ISBN 978-1-960740-54-0

INNOVATIVE FOOD PRODUCTS - NUTRACEUTICALS AND FUNCTIONAL FOODS

Editors

Muhammad Haseeb Ahmad & Farzana Siddique

Review Based Book Chapter

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February 21, 2025

doi: 10.5281/zenodo.14830038

Scientific Knowledge Publisher (SciKnowPub), USA

info@sciknowpub.com

REVIEW BASED BOOK CHAPTER

SAFETY AND QUALITY OF NUTRACEUTICALS

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Abstract

Nutraceuticals, derived from bioactive compounds, offer health benefits and serve as natural alternatives to traditional pharmaceuticals. Despite their appeal, these products face significant challenges in safety and quality due to less stringent regulations and inconsistent standards globally. The examination of current regulatory frameworks in various countries, utilizing official sources and databases, reveals the complexities of quality, safety, product development, regulatory discrepancies, and authenticity affecting nutraceuticals. The global expansion of the nutraceutical market further complicates regulatory enforcement and the substantiation of efficacy and safety claims. To address these issues, the establishment of an effective system promoting cooperation among consumers, healthcare professionals, and government entities is imperative. Such a system would contribute to the creation of international standards and botanical references, thereby increasing transparency and trust in both processes and products. Additionally, the role of emerging technologies in enhancing systems engineering through information sharing and resource utilization across nations is explored. In conclusion, the current state of nutraceutical regulation is insufficient, leading to questionable claims often unsupported by robust evidence. Strengthening regulatory frameworks and fostering a culture of integrity are crucial to guarantee product efficacy and safety, facilitate monitoring, and bolster the confidence of both consumers and healthcare providers.

Keywords
Nutraceutical, Therapeutic Effect, Quality, Safety, Regulations

1. Introduction

Nutraceuticals are products with naturally occurring, biologically active ingredients that are good for consumers [1]. Depending on the nation and its laws, they may be categorized as functional foods, medicines, dietary supplements, or therapeutic foods. Nutraceuticals can be obtained from a variety of sources, including dietary fibers, fatty acids that are polyunsaturated, antioxidant vitamins, probiotics, prebiotics, polyphenols,

or spices, and herbs. Nutraceuticals are said to have some physiological effects, including enhancing immunity, treating chronic pain, and enhancing general well-being [2]. Nonetheless, the business and authorities must address the significant issues surrounding the quality and safety of nutraceuticals. Nutraceuticals are not under stringent safety and efficacy testing or pre-market approval, in contrast to pharmaceuticals. Furthermore, there is a great deal of variation in the laws and guidelines governing nutraceuticals in various nations and areas, which leaves both producers and customers perplexed and inconsistent [3]. As a result, methods for quality assurance and control are required to guarantee the identity, potency, purity, equilibrium, and safety of nutritional supplements at every stage of the supply chain, which ranges from the raw material to the finished product. The present state and concerns regarding the safety and quality of nutraceuticals, as well as the most effective approaches and methods for enhancing the quality assurance process of these products, has been covered in this chapter.

Nutraceuticals including antioxidants, omega-3 fatty acids, plants like wheatgrass, aloe vera, and other types of seaweed, and algae, as well as teas and herbs like ginseng and Echinacea, continue to enjoy a healthy and expanding market. According to a recent assessment, the nutraceutical business is predicted to grow to a potential value of $340 billion by 2024, indicating that it is now experiencing global expansion [4]. From 2016 to 2024, the cumulative annual growth rate (CAGR) for nutraceuticals is projected to be 7.2% [5]. This increase in the nutraceuticals-based industry's growth is linked to a few variables, including an increase in consumer demand for nutraceuticals, increased knowledge of the health advantages of nutrition, and an incremental rate seen in the healthcare graph [6]. Over 90% of the worldwide nutraceutical industry is currently accounted for by Europe, the United States, and Japan. At a compound annual growth rate of 8%, the market is expected to grow from $247 billion in 2019 to $336 billion by 2023 [6, 7]. Now that the global markets have reached a certain level of maturity, developing economies, particularly those in Asia Pacific, including India, are the focus of nutraceutical companies. In 2017, the market share of the Indian nutraceutical industry was a mere 2% of the worldwide market [8].

2. Efficacy and Safety Aspects of Nutraceuticals

2.1. Efficacy

The efficacy of nutraceuticals is the degree to which they produce the desired health effects in the prevention or cure of various diseases. Nutraceuticals are natural substances that may have health benefits beyond their nutritional value, such as anti-inflammatory, anti-cancer, antioxidant, and prebiotic effects [9].

Figure 1 describes a few instances of how some nutraceuticals can be beneficial. After carefully weighing the costs and benefits and taking the preferences of the patient into account, a meta-analysis of 12 research revealed that cinnamic acid decreased inflammatory indicators and may be utilized as a potential adjunct in oxidative stress and inflammation [9]. A meta-analysis was conducted on 86 RCTs with 162,796 individuals to compare the effects of high versus low levels of omega-3 fatty acid intake on cardiac and circulatory illness over a minimum of one year. 8672 individuals in 31 RCTs were used in a meta-analysis to assess the effects of probiotic-treated adults and children on the incidence of Clostridium difficile-associated diarrhea (CDAD) [9, 10]. 23 RCTs involving 1513 participants were meta-analyzed to determine the effect of dietary fiber on coronary heart disease and associated risk variables. To ascertain if dietary iron therapy prevents and controls anemia in a healthy population, a summary of the data from 75 systematic reviews has been conducted. 19 RCTs were meta-analyzed to ascertain the effectiveness of antioxidant vitamins and/or mineral supplements in slowing the advancement of age-related macular degeneration (AMD) [11].

2.2. Safety: Issues and Potential Risk

Consumers use nutraceuticals, which are sold as over-the-counter products, as supplements [12]. As a result, their safety must be prioritized, or else fatal consequences could happen. The three most often reported problems are contamination, adulteration (deliberate or accidental), and deceptive labeling as shown in Figure 2.

Three distinct detection procedures can be used to show adulteration: (1) the existence of an undocumented drug; (2) the deviation of a component from its usual concentration (content); and (3) the likelihood that a profile will not occur [13]. One can intentionally or unintentionally commit adulteration. Various circumstances may

lead to unintentional adulteration. For example, contamination with chemical fertilizers, heavy metals, fertilizers, or microbiological agents may occur during storage, the formulation and manufacture of nutraceuticals, or the many stages of plant growth. Insects, rodents, parasites, fungi, mold, poisons, heavy metals, dust, pollens, artificial substances, and insects can all be used as adulterants [14]. Any of these contamination types could result in infections or even more serious ailments like gastritis and its aftereffects, liver damage, and even potentially fatal diseases. The stability of the active chemical or compounds, microbiological control, and specifications given in specific monographs may therefore be used to determine the need for raw material and finished product quality control. Intentional adulteration of vitamins or herbal treatments might have very negative effects. It frequently happens with synthetic substances, most of which are not reported [15]. It typically has the goal of changing the pharmacological response and generates financial gains. Nutraceuticals derived from plants are frequently very hard to come by, and extract manufacturing is expensive and time-consuming. Consequently, regulatory agencies do not permit these adulterations [16].

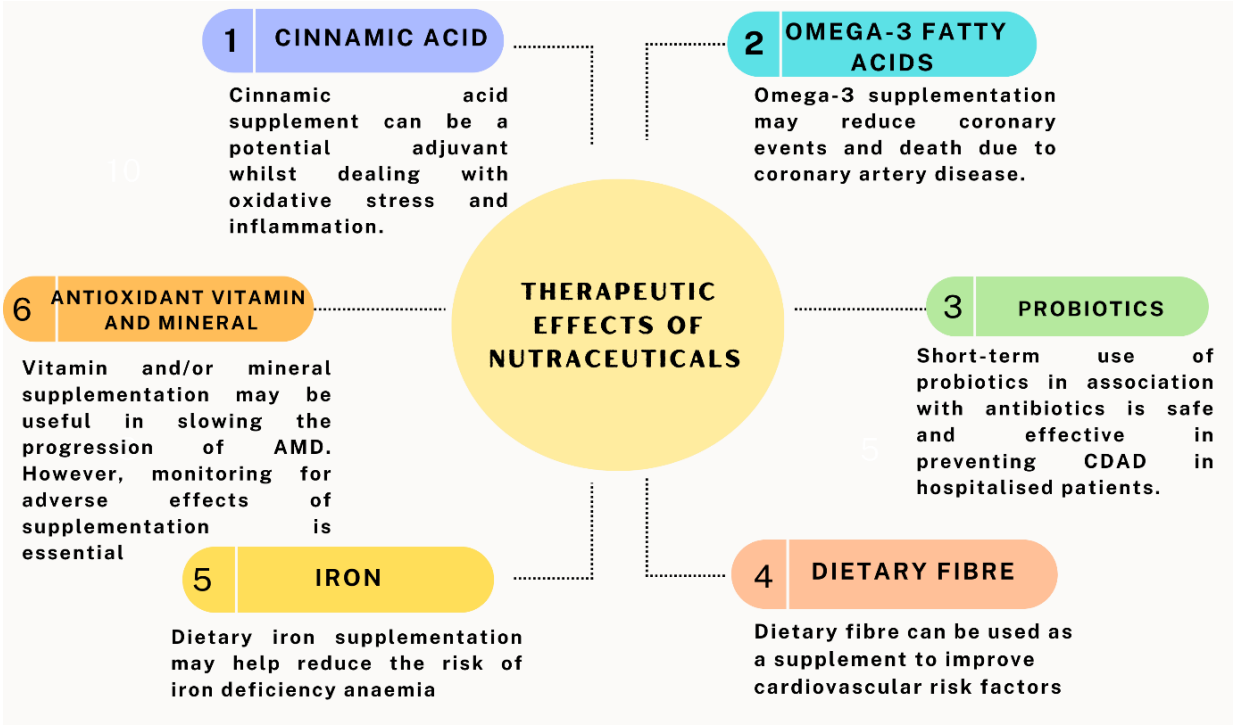

Figure 1. Potential Therapeutic Effects of Nutraceuticals [9]

Deceptive labeling is another source of harm to human health. In one study, the isoflavone content was analyzed and contrasted with the label information on five different types of dietary supplements made from soy [17]. Two of the alleged isoflavones, genistein and daidzein, were found to be missing from three of the five supplements [18].

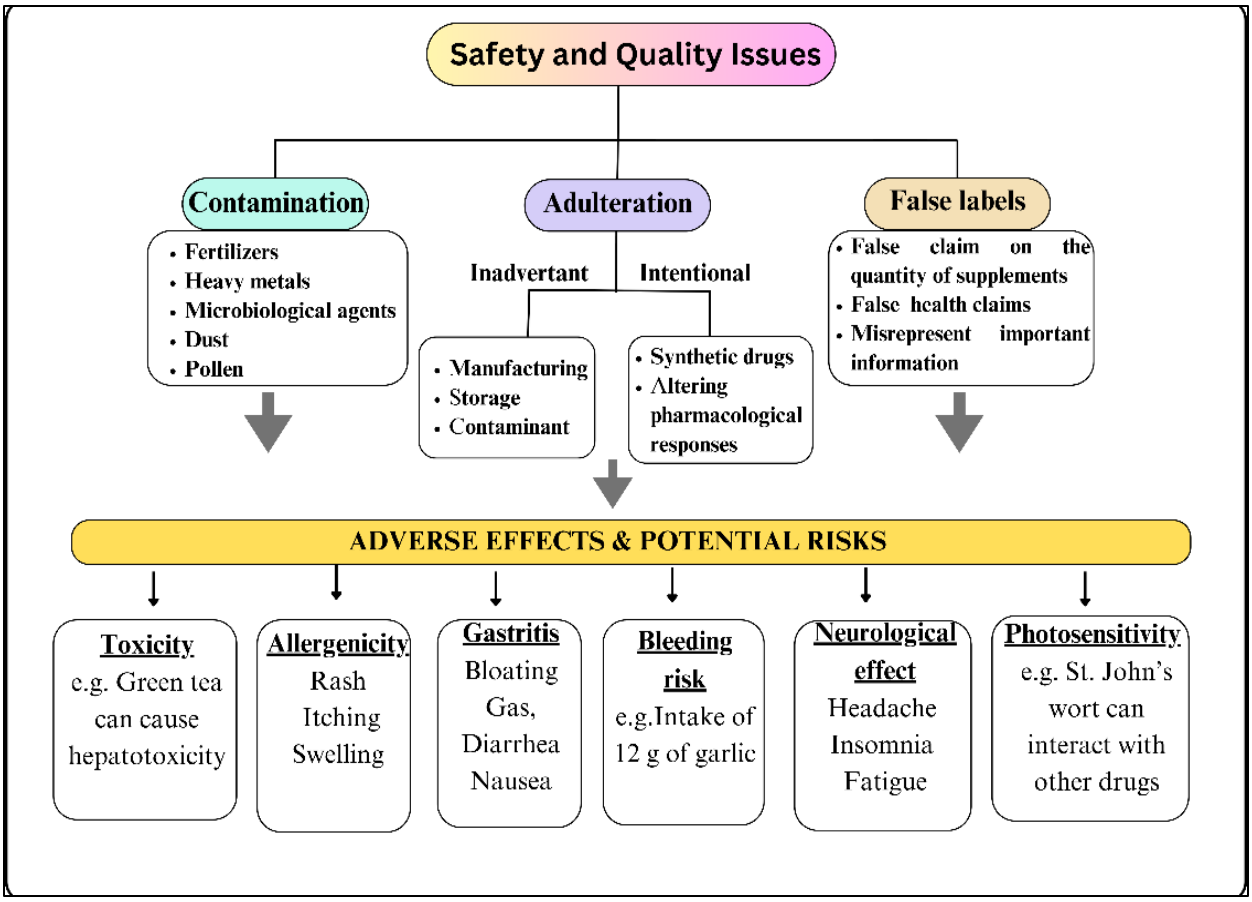

Figure 2. Schematic Illustration of Safety, Quality and Potential Effects and Risks of Nutraceutical [12-15]

Furthermore, an HPLC investigation of one of the compositions revealed that each pill contained 1.538 mg of genistein, rather than the 60 mg of isoflavone that had been calculated based on genistein [19]. However, nutraceuticals have the potential to cause toxicities even at recommended concentrations. The main reason for this is that there aren't enough controlled or long-term human clinical research studies to establish the ideal dosage [20]. For example, there have been reports of hepatotoxicity associated with green tea [21]. An everyday dosage of about 12 g of cloves of garlic

can have antiplatelet properties and induce abnormal bleeding. Your health may be at danger due to incorrect ingredient identification, incomplete ingredient lists, and dosage errors, in addition to potential allergic reactions. It may also have an impact on the effectiveness of other drugs and prescriptions. Supplements containing omega-3 and fish oil may intensify bleeding, which is particularly elusive for people on other anticoagulants [22]. For many supplements, there are recommended dosages available; nevertheless, they differ significantly. Nutraceuticals in pharmaceutical or a greater concentration of supplementation may have unexpected detrimental consequences through pro-oxidative or other mechanisms.

3. Safety Assessment of Nutraceuticals

FAO/WHO mandates that producers of nutraceuticals or functional foods carry out placebo-controlled clinical studies and evaluate the results in four phases [23].

1. Safety
2. Efficiency
3. Effectiveness
4. Surveillance

Investigating the safety of dietary supplements is still ongoing. Table 1 demonstrate that it is necessary to assess the possible dietary impact, the novelty of the constituents and preparation techniques, and both [24]. The safety of any innovative food ingredients and their production techniques is guaranteed by several rules [25].

To assess the safety of functional ingredients, which are added to foods for health benefits, four steps are followed: identifying hazards, characterizing hazards, assessing exposure, and characterizing risks [26].

- **Step 1: Hazard Identification**. This step aims to identify the potential hazards of the functional ingredients, such as their biological activity, toxicity, impurities, and interactions with other substances. Different types of functional ingredients have different safety issues, such as single compounds, herbal extracts, or novel products. Historical exposure and scientific studies can help identify hazards [27].

Table 1. Questionnaire for Healthcare Experts to Access the Safety of Nutraceuticals

A registered dietitian, a food scientist, a nutritionist expert, or another healthcare provider must be able to respond to several questions to assess the safety of a functional food	
i.	Which ingredient(s) serves a purpose?
ii.	What quantity of the substance is included in each serving?
iii.	How big of a serving is normal?
iv.	What is the average amount of eating the functional food? e) Has the company tested the ingredient(s) in both people and animals for safety?
v.	Are there any published, peer-reviewed studies on the substance or ingredients?
vi.	Will the company give you background on studies that have been published or safety information?
vii.	Does the active component conflict with medications prescribed by a doctor?
viii.	What is the scientific basis for the effectiveness of functional food?
ix.	What is the scientific basis for the effectiveness of functional food?
x.	Have carefully planned and supervised clinical intervention studies involving humans been carried out?
xi.	Do studies appear in journals that undergo peer review?
xii.	Should it be shown successful, is one serving sufficient to give the active ingredient in a way that is noticeable?

- **Step 2: Hazard Characterization.** This step aims to determine the dose-response relationship of the functional ingredients, that is, how the level of exposure affects the severity and probability of adverse effects [28]. Depending on the amount and mode of action, functional substances can produce a variety of effects in the body, ranging from therapeutic effects to outright toxicity. Research on animal toxicology can yield valuable insights into toxicological endpoints of interest, including but not limited to target organ assessment, genetic mutation, carcinogenicity, developmental toxicity, and so on.

- **Step 3: Exposure Assessment.** This step aims to estimate the amount and frequency of exposure to the functional ingredients, considering the intended use and probable experience [29]. The safe level of intake of functional ingredients must be compared to its purpose of use and exposure level. This can be done by looking at past data or using scientific studies (clinical trials, animal toxicology, digestion, distribution, metabolism, excretion, or ADME) to determine the safe level [30]. There may be very little safety buffer between the planned intake amount and a potentially dangerous level. The safe level may be very close to the toxic level, so there is a narrow margin of safety. Drug and food interactions could affect the exposure level and the risk.

- **Step 4: Risk Characterization.** This phase aims to integrate the data from the previous stages and assess the overall threat of the functional ingredients, considering the uncertainty and variability of the data [31]. Human clinical trials are essential to confirm the safety of functional ingredients, due to the limitations of animal models in predicting the effects in humans [32]. When deciding if the results of an animal study may be applied to humans, great effort must be taken to ensure that the design of the study—including the species being studied, dose level, duration, mode of administration, and control groups—matches the human scenario as closely as possible. The complexity and composition of the mixture that the functional ingredient is part of, as well as the presence of impurities, must also be considered [33].

4. Regulation of Nutraceuticals

Different countries have different regulatory bodies that set common principles and responsibilities for nutraceuticals and dietary supplements as explained in Table 2 [34]. These regulations aim to enhance the value of these products and safeguard their safety and effectiveness for consumers. The Table 2 below shows the product characterization and regulations applicable to each country.

4.1. European Union

Nutraceuticals are defined and governed by the European Food Safety Authority (EFSA) as food supplements, which are concentrated nutrient doses intended to

augment a regular diet and offer physiological and/or nutritional advantages [35]. The primary emphasis lies in the components of the supplement, such as minerals, vitamins, and amino acids, as well as the concentrations of each. The materials used in EU-produced nutraceuticals can only be those authorized and listed in Directive 2002/46/EC5 [36]. A corporation can apply to the EC for consideration if it wants to incorporate a nutritional supplement, minerals, or another material that isn't on this list [37].

This law provides the legal framework that food business operators utilize when they wish to emphasize on the goods labeling or in its advertising the specific health and nutritional benefits of their products. The Regulation's guidelines cover both nutrition and health claims, such as "low fat," "high fiber," and "Vitamin D is crucial for the usual development and growth of bone in children. These regulations aim to guarantee that any claims made about food in the European Union on its label, in its presentation, or its advertising are truthful, precise, and supported by data from science. The EU wants to safeguard food industry operators' quality standards and safeguard consumers [38].

4.2. USA

Depending on the claims and intended usage of nutraceuticals, the US has two primary authorities involved in their regulation. They're The government organization in charge of ensuring the efficacy, safety, and quality of medications, food, cosmetics, biologics, medical equipment, and animal products is the U.S. Food and Drug Administration (FDA) [39]. The government organization that oversees the promotion and marketing of goods and services as well as the enforcement of consumer protection laws is the government Trade Commission (FTC) [40].

The Federal Food, Drug, and Cosmetic Act (FD&C Act) was revised by the Dietary Supplement Health and Education Act of 1994 (DSHEA), creating a new legal framework in the US for the regulation of nutraceuticals [41]. Dietary supplements, as defined by the DSHEA, are goods that include one or more dietary elements, which include minerals, vitamins, herbs, proteins, enzymes, etc., and are meant to be taken in addition to a regular diet [42]. Additionally, the DSHEA gives the Food and Drug Agency

and the FTC the power to supervise the regulation of dietary supplements in areas like safety, labeling, and advertising.

4.3. Japan

Japan regulates nutraceuticals—products with health advantages beyond their nutritional value—under a complicated regulatory framework [43]. Numerous organizations and legal frameworks, including the Food Safety Commission (FSC), the Ministry of Health, Labour, and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA), the Food Sanitation Act, the Health Promotion Act, the Food Labeling Act, and others, regulate nutraceuticals [44]. Nutraceuticals are divided into four groups based on their claims and approval process: foods with function claims, foods for specific health uses, foods with health claims, and foods with nutrient function claims [45]. Notification and approval criteria vary for each category based on the type of claim, degree of scientific proof, and labeling regulations.

4.4. China

China's primary regulatory body for nutraceuticals is: The National Health Commission (NHC) oversees creating and upholding the rules and guidelines about food and medical supplies [46]. Food and healthcare product quality, safety, and efficacy regulations are handled by the State Administration for Market Regulation (SAMR), the central government organization that manages China's market administration and supervision. A wide range of rules and regulations covering all areas of nutraceuticals, including categorization, labeling, marketing, registration, and monitoring, make up China's extensive legal framework for these products [47]. Nutraceuticals are defined in China as health foods with health benefits or as vitamin or mineral supplements. Depending on their contents and claims, these foods may be certified or listed with the relevant authorities. Based on the product's components, claims, dose, intended purpose, target population, and other factors, China makes a distinction between healthy foods and other types of goods [48].

4.5. India

Nutraceuticals are regulated in India by two primary agencies: CDSCO for medicines and medical devices and Food Safety and Standards Authority of India (FSSAI)

concerning food and nutraceuticals [49]. India boasts an extensive legal framework pertaining to nutraceuticals, comprising multiple legislation and rules that establish guidelines and requirements for various categories and varieties of nutraceuticals. According to several variables like intended purpose, target demographic, dosage, claims, and ingredients, food items that offer health and medical advantages are classified as either novel foods, functional food items, dietary supplements, or nutraceuticals in India [50].

4.6. Australia

Nutraceuticals are regulated in Australia as either foodstuff or medicines, based on the contents, dose, claims, and intended application [51]. The Therapeutic Goods Administration, known as the TGA, oversees overseeing nutraceuticals with therapeutic claims. Pre-market authorization and post-market monitoring are necessary for these goods. Food Standards Australia New Zealand (FSANZ) regulates nutraceuticals without therapeutic claims. FSANZ establishes guidelines and standards for food and food additives. A few laws and regulations, including the Food Standards Code, the Therapeutic Goods Regulations of 1990, and the Therapeutic Goods Act of 1989, regulate nutraceuticals [52]. The standards and requirements for the categorization, labeling, promotion, registration, and oversight of nutraceuticals are outlined in these laws and regulations.

5. Quality Management of Nutraceuticals

A comprehensive strategy is required to ensure the quality of nutraceuticals, starting with improving the agricultural crop [53]. According to the ideology of smart product delivery systems, crop identification must be done botanically, using biodata documentation and agronomic practice data (Good Agricultural Practices), and farm site awareness (via Global Positioning Systems). Analyses and monitoring of the biologically active nutraceutical compounds and/or biomarkers are required for phytochemical fingerprinting data [54]. This data necessitates the creation of quick assay techniques and instruments to guarantee compliance and uniformity in real time, together with documentation and change detection during handling, harvesting, processing, and production (manufacturing into product). Rapid tests can also be used

to guarantee chemical and microbiological safety for the duration of the product's shelf life.

5.1. The Role of Intelligent Product-Delivery Systems in Optimizing Product Quality and Accountability

A program called IPDS uses IT to increase product value through the resource/product supply network [55]. Present-day global sourcing requires a certain level of scientific foundation, which traceability both facilitates and assures. Up until now, most of the standardization has relied on data from biomarkers and plants, paying little attention to the precise origin, the conditions there, or the article's "journey" through the market. Table 3 reveals the standardizations required for different aspects of the safety and quality of nutraceuticals [56]. A resource traceability system (RTS), which is a component of an intelligent product-delivery system (IPDS), can enhance the important quality attributes assuring safety (microbiological, chemical, and physical), as well as quality assuring the efficiency of the product (or its components) [56]. By having these processes in place from the field (farm gate) to the table and household disposal, the provider delivers a high degree of responsibility and significantly raises the chance that the product will meet predetermined requirements. Furthermore, if a recall is required, it may be carried out quickly and effectively. By gathering data (identification labels in the form of chips, portable data files, etc.) from point of origin to point of disposal, IPDS enables product tracking and, consequently, traceability. Incorporating I.D. tags with portable data and the compilation of relevant information detailing the product's origin, harvest, and history, IPDS enables fast traceability between agriculture and consumption.

Another issue is the lack of traceability. Three technologies currently in use can be combined to ensure traceability: (1) global origin positioning and lot tracking during transport phases; (2) bar-coding advancement from radiofrequency identity to chip coding; and (3) hazard analysis and critical control point (HACCP) management connection to FDA, or similar international databases, for adverse effect observation [57]. These could be used in conjunction with the quick development of marker assays based on nanotechnology.

Table 2. Nutraceuticals Regulations among Different Countries [34]

Region	Regulatory body	Regulations	Product Characterization
European Union	European Food Safety Authority (EFSA)	Directive 2002/46/EC, which establishes a harmonized list of vitamins and minerals Regulation (EC) No 1924/2006 on nutrition and health claims made on foods	Nutraceuticals are substances that have both nutritional and physiological effects, and can be used as food supplements, feed additives, or medicinal products
United States	Food and Drug Administration (FDA), DSHEA)	Dietary Supplement Health and Education Act of 1994, Federal Food, Drug, and Cosmetic Act, Federal Trade Commission Ac	Nutraceutical foods are supplements that contain one or more food ingredients, such as vitamins, minerals etc.
Japan	Ministry of Health, Labour and Welfare (MHLW)	Food with Health Claims, Food with Nutrient Function Claims, Foods for Specified Health Uses, Foods with Function Claims	Nutraceuticals are functional foods that have health benefits beyond basic nutrition, and can be classified into four categories based on their claims and approval process
China	NHC and the SAMR	Food Safety Law, Administrative Measures for Registration and Filing of Health Food, Administrative Measures for Registration and Filing of New Food Raw Materials	Nutraceuticals are health foods that have specific health functions or supplement vitamins or minerals, and can be registered or filed with the authorities depending on their ingredients and claims
India	Food Safety and Standards Authority of India (FSSAI)	Food Safety and Standards Act, 2006, Food Safety and Standards Regulations, 2011, Drugs and Cosmetics Act, 1940, Drugs and Cosmetics Rules, 1945	Nutraceuticals are dietary supplements that offer medical and health advantages, such as illness prevention and treatment and can be categorized as nutraceuticals, functional foods, dietary supplements, or novel foods
Australia	Food Standards Australia New Zealand (FSANZ)	Therapeutic Goods Act 1989, Therapeutic Goods Regulations 1990, Food Standards Code	Nutraceuticals are products that have both nutritional and therapeutic properties, and can be regulated as either foods or medicines depending on their ingredients, dosage, claims, and intended use

Table 3. Standardization for Quality and Safety Management [56]

To ensure safety and quality, standardization is essential for the following aspects:
1. The Latin name of the plant materials, the CAS number of the chemical entity, and the origin or synthesis location of the source
2. The GIS descriptors of the plant material
3. The sample verification of the plant material by a systematic botanist or a chemical certification
4. The certification of the tolerance levels below the limit for organics (such as pesticide residues)
5. Heavy metals (such as lead, and mercury) and microbiological pathogens
6. The content of bioactive(s)/biomarker(s), if identified
7. The digital documentation of GMPs, compliance with HACCPs, and monitoring of the US FDA database for adverse effects

6. Regulatory Reforms for Advancing Consumer Protection and Product Quality

A model for collaborative open database creation and nutraceutical development procedure modified from a suggestion by Santini et al. [41]. They suggest a safe development procedure that entails post-marketing monitoring, feedback to regulatory bodies for quality assurance, evaluation of effectiveness, and detection of adverse effects as illustrated in Figure 3 [41]. In addition to safeguarding consumers, this perpetual feedback loop aids in the production of superior analogs and nutraceuticals.

7. Nutraceutical Product Transparency: Challenges and Solutions from Serialization and Blockchain Technology

There is a trust gap between customers and nutraceutical makers, mainly stemming from the uncertainty of the origin and composition of the products, as well as the lack of sufficient proof for the alleged benefits of the products [58]. Regulatory oversight can mitigate the doubts regarding the benefits, but verifying the origin and composition necessitates inventive technological approaches. Serialization, which entails assigning distinct codes and security features to the products, has already demonstrated its effectiveness in preventing falsification in the pharmaceutical sector [59]. Blockchain

technology affords an extra level of security and clarity by generating a distributed, immutable ledger of transactions, enabling the tracing of products from origin to end-user [60]. Incorporation of blockchain with deep learning can yield supplementary advantages, such as forecasting adverse effects, suggesting withdrawals, and even customizing dosage prescriptions. With the global nutraceutical packaging market estimated to attain US$5 billion by 2029, the implementation of these technologies has the capacity to considerably augment trust and transparency in the sector, benefiting both consumers and producers [61].

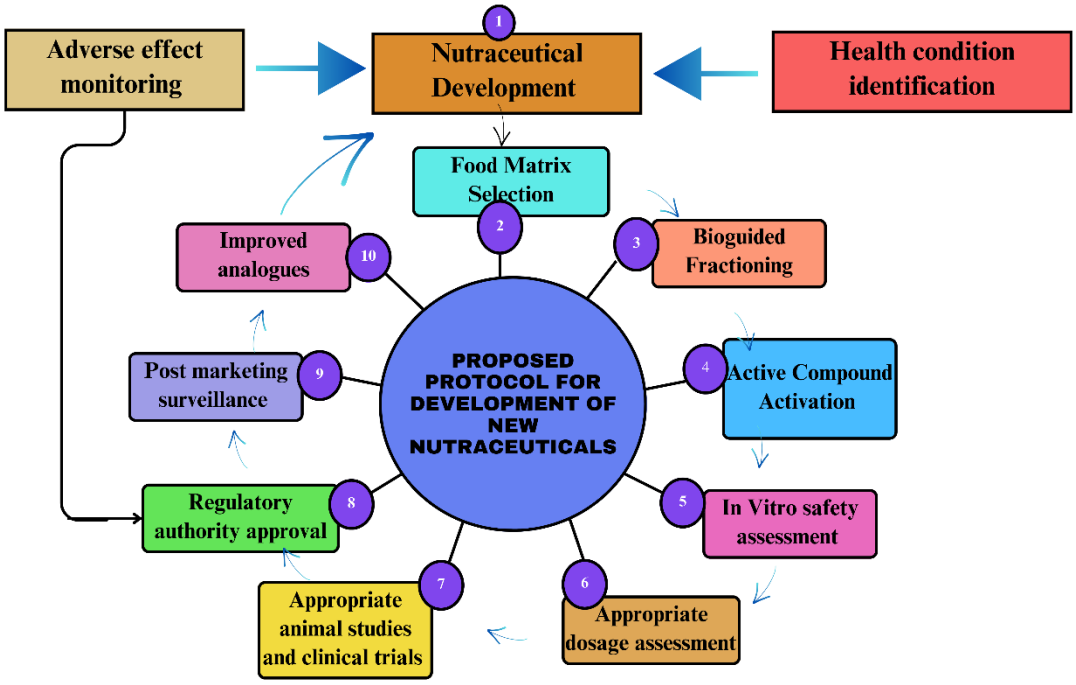

Figure 3. Proposed Protocols for the Development of New Nutraceuticals [41]

Practical examples are already reinforcing the argument for blockchain incorporation in nutraceuticals [62]. Carrefour SA, a French retailer, witnessed sales growth after employing blockchain to trace 20 items such as meat, milk, and fruit in partnership with IBM. They intend to extend that to 100 items, comprising baby and organic products, this year. Likewise, Walmart is experimenting with blockchain with 10 companies after effectively tracking mangoes and pork. This cooperative method, driven by blockchain,

can create the conditions for a future where consumers have ultimate trust in the genuineness and origin of their nutraceuticals.

8. Conclusion

In summation, consumers are interested in health-promoting products that contain dietary ingredients, such as dietary supplements and nutraceuticals. However, in various countries, these products are regulated differently, which creates gaps and challenges in quality and safety. Nutraceuticals have potential advantages, but they require an entire framework of integrity to accomplish them. This requires education, good manufacturing practices, monitoring, protocol development, harmonization, and risk assessment. Product traceability and blockchain technology can enhance transparency and security. The nutraceutical industry also needs novel quality management approaches, such as IPDS and RTS, to reduce chronic disease and healthcare costs and improve quality of life.

Acknowledgement
The authors are highly obliged to their departments and institutes for access to journals, books and valuable database.

Authors Contributions
Conceptualization, M.A.; writing—original draft preparation, Z.A, K.M and A.G.; writing—review and editing, F.Z, M.A and A.G.

Conflict of Interest
The authors declared that they have no conflict of interest.

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