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Review

The current use and evolving landscape of nutraceuticals

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ABSTRACT

The nutraceutical market is currently a high-impact multi-billion-dollar industry, and it is anticipated to grow rapidly over the next decade. Nutraceuticals comprise diverse food-derived product categories that have become widespread due to increased consumer awareness of potential health benefits and the need for improved wellness. This targeted review is designed to identify the current global trends, market opportunities, and regulations that drive the nutraceutical industry. Safety and efficacy concerns are also explored with a view to highlighting areas that necessitate further research and oversight. Key drivers of the nutraceutical market include aging populations, consumer awareness, consumer lifestyle, increasing cost of healthcare, and marketing channels. Although some nutraceuticals hold promising preventive and therapeutic opportunities, there is a lack of a universal definition and regulatory framework among countries. Moreover, there is a lack of adequate evidence for their efficacy, safety, and effectiveness, which was even further highlighted during the ongoing coronavirus pandemic. Future prospective epidemiological studies can delineate the health impact of nutraceuticals and help set the scientific basis and rationale foundation for clinical trials, reducing the time and cost of trials themselves. Together, an understanding of the key drivers of the nutraceutical market alongside a consistent and well-defined regulatory framework will provide further opportunities for growth, expansion, and segmentation of nutraceuticals applications.

1. Introduction

Over the last few decades, a new health paradigm has emerged that places an emphasis on diet and nutrition. A more health-conscious consumer pool with increased expendable income in the Western world has shifted consumer trends towards the purchase of dietary supplements, functional foods, and nutraceuticals with the intention of maintaining optimal health and preventing negative health

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consequences [1,2]. Nutraceuticals are an innovative concept and an umbrella term for nutritive supplement-like products with health benefits that go beyond their basic nutritional value. Over the past few decades, several bioactive constituents including food extracts or phytochemical-enriched extracts were developed and marketed as pharmaceutical formulations, such as capsules, solutions, powders, gels, etc. Epidemiological studies suggest an association between phytochemical constituents in nutraceuticals and an improvement in health to some extent [3]. On the same note, plant-derived and other natural compounds have demonstrated their potential, yielding a pool of molecules that may exhibit therapeutic properties [4–7] and are set to be a continuous source of new drugs for the foreseeable future [8]. Diverse food products based on the bioactivities of plant compounds are also being developed [9] with the intent maintain health and prevent disease, and to enhance overall health and well-being. However, the supporting scientific evidence for metabolism and health benefits of nutraceuticals is scarce overall. The nutraceutical market has received an unforeseen worldwide response and is currently a multi-billion industry [10]. The global nutraceutical market was valued at around USD 383 billion (EUR 311 billion) in 2016 and was expected to reach around USD 561 billion by 2022 (EUR 456 billion) [3] prior to the coronavirus diseases 2019 (COVID-19) pandemic. With the increase in health awareness, including lifestyle changes, across the globe, the nutraceutical industry is further anticipated to evolve offering new opportunities for innovative products based on consumer interest in health-enhancing foods.

Despite rising public interest in nutraceuticals, the lack of universally accepted definitions and diverse regulatory frameworks remains a challenge. Regulation of nutraceuticals varies across the globe and is unregulated in some countries. There is a need to understand the current market trends for nutraceuticals, along with variations in regulatory frameworks across different countries. This review identifies the current trends and regulations that drive the nutraceutical industry. It then explores opportunities to enhance the market value of nutraceuticals.

2. Defining nutraceuticals

Defining nutraceuticals has been challenging, whereby no one global definition is accepted despite the proposals for a framework to do so [11,12]. This is largely due to differences in legislation governing the sales, marketing, safety, and efficacy of such products in different regions around the world along with cultural influence on the use of these products. One challenge is that nutraceuticals, dietary supplements, and functional foods are often discussed together but it is important to recognize that these types of products differ in their classification, albeit fluid in their designation. Nutraceuticals contain nutrients or extracts that are generally derived from foods or sources of natural origin that are intended for prophylactic or therapeutic applications [11,13]. Nutraceuticals include diverse product categories such as herbal and botanical products, food-derived active compounds or related by-products, vitamin and minerals mixes, protein powders or even components of dietary supplements [14,15]. On the other hand, dietary supplements are nutrients or compounds that are intended to support nutrient intake, prevent deficiencies, and may occasionally exhibit therapeutic benefits even if that is not their intended function. Despite their common appearance as tablets, capsules, gels, syrups or extracts, nutraceuticals and dietary supplements are generally considered nonpharmaceutical and nonmedicinal products [13].

Functional foods can be loosely defined as foods that may exert positive health benefits upon consumption beyond their basic nutritional values. However, functional foods do not have the capacity to treat or prevent illnesses by themselves and these products are not essential to the diet [16]. Functional foods may naturally contain proponents or added ingredients that may promote optimal health or reduce the risk of disease. It is also possible that a food-derived component can be used to produce novel products that may fit into multiple categories. A bioactive constituent derived from a herb may be incorporated into a food to product a functional food or it could be encapsulated to manufacture nutraceuticals. Hence why these general distinctions between these products cause issues for regulatory authorities.

Other related food classifications do exist such as medical foods or fortified foods. Medical foods are formulated for the dietary management of diseases with distinct nutritional requirements that are otherwise not met by normal dietary intake alone, such as pancreatic exocrine insufficiency, cachexia, or hypercysteinemia [17]. This category of foods is considered therapeutic agents under the Orphan Drug Act of 1988 in the United States (U.S.) [17]. Whereas fortified foods are a public health intervention whereby everyday foods such as cereal, milk, bread, and pasta have had nutrients, vitamins or minerals added to them such as vitamin D, calcium or iron with the intention of preventing nutritional deficiencies. This has been a successful approach in the U.S. and other countries for the prevention of rickets and pellagra [18].

3. Insights into the global market

The nutraceutical industry is flourishing and diversifying rapidly (Fig. 1). The current market trends in healthcare are inclined towards preventive health care strategies, rather than treatment and disease management. This trend is anticipated to grow as healthcare costs increase in both developing and developed countries. Increasing occurrence of chronic diseases coupled with the high cost of healthcare interventions is creating a demand for personalized nutrition, along with a boost in demand for nutraceuticals. Additionally, there is a shift in consumer preference from synthetic pharmaceutical preparations to natural and organic nutraceutical ingredients [19]. According to a report by Klynveld Peat Marwick Goerdeler (KPMG), the nutraceuticals market was projected to be worth approximately $250 billion by 2018. In addition, the growth of nutraceutical industry was predicted to be at about 7.3% compound annual growth rate (CAGR) from 2015 to 2021, with the market anticipated to be valued over $275 billion by 2021. Indeed, we now know that by 2019 the nutraceutical market had exceeded these values and was worth $382 billion, and was worth $412 billion in 2020 [20]. Further, the value of the nutraceuticals industry is already more than 25% of the value of the pharmaceutical industry [21]. U.S., Japan, and Germany are key drivers of the nutraceutical market because of high product adoption rate in these developed economies [20]. Finally, an above average growth in nutraceutical market is expected for China, India, and Brazil over the coming decades with the fastest predicted CAGR [20].

3.1. North America

The U.S. is one of the largest consumers of nutraceuticals and has been the world's largest nutraceutical market for over a decade [32–34]. By all forecasts, the U.S. nutraceutical market is expected to experience an increase in the coming years as a result of a continuously growing demand [34]. Indeed, the U.S. market for nutraceuticals is anticipated to increase at a CAGR ranging from 5.5% to 6.0% from 2016 to 2022, with a value of more than USD 95 billion (~EUR 77 billion) [35]. The growth in nutraceuticals in the US is in large part due to innovations in the sector promoting wellness products including dietary supplements, immune-boosting supplements, energy drinks, protein supplements, probiotics, and prebiotics among a host of other products [36].

Canada has also emerged as a global supplier of nutraceuticals, with more than 750 Canadian companies specialized in functional foods and natural health products (FFNHP), attributing to more than USD 11 billion in revenue in 2011. Overall, there were over 32,000 FFNHPs on the market, with natural health products accounting for a majority of (85%) of these product lines (Statistics Canada, 2011). Between 2019 and 2024, the Canadian nutraceuticals market is expected to see a growth rate of 5.62%, due to the rising demand for nutraceuticals with potential health benefits [37]. The Natural Health Products Directorate

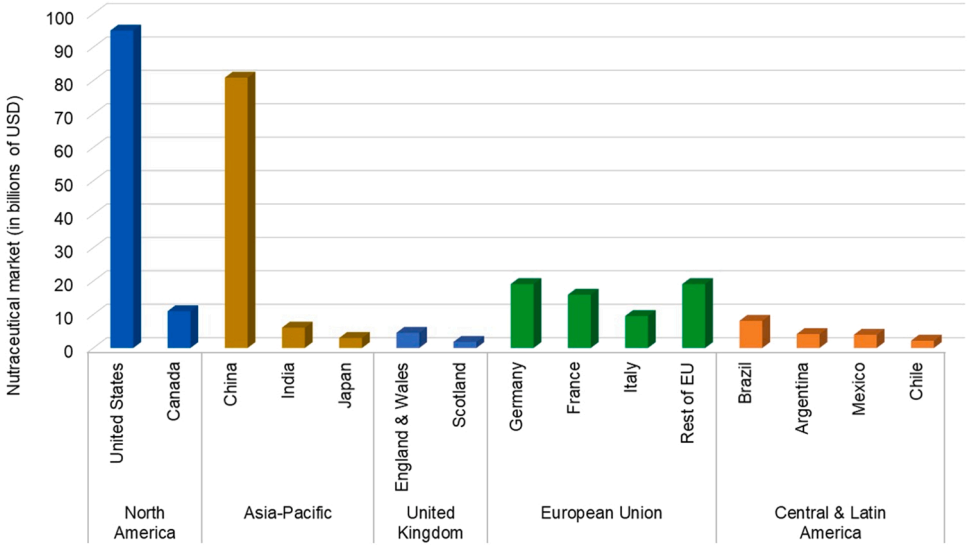

Fig. 1. The global nutraceutical market and major consumers approximated using 2017 estimates in billions of USD from the following Refs. [22–31].

(NHPD), now known as the Natural and Non-prescription Health Products Directorate (NNHPD) was introduced in 2004. In its first six years, the NNHPD granted over 27,900 product licenses, representing over 43,000 natural health products [38], indicating the great demand and market growth for natural health products in Canada in the late 2000's.

3.2. Asia-Pacific

The Asia-Pacific nutraceuticals product market is growing rapidly, accounting for 31% of the nutraceutical marker value in 2019 [20] and is estimated to reach USD 89.6 billion by 2021, increasing at a CAGR of 8.52% in the forecast period of 2016–2021 [39]. The functional food ingredients market is anticipated to increase at a CAGR of 5.9% between 2016 and 2026 and is anticipated to have a market share of USD 5.04 billion by the end of 2026 [39].

The nutraceutical market in China is now the second largest and one of the fastest growing markets in the world. Based on a 2017 report by Transparency Market Research, Cision, China generated 39.5% (80.9 billion USD), of the total nutraceuticals market worth USD 204.8 billion in the Asia-Pacific region. China is responsible for only 2% of retail nutraceutical products on the global market, however, China exports 65% of the raw materials the manufacturing of food health products internationally [22]. Despite such high rates of annual growth, its growth is obscured by ambiguities around the meaning and management of nutraceuticals. Cross-border e-commerce (CBEC) is used as a medium for retail distribution of nutraceutical products outside China. However, since April 2016, the Chinese government has implemented CBEC policies, such as eliminating imposing new customs clearance requirements, tax concessions, and restricting nutraceuticals sold without registration with CBEC. Because of the regulatory complexities and ambiguities surrounding nutraceuticals, it is difficult to provide true market estimates. Despite the regulatory stringencies, the concept of Yin-Yang may be a driving force for Chinese nutraceutical market, central to Chinese culture, diet, and traditional Chinese Medicine. In addition, a balanced regulatory and marketing environment will lay foundation for sustained growth [40].

Japan is another large continually growing market for nutraceuticals [34], accounting for approximately a fifth of the Asia-Pacific nutraceutical market share [41]. In 1991, the government of Japan introduced the Foods for Specified Health Use (FOSHU) regulatory process. Each FOSHU category of claims also includes non-FOSHU functional foods on the market that can use off-label health-related claims. The total retail sales of approved FOSHU products was 6.2 billion USD in 2007 [26]. The non-FOSHU functional foods market in Japan is considerably larger compared to FOSHU products [42,43].

The nutraceuticals industry in India is also another of the rapidly flourishing markets in the Asia-Pacific region. The nutraceuticals industry in India was estimated to be worth USD 2.2–2.8 billion in 2015 and was predicted to grow at 20% to USD 6.1 billion by 2019–2020. Such is the level of growth of India's nutraceutical market that is now projected to reach USD 8.5 billion by 2022 [23–25]. The expansion of this industry over the past decade is the result of significant lifestyle changes by the Indian population. Fast foods and packaged foods, along with sedentary lifestyles have resulted in the increased incidence of lifestyle diseases such as hypertension, hyperlipidemia, diabetes, cardiovascular diseases, and obesity. As a result, Indian consumers, predominantly those of higher socio-economic status, are inclined towards nutraceuticals as alternatives to drugs for improving health and/or preventing diseases [24].

3.3. United Kingdom and European Union

This region is the third largest market for nutraceuticals in the world, with Germany, France, and Italy being the key markets in this region. Further, the United Kingdom (UK) and Spain have emerged as key test markets [44]. The reason for restrained growth compared to North America and Asia-Pacific is due to its stringent regulatory approval procedures, along with high-cost of research and development, ultimately, resulting in higher product prices [27]. The European nutraceutical market was valued around USD 79.7 billion in 2016. Prior to the coronavirus pandemic, the European market was projected to increase at a CAGR of 6.39% from 2018 to 2023. Omega-3 fatty acids are among the most consumed nutraceuticals in this region [27]. Besides the scientific research tailored to the needs of the customers, technological developments are also driving the market for these products in Europe [28].

Germany is a major market, with the largest market share of 23.02% in Europe, followed by UK and France [27,28]. The German nutraceutical market was valued at USD 11.0 billion in 2016 with a CAGR of 6.37%. The contributing factor for Germany's growth is the increasing desire of Germans to support their general health and wellbeing or to target specific health conditions through supplements. Major companies in the nutraceuticals and functional food sector in Germany include Danone Deutschland GmbH and Wrigley GmbH. Consumers in UK are more inclined towards high protein products for their health-promoting properties [27], which is already a competitive market worth over USD

140 million that may now increase due to an increased interest in protein hydrolysates and their potential health benefits in the infant nutrition, sports nutrition, and the nutraceutical markets [29].

3.4. Central and Latin America

Latin America is considered the fourth largest market for nutraceuticals in the world, with Brazil and Argentina being the largest markets in Latin America. Nutraceuticals are a rapidly expanding market due to a growing trend of healthy living among people. The nutraceutical market in Brazil reached sales of USD 13 billion in 2005 [45] and a projected value of 13.25 billion was forecast for 2021 with a CAGR of 7.96% predicted over the coming years leading to a market value of USD 19.4 billion by 2026. [30]. The Latin American region has seen substantial growth opportunities in nutraceutical industry due to its favorable economic growth and changes in lifestyle over the past decades [30,45], in addition to abundance of natural resources, which have helped the nutraceuticals market in Brazil to flourish over the past few years, with a market share of 5.3% in the global revenues. Moreover, consumers inclination towards consumption of healthy foods and supplements has increased in the older and middle-class populations, further boosting the sales of nutraceuticals throughout the country [46]. The Amazon due to its incredible biodiversity may also be a source of natural health products and nutraceuticals in time if responsibly managed [31].

3.5. The impact of the COVID-19 pandemic on the global nutraceutical market

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 with devastating consequences worldwide. COVID-19 is a disease associated with a wide range of symptoms, that mostly affect the respiratory system. COVID-19 can range from an asymptomatic infection to severe disease, acute respiratory syndrome, and may be fatal [47]. Researchers have been scrambling to repurpose drugs and develop novel therapeutics with limited success [48]. Among those is dietary supplements and nutraceuticals [13,49], which has profoundly impacted their sales globally in 2020 [2]. Sales increased due to individuals seeking additional protection from infection and severe disease by purchasing nutraceuticals with potential health benefits against respiratory infections and related symptomology [50]. For example, in the U.S., sales of supplements and nutraceuticals grew by 51.2% at the start of the pandemic in March 2020 compared to 2019 and remained high as evident by the 16.7% growth in July 2020 [51]. In Europe [51], China [52], and India [53], similar trends were observed. The potential use of nutraceuticals and supplements during the pandemic was a topic of enthusiastic debate on social media [54] and in the literature [13,55,56]. In this context, intense debate on the efficacy and safety of nutraceuticals for the prevention and/or treatment of COVID-19 is ongoing, and sales of nutraceuticals are expected to remain high in the first half of 2021, albeit at much lower level than the sales achieved at the beginning of the pandemic [57]. While these levels of sales are unsustainable, they may still affect projections of market growth over the coming years.

4. Key drivers of the nutraceutical market

The nutraceutical industry is largely consumer driven and will continue to grow because it fits within the current lifestyle of developing and developed countries. An understanding of the key drivers of the nutraceutical market, will provide further opportunities for growth, expansion, and segmentation (Fig. 2).

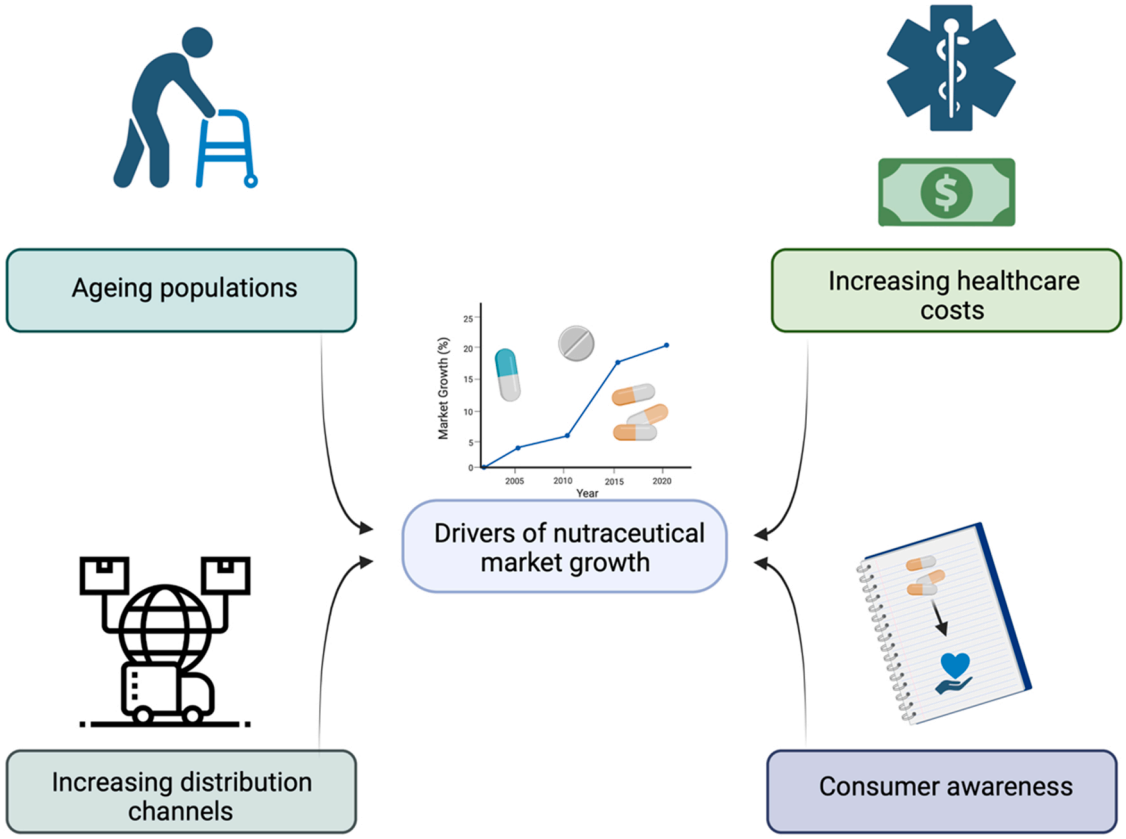

Fig. 2. Drivers of the growth of the global nutraceutical market are multifactorial but can be characterized by four main themes including an ageing population, increasing costs of healthcare, increasing distribution channels, and consumer awareness.

4.1. Aging population

Aging represents a natural biological process that results in certain ostensible chronic medical conditions, such as Alzheimer's disease, dementia, respiratory problems, hypertension, CVD, osteoporosis, and cataracts. Due to the increasing growth of elderly populations throughout the world, many healthcare systems will struggle to maintain a healthy lifespan for their elderly citizens. However, healthy aging can be greatly aided mainly by consuming a healthy and nutritious diet, along with an active and correct lifestyle [58–61]. Nutraceuticals have the potential to protect against aging and stress. In fact, they have shown to be beneficial in prevention of age-related chronic conditions, thereby promoting longevity and overall well-being for the elderly population [62].

4.2. Consumer awareness

This growth is being driven by an increase in consumer awareness of health; including awareness for the benefits of a nutritional diet, improved lifestyles, education programs, and accelerated health awareness information disseminated through social media. Indeed, consumer awareness has also driven the growth of "wellness" products [63]. This area of the nutraceutical market for the US and Canada is anticipated to grow steadily as consumers show increased interest in improving their lifestyles. In the Asia-Pacific region, the growth in nutraceuticals market is also attributed to rise in disposable income and middle-class consumers, urbanization, and increase in incidence of lifestyle-related diseases such as hypertension, diabetes, and cardiovascular diseases [39,64]. Consumer awareness is largely what drove the increased growth of the nutraceutical market at the beginning of the COVID-19 pandemic.

4.3. Increasing cost of healthcare

Changes in the healthcare industry, along with increasing healthcare and drug costs are also triggering the growth of the nutraceuticals market. Consumers are increasingly inclined to look towards nutraceuticals not only to improve their health, but also to save money on expensive over-the-counter and prescription drugs. In this sense, a substantial increase in the nutraceutical market has been seen in the U.S. and Canada, followed by Asia-Pacific and Mexico [65].

4.4. Increasing number of distribution channels

The use of different distribution channels provides opportunities for targeting different market segments and increasing nutraceutical sales. Different distribution channels currently being used include online selling, direct marketing, and business-to-business (B2B) channels and business-to-consumer (B2C) channels. The growth of online sales of nutraceutical products can be attributed to the growing number of internet users and growing interest of many of them in online shopping, even in case of health products due to convenience. Based on the Euromonitor International Research report, the global vitamin and supplement market accounted for about EUR 60.2 billion in internet sales contributing a substantial share in the growth of supplement demand. About 44% of the consumers purchase nutraceuticals online globally. Similar sales trends online are anticipated for India, being the second largest growing online population [66]. Some companies use direct marketing approaches with specialized retail stores for consumers. These specialized retail stores are positively perceived by consumers, and they often tend to buy food and health supplements from a specialized store rather than from medical or other stores. For example, Himalaya, an Indian company, successfully used this approach for its nutraceutical products. Digital marketing such as email marketing, social media, mobile applications (Apps), e-marketing, websites, virtual sales representatives, and closed platforms are becoming powerful tools for marketing nutraceuticals and nutritional supplements. These strategies enable the marketers to target and track various aspects of marketing, tailoring the market strategy based on consumer needs. B2B and B2C e-commerce had limited success in health-related products demonstrated promising growth [67]. In recent years, multi-level marketing of supplements and nutraceuticals has dramatically increased [63]. Multi-level marketing is a strategy whereby independent distributors sell products directly to the consumer from their own home, online, or via telecommunications. Distributors can be both rewarded for their sales and if they can recruit additional individuals to become distributors. However, while not illegal, this form of supplement distribution is highly unethical and some of the products may be unsafe or simply unnecessary [63,68].

5. Benefits of nutraceuticals

Nutraceuticals hold promising opportunities for improving underlying health conditions, alleviating symptoms, and improving overall well-being. Existing pre-clinical studies demonstrate beneficial effects of many nutraceuticals, including phytochemical enriched and food extracts as means of reducing inflammation and oxidation [69] and nutraceuticals of marine origin that go beyond omega-3 fatty acids [70,71]. There have also been attempts to formulate recommendations prepared by experts from the International Lipid Expert Panel (ILEP) for the application of nutraceuticals for different risk factors, conditions, and diseases such as lipid disorders, inflammation, statin intolerances or even heart failure [72–75]. With more research, there is also potential for nutraceuticals to be used as a prophylactic or adjunct treatment of a variety of chronic conditions, including heart diseases, cancers, Alzheimer's disease, mental health, and metabolic disorders, and in many cases robust clinical efficacy evidence is already available [74,76–79]. Contemporary consumers are educated, health conscious, and more aware of their lifestyle choices. Therefore, consumers want safe and effective nutraceuticals that enhance their health and well-being or act as preventive measures that will help them to combat the various non-communicable diseases associated with unhealthy living and aging.

6. Current regulations specific to nutraceuticals

The concept of nutraceuticals has been proposed as a modern approach leaning on nutritional science and its definition is still in the gray area between food, food supplements, and pharmaceuticals (Table 1). Therefore, the definition of nutraceuticals and an appropriate assessment of their potential in medicine is still the subject of debate and far from being consistent and accepted, which is a legislative challenge worldwide. The blurred lines between what is considered a nutraceutical versus a dietary supplement or functional food can contribute to how regulatory authorities view these products and legislate for them. For example, functional foods in Japan are defined based on their use of natural ingredients, whereas in the U.S., they can also contain ingredients produced with biotechnology. These discrepancies in definitions between the different accepted definitions of nutraceuticals across different countries and their regulatory aspects is a critical issue. Furthermore, the lack of globally harmonized legislation and regulations are another serious issue for nutraceutical growth and distribution. The existence of different regulations can result in ambiguity and inconsistency, especially when defining products present in multiple countries [11].

The milestone for examining the efficacy and safety of food was set by the United Nations Food and Agricultural Organization (FAO) and the World Health Organization (WHO) in the Codex Alimentarius in 1992. These internationally recognized guidelines establish general rules for producing and marketing foodstuffs and their derivatives are used by many countries. These guidelines define health claims in terms of nutrient function, enhanced function, and the reduction of risk [11]. Globally, there are various standards set among nations and regions.

Table 1
Regulatory framework and pertinent policies concerning nutraceuticals in some of the key global markets.

Country	Definition	Pertinent acts	Applicable to
Australia (Varghese and Mishal, 2014)	Complementary medicines	The Therapeutics Goods Act, 1989, implemented in 1991; governed by the Department of Health and Ageing.	• herbal medicines • vitamins and minerals • nutritional supplements • homeopathic medicines • aromatherapy products • traditional medicines
Canada ([11]; Varghese and Mishal, 2014)	Natural Health Products	The Natural Health Product Regulations (2004) by Health Canada; governed by the Food and Drugs Authority of Canada and the Natural and Non-prescription Health Products Directorate (NNHPD).	• vitamins and minerals • herbal remedies • homeopathic medicines • traditional Chinese medicines, probiotics • amino acids and fatty acids
China (Varghese and Mishal, 2014; [22])	Common foods in standardized dose and method of delivery to improve efficacy and health benefits	No specific act. China's State Food and Drug Administration (CFDA) conducts all affairs relating to health foods. Testing protocol such as complete animal or human clinical study is required for approval. A "blue hat" label is applied to foods deemed functional.	• any common food deemed to be functional
European Union [14]	Food supplements, which are defined as concentrated sources of nutrients and other substances with nutritional benefits	European Food and Safety Authority (EFSA) Directive 2002/46/EC	• proteins • vitamins and minerals • other substances with nutritional benefits
India (Varghese and Mishal, 2014)	Foods for special dietary use, specially processed or formulated, to satisfy particular dietary requirements, not including any drug and can only be used for oral administration. They can be used as conventional foods, which cannot claim to cure any specific disease, but can claim indirect health benefits.	Food Safety and Standards Act (2006)	• plants or botanicals or their parts in the form of powder concentrate or extract in water, ethyl alcohol or hydro-alcoholic extract, single or combination. • minerals or vitamins or proteins or metals or their compounds or amino acids in amounts not exceeding the recommended daily allowance for Indians or enzymes (within permissible limits) • substances from animal origin.
Japan [90]	Food for Specified Health Uses	The Foods for Specified Health Use (FOSHU) regulatory process	• dietary substances for use by humans that supplement the diet by increasing total dietary intake. • food with health function (not substantiated on scientific evidence) • food with certain effectiveness, but without established mechanism of the effective element for the function
Latin America (Colombia, Brazil, Argentina) [45]	Functional foods	ANVISA (Agencia Nacional de Vigilancia Sanitaria) in Brazil.INVIMA (The National Food and Drug Surveillance Institute) in Colombia.	• fiber • probiotics • flavonoids • plant sterols • fatty acids.
Russia (Varghese and Mishal, 2014)	Foodstuffs with clinically proven effectiveness that are recommended prophylactically and for the prevention of pharmaceutical therapy induced side-effects and the achievement of complete remission.	Ministry of Healthcare and Social Development's #1898, (1997): The Procedure for the Examination and Health Certification of Active Dietary Supplement regulated under Biologically Active Dietary Supplements (BADS)	• vitamins and minerals • amino acids • dietary fibers • bioflavonoid • alkaloids • essential oils • polysaccharides
United States (Varghese and Mishal, 2014)	Dietary supplements, products (other than tobacco) intended to supplement the diet that contains one or more of the main dietary ingredients.	Dietary Supplement, Health and Education Act (DSHEA) of 1994	Concentrates, metabolites, constituent, extract or combination of: • vitamins and minerals • amino acids • herbs or other botanicals

Current European regulations monitored by the European Food Safety Authority (EFSA) include food supplements but do not officially mention or recognize the term nutraceutical. There is also no distinction between food supplements and nutraceuticals for the purpose of obtaining a beneficial health claim application on new products. Indeed, medicinal claims for nutraceuticals are required to conform with regulatory requirements (efficacy, safety, and quality testing) of other medicinal products. Therefore, nutraceuticals can either be monitored as a food component under Directive 2002/46/EC [81] or a medicinal product under Directive 2004/27/EC [82]. The safety of supplements is monitored under Directive 2002/46/EC by EFSA and the European commission [81]. In an effort to synchronize various legislations in relation to nutrition health claims, Regulation EC 1924/2006 was put into effect [83]. The aim of this regulation was to instill confidence among consumers by providing understandable information and assuring the safety and efficacy of products. Health claims can now only be

placed on product labels or packaging if they are compliant with EFSA guidelines [83,84]. Europe is also home to the European Nutraceutical Association (ENA) since 2005, which serves as a non-profit organization to evaluate emerging evidence in relation to nutraceuticals [85].

In the U.S., the Food and Drug Administration (FDA) are not entirely responsible for nutraceuticals, but they are monitored by the Dietary Supplement Health and Education Act [86] and the Food and Drug Administration Modernization Act of 1997 (FDAMA) [87]. Notably, in the case of a botanical preparation, they do not require clinical testing before marketing, separate from a botanical drug. For a botanical preparation to be considered a drug substance, intended for diagnostic, preventive, or curative purposes, the manufacturer must provide clinical efficacy and safety data for over-the-counter drug review. According to the DSHEA, the manufacturer bears the responsibility to ensure the safety of nutraceuticals. The nutraceutical intended for marketing should comply with the following criteria: *(i) be intended for ingestion in form of pill, capsule, tablet, powder or liquid form, (ii). not be represented for use as a conventional food or as sole item of a meal/diet, and (iii) be labeled as a "dietary supplement"*. Due to the need to increase surveillance on the growing supplement and nutraceuticals markets, the FDA established the Office of Dietary Supplement Programs (ODSP). However, there is significant concern that these legislations do not provide adequate protection to consumers as the manufacturers are responsible for ensuring a product's safety and efficacy before production and marketing [11,13]. Manufacturers are not required to seek approval or register their product with the FDA prior to reaching the market. This potentially place the consumer at risk to unsafe on inefficacious products that lack preclinical and clinical evidence.

On the contrary, in Canada, the regulation of nutraceuticals is governed by the Food and Drugs Authority of Health Canada and is regulated more like a drug than as a food category. The category comprises homeopathic medicines, herbal remedies, vitamins and minerals, traditional Chinese medicines, probiotics, and other products (e.g., amino acids and fatty acids) [11].

Other countries do not have any specific regulations. For example, Indian regulations do not provide any specific legal status to nutraceuticals. The Food Safety and Standards Act (FSSA) established in 2006 does not distinguish between functional foods, nutraceuticals, and dietary supplements [88]. Each of these products is indicated as food for a special dietary application. In India, Ayurveda is an entire field of natural medicinal products that has been practiced for thousands of years and is considered a tested system for supervised administration of natural products [89]. In Asia-Pacific region, Japan, was among the first countries to face the issue of regulating food supplements and foodstuff by their regulatory authority, the Foods for Specified Health Use (FOSHU) [90].

Many other countries, such as Australia or China, regulate nutraceuticals simply as a category of food. For some countries including Colombia, Brazil, and Argentina, a simple registration-based approach to local authority is used, and a notification-based approach is valid in Mexico and Chile [11]. Brazil, China and Taiwan, also have stricter requirements, where prior to registration, a complete animal or human clinical study is required [11].

The Russian Federation Food Security Doctrine regulates nutraceuticals under Biologically Active Dietary Supplements (BADS) [91]. Nutraceuticals are defined as foodstuffs with clinically proven effectiveness recommended for prophylactic use to prevent side effects induced by pharmaceutical products and the achievement of complete remission. The definition includes vitamins, minerals, amino acids, dietary fibers, and para-pharmaceuticals (bioflavonoid, alkaloids, essential oils, polysaccharides) [91].

The COVID-19 pandemic has highlighted that greater regulatory oversight and enforcement is required for nutraceuticals, dietary supplements, and functional foods internationally. During the pandemic, several products were advertised as prophylactics, therapeutics, and even cures for COVID-19 despite a clear lack of evidence for safety or efficacy. In the U.S. for example, oleandrin was proposed as a supplement, which could have been lethal if consumed [13]. This along with many other examples prompted the FDA and Health Canada to issue several warnings to various companies for false advertising and mislabeling their products, and to prevent harm to consumers [13,92]. While this shows an example of enforcement of regulatory oversight in action in the U.S. and Canada, there is certainly room for improvement to prevent such products from reaching consumers in the first place.

7. Concerns regarding nutraceutical safety and efficacy

Nutraceuticals have the potential to partially prevent or co-treat various health conditions. However, there is often a lack of adequate information to properly substantiate the efficacy, safety, and effectiveness of nutraceuticals, presenting concerns regarding nutraceutical use and there can be issues with how to classify such a product if being used for medicinal purposes. Most medicinal or nutritional claims are uncorroborated due to a lack of evidence on possible mechanisms of action and a lack of randomized clinical trials to confirm the claimed beneficial health effects of the specific pathological conditions. Furthermore, in vitro data reported in the literature, often focus on single food constituents (micronutrients or secondary metabolites). Such studies assume that the studied micronutrients or secondary metabolites can be generally considered safe as they are derived from commonly used food components; this, however, needs to be validated by rigorous studies. Therefore, it is crucial to conduct clinical trials to thoroughly study both the efficacy and safety, and to gain a better understanding of the mechanism of action and bioavailability of nutraceuticals. Monitoring the production of nutraceuticals is a critical step that lacks considerable oversight worldwide.

Nutraceuticals can be toxic to consumers if they become contaminated with heavy metals, metalloids, mycotoxins, allergens, fertilizers, pesticides or non-product residues from toxic plants during production. The risk of adverse pharmacokinetic or pharmacodynamic interactions between nutraceuticals and therapeutics can occur [93,94], which is worrying considering that patients rarely disclose their consumption of supplements to their physicians [95]. Indeed, several common examples exist. Products containing peppermint oil can interact with cytochrome P450 isoforms, which may modify the metabolism of various drugs [96,97]. Some foods and their nutraceutical products that contain tyramine in high doses (>10 mg), such as yeast containing supplements, are known to interact with monoamine oxidase drug inhibitors that are used to treat depression. These adverse interactions can lead to cardiac arrhythmias, hyperthermia, cerebral hemorrhage, or fatal hypertensive crisis [98]. Moreover, toxic element contamination was detected in several natural health products and supplements [99]. Natural botanical toxicants are also of serious concern whether used as herbal remedies or incorporated into foods, tonics, supplements, or nutraceuticals. For example, *Aristolochia* are a family of herbs that have been consumed for the treatment of seizures among other conditions particularly in traditional Chinese medicine. These plants are known to be toxic and carcinogenic in some individuals if consumed, a history that has been well documented by Grollman and Marcus [100]. Indeed, the oleandrin example during the coronavirus pandemic is just another example of the potential danger of unregulated use of plants, herbs, and derived products that may contain natural botanical toxicants. These examples highlight the importance of monitoring the production, consumption, safety, and efficacy of nutraceuticals that may contain these constituents. Indeed, good manufacturing practices and safety monitoring should be enforced to ensure that consumers can trust the products they consume.

Rapidly emerging novel products have also become an area of concern, particularly in relation to how legislation should view the product with regards to regulation and safety. One emerging area of product development that has caused concern and can serve as an example of how legislating the field has become difficult is the

cannabidiol (CBD) industry. Cannabidiol is a phytocannabinoid extracted from *Cannabis* plants and mixed with an edible oil such as sunflower oil. Cannabidiol differs from marijuana products as it does not contain the psychoactive isomer of Δ^9-tetrahydrocannabinol (THC) [101]. Increased interest in the use of CBD for medicinal purposes means the CBD market is currently worth USD 9.67 million but is expected to rise to USD 5.3 billion by 2025 with a staggering CAGR of 40.4% [102]. CBD is believed to have therapeutic effects for numerous conditions and has been used so alleviate pain for various diseases such as cancer [103]. In June 2018, the first plant-derived pharmaceutical grade CBD oil (Epidiolex®) was approved for use by the FDA for epileptic disorders such as Dravet syndrome or Lennox-Gastaut syndrome in children [104,105]. Additional medical indications that have some supporting evidence for the use of CBD products include anxiety disorders, schizophrenia, and Parkinson's disease [101]. While this is very positive, many popular uses of CBD are not supported by clinical research. Indeed, it is not unheard of that CBD products have been a cause of serious adverse reactions [106] and there is a paucity of human clinical trials. For trials that have occurred, it appears that CBD is mostly well tolerated and non-toxic, but there may be cause for concern for interactions with other medications as demonstrated in clinical trials of epileptic conditions [107].

The CBD industry has created a difficult situation with regards to how these products should be classified and health claims, concerns of safety and efficacy, and murky legality has been a considerable issue to date [108]. One issue is that CBD can now be purchased as oils, capsules, ointments, creams, or gummies, it can be incorporated into fruit drinks and coffee, and it is even available as a product for pet consumption. This causes a classification conundrum for regulatory authorities. Defining whether these products are supplements, nutraceuticals, functional foods or medicinal products is a challenge. In 2018, industrial hemp (*Cannabis* plant with less 0.3% THC or less by dry weight) was removed from the U.S. Agriculture Improvement Act from Schedule I of the Controlled Substances Act. This allowed hemp to be classified as an agricultural commodity, which lead to an increase in the sales of hemp-derived CBD supplements for consumption with purported benefits that far exceed the available evidence to support such claims [109]. Approval of Epidiolex® by the FDA, appears to inadvertently give some credibility to claims for CBD in relation to other conditions such as cancer [101,109]. In Europe, all CBD products are currently classified as "novel foods" by the EFSA as a history of safe consumption has not been demonstrated [110] as required by the recently amended Regulation (EU) 2015/2283 and previous iterations [111]. Currently, no CBD products have been approved by EFSA, despite several products being readily available for purchase in E.U countries.

In the U.S., products containing THC or CBD cannot be defined as dietary supplements and cannot be added to foods intended for human or animal consumption under the Federal Food, Drug, and Cosmetic Act [112]. However, the FDA does allow for some use of non-THC-containing CBD constituents in foods and dietary supplements if all other stipulations under the Federal Food, Drug, and Cosmetic Act are met [113]. Indeed, inappropriate use, sale, production, and marketing of such products has prompted the FDA to act and issue several warnings to noncompliant companies and individuals [114]. While there appears to be a considerable gap in the regulatory framework of these products, in an acknowledgment of the growth and interest in the field, the FDA has issued guidance to support those in the industry including guidance on how clinical trials should be conducted [115]. At a governmental level, the Hemp Access and Consumer Safety Act has been filed by Senators in May 2021 [116], indicating that there will be considerable shifts in legislation in this product area over the coming years. To summarize, regulation of CBD products as supplements, foods, or medicines, is challenging but an unregulated CBD market is a potential threat to public health. As stated by Hurd et al. at a minimum, products must have proper and controlled manufacturing, standardized testing, accurate labeling, and the industry must follow regulations set in place [107].

While the regulation of dietary supplements and nutraceuticals is challenging, there is a pathway for the approval of some nutraceuticals that can provide evidence of safety and efficacy. One such example of a successful product is Fruitflow® manufactured by Provexis. This is an antiplatelet tomato-based nutraceutical that has been granted permission to apply a health claim on the product by EFSA for the maintenance of normal platelet aggregation [117,118]. This was the first product of its kind to be granted such a health claim and it won't be the last. However, multiple clinical trials were conducted in order to be granted a health claim and the product is not necessarily recognized as a nutraceutical but rather a novel food or functional ingredient [119]. In 2018, EFSA approved a novel shrimp (*Pandalus borealis*) peptide concentrate as a novel food, with the intention of making nutraceuticals [120] based on the unpublished clinical trial evidence provided that indicated the product was safe to consume [121]. The product is manufactured by protein proteolysis of the heads and shells for hypotensive management. The peptide formulation is made by Medfiles for Marealis AS, a Norwegian company. However, failed attempts for novel foods and health claims have also been documented. Recently, the MegaNatural®-BP grape seed extract produced by U.S. company Polyphenolics was rejected for a health claim relating to maintaining normal blood pressure due to weak clinical evidence provided [122].

These examples highlight the requirement of well-designed clinical trials currently required to approve a novel food or health claim in Europe. Although these clinical trials are necessary, they may also pose a burden to the nutraceutical industry as they may be a constraint for small companies wishing to bring an innovative product to market with a health claim due to the cost of running such rigorous clinical trials.

8. Looking to the future of nutraceuticals

Nutraceuticals offer potential preventive care and in some cases treatment for diseases at a low cost. Nutraceuticals can offer faster development times and occasionally they can be administered as native compounds in herbal form or as core food ingredients. Their health impacts can be conveniently determined because epidemiological studies can establish their safety profiles, cutting down the time and cost of clinical trials. Disease prevention strategies are expensive and highly regulated. Nutraceuticals could help improve disease prevention, while cutting down cost, time, unpleasant medication, and clinical procedures.

8.1. Clinical recommendations

Nutraceuticals may be applicable for several different indications due to their multi-targeted actions. For example, curcumin from turmeric has lipid-lowering, blood pressure reducing, antioxidative, and anti-inflammatory reducing properties along with the capacity to improve insulin sensitivity [123,124]. This necessitates elucidation of the various underlying mechanisms, pharmacokinetics, and pharmacodynamics of the active compounds. Preclinical research with active compounds would provide clarity for quality, efficacy, and mechanisms of action. Clinical evaluation of these natural compounds can provide further evidence of efficacy and safety of nutraceuticals [125]. Clinical assessment will also provide a paradigm shift in nutraceutical classification as drugs rather than as supplements [125]. Furthermore, drug discovery, development, preclinical and clinical testing receives significant funding internationally, whereas funding for research on nutraceuticals and supplements, which are consumer by over 170 million Americans [126], receives little investment. Further investment in clinical research for nutraceuticals will increase their status among scientists and increase consumer trust, thus also potentially increasing market value.

8.2. Regulatory recommendations

It is important to clearly identify nutraceuticals' specificity in view of

their possible clinical use and utility in the pharmaceutical arena. The focus on food supplement legislation has thus far addressed multiple issues regarding safety and labeling. However, little emphasis has been placed on a nutraceuticals' clinical benefits. A regulatory system should allow identification and classification of these products and would provide clarity for quality, efficacy, mechanism of action, and safety to potential consumers. While EFSA's novel food and health claim application does ensure consumer safety and product efficacy, the level of evidence required may prevent small innovative companies from applying for novel food status or health claims on their products.

Medical and regulatory guidelines will offer essential tools moving forward to capture nutraceuticals' benefits and safety, will create awareness about nutraceuticals, and provide them a more appropriate status within the healthcare industry. Nutraceuticals' manufacturers need to focus on the quality of the available products [127]. This can be achieved by identifying and classifying active compounds in the natural products and providing detailed product specifications on labels. Further, it is likely that nutraceuticals will only be used as an add-on to pharmacotherapy and not as a first-line therapy to void the situation that patients would prefer using nutraceuticals and not drugs (e.g., statins) [72,73]. As discussed previously, this has been a concern for some physicians treating patients who turn to unproven CBD products instead of medical standard-of-care. Therefore, clear guidelines need to be proposed to support the use of nutraceuticals and to enhance their value as they proceed through clinical trials to market.

8.3. Future research recommendations

Considering the current regulatory frameworks surrounding nutraceuticals and growing public interest in this market, there is a need to identify and systematically summarize existing literature on the benefits and safety of nutraceuticals. Future studies need to identify opportunities and gaps in medicinal properties of nutraceuticals, key target markets, and propose steps to improve health using nutraceutical products. Epidemiological/observational studies can shed light on the effectiveness of these products as well as develop a safety profile for further clinical assessments. In this regard, meta-analysis of available clinical trials and/or pilot studies can be a useful tool to compare the effectiveness of two or more nutraceutical formulations. Collectively, these studies can provide the foundation for providing clinical recommendations and robust guidelines for effective nutraceutical marketing.

CRediT authorship contribution statement

AC and **IC** conceptualized the study, conducted literature search, and drafted the manuscript. **RL**, **OKH** and **AGA** substantially revised the first draft. **JH**, **AJ**, **LH**, **VP**, **MB** and **MB**, contributed toward revising the papers and agree to be accountable for all aspects of the work. **NA** and **RL** reviewed the draft manuscript. All authors agreed on the final submitted version of the manuscript.

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Conflict of Interest

The authors did not declare any conflict of interest for this manuscript.

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