assessment of the highest possible standard is carried out by the European Food Safety Authority (EFSA). The EU Register of nutrition and health claims lists all authorized health claims and it is publicly available at the following webpage: https://ec.europa.eu/food/food-feed-portal/screen/health-claims/eu-register/details/POL-HC-6467.

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Measuring powdered food supplement

According to Article 11, health claims which: 1) suggest that health could be affected by not consuming the food; 2) make reference to the rate or amount of weight loss; 3) make reference to recommendations of individual doctors or health professionals and other associations; and 4) not referred to in Article 11, shall not be allowed.

However, there are certain exceptions known as "pending claims". These are claims on a closed list under review by regulatory authorities and have not yet received official authorization. Those claims may be used on the EU market under the responsibility of the business operators provided that they comply with the general principles and conditions of the Claims Regulation and the relevant national provisions.

4.2.4 Regulatory landscape in Latin America and the Caribbean

4.2.4.1 Regulation of food supplements and functional food in Argentina

Classification

Food supplements, referred to as "suplementos dietarios" in Argentina, fall under the classification of foods and are regulated by Article 1381, as "Food for special diets" included in the Argentinian Food Code (Código Alimentario Argentino – CAA).

Their objective is to increase the usual dietary intake, supplementing the incorporation of nutrients and/or other ingredients in the diets of healthy people, and they are available in various formulations such as solid forms (e.g. tablets, capsules, granules, powders) or liquid forms (e.g. drops, solutions), and other forms for gastrointestinal absorption. Their purpose does not extend to treating or curing diseases, nor are they intended for therapeutic use. Instead, their focus is squarely on promoting health and addressing nutritional deficiencies (Ministerio de Salud, 2020).

Labelling

The labelling of food supplements in Argentina must adhere to the overarching regulations governing food labelling. In addition to the general labelling mandates, food supplements are subject to specific regulations outlined in Article 1381 of the CAA.

Key elements that must be included on the label comprise of the following: the legal designation "suplemento dietario", the brand and/or trade name of the product, the net weight, the complete ingredient list, the allergens, the name and the address of the manufacturer and the importer, the national Registry of Establishment number (RNE), the country of origin, the preparation and instructions for use, the daily recommended intake, the mandatory legends and warnings, the required use by/best before date, and the batch number/lot identification (Ministerio de Salud, 2020).

Composition

Food supplements in Argentina should contain in simple or combined form the following: amino acids, proteins, lipids, carbohydrates, probiotics, vitamins, minerals, and fibres and/or other ingredients with a nutritional or physiological role. Vegetable herbs and other ingredients may be added, which shall comply with the specifications, requirements and limitations set in this Code.

The proposed vitamins and minerals shall cover not less than 30 percent of the recommended daily intake (RDIs), established by the manufacturer according to the values given in the Tables in Article 1387 of this Code. Content vitamins and minerals in food supplements cannot exceed, in daily consumption, the values of tolerable upper limit (UL) in Table I of the article. "tolerable upper limits" (UL) is understood as the highest level of daily intake of nutrients that probably do not cause any risk of adverse effects.

The vitamin and mineral content of food supplements for pregnant women, breastfeeding women and children may not exceed the RDI values established in Tables II and III (recommended daily intake of protein, vitamins and minerals for pregnant or breastfeeding women, and children), listed in article 1387 of this Code (Ministerio de Salud, 2020).

Registration

Before food supplements can be introduced into the Argentinian market, they must first be authorized in the National Register of Foodstuffs (Registro Nacional de Productos Alimenticios – RNPA).

To obtain this authorization, a comprehensive dossier must be submitted to the competent food safety authorities in Argentina (Ministerio de Salud, 2020). This dossier should contain a variety of information, including but not limited to:

- a certificate of free sale issued by the competent authorities from the country of origin;
- the label of the product;
- detailed information about the ingredients used in the product and their nutritional composition;
- product and ingredient specifications;
- information about the storage conditions and shelf-life of the product.

Claims

Nutrient content claims are addressed under the CAA (Article 235 fifth), referencing the Technical Resolution No.01/12 on complementary nutritional information. This resolution provides a framework ensuring the scientific accuracy and non-misleading nature of nutrient content claims. It delineates the criteria for making such claims, specifying the eligible nutrients, conditions for claim validity, and requisite scientific evidence for substantiation (ANMAT, 2012).

Health claims, which attribute specific health properties to a food, are not allowed on the labelling of food supplements. However, this regulation is currently under review. Health claims are allowed for other foods with some exceptions set out in the regulation itself. Their authorization either for advertising or for food labelling is regulated by Provision No.7730/2011, modified by ANMAT Provision 8095/23, if they are scientifically justified and do not mislead the consumer (ANMAT, 2023).

It is important to note that Regulatory Decree No.151/2022 (article 6) of the Law for the Promotion of Healthy Eating (Law No.27,642) establishes that front-of-pack labelling in Argentina does not apply to food supplements (Ministerio de Salud, 2022).

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Papayas. Papain, an enzyme found in papayas, is used as an ingredient in food supplements. Brazil

4.2.4.2 Regulation of food supplements and functional food in Brazil

Classification

As per the Resolution (Resolução) RDC No.243/2018, food supplements (known as "suplementos alimentares") are characterized as products intended for oral consumption, available in various forms, and designed to supplement the diet of healthy individuals with nutrients, bioactive substances, enzymes, or probiotics, either in isolation or in combination. The approved forms can range from solid to semi-solid or liquid, encompassing a variety of forms such as capsules, tablets, liquids, powders, bars, gels, lozenges, chewing gum, and more (ANVISA, 2018).

Labelling

Specific labelling provisions for food supplements are outlined in RDC No.243/2018 and Normative Instruction (Instructiva Normativa – IN) No.28/2018. The labelling of food supplements must include the name "Suplemento Alimentar", followed by the form of presentation. Optionally, the individual names of nutrients, bioactive substances, or enzymes, their classes or sources, or the name of the probiotic strain, can be included. Instructions for use and storage must also be included on the label together with the warnings "This product is not a medicine", "Keep out of the reach of children" and "Do not exceed the recommended daily intake indicated on the packaging". Specific warnings for certain nutrients, bioactive substances, enzymes or probiotics should be also included according to IN No.28/2018. Additionally, the nutritional label must declare the portion as the daily amount recommended by the manufacturer for each of the population groups and specific age groups (ANVISA, 2018).

However, the labelling of food supplements must not include any representation, even in other languages, that explicitly or implicitly asserts, suggests, or insinuates that 1) the product serves medicinal or therapeutic purposes, 2) contains substances that are unauthorized or prohibited, 3) the food is incapable of supplying the necessary components for health, or 4) that the product is equivalent to or superior to traditional foods.

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Medicinal herbs in jars. Uzbekistan

Composition

The Resolution (Resolução) RDC No.243/2018 and IN No.28/2018 regulate the composition of food supplements. Specifically, Annexes I and II provide a comprehensive list of ingredients approved for use in food supplements. This list is tailored to various demographic groups and includes the sources of nutrients, bioactive substances, enzymes, and probiotics. On the other hand, Annexes III and IV establish the minimum and maximum permissible levels of these substances and microorganisms in food supplements, based on the specific demographic group (ANVISA, 2023).

Herbal substances, which are concentrates and plant extracts, can be used in supplements. However, permitted plant extracts must be previously approved regarding their safety for use as a novel ingredient and be a source of specific nutrients or bioactive substances.

In Brazil, the National Health Surveillance Agency (ANVISA) defines novel foods or novel ingredients as those that do not have a history of safe consumption in the country. In order to be included on the list of ingredients approved for use in food supplements, novel ingredients must be submitted to premarket risk assessment according to the procedure described by Resolution RDC 839/2023, which modernizes the standards, flows and procedures to verify safety and authorize the use of novel foods and ingredients.

Registration

Resolution (Resolução) RDC No.843/2024 and IN No.281/2024 regulates the registration process for foods in Brazil. Food supplements are exempt from registration, but must be notified to ANVISA, according to the aforementioned regulations (ANVISA, 2024).

Claims

Annex V of the IN No.28/2018 regulation stipulates the catalogue of nutrition and health claims that are allowed for use in food supplements. The application of these claims is discretionary, except for food supplements containing probiotics or enzymes, where it is mandatory.

In the case of probiotics, food with functional claims and or health properties claims require a premarket approval by ANVISA as established in Resolution RDC No.18/1999 and Resolution RDC No.241/2018 and must be notified to ANVISA, according to Resolution RDC No.843/2024 and Normative Instruction No.281/2024 (ANVISA, 2018).

4.2.5 Regulatory landscape in the Near East

4.2.5.1 Regulation of food supplements in Egypt

Classification

In Egypt, food supplements contain concentrated sources of nutrients like vitamins and minerals, or other substances with nutritional or physiological effects, either individually or in combination and are designed to augment the regular diet. They are marketed in various forms such as solutions, capsules, powders, tablets, drinkable ampoules, drops, or other similar forms, which are intended to be consumed in small, measured unit quantities as a part of conventional food intake. A wide range of nutrients and other ingredients might be present in food supplements, including, but not limited to, vitamins, minerals, amino acids, essential fatty acids, fibre, and various plants and herbal extracts (NFSA, 2018).

Labelling

In Egypt, the label for food supplements should include the following details (NFSA, 2018):

- the product's name and the description "Food or Dietary Supplement";
- the list of ingredients;
- net weight or size of the product;
- the name, address, and brand of the producer, and if the product is imported, the importer's details;
- the country of origin;
- the batch/lot identification number;
- the expiration date and storage instructions;
- nutritional facts;
- the name(s) of nutrients or substances that characterize the product and have nutritional and/or physiological effects;
- the recommended daily dose, along with a warning not to exceed this dose;
- a statement indicating that food supplements should not be used as a substitute for a varied diet;
- a statement advising that the product should be kept out of the reach of children;
- any warnings specific to an active or inactive ingredient of the food supplement;
- a statement indicating that the product should not be used by pregnant or lactating women except under the supervision of the physician.

Composition

The CAC/GL 23 "Guidelines for Use of Nutrition and Health Claims" and "Guidelines for Vitamin and Mineral Food Supplements" list the vitamins and minerals permitted in food supplements, along with their chemical forms (FAO and WHO, 2004). Herbs and other ingredients such as enzymes and active ingredients typically used in food supplements are authorized according to their relevant approval by a joint committee with the Egyptian Drug Authority (EDA) and other regulatory bodies.

Registration

All food supplements intended for marketing in Egypt must be registered. The National Food Safety Authority (NFSA) of Egypt is the governing body responsible for these registrations. As per the NFSA Decree of the Board of Directors No.1 of 2018, which outlines the rules for the registration and handling of foods for special dietary uses, food supplements, whether produced domestically or imported, cannot be handled or advertised unless they are registered and licensed for handling by the NFSA. They can only be manufactured, processed, or prepared in factories that are licensed and meet the hygiene requirements for food factories, or in pharmaceutical factories approved by EDA (NFSA, 2018).

Claims

Nutrition and health claims are regulated in Egypt. These claims are prohibited if: 1) they are false, ambiguous, or misleading; 2) if they cast doubt on the safety of the food or the nutritional adequacy of other foods; 3) if they encourage or condone excessive consumption of a food; 4) if they state or imply that a balanced and varied diet cannot provide appropriate quantities of nutrients in general; and 5) if they refer to changes in bodily functions which have not been globally approved or acclaimed and could cause doubt in the consumer (NFSA, 2018).

A shopkeeper selling beans and spices. Egypt

4.2.6 Regulatory landscape in North America and the Southwest Pacific

4.2.6.1 Regulation of food supplements and functional food in Australia

Classification

In Australia, food supplements may be regulated as a therapeutic good or as a food, while functional foods are generally regulated under food regulatory provisions.

Products that fall under the broad category of "Therapeutic Goods" include medicines, biologics, and medical devices regulated by the Therapeutic Goods Act of 1989 and under the jurisdiction of the Therapeutic Goods Administration (TGA) (Australian Government, 1989). The TGA's regulatory activities include premarket assessment, post-market monitoring, and enforcement of standards. Additionally, the TGA is responsible for the licensing of Australian manufacturers and verifying that overseas manufacturers comply with standards equivalent to those in Australia. Complementary medicine is the regulatory term used within the therapeutic goods category to include herbs, vitamins, minerals, and various nutritional supplements.

If there is an applicable food standard in the Australia New Zealand Food Standards Code (the Code), then the definition of therapeutic good does not apply to the good, and the product is regulated as a food. Food Standards Australia New Zealand (FSANZ) is responsible for developing and maintaining standards in the Code (FSANZ, 2024a). Food standards are implemented and enforced by government food agencies and local councils in the Australian states and territories through their respective food laws. Supplemented foods regulated under the Code are categorized as formulated caffeinated beverages, electrolyte drinks, formulated supplementary sports foods, and formulated supplementary foods.

Functional foods also fall under the jurisdiction of the Code but are not a discrete food category in food regulation. Instead, they are controlled by provisions in the Code that regulate fortification with vitamins and minerals and the addition of substances that are used for a nutritive purpose. These are substances added to foods to achieve a functional or nutritional purpose, and they would not otherwise be present in traditional foods at all or within the quantities sought.

These substances require premarket assessment by FSANZ and a specific permission in the Code.

Where there is potential overlap between food and therapeutic good regulations, determination of whether the product is a food or a therapeutic good depends on a number of factors, such as the product's ingredients, marketing and labelling claims, and the presentation (e.g. presentation as a pill, food bar, powder, and so on) (Australian Government, n.d.).

Labelling

In Australia, the regulatory framework for the labelling of complementary medicines includes several mandatory requirements which encompass the following information: the product name, the names and quantities of all active ingredients, the batch number, the expiry date, relevant warning or advisory statements, storage conditions, directions for use and, the indications for which the product is used. All this information must be presented in English, using durable and legible lettering.

For foods regulated under the Code, general labelling requirements which are applicable to all foods are listed in Chapter 1 standards of the Code. These standards set requirements for food identification, warning or advisory statements, ingredient information, direction for use, nutrition information requirements and claims. Specific labelling and information requirements may also apply, as required in the standard for a specific food category (e.g. formulated caffeinated beverages, electrolyte drinks, formulated supplemented sports foods, and formulated supplemented foods).

Composition

The TGA regulates complementary medicines and maintains a positive list of allowable ingredients in complementary medicines that are listed (low risk) in the Australian Register of Therapeutic Goods (ARTG) including excipients and actives. Active ingredients for complementary medicines include amino acids, charcoal, choline, essential oils, herbal materials, homeopathic preparations, microorganisms, minerals, mucopolysaccharides, ingredients of animal origin, lipids, substances produced by/obtained from bees, polysaccharides or carbohydrates, and vitamins.

Authorization for the incorporation of new ingredients into the Therapeutic Goods (Permissible Ingredients) Determination is granted by the Delegate of the Minister of Health after the assessment of these components by the TGA. Safety and quality assessments of new ingredients are conducted by the TGA upon receipt of an application with supporting data. The TGA might also conduct safety assessments of existing permitted ingredients if a safety concern comes to their attention. For instance, reports of severe adverse incidents like liver failure may prompt the TGA to investigate, as this could indicate potential adverse effects on consumer safety.

Based on the findings of the assessment, the TGA will introduce a new ingredient if the substance has been demonstrated to be safe for use in low-risk listed medicines. Where the safety of an existing ingredient has been reviewed, the TGA may alter restrictions, or revise precautionary statements as required. If concerns regarding safety persist despite restrictions or warnings, or if there is insufficient data for the Delegate to ascertain safety, the TGA may remove the ingredient from the Determination.

For food products regulated under the Code, compositional requirements are set to the specific standard for that food category. Substances that are regulated include vitamins, minerals, amino acids, and substances that are used for nutritive purposes. Changes to composition requirements, such as a permission to add a new substance or a change in the permitted amount of a substance, are achieved through an application to change the Code. Applications must meet certain information requirements to enable FSANZ to evaluate any potential public health and safety risk. Any identified risks can be addressed through, for example, new labelling requirements or restrictions on amounts permitted to be added, or foods it can be added to. If risks cannot be addressed through risk management approaches, the application may be rejected.

Registration or approval

Before they can be sold, complementary medicines must be registered or listed on the Australian Register of Therapeutic Goods (ARTG). Hence, the Complementary Medicines category has premarket approval requirements like those for foods and supplements in other countries, but with more stringent, drug-like requirements dependent on the level of risk of the product.

Applications to list or register a medicine on the ARTG follow different pathways, depending on the level of risk involved.

Products with lower risk can be "listed" in the ARTG by meeting certain criteria, such as containing low-risk ingredients, which are included in the Therapeutic Goods (Permissible Ingredients) Determination, adhering to good manufacturing practice (GMP) standards, only using low-risk indications which are included in Therapeutic Goods (Permissible Indications) Determination. These products are not premarket evaluated by the TGA and are included in the ARTG based on a certification from the product owner that the product meets all regulatory requirements.

The TGA also has a "listed assessed" pathway. Products in this pathway must meet the same requirements as listed medicines with the exception that, in addition to permitted indications, they can make "intermediate" level claims. The efficacy of these medicines is assessed by the TGA premarket.

Products containing higher-risk ingredients and/or making higher level health claims are registered in the ARTG. The application pathway involves an evaluation by the TGA of the safety, quality and efficacy of the medicine before it can be registered on the ARTG (Australian Government, 2019).

The TGA's approval and regulation of products are grounded in a risk-benefit assessment, which applies its scientific and clinical expertise to decision-making, ensuring that the benefits of a product outweigh any associated risks. When assessing the risk level, factors such as side effects, potential harm from prolonged use, toxicity, and the seriousness of the medical condition for which the product is intended are all considered. The level of TGA regulatory control intensifies in proportion to the level of risk posed by the product, and the TGA holds the authority to act if an issue arises. The spectrum of possible regulatory actions ranges from ongoing monitoring to the withdrawal of a product from the market.

For foods, applications to change the Code are assessed by FSANZ though an established risk analysis framework (FSANZ, 2024b). For a new substance or proposed changes, the full assessment includes consideration of toxicological, microbiological and nutritional safety risk, dietary exposure assessment, functional purpose and efficacy, consumer research, and cost-benefit analysis. All FSANZ assessments undergo a public consultation process to ensure views of stakeholder groups are canvassed and addressed. New or amended standards are approved though the FSANZ Board and the Food Ministers' Meeting, which oversees the food regulation system.

Claims

In Australia, the "TGA assessed" claim can be used for assessed listed medicines and registered complementary medicines. This claim indicates that the TGA has evaluated the efficacy of a medicine's indications through a premarket evaluation.

The "TGA assessed" claim aims to enhance transparency about the independent assessment of efficacy claims for certain medicines by the TGA, thereby supporting consumers in making more informed purchasing decisions. However, it is important to note that the "TGA assessed" claim is not a recommendation by the TGA and does not suggest that a product with the claim is better than other products without the claim.

Nutrition, health and related claims for foods are regulated in the Code under Standard 1.2.7. Health claims can be pre-approved or self-substantiated, but both must be supported by scientific evidence to the same degree of certainty. Health claims are not permitted on foods of poor nutritional quality, as determined by nutrient profiling scoring criterion (NPSC) (FSANZ, 2023).

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Powdered food supplement in a sachet

4.2.6.2 Regulation of natural health product and supplemented food in Canada

Classification

In Canada, food supplements are regulated by Health Canada and are classified as either a food, a non-prescription drug, or a natural health product (NHP). NHPs encompass a wide range of products including vitamins, minerals, herbal remedies, homeopathic medicines, traditional medicines such as traditional Chinese medicines, probiotics, and other products like amino acids and essential fatty acids. The regulation of NHPs falls under the jurisdiction of the Food and Drugs Act and the natural health products Regulations. NHPs are normally available in dosage formats that are not typical of conventional foods, such as capsules, tablets, solutions, creams, ointments, drops and tinctures (Health Canada, 2021).

Labelling

The general labelling requirements for NHPs stipulate that the label must contain a principal display panel which includes brand name, product number, dosage form, and net amount.

The label should also show the name and address of the product licence holder and, if the product is imported, the name and address of the importer. The common and proper names of each ingredient it contains should be listed.

The label should also provide the recommended use or purpose, route of administration, dose, and duration of use, if any. Risk information including cautions, warnings, contra-indications, or known adverse reactions associated with its use should be clearly stated. Recommended storage conditions, along with the lot number, expiry date, and a description of the source material of each medicinal ingredient contained should also be included.

In 2022, amendments to the labelling requirements in the natural health product regulations were published with implementation of the new requirements beginning in 2025. The new requirements aim to make NHP labels more legible and easier to understand. Key highlights of the new requirements include more clearly and prominently displayed text, a standardized facts table, and the inclusion of new warning statements for allergens (Health Canada, 2022).

Composition

NHPs are naturally occurring substances that are used to restore or maintain good health. They are made of substances such as plant material, alga, bacterium or fungus, vitamins, amino acids, essential fatty acids, minerals or probiotics (Health Canada, 2021).

Monographs contain information supporting the safety, efficacy or quality of a medicinal ingredient or NHP that Health Canada has reviewed and determined to be acceptable. Health Canada has developed a compendium of monographs including single ingredient monographs which indicate only one medicinal ingredient, and product monographs, which indicate multiple ingredients or describe the conditions of use for a product category.

Market authorization

The oversight of NHPs is the responsibility of the natural and non-prescription health products directorate (NNHPD). A prerequisite for NHPs is the completion of a premarket approval process and the acquisition of a licence before entering the market. The NNHPD assesses product licence submissions. To gain approval, applicants must provide details on the product's ingredients, manufacturing procedures, intended claims, and substantiate evidence on safety, efficacy and quality. Health Canada considers a wide range of evidence to validate the safety and effectiveness of NHPs including clinical trial data, literature references (e.g. published research, journals), pharmacopeias, and traditional knowledge. The type and amount of supporting evidence required depend on the health claim proposed for the product and its associated risks. Additionally, manufacturers are required to hold a site licence for production, and licence holders have an obligation to monitor and report to Health Canada any adverse reactions, associated with their products.

Supplemented foods

Supplemented Foods (SF) are defined as prepackaged products in food formats that contain one or more specific added vitamins, mineral nutrients, amino acids, or other ingredients which are added for reasons other than nutritional purposes. They include beverages enhanced with vitamins and/or minerals, caffeinated energy drinks, snack bars with added vitamins, and so forth. These products may not be suitable for unrestricted consumption or for vulnerable populations, such as children, pregnant or breastfeeding individuals and therefore require specific conditions.

Distinct from NHPs, supplemented foods (SF) are governed by the Food and Drug Act and Regulations. In July 2022, Health Canada published the Supplemented Foods Regulations in the Canada Gazette, Part II (CGII) (Government of Canada, 2022). This regulatory framework provides a comprehensive guideline for the use of supplemental ingredients in foods. For each supplemental ingredient (e.g. vitamins, minerals, amino acids, and caffeine), the regulations specify the food categories in which it can be added, the maximum permissible amount, and any required cautionary statements on the product label. The regulatory framework provides flexibility through a premarket submission process that permits additions of new supplemental ingredients, modifications to conditions of use of existing supplemental ingredients or additions of new food categories for use as supplemented foods (Government of Canada, 2022).

Claims

In Canada, health claims on food products are not mandatory but can be included voluntarily in labelling or advertising. However, these claims must strictly adhere to the guidelines set forth by the Food and Drugs Act (FDA), the food provisions of the Food and Drug Regulations (FDR), and any relevant guidance provided by Health Canada. All health claims must be truthful and not misleading, and health claims that refer to a Schedule A.1 disease in the FDA require a mandatory review by Health Canada and a regulatory amendment before their use.

Health claims not pertaining to diseases listed in Schedule A.1 of the FDA do not require a review by Health Canada or a regulatory change. For these claims, manufacturers and importers are required to disclose, upon request by the Canadian Food Inspection Agency when warranted, the evidence for the health claim in accordance with Health Canada's health claims guidance documents. Nutrient Content Claims, which describe the energy value or nutrient content of a food (e.g. "free," "reduced," "source," "excellent source"), must meet specific conditions outlined in regulations and guidelines (Health Canada, 2023).

Pregnant woman taking liquid food supplement

4.2.6.3 Regulation of food supplements and functional food in the United States of America

Classification

In the United States of America, the Food and Drug Administration (FDA) regulates dietary supplements as foods under the Federal Food, Drug, and Cosmetic (FD&C) Act, which defines dietary supplement, in part, as:

> a product (other than tobacco) that is intend to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combination of these ingredients (21 U.S.C. 321[ff][1]) (U.S. Department of Health and Human Services, 1994).

It is important to note that, in the United States of America, dietary supplements must be intended for ingestion only; therefore, dietary supplements cannot be taken for use through other routes of administration (e.g. injection, sublingual inhaled, and so forth) (21 U.S.C. 321[ff][2]).

The primary regulations that govern dietary supplements in the United States of America are 21 CFR part 101, which encompasses labelling; 111, which encompasses good manufacturing and distribution practices, packaging, and record-keeping requirements; and 190, which encompasses the premarket safety notifications.

Labelling

FDA regulations require dietary supplement labels to bear five statements: 1) the product name and a statement that identify the product as a "dietary supplement" or equivalent term replacing "dietary" with the name or type of dietary ingredient in the product (e.g. "iron supplement" or "herbal supplement"); 2) the name and place of business of the manufacturer, packer, or distributor; 3) nutrition labelling in the form of a "Supplement Facts" panel; 4) a list of "other ingredients" not declared in the Supplement Facts panel; and 5) the net quantity of contents. The Supplement Facts panel must list the serving size and number of servings per container, declare each dietary ingredient in the product, and except for dietary ingredients that are part of a proprietary blend, provide information on the amount of the dietary ingredient per serving. Depending on the type of ingredient, the amount per serving must be declared as a quantitative amount by weight,

Effervescent tablets as a form of food supplement

as a percentage of the Daily Value, or both. Finally, dietary supplement labels must provide a domestic address or domestic phone number for reporting serious adverse events to the manufacturer, packer, or distributor whose name and place of business are listed on the label, who are required by law to keep a record of all adverse events and to report serious adverse events to the FDA within 15 days of receipt (U.S. FDA, 2024).

Composition

Dietary supplements marketed in the United States of America can be composed of both dietary and non-dietary ingredients. As defined by the FD&C Act, a "dietary ingredient" can be a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance used to supplement the diet by increasing total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any of these substances (21 U.S.C. 321[ff][1]).

Ingredients in dietary supplements that do not fall under the category of dietary ingredients are referred to as "non-dietary ingredients." These can include elements such as flavours, excipients, and fillers. Non-dietary ingredients used in dietary supplements, like conventional food ingredients, must be authorized for their intended use by a food additive regulation or generally recognized as safe (GRAS) (U.S. Department of Health and Human Services, 1994).

Premarket safety review

Companies are not required to provide the FDA with evidence supporting the safety or effectiveness of their food products before or after they are marketed. However, an exception is made for dietary supplements that contain certain new dietary ingredients. In the United States of America, dietary ingredients introduced after 1994 must undergo a safety review through the new dietary ingredient notification (NDIN) process, which includes providing safety information and details about the new ingredient and the dietary supplement in which it will be marketed. The notification must be submitted to the FDA at least 75 days prior to the product's introduction to the market. This notification, which is mandatory, is based on substantiation that the manufacturer or marketer considers the NDI safe in the product under its intended conditions of use (U.S. FDA, n.d.). Dietary ingredients marketed before October 1994 are exempt from notification; however, there is no official compilation of these ingredients in the United States of America (21 U.S.C. 350b[d]). Additionally, there is an exception to the notification requirement for NDIs that have been in the food supply (21 U.S.C. 350b[a][1]).

Registration

Unlike drugs, which must be proven safe and effective for their intended use before marketing, dietary supplements are overseen by the FDA primarily through post-market surveillance. Under the FD&C Act the FDA does not have the authority to approve dietary supplements before they are marketed. Firms are indeed responsible for ensuring that the dietary supplements they manufacture or distribute are not adulterated or misbranded. Hence dietary supplements do not need premarket approval, but the manufacturer is responsible for ensuring that the products are safe. In the United States of America, the primary prerequisite for introducing a product into the marketplace is that any facilities involved in manufacturing, processing, packing, or holding dietary supplements or dietary ingredients for consumption within the country must be registered with the FDA. Additionally, FDA requires those who manufacture, package, or hold dietary supplements to follow current good manufacturing practices (cGMPs) to ensure the identity, purity, quality, strength, and composition of the products (U.S. FDA, 2024).

Functional foods

It is important to note that while the FDA has established regulatory frameworks for ingredients added to conventional foods (products that are not dietary supplements), dietary supplements, and medical foods, it does not have a specific regulatory category for functional foods. Thus, multi ingredient foods marketed as "functional" would need to meet the same regulatory requirements as any other multi-ingredient with respect to the safety of the ingredients and labelling food. For manufacturers seeking to make labelling claims for specific functional health effects, the FDA oversees regulatory programmes for authorized or qualified health claims. Under these programmes, manufacturers must substantiate their health claims with scientific evidence (U.S. FDA, 2017).

Claims

The FDA in the United States of America classifies claims pertaining to food supplements and functional foods into three categories: 1) structure/function claims, 2) health claims, and 3) nutrient content claims. The first category delineates the function of a bioactive ingredient within the human body; the second one highlights the link between a bioactive ingredient or a food and the reduction of disease risk, and the third type describes the level of nutrients in a product. The first and third types of claims listed above are not approved by the FDA and do not require FDA evaluation before they are used on the labelling. Health claims do require FDA evaluation (U.S. FDA, 2024). Manufacturers are responsible for ensuring the accuracy and validity of these claims. When a dietary supplement label includes a structure/function claim, a disclaimer is required informing consumers that the FDA has not evaluated it. Further, the dietary supplement firm marketing a dietary supplement containing a structure/function claim must notify the FDA about the claim within 30 days of first marketing the dietary supplement with that claim (21 U.S.C. 343[r][6]) (U.S. FDA, 2024).

5. CONSUMER PERCEPTION OF THE SAFETY OF FOOD SUPPLEMENTS AND FUNCTIONAL FOODS

Consumers are increasingly turning to food supplements and functional foods to prevent illness and enhance their well-being (Wang, 2023). This trend, combined with regulatory flexibilities in some jurisdictions (as highlighted in Section 4), has facilitated the rapid global expansion of the food supplements and functional foods industry. Consequently, these products are now extensively distributed and advertised through multiple channels, including internet marketing (Wang, Neilson and Ji, 2023).

Navigating this landscape can be challenging for consumers, who often struggle to make well informed choices about which products to use, how to use them, and whether they are necessary (Pullon *et al.*, 2019). Additionally, the benefits of food supplements and functional foods are not always supported by consistent scientific evidence. While some products have demonstrated positive nutritional outcomes, others have been linked to negligible or even adverse effects (see Section 3).

Yet, many consumers continue to use food supplements and functional foods regularly, even when they are aware that the products may be ineffective (Blendon *et al.*, 2001) or could pose potential food safety issues (see Section 3). This underscores the importance of understanding consumer perceptions of the safety of these products. By exploring why consumers use these products and the factors influencing their decisions, it is possible to gain insights into the consumption behaviours and the socio-cultural mechanisms underlying them (Wang, Neilson and Ji, 2023).

In this section, consumer perceptions of the safety of food supplements and functional foods are addressed, underscoring the important role of traditional knowledge and traditional medicine related to these products. The motivations behind the use of these products, and the impact of the regulatory and marketing environment on their use are examined.

5.1 Why consumers choose to purchase and consume food supplements and functional foods

The literature demonstrates that a wide range of motivations drive the purchase and consumption of food supplements and functional foods, making understanding them a key component in decoding consumer behaviour within this market. There is a broad spectrum of reasons for consumption of these products, ranging from internal factors like an increased awareness of the impact of food on health to external influences such as media messaging. Health consciousness drives individuals towards preventive health care, fostering positive attitudes about the purchase of health-related food products (Black, 2018; Thompson, 2016). Social influences also play a pivotal role, with family, friends, and health professionals often guiding individual choices. Furthermore, sociodemographic factors, including age, gender, education, and financial status, significantly mould individual perceptions and behaviours in relation to food supplements and functional foods (Kim, Lee and Park, 2021; Nguyen, Tran and Pham, 2019; Lee and Lin, 2020). The theory of planned behaviour (TPB) further deepens the understanding of these motivations by exploring how attitudes, subjective norms, and perceived behavioural influence the intention to purchase and consume these products (Conner *et al.*, 2003). According to TPB, a consumer's intention to buy food supplements and functional foods is driven not only by their positive attitudes toward health and well-being but also by perceived social pressures (subjective norms) and the degree of control they believe they have over their behaviour (Ajzen, 1991). For instance, an individual who believes that consuming food supplements will significantly improve their health and who perceives strong social encouragement from friends or health professionals is more likely to follow through on that intention. Additionally, if individuals feel confident in their ability to access and regularly use these products (perceived behavioural control), their likelihood of purchasing increases. The allure of these products is frequently linked to the symbolic and cultural connotations through which these products are seen as a more accessible route to achieving healthier lifestyles, circumventing the need for drastic dietary changes (Garcia and Lopez, 2018). Moreover, the rise of personalized nutrition, driven by advancements in technology and a better understanding of human genetics, is likely to further shape consumer behaviour in this market. Some of the key motivations driving consumers' purchase of food supplements and functional foods are listed below:

1. Influence of media

The internet and social media play significant roles in shaping consumer beliefs about supplements and functional foods. For example, poor eating habits are often highlighted, convincing many that their daily diets lack adequate vitamins and minerals, creating the perception that supplements are necessary to meet nutritional needs (Smith, 2021). Moreover, social media platforms and influencers have become powerful drivers in the decision-making process for purchasing and consuming food supplements (Patel and Kumar, 2020; Smith and Johnson, 2021).

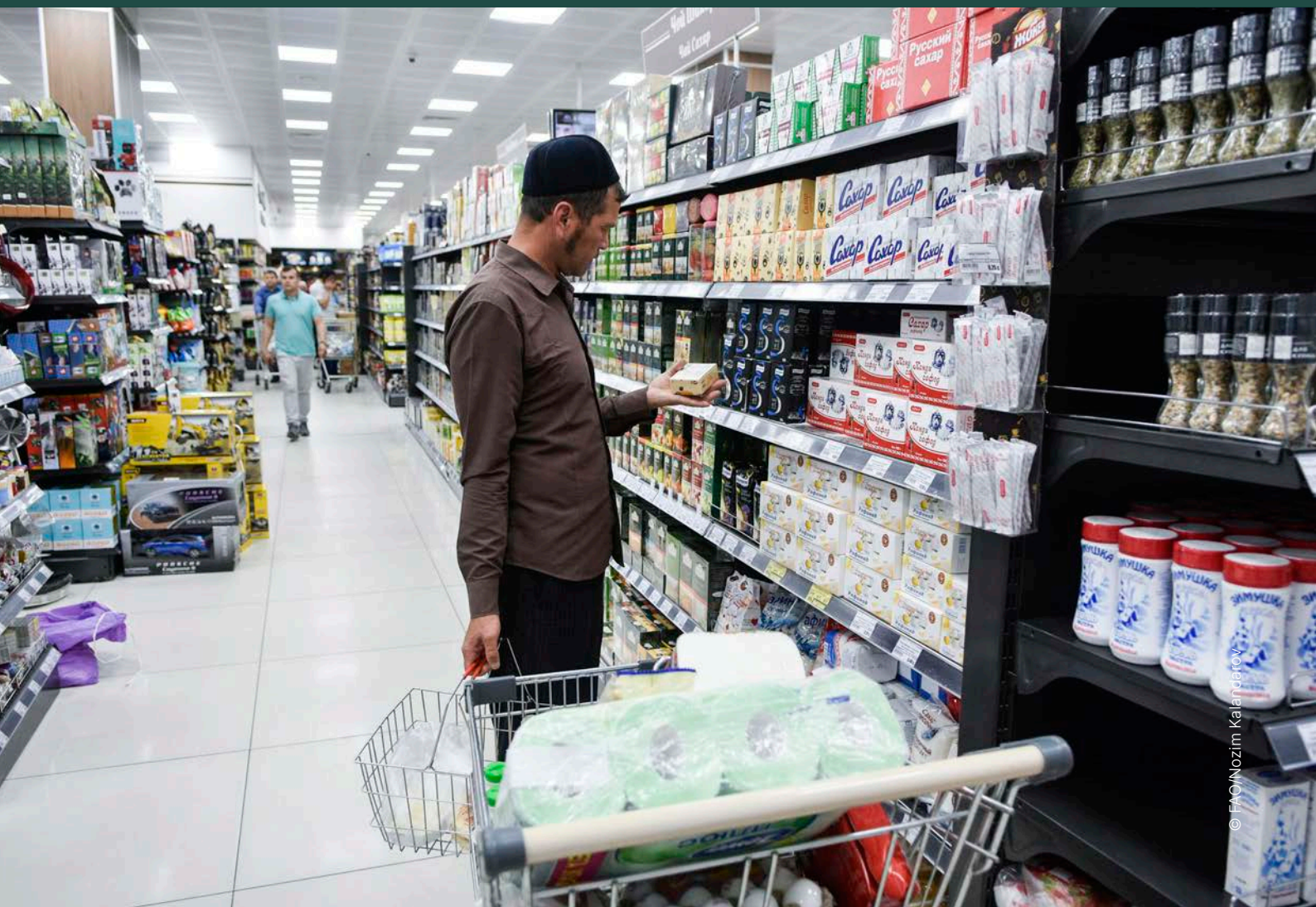
2. Inputs from the health marketplace

Consumers navigate a highly complex market of food supplements and functional foods, where reliable information and effective communication are crucial to aid decision-making. The diversity and volume of products, coupled with varying degrees of scientific evidence for their safety and effectiveness, make it challenging for consumers to discern which products meet their needs and are safe to use. Consequently, marketing communications, especially product labelling and advertising, play a pivotal role in shaping consumer perceptions and choices. For example, health claims on product labels can exploit consumer anxieties about health and nutrition or leverage well-known traditional beliefs or practices arising from the local culture. In an era where there is increasing awareness of diet-related diseases and a growing emphasis on preventive health measures, food supplements are marketed as convenient solutions to fill nutritional gaps and enhance overall well being. This marketing strategy taps into consumer fears and desires, making health claims particularly effective (Verbeke, Scholderer and Lähteenmäki, 2009).

3. Influence of family and friends

Individual perceptions and decisions regarding the use of supplements and functional foods are often profoundly influenced by family members and close friends. This social influence plays a critical role in shaping attitudes and behaviours towards health and nutrition. Research has shown that family habits and discussions about health can significantly impact an individual's dietary choices and the likelihood of incorporating supplements into their daily routine. For example, if their family members regularly use supplements, individuals are more likely to perceive these products as beneficial and necessary for their health (Brown *et al.*, 2018). Friends also play a role in influencing supplement consumption. Peer recommendations and shared experiences can reinforce positive attitudes towards supplements. When friends discuss the benefits, they believe they have derived from using specific supplements, it can create a ripple effect, encouraging others within the social circle to adopt similar practices (Conner *et al.*, 2003; Jones and Smith, 2020).

A customer reading a product label at the supermarket. Tajikistan



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4. Sociodemographic factor, socioeconomic status and social role

Traditional sociodemographic factors such as age, gender, education, and financial status significantly impact individual purchase and use of food supplements and functional foods. For example, higher educational levels often correlate with greater awareness and usage of these products (Lee and Lin, 2020). Additionally, food plays a symbolic role in society, and consuming functional foods can contribute to a positive social image and desired lifestyle (Conner *et al.*, 2003; Davis, 2017; Miller, 2019).

5. Influence of health professionals

Health professionals such as doctors, pharmacists, dietitians, and nurses play a significant role in influencing consumers' purchases and use of food supplements. Their recommendations are often trusted and can greatly impact consumer behaviour (Nguyen, Tran and Pham, 2019). This influence is particularly important for specific populations such as the elderly and pregnant women, who may have unique nutritional needs that can be effectively addressed through supplementation. By assessing individual health needs, professionals can provide personalized advice on the types and dosages of supplements that are most appropriate. This tailored approach can enhance the benefits of supplementation and prevent potential risks associated with inappropriate use (Dickinson *et al.*, 2014).

6. Positive expectations and healthier lifestyles and preventions

Individuals who maintain a healthier lifestyle and possess greater health awareness are more inclined to use food supplements and functional foods (Dickinson and MacKay, 2014). These individuals often believe that supplements can further enhance their well-being, supporting their efforts to maintain or improve health. This belief is reinforced by the perception that supplements can fill nutritional gaps and provide additional health benefits, despite the adequacy of their current diet. However, the literature shows that for those who already have a balanced and nutrient-rich diet, additional supplementation may not provide any significant benefits, and the perceived benefits of supplements may be attributed to the placebo effect, where individuals experience positive outcomes simply because they believe they will (Rawdon *et al.*, 2012).

7. Easier alternatives and guilt alleviation

Food supplements and functional foods offer an easier alternative for individuals seeking to lead a healthier life without drastically changing their eating habits. These products are convenient and often marketed as quick fixes for nutritional inadequacies. Some studies indicate that consumers use functional foods to alleviate guilt associated with unhealthy eating patterns, allowing them to balance indulgence with perceived health benefits (Roberts and Taylor, 2018; Hall, 2019). This behaviour, known as compensatory behaviour, involves actions taken to counterbalance or mitigate apparent nutritional deficiencies or health risks due to lifestyle or dietary habits. For example, individuals with poor dietary habits may turn to multivitamins to ensure they receive necessary nutrients and to offset negative health effects (Smith, 2021; Bailey *et al.*, 2013).

8. Spread of sustainable diets

The increasing popularity of sustainable diets, including vegan, vegetarian, and flexitarian, has led to a heightened demand for food supplements and functional foods. These diets often exclude or limit animal products, which are primary sources of certain nutrients such as vitamin B12, iron and calcium. As a result, individuals adhering to these diets may require supplementation to ensure they meet their nutritional needs (Craig, 2009).

9. Symbolic meanings and cultural beliefs

For some consumers, the value of food supplements extends beyond their functional benefits and is deeply rooted in symbolic meanings that resonate with their identity. Supplement use can be an expression of deep-rooted ideological values and cultural beliefs (Garcia and Lopez, 2018). This is particularly evident among individuals who incorporate traditional medicine and cultural practices into their health regimes. For instance, Ayurveda and traditional Chinese medicine (TCM) are ancient systems of medicine that have long used herbs and natural substances to promote health and treat diseases. Additionally, western herbal medicine and naturopathy, which are practiced in over 100 countries, utilize herbal remedies as a fundamental therapeutic approach (Lloyd and Hausser, 2022b). Supplements incorporating Ayurvedic herbs like ashwagandha or TCM herbs like ginseng, as well as those rooted in western herbal traditions, are popular among consumers who value these traditional practices (Patwardhan *et al.*, 2005; Barnes, Bloom and Nahin, 2007).

A elderly woman taking supplements during a meal

5.2 The blurred line between food supplements and drugs: common misconceptions

There is a common misconception among the public that supplements can be used as treatments for various medical conditions, which blurs the line between food supplements and pharmaceuticals (White and Green, 2019). In many jurisdictions, the primary distinction between drugs and supplements is that supplements cannot claim to prevent, treat, or cure diseases, which are claims reserved for pharmaceuticals (see Section 4). Consequently, the labelling and advertising of food supplements and functional foods in many countries cannot suggest or state that the products can diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases (see Section 4). However, this clear-cut distinction is being challenged as certain foods and food supplements are found to have significant health benefits. This overlap between the domains of food and drugs raises important questions about the regulation and safety of these products, which is crucial in the evolving landscape of "food as medicine". Health claims on supplement labels often imply significant health benefits, which further confuses consumers (Wierzejska, 2021), contributing to people struggling to distinguish between supplements and drugs (Wawryk-Gawda *et al*., 2019). For example, health claims such as "supports immune health" or "promotes heart health" can lead consumers to believe that supplements offer the same therapeutic benefits as drugs. This is particularly problematic when these claims are not adequately substantiated by scientific evidence, resulting in an overestimation of a supplement's efficacy (Dickinson and MacKay, 2014). Additionally, as mentioned in Section 3, individuals already undergoing pharmaceutical therapy for specific medical conditions may experience adverse effects if they take supplements concurrently with drugs in the belief that these will enhance the beneficial effects of their medication.

5.2.1 The influence of "Natural" labelling on consumer perceptions

Marketing tactics frequently emphasize the natural qualities of food supplements and functional foods on labels, thereby influencing consumer preference. The depiction of food supplements as "Natural" products resonates with a widespread belief that natural substances are inherently safer and healthier than synthetic ones. Studies suggest that consumers often equate natural products with a reduced risk of side effects compared to traditional medications (Lobell *et al.*, 2019), and this belief can lead to the false assumption that supplements are a safer alternative for health maintenance and disease prevention.

While supplements can be beneficial when used correctly, the perception that they are safer and more natural than drugs can lead to potential hazards. For instance, individuals may choose supplements over prescribed medications, believing them to be equally effective but without the associated risks of pharmaceuticals, resulting in delayed treatment and exacerbation of medical conditions (Loya, Gonzalez-Stuart and Rivera, 2009).

5.2.2 Food supplements in complementary and alternative medicine

Complementary and alternative medicine (CAM) has gained significant popularity worldwide among both the general public and some medical professionals (Phutrakool and Pongpirul, 2022). Many individuals perceive CAM as offering potential health benefits, such as treatment of illnesses, alleviation of symptoms, reduction of side effects from conventional treatments, and promotion of overall well-being. CAM practices often involve more time with practitioners and an individualized approach, which can appeal to those who feel underserved by conventional health care systems. However, while CAM emphasizes a holistic approach that includes the mind-body connection and preventive care, its treatments are not always supported by the same level of rigorous scientific evidence as conventional medicine (Corp, Jordan and Croft, 2018).

Phutrakool and Pongpirul (2022) define CAM as a form of medicine or treatment that is not considered conventional or standard medicine. The National Center for Complementary and Integrative Health (NCCIH) categorizes most types of complementary medicines under two primary categories: mind-body practices and natural products. Mind-body practices encompass yoga, chiropractic, massage, acupuncture, and meditation therapy, while natural products include herbs, vitamins, minerals, and probiotics, often consumed in the form of food supplements (NCCIH Strategic Plan FY 2021–2025, n.d.).

Traditional medicine systems such as traditional Chinese medicine (TCM), Ayurveda, naturopathy (Lloyd and Hausser, 2022a) and various indigenous healing practices have long incorporated natural substances and herbs to promote health and treat diseases. In contemporary times, this integration has expanded to include food supplements, which can be perceived as an extension of these traditional practices. These traditional medicines emphasize a holistic approach to health, focusing on maintaining balance within the body and preventing disease through natural means (Smith and Atalan-Helicke, 2020). In many cultures, the use of traditional medicines is passed down through generations, creating a deeply ingrained trust in natural remedies. Consumers familiar with traditional medicine practices are more likely to use herbal supplements as part of their health regimen, believing in their efficacy based on cultural knowledge and historical usage (Cohen, 2014).

However, the intersection of traditional medicine and food supplements can raise some concerns. The efficacy and safety of many traditional remedies, when repackaged as food supplements, may not be adequately supported by traditional evidence, given the alterations required to turn it into a manufactured product (Steel *et al.*, 2023; Foley *et al.*, 2023). Therefore, health care providers play a key role in educating consumers about integrating traditional practices with modern scientific insights, helping consumers make informed decisions that maximize health benefits and minimize risks (Bent, 2008; Cohen, 2014; Ekor, 2014).

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A Kenyan herbalist preparing herbal remedies. Kenya

5.2.3 Integrating traditional medicine with conventional medicine

The integration of traditional medicine with conventional medicine can potentially enhance patient care. This integrative model acknowledges the inherent value of time-honoured traditional practices while simultaneously leveraging the cutting edge advancements of contemporary medical science.

Research has consistently demonstrated that certain traditional therapies could potentially complement conventional treatments. For instance, herbal medicines such as ginger and turmeric largely used in TCM and Ayurveda, have been proven to possess anti-inflammatory and antioxidant properties. These natural remedies can potentially bolster conventional treatments for various inflammatory conditions, potentially leading to improved patient outcomes (Tapsell *et al.*, 2006).

However, the effective integration of traditional and conventional medicine is not merely about combining different treatment modalities. It also requires the development of a framework that ensures the seamless incorporation of traditional and complementary medicine into mainstream health care (Steel *et al.*, 2023).

5.3 The impact of health claims on consumer behaviour in the food and supplements industry

The food and supplement industries recognize that consumers are significantly motivated to purchase products that feature Qualified Health Claims (QHCs). These claims describe the relationship between the consumption of dietary substances and the reduced risk of disease or health conditions, though they are based on emerging rather than fully conclusive scientific evidence, as required for standard health claims. QHCs, accompanied by disclaimers, are designed to increase consumer confidence and drive sales. Research indicates that consumers are willing to invest more in products that promise health benefits (Berhaupt-Glickstein and Hallman, 2021). For example, a study by Steinhauser, Janssen and Hamm (2019) found that consumers are not only more likely to purchase products with health claims but are also willing to pay a higher price for them. Similarly, Andrews, Netemeyer and Burton (2009) found that health claims on food products can enhance perceptions of product quality and increase the perceived value, thereby justifying a higher price point. Furthermore, McKeon and Hallman (2024) discovered that front-of-package protein labels on cereal can create "health halos", causing consumers to view these products as healthier than they might be.

This highlights the powerful influence of label claims on consumer perceptions and purchasing choices.

According to Berhaupt-Glickstein, Hooker and Hallman (2019), the nuanced language of health claims can significantly influence consumer purchase intentions. Their study demonstrated that the way health benefits are communicated can have a substantial impact on consumer behaviour, particularly in the context of products like green tea. Further, Berhaupt-Glickstein and Hallman (2021) emphasized the importance of clear and accurate health claims in their research on disputed qualified health claims for green tea and cancer. Their findings reveal that ambiguous or contested claims can lead to consumer confusion and underscore the necessity for stringent regulatory oversight to protect consumer interests.

These insights are critical for the food and supplements industries, which can leverage health claims to enhance product appeal and justify premium pricing. However, it is important for regulatory bodies to ensure that these claims are substantiated and clearly communicated to avoid misleading consumers and to maintain trust in health-related marketing.

A child eating breakfast cereal. This food can be enriched with soluble fibres, vitamins, and minerals

5.4 Enhancing consumer trust through transparency and effective communication

Consumer trust in food products, especially in the realm of food supplements and functional foods, necessitates a comprehensive strategy that hinges on transparency and effective communication.

- **Transparency** is about offering clear, precise, and easily accessible information about various aspects of a product. This includes details about the ingredients used, their sourcing, the manufacturing processes involved, and the scientific evidence that supports any health claims made.
- **Effective communication**, is about ensuring that this information is relayed in a manner that is both comprehensible and trustworthy to consumers. Verbeke's research in 2008 underscores the significance of transparency in labelling and the provision of detailed product information as key factors in rebuilding consumer trust.

However, food scandals can significantly impact consumer trust, leading to heightened scepticism and reluctance towards purchasing or consuming food supplements and functional foods. Instances of contamination, mislabelling, and fraudulent claims can severely erode public trust in these products and the wider food industry. In such scenarios, swift and transparent responses from both the industry and regulatory bodies are crucial. These responses can help manage the crisis and reassure the public. For example, openly communicating about the steps taken to rectify contamination issues and prevent future incidents can restore confidence, as suggested by van Rijswijk and Frewer in 2008. By prioritizing clear information, proactive engagement, and consumer education, the food supplement and functional food industries, in collaboration with regulatory bodies, can work towards restoring and maintaining public trust in their products. This comprehensive approach not only addresses immediate concerns but also fosters a long-term relationship based on trust and transparency with consumers.

Packing medicinal herbs. Uzbekistan

6. WAY FORWARD: ENSURING THE SAFETY OF FOOD SUPPLEMENTS AND FUNCTIONAL FOODS

Raising awareness and understanding the importance of personalized nutrition in optimizing health outcomes are essential for effective oversight and regulation of food supplements and functional foods. In this context, it is also important to recognize that these products, central to the personalized nutrition paradigm, have undergone significant evolution, reflecting broader trends in consumer demand, scientific advancements, and regulatory landscapes.

The present report underscores that the safety of food supplements and functional foods is a multifaceted and highly complex issue. This complexity arises not only from the regulatory challenges associated with these products but also from the significant role that consumer perception plays in their use and acceptance. The interconnections between product safety, regulatory oversight, and consumer behaviour are profound, underlining the need for a holistic approach to ensure the safety of these products.

This section synthesizes and recaps the discussions presented throughout this publication, highlighting key insights into product development trends (see Section 2), quality and safety concerns (see Section 3), regulatory frameworks (see Section 4), and consumer behaviour (see Section 5). Integrating these insights, it provides a structured approach towards the development of actionable strategies that food competent authorities can consider in navigating the complex interplay of factors that impact the quality and safety of food supplements and functional foods with the aim of enhancing the safety of these products and protecting public health.

6.1 Addressing food safety challenges in supplements and functional foods: possible actions for food competent authorities

6.1.1 Embracing technological innovation

As described in Section 2, the innovation in the formulation and delivery of food supplements and functional foods has led to significant improvements in the bioavailability and stability of bioactive ingredients. Technologies such as microemulsions, nanoparticles and biopolymers are changing the way these ingredients are absorbed and utilized by the body. However, these technological advancements also introduce new safety challenges that must be addressed through rigorous safety evaluations. Therefore, it is important for food competent authorities to carry out comprehensive safety assessments specifically tailored to the challenges posed by these new technologies, considering their unique characteristics. To keep pace with the rapid advancements in this field, collaborating with stakeholders, including manufacturers, researchers, and developers, is key to staying informed about the latest innovations and understanding their implications for food safety. This ensures that the risk assessment reflects the latest scientific and technological advances bridging the gap between innovation and regulation.

Brazil nuts naturally containing selenium. Brazil

A woman examining the leaves and phenotype of medicinal herbs under a microscope. Uzbekistan

6.1.2 Managing potential food safety issues

As detailed in Section 3, food supplements and functional foods, while offering potential health benefits, may also pose significant safety concerns that food competent authorities in some jurisdictions are already addressing. These concerns include but are not limited to the risks of interactions between food supplements and pharmaceutical drugs; the presence of highly concentrated or chemically modified bioactive ingredients; the dangers of adulteration and contamination; and the potential for overdose and toxicity.

Interactions between food supplements, functional foods, and pharmaceutical drugs

One of the most critical safety concerns in the field of food supplements and functional foods is their potential interaction with pharmaceutical drugs. These interactions can significantly impact drug metabolism, potentially diminishing the efficacy of medications or, conversely, increasing their toxicity to harmful levels. To address and mitigate these risks, it is important for food competent authorities to implement labelling requirements that explicitly detail potential interactions between supplements and prescribed medications to empower consumers with the information needed to make safer choices. Explicit warnings on labels can play an important role in preventing consumers from inadvertently compromising their health by taking supplements that may interfere with or intensify the effects of their prescribed treatments. This practice has already been applied in certain countries and serves as a valuable example of how clear labelling can enhance consumer safety and awareness.

Ensuring the safety of bioactive ingredients

Bioactive ingredients, especially when concentrated or chemically modified for inclusion in food supplements or functional foods, can potentially introduce a set of safety challenges that require careful consideration. While ingredients like curcumin and catechins are widely regarded as safe in their natural, traditional food forms, their safety profile can change significantly when these compounds are consumed in higher concentrations or altered through processing. Given these complexities, it is important for food competent authorities to establish safety assessments tailored

Tomatoes, naturally containing lycopene. Italy

specifically for bioactive ingredients in their concentrated or modified forms which should go beyond the standard evaluations used for conventional food ingredients.

Preventing adulteration and contamination

Adulteration and contamination are significant challenges that can severely compromise the safety of food supplements and functional foods. The inclusion of unauthorized active pharmaceutical ingredients (APIs) or the presence of environmental contaminants such as heavy metals and mycotoxins could pose significant health risks to consumers. To address these, food competent authorities in some jurisdictions have implemented advanced analytical techniques for routine testing and established clear guidelines for manufacturers. These guidelines define acceptable contaminant levels and outline best practices to maintain product safety and integrity throughout the supply chain, serving as a foundation for ensuring consumer protection and product reliability.

Mitigating overdose and toxicity risks

The potential for overdose and toxicity is a critical concern, especially given the popularity of food supplements containing vitamins, minerals, and other bioactive compounds. Excessive intake of these substances can lead to serious health issues, such as hypervitaminosis or mineral toxicity. Clear dosage recommendations and explicit warnings about the risks of overconsumption could have a significant positive impact on consumers. Additionally, public education campaigns could raise awareness about the dangers of exceeding recommended dosages, particularly for vulnerable populations such as children, pregnant women, and the elderly.

Tailoring safety assessments for new and novel ingredients

As the market for food supplements and functional foods rapidly expands, there is a parallel increase in the introduction of new and novel food ingredients. These ingredients, which often lack a long history of safe consumption, present unique challenges and require rigorous safety evaluations before they can be deemed suitable for human consumption.

The novelty of these ingredients means that their potential effects on health are not fully understood, making thorough safety assessments crucial to limit unforeseen risks. In response to this growing trend, food competent authorities in various jurisdictions have developed clear and structured pathways for the approval of these ingredients. These pathways are designed to ensure that all necessary safety data such as toxicity, bioavailability, allergenicity, and potential interactions with other substances are reviewed and validated before any new food ingredient is allowed to enter the market. As products evolve through technology or manufacturing, they could be considered novel products. Therefore, the safety evaluations of such products may not rely too heavily on traditional evidence.

6.2 Addressing regulatory challenges and opportunities for food supplements and functional foods

As highlighted in Section 4, the regulation of food supplements and functional foods faces significant challenges due to a lack of clarity and consistency among countries regarding regulatory requirements, definitions, and terminology across different jurisdictions. This ambiguity creates a complex landscape that food competent authorities must navigate when applying or initiating regulatory processes for these products. Addressing these challenges is essential to ensure consumer safety, facilitate international trade, and protect public health.

For example, a product classified as a food supplement in one country might be considered a pharmaceutical product in another, depending on its composition, intended use, and claimed benefits. In addition, the evolving concept of "food as medicine" further blurs the traditional boundaries between food supplements and pharmaceutical drugs. Traditionally, the key distinction lies in their intended use: drugs are designed to prevent, diagnose, treat, or cure diseases, while food supplements are meant to support overall health and nutrition. However, advancements in nutritional science and emerging research on personalized nutrition have highlighted the therapeutic potential of certain foods and food supplements. Research has shown that specific nutrients and bioactive compounds can significantly contribute to managing health conditions and reducing disease risk. This emerging evidence raises critical questions about how to effectively regulate products that blur the line between food and medicine, ensuring they are both safe and effective without misleading consumers.

The integration of traditional medicines into modern food supplement regulations presents another layer of complexity. Many cultures have long histories of using herbal remedies and natural products for health purposes, and these traditional medicines are increasingly entering mainstream markets as food supplements. Hence, incorporating traditional knowledge while applying rigorous scientific evaluation to ensure product safety is an important factor to consider.

Furthermore, the increasing prevalence of chronic diseases, aging populations, and a more health conscious public, drive the demand for innovative food supplements and functional foods. Regulators should aim to balance encouraging innovation with ensuring consumers are protected from potential risks linked to new ingredients and formulations. Implementing robust yet flexible regulatory frameworks that can adapt to scientific advancements and market changes is crucial for supporting industry growth while maintaining high safety standards.

Efforts to address these challenges are underway, with international organizations such as the Codex Alimentarius Commission playing a pivotal role. These standards, once widely adopted, could help reduce trade barriers, ensure product safety, and provide clearer guidance for manufacturers and consumers alike. However, more work can be done in this field to fully realize these goals and address the evolving complexities of the market. It is important for national food competent authorities to collaborate closely with their counterparts in other countries, fostering a robust global food safety network that can respond effectively to emerging challenges and ensure the safety of these products worldwide.

Pineapple. Bromelain, an enzyme found in pineapple, is used as an ingredient in food supplements. Kenya

6.3 Building consumer trust

As described in Section 5, consumer perception of the safety of food supplements and functional foods is a critical factor that significantly influences purchasing decisions and overall public health. Building consumer trust hinges on transparency. It is essential to provide clear, detailed information about product ingredients, their sourcing, manufacturing processes, and the scientific evidence supporting health claims. This transparency not only empowers consumers to make informed choices but also strengthens their confidence in the safety and quality of these products.

Misleading or scientifically unsupported health claims on food supplements can erode consumer trust and blur the distinction between supplements and pharmaceuticals. To maintain credibility, providing strong scientific evidence can help consumers make informed decisions and clearly differentiate supplements from pharmaceutical products.

Given the significant influence of social media and online platforms on consumer behaviour, these channels play a pivotal role in shaping perceptions of food supplement safety and efficacy. Proactive consumer engagement by food competent authorities can be a valuable strategy for disseminating accurate information and effectively countering misinformation.

A comprehensive strategy that prioritizes transparency in product details, clear differentiation between supplements and pharmaceuticals, and proactive communication with consumers is key to building and sustaining public trust.

Two women at a fruit market, Morocco

6.4 Potential follow-up activities for food competent authorities

This report has highlighted the complexities, and the efforts needed, to ensure the safety of food supplements and functional foods. These efforts are especially critical in low- and middle-income countries (LMICs), where regulatory capacity may be limited, and the rapid influx of new products can pose potential risks to public health. To address these challenges, some follow-up activities can be considered for food competent authorities, for instance:

- Invest in **capacity-building initiatives** to enhance the regulatory capabilities of food competent authorities. This includes training programmes for regulatory personnel on the latest safety assessment methodologies, international best practices, and risk management strategies.
- Invest in **research initiatives** to better define human nutrient requirements and recommended nutrient intakes.
- Encourage the adoption of **international standards**, such as those developed by the Codex Alimentarius Commission, to harmonize regulatory approaches and facilitate global trade.
- Launch public **education campaigns** aimed at informing consumers about the safe use of food supplements and functional foods. These campaigns should focus on the importance of following dosage recommendations, understanding potential interactions with medications, and recognizing credible health claims.
- Support the development of a **regulatory framework** that encourages clear and comprehensive labelling, providing consumers with detailed information about product ingredients, sourcing, and the scientific evidence backing health claims.
- Encourage **collaboration between food competent authorities** in LMICs and their counterparts in higher-income regions. This can include sharing data on safety assessments, regulatory practices, and adverse events to build a more robust global safety network.
- Support **research initiatives** that explore the safety and efficacy of traditional medicines and novel ingredients in food supplements. This research can provide valuable insights into the cultural context of supplement use and help integrate traditional knowledge with modern scientific standards.
- Establish **innovation hubs** that bring together researchers, manufacturers, and regulators to develop safe and effective food supplements that meet local needs while adhering to international safety standards.

6.5 Conclusions

The future of food supplements and functional foods will likely be influenced by significant advancements in biotechnology, rising consumer demand for personalized products, and evolving regulatory landscapes. As the fields of nutrigenomics continue to progress, we can expect the development of even more precisely tailored products that address individual health needs at a molecular level. Ensuring the safety of these increasingly sophisticated products will require the integration of robust safety protocols alongside cutting-edge innovations.

As the food supplement and functional food sector continues to advance, regulatory frameworks must evolve in tandem. While significant progress has been made in regulating these products, ongoing efforts are essential to address the challenges posed by a rapidly changing market. By working towards greater harmonization and developing new regulatory approaches for emerging areas such as personalized nutrition, regulators can help to ensure that these products continue to be safe and beneficial for consumers worldwide. In this context, FAO will continue to monitor and remain actively engaged in the evolving field of personalized nutrition, providing proactive guidance to its Members to support safety and quality in the field of food supplements and functional foods while ensuring consumer protection.

Children eating a school meal. Lao People's Democratic Republic

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Rome, Italy

ISBN 978-92-5-139611-7

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CD4280EN/1/04.25