

## MINI REVIEW



# Nutraceuticals: a promising, yet unregulated Frontier in Healthcare

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Nutraceuticals, with their potential health benefits, are increasingly being used to manage a variety of health conditions. The global market for nutraceuticals, valued at USD 540 billion in 2022, is projected to reach USD 1025 billion by 2030. This paper delves into the beneficial impacts of emerging nutraceuticals on a spectrum of medical disorders, drawing from credible sources from the National Library of Medicine. We have scrutinized studies on the application of nutraceuticals in treating conditions like sleep disorders, migraines, oxidative stress, mental health issues, pain disorders, obesity, gastrointestinal disorders, and even COVID-19. Our analysis indicates that nutraceuticals hold promise for addressing various health issues. However, this paper also sheds light on the health risks associated with nutraceuticals. Despite their widespread use, the safety and efficacy of nutraceuticals are still uncertain due to the lack of stringent regulations, unlike pharmaceutical drugs. This raises concerns about potential health risks and misleading claims. Research indicates that some supplements can cause adverse effects and interact with medications. Therefore, to ensure safe usage, it is imperative to implement stricter regulations, enhance reporting systems, and boost consumer awareness.

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## INTRODUCTION

Nutraceuticals are products derived from food sources that offer both nutritional and medicinal benefits. In 2022, the worldwide market for nutraceuticals was valued at USD 540 billion and it is projected to grow to USD 1025 billion by the year 2030 [1]. They can be classified into several categories. Functional Foods are fortified with specific nutrients like vitamins or omega-3 fatty acids to provide health benefits. Dietary Supplements are products that contain dietary ingredients like vitamins, minerals, herbs, amino acids, and other substances intended to supplement the diet. Medicinal Foods are specially formulated for the dietary management of a disease that has distinctive nutritional needs. Pharmaceuticals are medically valuable components produced from modified agricultural crops or animals. Nutraceutical Beverages are drinks fortified with health-promoting additives like probiotics and prebiotics. Lastly, there are Nutraceuticals in Pharmaceutical Form which are in the form of tablets, capsules, and powders. It's important to note that the definition and classification of nutraceuticals can vary from country to country depending on their categorization and regulation [2].

This paper explores the beneficial impact of emerging beneficial trends in nutraceuticals on a variety of medical disorders, including sleep disorders, migraines, oxidative stress, mental health issues, pain disorders, obesity, and gastrointestinal disorders using publications from the National Library of Medicine which is the largest trusted peer-review database in the world. This paper further delves into the potential health risks associated with nutraceuticals. To mitigate these risks, it is imperative that suppliers furnish accurate guidance on the ideal

dosage of nutraceuticals, tailored to individual conditions and requirements.

To address the lack of regulation for nutraceuticals, it is crucial to establish comprehensive guidelines that ensure consumer safety and product efficacy. Potential health risks should be clearly depicted, and suppliers must furnish accurate guidance on the ideal dosage of nutraceuticals, tailored to individual conditions such as gender, weight, and past and present health conditions. Furthermore, regulatory bodies should implement stringent quality control measures, including regular inspections and testing of nutraceutical products to verify their composition and potency. Mandatory labeling requirements should be enforced to provide consumers with transparent information about the ingredients, potential allergens, and any possible side effects. Additionally, a centralized database could be established to track adverse reactions and efficacy reports, enabling continuous monitoring and timely updates to regulations. Collaboration between government agencies, healthcare professionals, and industry stakeholders is essential to develop and enforce these regulations effectively. By adopting these measures, we can ensure that nutraceuticals are safe, effective, and beneficial for consumers.

We recommend highlighting the lack of consumer awareness in the Introduction chapter as a key motivation for this research. Many consumers use nutraceuticals without fully understanding their ingredients, side effects, and risks, which compromises their safety. Additionally, they often do not comprehend the interactions with other medications and miss the opportunity to receive expert advice by not disclosing their nutraceutical use to healthcare providers.

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## BENEFITS OF NUTRACEUTICALS

### Sleep disorders

In a 6-week randomized trial, adults with impaired sleep were given either a nutraceutical blend or a placebo [3]. Sleep quality was measured using an actigraphy device. The trial involved 64 participants, with 31 in the active group and 27 in the placebo group. Their results showed no significant difference between the two groups in terms of sleep efficiency, total sleep time, wake after sleep onset, and other parameters. Both groups saw a decrease in the Pittsburgh Sleep Quality Index, but the placebo group had a greater increase in the SF-36 score. No serious adverse events were reported [3]. The SF-36, or the Short Form (36) Health Survey, is a patient-reported survey of health status. It's a set of generic, coherent, and easily administered quality-of-life measures.

Sleep is essential for mammals, promoting daily functions and preventing chronic diseases like Alzheimer's [4]. Insufficient sleep can lead to accidents and reduced efficiency. The gamma-aminobutyric acid (GABA)ergic system, the primary inhibitory neurotransmitter system in the central nervous system, counter-balanced excitatory neurotransmitters, affecting sleep. Dysfunction of this system was linked to insomnia. Modulating the GABAergic system, which includes the GABA neurotransmitter, GABA receptors, and GABA synthesis and degradation, could be a promising approach for insomnia. Varintra et al. reviewed the significance of sleep, insomnia classification and pathology, the impact of GABAergic system changed on sleep, and medications such as Chinese herbal medicines targeting the GABAergic systems [4].

### Migraine

Nutraceuticals, derived from food or plants, were increasingly used for migraine treatment as they offer a natural, effective, and safe alternative to conventional therapies [5]. They included phytomedicines, diets, and vitamin, mineral, and supplement-based treatments. Options included vitamins like riboflavin, antioxidants, and plants like feverfew, butterbur, cannabis, St. John's Wort, Rosa x damascena, and Gingko biloba. Dietary interventions and supplements like polyunsaturated fatty acids, l-carnitine, pre/probiotics, and melatonin were also used. While some therapies have strong evidence, others like cannabis have limited evidence. Future studies may explore traditional medicines and larger trials in partnership with industry [5].

Nutraceuticals, as part of the diet, offer a safe, non-pharmacological approach for migraine treatment [6]. They inhibited oxidative stress, suppress inflammation, and maintain gut microbiome health, all implicated in migraine pathology. Enriched in polyphenols and phytosterols, nutraceuticals reduced harmful effects of reactive oxygen species and inflammation. They also prevented dysbiosis and maintained intestinal bacteria that produce anti-inflammatory molecules like short-chain fatty acids, contributing to a healthy nervous system. Thus, nutraceuticals provided a complementary strategy for migraine, exhibiting antioxidant, anti-inflammatory, and anti-nociceptive properties while maintaining gut microbiota [6].

### Oxidative stress

The rising prevalence of metabolic and cardiometabolic disorders globally, characterized by oxidative stress and chronic inflammation, posed significant health challenges [7]. Traditional therapeutic approaches sometimes fall short, leading to growing interest in nutraceuticals. These natural compounds show potential to support or even replace pharmacological treatments. Nutraceuticals like polyphenols, omega-3 fatty acids, and antioxidants exhibit antioxidative and anti-inflammatory properties, offering a promising strategy to mitigate oxidative-stress- and inflammation-associated metabolic diseases. This review highlights their potential to restore redox balance and temper chronic inflammation, while discussing challenges and prospects of nutraceutical-

based interventions, including bioavailability enhancement, personalized treatment approaches, and clinical translation [7].

Nutraceuticals, offering both nutritional and therapeutic benefits, can slow aging and shield against diseases [8]. Interest has shifted from allopathic to Ayurvedic to nutraceuticals due to their safety and lack of adverse effects. However, conventional forms like pills have poorer bioavailability and stability. Nanotechnology has emerged as a promising field, creating more bioavailable, less toxic, and sustainable nutraceuticals. Nano-pharmaceuticals for oxidative stress have shown improved antioxidant delivery, reduced leakage, and increased targeting precision. They effectively treated oxidative stress-related illnesses by lowering ROS levels. Their review outlined the major uses of nano-nutraceuticals, emphasizing their role in reducing oxidative stress [8].

### Mental health

Correct nutrition and diet were linked to mental health, immune system functions, and gut microbiota composition [9]. Diets rich in fibers, phytochemicals, and omega-3 fatty acids have anti-inflammatory and protective effects on the nervous system. Nutraceuticals, particularly probiotics and omega-3 fatty acids, can improve symptoms of various mental disorders. This review gathers data on the efficacy of nutraceuticals in treating schizophrenia, autism spectrum disorders, major depression, bipolar disorder, and personality disorders, providing an overview of recent evidence and future research directions [9].

Medicine used the 4Ps model to identify influences on illness states and guide patient care [10]. Mental health, a complex mix of biological, psychological, environmental, and social factors, was a significant global concern. The 4Ps model in medicine was a tool utilized in psychology, psychiatry, and psychological medicine. It served to transform a patient's narrative into a coherent and concise record. Their model was composed of four key elements: Predisposing Factors, which are factors that make a person susceptible to a disorder; Precipitating Factors, which trigger the onset of the disorder; Perpetuating Factors, which maintain the disorder once it has started; and Protective Factors, which prevent the onset or reduce the severity of the disorder. The gut-brain-microbiome (GBM) axis and its impact on mental health was gaining interest. Their model explored the connection between nutrition and the GBM axis and its risks for mental health problems in emerging adults, a common stage for mental illness onset. Their review discussed the impact of dietary trends on the GBM and mental health, the role of gut microbiome-based interventions, and implications for clinical intervention [10].

Obesity and depression, interdependent disorders with strong inflammatory effects, were global health issues [11]. The gut microbiota's role in treating these conditions was increasingly recognized. Research suggests that prebiotics, probiotics, or symbiotics can effectively treat obesity and alleviate mood dysregulation. Their review highlighted the role of intestinal microbiota in treating depression and obesity, and pointed to the potential benefits of probiotics, including psychobiotics and prebiotics, in supporting the treatment of these diseases [11].

Schizophrenia affected approximately 1% of the global population, necessitating innovative therapeutic strategies [12]. Recent insights into neuroinflammation, the gut-brain axis, and microbiota in schizophrenia pathogenesis have led to the exploration of psychobiotics as a new treatment. These interventions target the gut microbiome, promising to alleviate psychiatric symptoms. Advancements in artificial intelligence and nanotechnology were set to revolutionize psychobiotic development, enhancing their production, precision, and effectiveness. Their interdisciplinary approach marked a new era in schizophrenia management, potentially transforming patient outcomes and offering hope for those afflicted by this complex disorder [12].

### Cognitive performance

Regular consumption of edible mushrooms may offer cognitive health benefits, according to previous literature [13]. An analysis of the EPIC-Norfolk cohort data revealed a significant reduction in mushroom intake over time. However, mushroom consumers displayed better cognitive performance than non-consumers at the final health check, with those consuming one or more portions per week showing the highest cognitive scores. These findings suggested that regular mushroom consumption may benefit cognitive function during aging. Further trials were needed to confirm these potential benefits and promote mushroom consumption among older adults [13].

Alzheimer's disease (AD), the most common form of dementia, was characterized by  $\beta$ -amyloid plaques, neurofibrillary clusters, and decreased brain acetylcholine levels [3]. Abnormal phosphorylation of tau protein also contributed to AD pathogenesis. These effects lead to cognitive decline, brain atrophy, and neuronal death. Malnutrition and weight loss, common in AD, were associated with greater cognitive decline. A balanced low-calorie diet and proper nutritional intake can counteract or slow AD progression, while a high-fat diet increases AD risk. Fruits, vegetables, antioxidants, vitamins, polyunsaturated fatty acids, and micronutrients can positively affect brain changes due to their antioxidant, anti-inflammatory, and radical scavenging properties. Their review summarized nutritional factors that may influence AD progression or prevention, the role of nutrition in A $\beta$  plaque formation, and potential therapeutic strategies involving natural compounds [3].

Chatzikostopoulos et al. highlighted the benefits of pomegranate seed oil (PSO), rich in antioxidant and anti-inflammatory fatty acids, in preventing brain neurodegeneration [14]. Their study investigated the effects of PSO on cognition in people with mild cognitive impairment (MCI). Eighty participants were randomized to take PSO and follow the Mediterranean Diet or just follow the diet. After a year, those who took PSO showed significantly better global cognition, verbal episodic memory, and processing and executive functions. PSO, a natural product, can be beneficial for people with MCI and could be a promising part of holistic approaches for dementia prevention [14].

### Neurodegenerative diseases

Neurodegenerative illnesses were influenced by the polarization regulation of microglia and macrophages [15]. Nutraceuticals targeting these cells' M1/M2 phenotypes offered a defense against neurodegeneration. Various nutraceuticals have shown promise in reducing M1 microglial inflammatory markers and increasing M2 indicators in Alzheimer's disease, suppressing amyloid beta-induced microglial M1 activation, reducing oxidative stress and pro-inflammatory cytokines in Parkinson's disease, and protecting against activated macrophages and microglia in multiple sclerosis. Their review highlighted the potential of nutraceuticals in treating neurodegenerative diseases involving microglial-related pathways [15].

### Pain disorders

Nutraceuticals, including herb extracts and natural compounds, were considered for treating gut-brain interaction disorders in children [16]. Limited pediatric trials showed reductions in colic episodes and crying time with fennel, multiple herbal extracts, *Mentha piperita*, and probiotics like *Lactobacillus reuteri* DSM 17938 and *Bifidobacterium lactis* BB-12. For functional abdominal pain or irritable bowel syndrome, supplements like peppermint oil capsules, psyllium fibers, corn fiber cookies, partial hydrolyzed guar gum, a specific multiple herbal extract (STW-5), or vitamin D have shown pain reduction. More large-scale, well-designed studies were needed to confirm the efficacy and safety of these treatments [16].

### Obesity

Obesity is a global health issue, with limited success in treatment through reduced food intake and physical activity, especially for elderly people with chronic diseases [17]. Nutraceuticals, naturally derived and used for their health benefits, could be an alternative to help lose weight and reduce obesity-related metabolic disorders. They can improve health, delay aging, prevent chronic diseases, increase life expectancy, and support body functions. Their study discussed the role of nutraceuticals in managing obesity and related comorbidities, supported by molecular docking studies. It attempted to optimize and widen the use of nutraceuticals in treating this chronic disease [17].

### Gastrointestinal disorders

Intense physical exercise can lead to gastrointestinal symptoms due to changes in blood flow, sympathetic nervous activation, and hormonal responses affecting intestinal function [18]. This can result in inflammation and disruption of the intestinal microbiota. Common symptoms included abdominal cramps, flatulence, and nausea. Maintaining microbiota stability can help manage these symptoms. The literature documented various microbiota alterations following different activities. Nutraceuticals like curcumin, green tea catechins, boswellia, berberine, and cranberry PACs can control inflammation and stabilize the microbiota, offering potential benefits in managing these situations [18].

### COVID-19

Curcuminoids, including Me23 and Me08, derived from turmeric extract, have been shown to possess antiviral properties [19]. Their study investigated their effects on human neurons infected with SARS-CoV-2, the virus causing COVID-19. Me23 significantly reduced proteins that enable the virus to enter cells and antioxidants protected against cellular damage. Both Me08 and Me23 lowered virus replication, while all curcuminoids reduced inflammatory molecules. These findings suggested Me23, in particular, has potential to lessen the impact of COVID-19, especially on the nervous system (Nicoliche et al. [19]).

### Skin aging

Skin aging is influenced by internal and external factors like cell progression, UV radiation, tobacco, nutritional deficiencies, and hormonal imbalances [20–22]. These factors degrade skin cells, leading to collagen and elastic fiber breakdown, resulting in roughness, wrinkling, pigmentation changes, and loss of elasticity. Nutraceuticals may help combat these effects [20–22].

### Cardiovascular disease and cancer

Vitamin and mineral supplementation showed little benefit in preventing cancer, cardiovascular disease, and death, except for a small reduction in cancer incidence with multivitamin use [23, 24]. Beta carotene increases lung cancer risk and other harmful outcomes in high-risk individuals. Evidence for other supplements is minimal or absent [23, 24].

### HEALTH RISKS OF NUTRACEUTICALS

Over 70% of Americans consume dietary supplements daily, contributing to a \$28 billion industry [25]. Unlike food or drugs, these supplements aren't FDA-approved before sale. Under the 1994 DSHEA, the FDA only monitors adverse reports post-marketing. Despite their popularity, there's limited evidence of health benefits for well-nourished adults. Some products can cause significant toxicity. Patients rarely disclose supplement use to physicians, increasing the risk of adverse drug-supplement interactions. It's crucial to understand the major supplement classes, their potential toxic effects, and possible drug interactions [25].

Similar to how pharmacovigilance monitors drug safety, nutravigilance tracks adverse effects from dietary supplements and nutraceuticals [26]. These products, gaining popularity, raise concerns due to lax regulations and potential for harm. The US relies on voluntary reporting by manufacturers and consumers, while Europe has a patchwork of national systems. To ensure safe use, all stakeholders—manufacturers, healthcare providers, and consumers—need to work together. Improved reporting systems and public awareness campaigns are vital for effective nutravigilance [26].

Epidemiologic studies have shown that patients with Congenital Heart Disease who consume a diet rich in antioxidants experience fewer instances of illness and death [27]. Supplements containing antioxidant vitamins C and E have been found to help prevent Congenital Heart Disease. However, supplementation with  $\beta$ -carotene can lead to negative effects and is therefore not recommended [27].

Holeček studied the side effects of increased intake of amino acids, commonly used as dietary supplements [28]. It focused on toxicity, mutagenicity, carcinogenicity, renal and gastrointestinal functions, ammonia production, and competition with other amino acids. Amino acids like arginine,  $\beta$ -alanine, branched-chain amino acids, carnosine, citrulline, creatine, glutamine, histidine,  $\beta$ -hydroxy- $\beta$ -methylbutyrate, leucine, and tryptophan were examined. Holeček suggested that a high intake of most amino acid supplements can lead to detrimental side effects. Further research is needed to understand the effects of high doses and long-term consumption of these supplements, their suitability under certain circumstances, and the consequences of discontinuing supplementation [28].

More patients with chronic conditions are using nutraceuticals, but there's no global consensus on their regulation [29]. Komala et al. summarized the current regulations in the USA, Europe, and Australia, highlighting efficacy and safety concerns, product development, regulatory gaps, and authenticity challenges. The data underscored the complexity of global nutraceutical regulation and the need for an effective system to increase collaboration between consumers, healthcare practitioners, and government agencies. Emerging technologies could improve system engineering through information sharing. In their conclusion, due to poor regulation, nutraceuticals have led to spurious claims, necessitating more stringent regulation and system integrity to ensure efficacy, safety, and increased confidence [29].

Jabbari et al. explored the potential harmful effects of dietary supplements, including an increased cancer risk [30]. Despite marketing campaigns promoting their health benefits, long-term use of these supplements may lead to toxicity and cancer. Their research focused on the correlation between high micronutrient intake from supplements and cancer development. They emphasized the need for quality research to investigate these risks and inform consumers and healthcare professionals about the potential dangers of extensive supplement use [30].

Dietary supplements, rooted in ancient medicinal practices, enhance nutritional value and are used by over 50% of the US population [31]. Many believe they're as effective as evidence-based therapies for lowering lipids. Supplements like red yeast rice, omega-3 fatty acids, garlic, cinnamon, plant sterols, and turmeric are marketed for "cholesterol health." However, they lack the FDA scrutiny that pharmaceutical drugs undergo, leading to variability in contents and efficacy. While they offer a holistic approach to reducing cardiovascular disease risk, their use shouldn't replace proven therapies. Grant et al. provided a historical and evidence-based perspective on dietary supplements for lipid-lowering [31].

Januszewski et al. reviewed the impact of 14 nutritional compounds, commonly used in food and pharmaceutical industries, on skin conditions [20]. These micronutrients, including

vitamins A, C, D, E, curcumin, chlorella, Omega-3, biotin, *Polypodium leucotomos*, *Simmondsia chinensis*, gamma oryzanol, olive leaf extract, spirulina, and astaxanthin, are believed to reinforce the skin's barrier and offer potential benefits like photoprotection. Regular intake may positively influence skin diseases like atopic dermatitis or psoriasis and provide UV protection, beneficial during chemotherapy or in melanoma prevention. However, further research is needed to establish effective dosage for desired skin effects [20].

Omega-3 fatty acids are essential for humans and come from fish, plants, or supplements [32]. While the body can convert some plant-based omega-3s (ALA) to the beneficial forms (DHA and EPA), this conversion is limited. Omega-3 supplements come in various forms (ethyl esters, free fatty acids) and are FDA-approved to treat high triglycerides. These supplements are generally safe with side effects like fishy taste, burping, and upset stomach. They may prolong bleeding time, so caution is advised for those on blood thinners [32].

In June 2021, the FDA approved semaglutide (Wegovy) for chronic weight management. Demand for Wegovy and Ozempic (same drug) has caused shortages [33]. On November 8, the FDA approved tirzepatide (Zepbound) for weight management, a new anti-obesity drug also sold as Mounjaro for diabetes. As the popularity of semaglutide rises, rare but serious adverse effects are being reported. Glucagon-like peptide-1 (GLP-1) receptor agonists, used for obesity treatment, show promising weight loss outcomes but come with tolerability issues, side effects, and risks. A pharmacovigilance study using the FDA Adverse Event Reporting System highlights mortality and serious adverse events associated with GLP-1 receptor agonists [33].

A study in *The New England Journal of Medicine* found that dietary supplements cause about 23,000 emergency department visits annually [34]. Weight-loss products, energy boosters, and vitamins are common culprits. Supplements can cause adverse effects, especially in children and older adults. Always consult healthcare providers before using supplements to ensure safety [34].

By the early 21st century, nutraceuticals gained popularity due to their accessibility, cost-effectiveness, and safety [35]. However, some have toxic potential, and many lack safety data. Contamination and interactions with drugs can compromise safety. Pharmacokinetic and toxicokinetic studies are crucial for assessing their safety and toxicity [35].

### Nutraceuticals recommendations

Nutraceuticals, such as prebiotics, fiber, polyunsaturated fatty acids, probiotics, and antioxidants, are essential for maintaining health and managing conditions like COVID-19 and diabetes [36]. Driven by global trends, the nutraceutical sector is growing, with the food industry increasingly focused on research to enhance health and medicine [36]. Nutraceuticals lack a distinct definition from other food-derived categories [37]. While studies show their potential health benefits, clear information and substantiated claims are often missing. An official definition and shared regulations are needed. Assessing their safety, mechanisms, and efficacy with clinical data is crucial, as they reside between pharmaceuticals and food, facing regulatory challenges [37].

Using the input-process-output (IPO) model, this paper reviews 174 studies on dietary supplement (DS) consumption, identifying key topics and themes [38]. DS consumption is a social-cultural process involving lifelong self-learning and socialization. Understanding consumers' motives and social mechanisms is crucial for guiding health consumption decisions and stakeholders in the health marketplace [38]. Consumers should be informed about the correct usage of the product, the appropriate timing for inoculation, and how to avoid interactions with other medications [39]. To increase consumer awareness of health risks and safety, it



is essential to provide comprehensive information about dietary supplements [40]. Consumers should be well-versed in reading labels and understanding third-party certifications [41].

Recently in Japan, a tragic incident occurred when a supplement from Kobayashi Pharmaceutical Inc. was contaminated with an unanticipated toxin, leading to the death of a consumer. As the nutraceutical market expands and competition intensifies, the risk of distributing substandard products increases. To ensure safety, it is crucial to implement laws and regulations that hold manufacturers accountable [27, 29].

## CONCLUSION

Nutraceuticals, products blending food and medicine, are gaining traction for their potential to address various health concerns. From sleep disorders and migraines to mental health and obesity, these include fortified foods, vitamin supplements, and herbal remedies. Studies suggest nutraceuticals may improve sleep quality, ease migraines, combat oxidative stress, and support mental well-being. They might even enhance cognitive function, manage neurodegenerative diseases, and reduce pain and weight. However, lax regulations raise safety concerns, with potential adverse effects and drug interactions. Additionally, misleading claims can be rampant. To ensure safe and effective use, stricter regulations, more research, and improved consumer awareness are essential.

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### **AUTHOR CONTRIBUTIONS**

Yoshiyasu Takefuji completed this research and wrote this article.

### **COMPETING INTERESTS**

The author declares no competing interests.

### **ADDITIONAL INFORMATION**

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