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PHARMACEUTICAL ASPECTS OF NUTRACEUTICALS: A GROWING TREND IN PATIENT CARE

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Abstract

The growing incorporation of nutraceuticals into patient care signifies a notable transformation in the health and wellness paradigm. The term “nutraceutical,” introduced by Stephen DeFelice in 1989, refers to food products that provide medical or health advantages, including the prevention and treatment of diseases. This paper delves into the pharmaceutical dimensions of nutraceuticals, emphasizing formulation challenges, innovative delivery mechanisms, and their effectiveness in disease management. High-quality nutraceutical formulations presents key challenges, such as the intricate nature of botanical ingredients, their chemical instability, and the necessity for age-appropriate dosage forms. To tackle these challenges, advanced drug delivery systems, including nanocarriers, liposomes, and pH-responsive formulations, are investigated to improve the bioavailability and therapeutic efficacy of bioactive compounds. The paper highlights the effectiveness of nutraceuticals in disease prevention and management, particularly using antioxidant-rich compounds, with evidence indicating their role in mitigating risks associated with conditions such as heart disease, diabetes, and certain cancers. The regulatory frameworks governing nutraceuticals differ across regions, influencing their safety and marketing practices. While nutraceuticals are generally regarded as safe, potential adverse effects warrant careful consumption. Looking to the future, the prospects for nutraceuticals appear bright, propelled by advancements in personalized nutrition and digital health technologies that can enhance product effectiveness and consumer trust.

Keywords:

Nutraceuticals

Pharmaceutical aspects

Patient care

Formulation challenges

Bioavailability

Drug delivery systems

Safety and toxicity

Regulatory framework

Disease prevention

Personalized nutrition

Introduction

In 1989 Stephen DeFelice MD, founder and chairman of the Foundation for Innovation in Medicine (FIM) coined the term nutraceutical from 'nutrition' and 'pharmaceutical'. According to him nutraceutical can be defined as, *"a food or part of a food that provides medical or health benefit including the prevention and treatment of a disease"[1]*.Compounds derived from animal or plant foods are used to manufacture nutraceuticals which are concentrated to deliver therapeutic and nutritional benefits in a suitable dosage form. These nutraceuticals include food products like dietary fiber, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, polyphenols, spices and other herbal foods[2].

Table 1 Classification of Nutraceuticals[3]

Classification	Examples
Dietary Supplements	Minerals (Calcium, Iron, Magnesium), Vitamins (Vitamin C, D), Herbal Extracts (Ginseng, Echinacea), Amino acids (Glutamine, L-Arginine)
Herbal Products	Curcumin, Green Tea Extract, Phytochemicals (Flavonoids, Carotenoids)
Probiotics	Lactobacillus, Bifidobacterium
Prebiotics	Oligosaccharides, Resistant starch
Genetically Engineered Foods	Omega-3 Canola Oil, High-Oleic Soybean Oil, Golden Rice (Vitamin A), Iron-Enriched Beans
Medicinal Foods	Diabetic Meals, Low-Sodium Diets, Phenylketonuria (PKU) Formulas, Glucose-Free Meals
Pharma Foods	Docosahexaenoic acid (DHA) Capsules, CoQ10 Supplements

The nutraceutical market, which comprises functional foods, dietary supplements, and herbal/natural products, has consistently grown since 1995 when it was pegged at $80 billion. In 1997, it was valued at $91.7 billion, dietary supplements and herbal products were the drivers of growth at 19.5% and 11.6% respectively. In the global market, it attained $46.7 billion in 2002 and has been growing at 7% annually. In 2017, the U.S. herbal dietary supplement market surpassed $8 billion with sales leaders' horehound and echinacea. In China, the herbal health market had reached $120 billion by 2014 led by goji, reishi mushroom, and ginseng[4].

Nutraceuticals Formulations and Challenges

There are numerous obstacles to overcome to create a high-quality nutraceutical formulation that is safe, effective, technologically feasible, and still affordable. Botanicals are complex substances having various chemical constituents, and typically multiple classes of compounds are contained in a single product, in contrast to medication molecules, which are well-defined chemical entities. Most of these plants are sensitive to high humidity, alkaline pH, heat, light, and oxygen. These typically have inconsistent particle size distribution, bulk density, and poor flow. Therefore, understanding the basic physicochemical characteristics of the various ingredient types, using appropriate manufacturing techniques, choosing the right excipients, and adding appropriate manufacturing overages based on critical stability studies are all necessary for the successful development of nutraceutical formulations [5]. Here, emphasis is given on:

- Challenges with various dosage forms
- Approaches to deal with formulation challenges.

Challenges

The high melting point, poor water solubility and chemical instability of chemical ingredients provide challenges when creating nutraceuticals. For instance, the high melting point of carotenoids, fatty alcohols and phytosterols could make formulation unstable [6]

Another problem is chemical instability. For instance, carotenoids like lycopene or curcumin, as well as omega-3 rich fatty acid oils like salmon, flax seed and cod liver oil all have stability issues. Bioactive product's composition, ambient factors like temperature, pH, pressure, etc., and the presence of metals and other oxidation promoting chemicals all have a direct impact on how much chemical degradation occurs. The creation of all nanoscale products is crucial for these chemicals to prevent their degradation [7].

Lastly creating dosage forms for dietary supplements and nutraceuticals that are suitable for various aging demographic groups presents a problem, particularly children and older adults. They face difficulties in swallowing solid dosage forms and cause dysphagia[8].

Approaches to Deal with Formulation Challenges

Isolation or manufacture of nutraceuticals concentrate from natural sources is one of the most used methods. It is beneficial because most of the herbal nutraceuticals high dosage per serving each day. Furthermore, different sources include different ingredients. Within a single dosage form, the compression and flow properties of active ingredient vary greatly. Within a same composition, the components sensitivity to heat and moisture varies greatly[9].

Changing the delivery systems is another promising strategy. To create new generations of therapeutic compounds, different compounds' characteristics have been altered using novel drug delivery systems. They are also involved in the food sector and several types of dietary supplements. There have been reports of some supplement formulations made using nanotechnology, known as "nano formulations," which have improved absorption, decreased adverse effects, and shielded the active ingredients from deterioration[10]

Advancement in Drug Delivery System with Medicated Herbs

Scientists and researchers searched for effective delivery systems because of customers' growing preferences for eating healthy food products and the discovery that nutraceuticals were beneficial in both preventing and treating a variety of ailments. Researchers are becoming increasingly interested in using innovative medicine delivery

systems to address product effectiveness concerns. When administering active phytochemical components to the human body, the right vehicle must be used to deliver enough of the active ingredient undamaged to the intended location within the body. The target location varies and could include the bloodstream, organs, cells, etc. Many phytochemicals, including carotenoids and polyphenols, are either lipophilic or weakly soluble compound[11].

Fig.1 Different Nano based delivery systems employed for nutraceuticals[12]

Nanospheres and Nano-capsules

Polymeric nanoparticles having a diameter of less than 1 μm are what make up nanospheres and nano capsules. The vesicular structure of a nano capsule is encased in a polymeric membrane. The active component is contained within a nano capsule. The active substance in nanospheres is disseminated across a polymeric matrix to create a polymeric nanoparticle, which is then conjugated with chitosan. Curcumin was loaded into this system for use as an antioxidant [13]

Micellar encapsulation system

Aqueous solution, an amphiphilic molecule (either low or high molecular weight) with a concentration above carboxymethyl cellulose (CMC) and encapsulated bioactive make up the relatively easy micellar encapsulation technique in contrast to nano emulsion. The loading procedure in micellar encapsulation may be challenging and impact the encapsulation capacity and efficiency, despite the formulation being easier. In the literature, at least four techniques are frequently employed to encapsulate bio actives: (i) solvent dialysis, in which bioactive and amphiphiles are dissolved in a typical water-miscible solvent and the solvent is then dialyzed against water or an aqueous solution; (ii) Solvent evaporation: bio actives and amphiphiles are extracted into an aqueous solution by dissolving them in a typical volatile solvent. After that, the solvent is eliminated by evaporation; (iii) co-precipitation, in which bio-actives and amphiphiles dissolve in a common solvent and the solvent is subsequently evaporated to create an A–B mixture, to which the aqueous solution is added; and (iv) emulsification, in which bio-actives dissolve in a water-immiscible volatile organic solvent and amphiphiles dissolve in aqueous solution before being introduced into the aqueous solution via emulsion[11]

Dendrimers

Dendrimers are hyperbranched, monodispersed, three-dimensional molecules with host-guest and molecular weight characteristics. A dendrimer's three-dimensional (3D) structure is made up of surface or end groups, branching units, and a multipurpose inner core. Cavities in the core structure produce cages and channels that

make it easy to create branching units and hold the bioactive chemicals. The branches endow dendrimers with certain properties, including strong reactivity, solubility, and miscibility. Many active substances can complex with the surface of dendrimers[14] .

Lipid-Based Carriers

Lipid-based nano-capsules with a greater surface area than micro-sized carriers can improve the solubility, bioavailability, and controlled release of phenolic chemicals that have been nano-encapsulated. They may also find successful use in functional foods. For instance, β-Car nano-capsules (>300 nm) exhibited little alterations in physical stability over storage, indicating that they could be utilized in nutraceutical goods, functional foods, and drinks[15]

Nano emulsions

With the aid of an emulsifying agent, two immiscible liquids are combined to create a single phase, thermodynamically stable isotropic system in a nano-sized formulation known as a nano emulsion. The droplets are between 20 and 200 nm in size. Red grape skin, peanuts, and blueberries are natural sources of resveratrol, a substance that has been shown to have potent antioxidant qualities. Nevertheless, the compound's low bioavailability is its issue. Consequently, it has been encapsulated in the nano emulsion created using the spontaneous emulsification method to solve the issue and improve the effect, which has improved the system's retention and qualities[16]

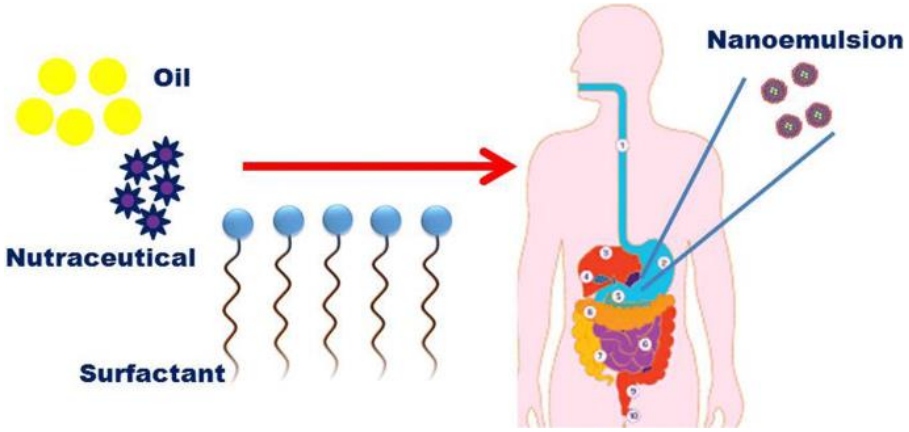

Fig.2 Optimized encapsulation and delivery of lipophilic nutraceuticals using oil-in-water nano- emulsion technology for enhanced bioavailability[17]

Nanoliposomes

Because they can simultaneously encapsulate lipophilic and hydrophilic materials, ensuring a synergistic effect, and because they can protect sensitive bioactive compounds, enhance their bioavailability, ensure sustained-release, and improve storage stability, nanoliposomes, also known as nanometric bilayer phospholipid vesicles, have a very promising future in the nutraceutical industry. Nanoliposomes' special qualities make them ideal for use in drug incorporation systems for efficient illness prevention and health promotion[18].

pH Responsive Formulations

A pH responsive system is a delivery technique that uses a particular pH shift to regulate the release of active substances. The pH ranges of the human body's many organs vary, including the colon (pH 6.4-7.0), small intestine (pH 5.5-6.8), and stomach (pH 1.5-3.5). Additionally, the tumor has a certain pH (about 7.4). Therefore, a pH-responsive system is a great option for site-specific targeting. As a result, the nutraceutical business has adopted this system[19]

Protein based carriers

To optimize the encapsulation, retention, protection, and release of bioactive substances, the most advanced protein-based nanoencapsulation techniques and protein modification techniques are being used in nanocarrier systems. An overview of the most recent research on the denaturation and aggregation of whey protein at the nanoscale, which may help create protein nanostructures with enhanced or novel qualities for the release and integration of nutraceuticals in food matrices. One intriguing method to improve the oral bioavailability of weakly water-soluble bioactive substances, such as vitamin E, is to use whey protein isolate as an encapsulating ingredient in a spray freeze-drying based microencapsulation approach[20]

Nanohydrogels

Different kinds of polymers, either natural or manufactured, make up nanogels or nanohydrogels (NGs). With diameters ranging from 1 to 100 nm, nanohydrogels combine the special qualities of hydrogel with nanoparticles. Intramolecular crosslinking is primarily found in nanohydrogels. Because nanohydrogels are smaller than macro or micro hydrogels, which are relatively larger, they are better able to hold onto integrated medications. Because nanohydrogels have benefits over traditional hydrogels, including a longer half-life in plasma, a higher loading capacity, and greater tissue uptake, they are being researched for the fast delivery of bioactive chemicals. Furthermore, because nanohydrogels are smaller and may enter tiny capillaries, they are more appropriate for the parenteral mode of delivery[21]

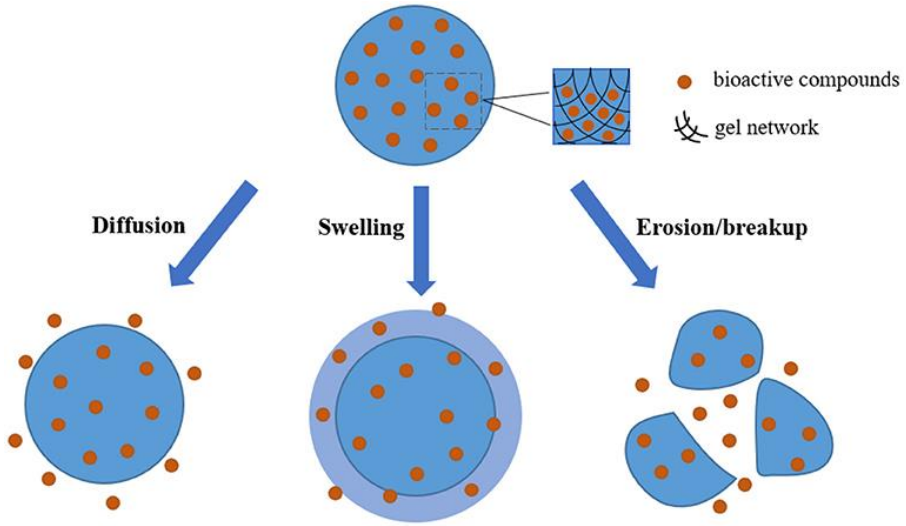

Fig.3 Release of bioactive compounds by nanohydrogels for targeted therapeutic applications[22]

Transferosomes

Another name for transferosomes is ultra-deformable vesicles which have an aqueous phase at their core encircled by a lipid bilayer complex that allows the formulation to self-optimize and self-regulate. The formulation of colchicine transferosomes has been researched to offer improved penetration and thus more sophisticated gout treatment. There have also been reports of improved efficiency and increased skin penetration with transdermal formulations of curcumin transferosomes which enhances curcumin's anti-inflammatory effects[23].

Bioavailability and Pharmacokinetics of Nutraceuticals

Most nutraceuticals have low bioavailability. Poor bioavailability of nutraceuticals is mainly attributed to physiochemical and physiological factors such as limited release from the food matrix, poor solubility in GIT fluids, formation of insoluble complexes with other constituents, poor permeation through the mucous layer or epithelial cells and molecular changes during the transit through GIT[24]

Phytosome technology is one of the most advanced drug delivery systems with the aim of improving the bioavailability of water-soluble phytoconstituents. This technology transforms highly water-soluble phytoconstituents in nutraceuticals through complexation with phospholipids into a carrier for absorption enhancement. This aspect was chosen to strike a balance between hydrophilicity to dissolve in intestinal fluids and lipophilicity to cross lipid-rich membranes. Phospholipids act as emulsifiers, thus improving the absorption of several high-efficacy nutraceutical-formulated products such as those with Ginkgo biloba, Silybum marianum, grape seed, and olive oil flavonoids[25].

Another technology known as encapsulation technology is extremely used in different industries such as nutraceutical and food industries to enhance and improve the stabilization, shelf-life, and bioavailability by providing active ingredients protection, controlling their release, and segregating the reactive components. Nanocarriers, including liposomes and their nano-scale versions (nanoliposomes), help to bring the benefits of less nutritional loss, time-release mechanisms, flavor and aroma protection, and liquid-solid transformations[26]. Liposome is one of the most popular technologies for encapsulating cells. It is a spherical vesicle composed of a two-phospholipid bilayer with a hydrophilic core and therefore is ideal for the incorporation of hydrophilic and hydrophobic substances. Previously, the study mentioned that nutraceuticals of opposite polarities can be co-encapsulated in liposomes, by using curcumin and resveratrol as an example. This study concluded that curcumin has its major part localized in the hydrophobic acyl-chain regions of liposomes, while resveratrol is associated with the polar head groups[27]

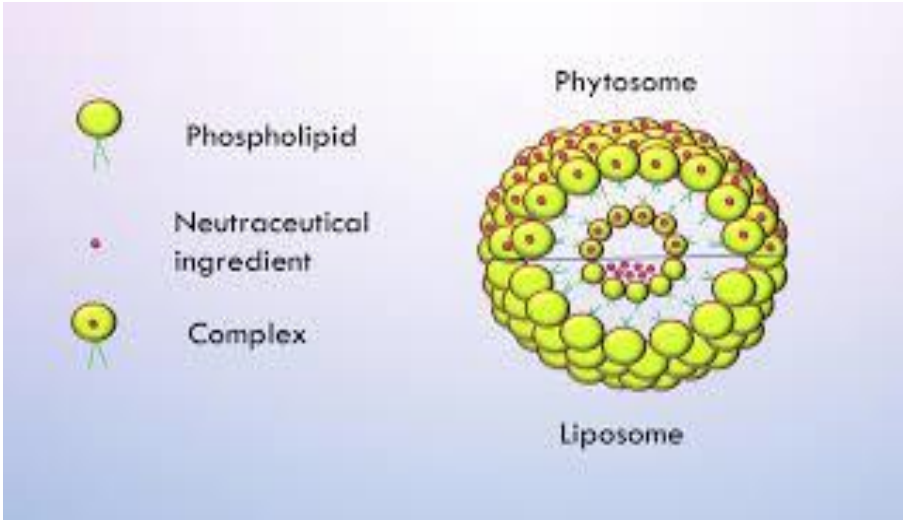

Fig.4 shows two innovative technologies Liposomes and phytosomes. Phytosomes enhance bioavailability by forming complex with phospholipids while liposomes encapsulate nutrients in lipid bilayer for targeted delivery[28].

Nutraceuticals are absorbed into the GI tract according to their chemical form (natural forms absorb better), and solubility (fat- or water-soluble), as well as individual elements that vary between persons, such as genetics, age, and health. Digestion occurs in the mouth and continues in the stomach and small intestine, where the absorption by the bloodstream is done by secretions of enzymes and bile. Prior to systemic circulation, the liver metabolizes them and alters their constituent parts. In the circulating blood, nutraceuticals couple to carrier proteins and target different tissues using specific mechanisms like receptor-mediated endocytosis. Their therapeutic effects are borne over by a complex of factors that include tissue specificity, residence time, and biotransformation[29]. Biotransformation takes place mainly in the liver by cytochrome P450 enzymes (e.g., CYP3A4, CYP2D6) in which Phase I (oxidation) and Phase II (conjugation) reactions for excretion are involved. Extrahepatic

metabolism would happen in other organs like intestines and kidneys, which contribute largely to the biotransformation of specific drugs. Genetic variations among enzymes impact efficacy, safety, and health outcomes. The primary excretion routes for nutraceuticals are via urine (for water-soluble ones) or bile (for lipid-soluble). Renal function and its related glomerular filtration rate (GFR), hepatic metabolism (mainly cytochrome P45 enzymes), protein binding, aging, gender, and body composition are some of the factors that affect the excretion efficiency[29].

Efficacy in Disease Prevention and Management

Recent studies have shown that several common diseases, such as heart diseases, diabetes, cataracts, high blood pressure, infertility, respiratory infections, and rheumatoid arthritis, are significantly influenced by deficiencies in tissue and/or low dietary levels of known antioxidants. For this reason, they form an integral component of the nutraceutical market. Moreover, oxidative stress has been found to play an important role in the progression of neurodegenerative conditions such as Huntington's disease (HD), Parkinson's disease (PD), and Alzheimer's disease (AD). Aging and deficiency in antioxidants in diet increase oxidative stress. There are several studies that have established a relation between high antioxidant levels in the diet and less risk for AD; this is since prevention is always easier than treatment. Research shows that AD can be prevented, and antioxidants promise that it may be the way to delay the fate of the disease[30].

In recent times, there's also been a lot of attention paid to phytochemicals with cancer-preventing properties. Many of these phytochemicals found in fruits and vegetables have chemoprotective value; some may also have properties that can prevent mutagenesis and carcinogenesis. For preventive purposes in breast cancer and prostate cancer, they advocate a whole bunch of said phytopharmaceuticals known as "Phyto-estrogens," purportedly having some hormonal activities[31]

Epigallocatechin gallate (EGCG) is one of the most important compounds of green tea and has potential therapeutic applications. In the management of oral potentially malignant disorder, i.e., lichen planus, as well as the promising activity toward COVID-19 and antimicrobials appearing through inhibition of dihydrofolate reductase disrupting folic acid metabolism in bacteria and fungi, EGCG has a wider application. Besides, EGCG inhibits biofilm formation, thus being a very effective compound against resistant pathogens such as Enterococcus faecalis and Candida species[32].

Lycopene and carotenoids are also very important substances with respect to human health. Lycopene is known as a potent antioxidant and reactive oxygen species (ROS) scavenger due to its unsaturated nature. Recently, lycopene-containing fruits and vegetables have been reported to prevent cancer by decreasing oxidative and other DNA damage in humans. beta-Carotene is one of the most efficacious antioxidants available among carotenes. The most common type, β-carotene, is found in leafy green as well as orange and yellow fruits and vegetables[30].

Flavonoids inhibit 'suicide' enzyme cyclooxygenase, which is responsible for degradation of prostaglandins, thus reducing the adhesiveness of platelets and eventually, their aggregation, preventing action of angiotensin-converting enzyme (ACE) which elevates the blood pressure. In addition, flavonoids reinforce the hair-thin capillaries which provide oxygen and critical nutrients to all cells and offer storage to the vascular succor system. Diminishing incidence of estrogen-dependent cancers can be done through flavonoids as inhibitors of estrogen-synthesizing enzymes[30].

In recent years, polyphenols, including phenolic acids, flavonoids, stilbenes, lignans, and polymeric lignans, have shown positivity toward improving metabolic disorders and complications arising from diabetes. Evidence is

piling up that plant-food polyphenols would serve as nutraceuticals and adjunct therapeutics for different aspects of type 2 diabetes mellitus, because of their biological properties[33].

Regulatory Framework for Nutraceuticals

Nutraceuticals and food supplements are governed differently in different countries, with guidelines set by bodies such as the Food and Agriculture Organization (FAO)/ World Health Organization (WHO) via the Codex Alimentarius. For instance, the FDA in the USA compels manufacturers to prove safety in the use of nutraceuticals prior to marketing them with surveillance for unsafe products; however, no prior Food and Drug Regulatory Authority (FDA) approval is required for production[34]. In contrast, the EFSA in Europe demands authorization for health claims prior to product marketing. Canada is an example where nutraceuticals are subjected to stricter regulations, almost like that of drugs while India's legislation considers nutraceuticals as special dietary foods whose regulations were introduced by Food Safety and Standards Act (FSSA). Indeed, Japan is the pioneer in the legislation on nutraceuticals as it grants approval to foods with health effects even without scientific evidence under its 'Foods for Specified Health Use (FOSHU). Other countries such as Australia, China, and some Latin American countries treat nutraceuticals as food, but some require prior clinical studies to be conducted before registration. Generally, proper assessment of safety with consequent clinical studies precedes the commercialization of nutraceuticals with health claims being authorized only after sufficient evidence of efficacy and safety has been provided[35].

Safety and Toxicity

Although commonly regarded as safe, some nutraceuticals have been proved to cause damage to the liver in the case of epigallocatechin gallate in green tea. Soy-derived iso-flavonoids genistein and daidzein have been shown to induce reproductive effects, and reduced fertility, also stimulation of estrogen-sensitive tumor growth due to their estrogenic activity. Purified isoflavones often consumed by menopausal women can have a higher risk of estrogen-sensitive cancers than whole soy foods. This suggests that concentrated or purified forms of these products should be cautiously used[36].

Future Prospectives

Nutraceuticals indeed have bright prospects with the ongoing progress in personalized nutrition, innovative delivery systems, and the growing importance of preventive health. This will entail when integrated with nutrigenomics and technologies enabled by digital health for individualizing solutions based on individual requirements with nanoencapsulation and bioavailability enhancements that would bring product efficacy. In addition, standardized measures for safety and efficacy by evolving regulatory frameworks will strengthen consumers' confidence. This will, further create additional space for growth with an increase in demand for wellness products from most emerging markets, as well as from growing populations of aging people. Further nourishment in an individual's health journey using health apps and wearables will also be accomplished with nutraceuticals[37].

Conclusion

Incorporating nutraceuticals into patient treatment marks a noteworthy progress in the strategy towards health and wellness. This review emphasizes the complex challenges involved in creating nutraceuticals, including concerns regarding chemical stability, bioavailability, and the creation of appropriate dosage forms for various demographic segments. Cutting-edge drug delivery methods, including nanocarriers and pH-sensitive formulations, provide hopeful options to improve the effectiveness and stability of these products. Moreover, the significance of

nutraceuticals in preventing and managing diseases highlights their role in modern healthcare. Nonetheless, the regulatory environment continues to be intricate, requiring thorough safety evaluations and clinical research to guarantee consumer safety. With the progression of the field, the outlook for nutraceuticals seems promising, especially with the rise of personalized nutrition and progress in digital health technologies, which can enhance their therapeutic advantages. Ongoing research and development in this field will be vital to satisfy the increasing need for safe and effective nutraceutical products, particularly among older adults pursuing comprehensive health options.

Abbreviations

FIM	Foundation for Innovation in Medicine
PKU	Phenylketonuria
DHA	Docosahexaenoic acid
CMC	Carboxymethyl cellulose
NGs	Nanogels
GFR	Glomerular Filtration Rate
HD	Huntington's disease
PD	Parkinson's disease
AD	Alzheimer's disease
EGCG	Epigallocatechin gallate
COVID-19	Corona virus disease 19
ROS	Reactive oxygen species
DNA	Deoxyribonucleic acid
ACE	Angiotensin converting enzyme
FAO	Food and Agriculture Organization
WHO	World Health Organization
FSSA	Food Safety and Standards Act

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MN: Conceptualization, Writing-Original draft, Supervision. FP: Writing-Original draft, Writing -review & editing. MK: Writing -Original draft, Writing review & editing. ST: Validation, Writing-review & editing. All authors read and approved the submitted version.

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