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# EXPLORING THERAPEUTIC EFFICIENCY AND FORMULATION STRATERGIES IN NUTRACEUTICALS: A COMPREHENSIVE REVIEW

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Abstract: Nutraceuticals are the nourishing components (Hybrid of nutrition and pharmaceuticals) that are biologically active and possess capability for maintaining optimal health and benefits. This product plays a significant role in human health care and its endurance, most importantly for the future therapeutic development. Nutraceuticals have received recognition due to their nutritional benefits along with therapeutic effects and safety profile. Nutraceuticals are globally growing in the field of services such as health care promotion, disease reduction etc. Various drug Nutraceuticals interaction have also been elaborated with various examples in this review. Several patents on Nutraceuticals in agricultural applications and in various diseases have been started in last section of review, which confirms the exponential growth of Nutraceuticals market value. Nutraceuticals have been used not only for nutrition but also explore the therapeutic efficacy to prevent and treat the various diseases, such as to reduce side effects of cancer chemotherapy and radiotherapy. Diverse novel an formulation approaches tend to overcome challenges involved in formulation development of Nutraceuticals. Prior information on various interactions with drugs may help in preventing any deleterious effects of Nutraceuticals products. Nanotechnology also leads to generation of micronized dietary products and other Nutraceuticals supplements with improved health benefits. In this review article, the latest key findings(clinical studies) on Nutraceuticals that show the therapeutic action of Nutraceuticals that show the therapeutic action of Nutraceuticals bioactive molecules on various diseases have also been discussed.

IndexTerms - Cardiovascular diseases, Interactions, nutrition, prevention therapeutics.

## I. INTRODUCTION

II. Nutraceuticals are characterized as 'specially designed preparations', formulated with the aim of fulfilling specific dietary requirements and/or offer preventive health care. Nutraceuticals are the formulation of nutrient/nutrients which helps in prevention and treatment of some diseases, in addition to a supplement diet. Nutraceuticals is a term given by Dr. Stephen De Felicia in 1989 and came from two words "nutrition" and "pharmaceutical". These are foods or a part of foods that are beneficial in providing various health benefits including the treatment and/or prevention of the disease. Science of nutrition has increasingly achieved new horizons, starting from the anticipation of deficiencies in nutrients to prominence on human health and prevention and treatment of chronic ailments. Terms 'Nutraceuticals, 'food supplements', 'dietary supplements' have evolved after the concept was originated by Dr. De Felicia. There is no sharp demarcation between food supplements and Nutraceuticals given by regulatory authorities. Literature of recent years emphasizes on redefining the concept of Nutraceuticals, taking into consideration the efficacy, safety and toxicity of these products. Food products are nourishing substances that are eaten, drunk or otherwise taken to sustain life, provide energy and promote growth. Currently, isolation of nutrients from these food products are well recognized and used. The starting point to differentiate food/dietary supplements and Nutraceuticals is the identification of an epidemiological target, followed by safety and efficacy studies that understand the mechanism of action. One approach to differentiate these two types of formulations is describing ‘food supplements’ as agents to compensate deficiencies in micro- or macronutrients; in addition, the use of a “Nutraceuticals” in the treatment of a pathological disease must be supported by strong scientific evidence[1]. With adequate clinical evidence, nutritional supplements should have a strong safety profile with few undesirable side effects and better bioavailability. There is a very fine line of demarcation between two type of formulations: the same ingredients may work as a Nutraceuticals or food supplement, but may be demarcated on the basis of claims. Nutraceuticals include single or combinations of pro- and pre-biotic foodstuff and food for special medical uses; and food supplements includes single or combinations of mineral, vitamins, protein supplements, functional foods and herbal products. By prolonging or eliminating the need for pharmaceuticals in subjects to fit for an alternative no pharmacological treatment to a pathological condition, the incorporation of Nutraceuticals into daily diet may aid in the prevention of pathological disorders. There are claims that foods including spices and herbs possess the tendency to decrease the risk of many diseases and can be highly beneficial in improving the quality of life[2]. There is a plethora of benefits that Nutraceuticals have provided, including their promising results in the prevention and treatment of complicated diseases. However, there is a need of administration and prescription of Nutraceuticals and they should be strictly regulated in order to prevent their uncontrollable use and side effects[3]. Several researchers have studied drug compound-based nutraceuticals to improve the efficacy as well as bioavailability. The safety and efficacy of various statins have been used in the prevention of cardiovascular diseases even in pregnant women. Nutraceuticals with an effective safety profile and well-established impact on pregnancy might be a suitable therapeutic option for preventing diabetes mellitus and hypertensive disorders, or as an adjuvant to therapy with standard medications. Calcium, omega-3 polyunsaturated fatty acids, vitamin D, folic acid, resveratrol, alpha-lipoic acid, zinc, inositol, and probiotic supplements are potentially proven candidates as novel Nutraceuticals[4]. The Nutraceuticals and functional food industries are in a good position to take advantage of consumer interest in these products. Whether it's a big pharmaceutical corporation, a nutritional company, a large food multinational, or a tiny vitamin-selling company, all are aware of changing patterns and the growing health- conscious customer trend. As a result, there is a proliferation of these value-added goods targeted at not only maintaining one's health but also the prevention and treatment of a variety of conditions ranging from heart disease to cancer [5]

III. Researchers have evaluated the Nutraceuticals associated with the drug compound ezetimibe for patients at risk of elevations of statin level, which further leads to cardiovascular diseases [17]. The use of a novel Nutraceuticals in blend with non- steroidal anti-inflammatory drugs (NSAIDs) has been proven a potential candidate for osteoarthritis, thus improving its efficacy and safety for commercial use[18].

IV. The market remains robust and ever-growing for Nutraceuticals such as antioxidants; omega-3 fatty acids; plants such as algae, aloe-Vera, seaweed, and wheatgrass; teas and herbs such as ginseng and Echinacea. A detailed findings including clinical data on Nutraceuticals are shown in Table 1[19,20]. A recent survey suggested that the Nutraceuticals market is expanding globally and the probability states that it may reach up to $340 billion by the year 2024. The compound annual growth rate (CAGR) of nutraceuticals is estimated to be 7.2% in the year 2016 to 2024. This increment in the growth of the nutraceuticals-based industry is associated with various factors such as a rise in demand for Nutraceuticals, an awareness among people for the benefits of nutrition and an incremental rate observed in the healthcare graph[21,22]. Currently, Europe, USA and Japan account for >90% of the total global nutraceutical market and the global market is supposed to reach $336 billion by 2023 from $247 billion in 2019 at a CAGR of 8%. With this attainment of maturity of global markets, now the focus of nutraceutical players has been shifted towards developing economies, especially those across Asia Pacific, including India. The Indian market had only 2% market share of total global nutraceutical market in 2017. It is estimated to reach $11 billion by 2023, increasing at a CAGR of 21%. By 2023, India is also expected to hold at least 3.5% market share of the global market[23,24].

CLINICAL DATA ON NUTRACEUTICALS.

| Nutraceuticals | Bioactive Molecule | Dosage | Formulation | Duration of Study | Action | Population Size (Volunteers) | References |
|---|---|---|---|---|---|---|---|
| Omega- 3 | Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) | 60 mg/kg/day | Capsule | 12 Months | Cystic fibrosis | 15 | [6] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Omega- 3 | Eicosapentaen oic acid (EPA) and Docosahexaen oic acid (DHA) | 900 mg in omega- 3 rich group and 250 mg in omega- 3 poor group | Capsule | 15 days | Reduct ion of chemo - therap y related toxici- ties | 61 | [7] |
| Omega- 3 | Eicosapentaen oic acid (EPA) and Docosahexaen oic acid (DHA) | 2000 mg/day | Capsule | 21 days | Appeti te | 72 | [8] |
| Aloe Vera | Aloe-emodin, aloin, aloesin and acemannan | - | Gel | 2 months | Acute dermat itis | 120 | [9] |
| Aloe Vera | Aloe-emodin, aloin, aloesin and acemannan | 60 mL | Juice | 5 months | Irritabl e bowel syndro me | 110 | [10] |
| Seaweed | Polysaccharide s, proteins, lipids and | 2000 mg/day | Extract | 12 weeks | High- densit ylipop | 34 | [11] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | polyphenols | | | | rotein (hdl) cholest erol | | |
| Wheatgrass | Vitamins, (A,B,C and E), minerals such as iron, calcium, magnesium, benzo(a)pyrene , ferulic, gallic, caffeic, syringic and p-coumaric acid | - | Cream | 12 weeks | Plantar fasciiti s | 134 | [12] |
| Ginseng | ginsenosides | 100 mg twice a day | Capsule | 12 weeks | Psych omoto r functio ns | 16 | [14] |
| | | | | | | | |
| Echinacea | Polysaccharide s, | 20 mg or 40 mg | Powder | 6 weeks | Anti- anxiet | 104 | [16] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | glycoproteins, alkamides,cich oric acid, caftaric acid and chlorogenic acids | twice a day | | | y and anti- depres sant | | | |

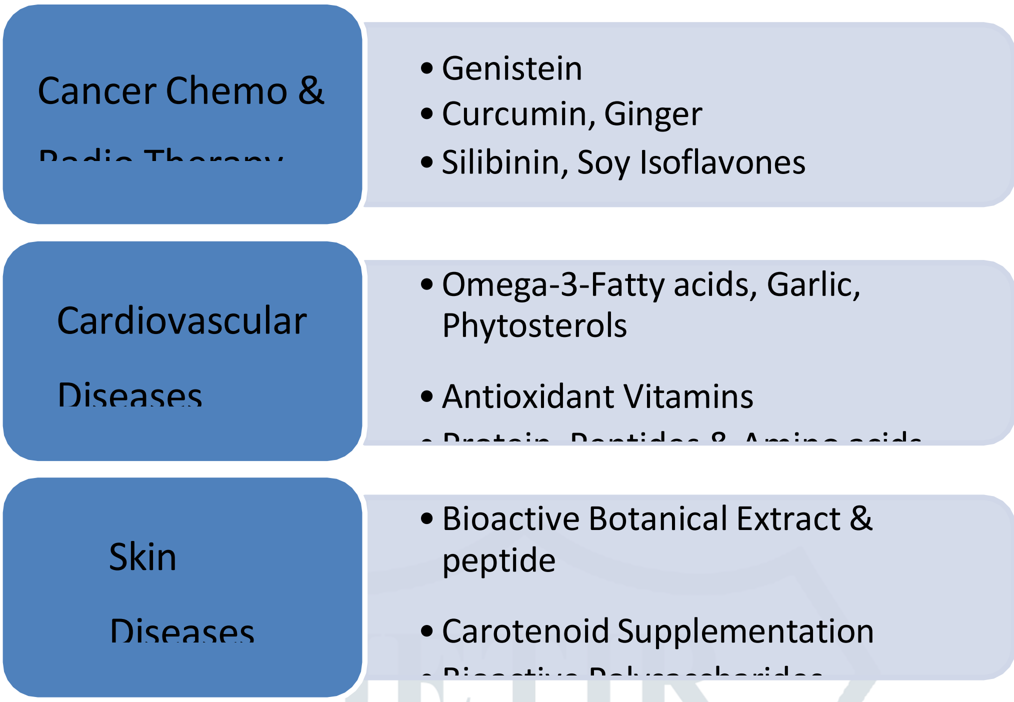
**Table 1: Clinical data of Nutraceuticals.**

Nutraceuticals industry is not able to bridge the gap between high demand and low supply as 75–80% of raw material used in nutraceuticals was sourced from China in North America, Europe and Asia Pacific. Due to China's manufacturing shutdown, and the sudden recessive conditions in native regions, the nutraceutical production has reduced. The sharp surge in demand was observed for dietary supplements from consumers, as they provide a strong immune function and decrease possible health threats[25].

However, an officially shared and accepted definition of Nutraceuticals is missing; these are also referred as ‗pharma food'—a powerful toolbox that is beyond the diet but before the drugs. Various formulations containing macronutrients (required in large amounts, e.g., omega-3 fatty acids, magnesium, potassium and calcium)[26], micronutrients (required in lesser amounts, e.g.,minerals or vitamins)[27] and phytochemicals that are present inthe food source[28] and are available at drug stores. Further,probiotics[29], minerals[30],polyunsaturated fatty acids[31], carotenoids[32], amino acids and proteins[33], vitamins[34], dietary, Fibers[35], spices and phytochemicals[36] have also become part of these formulations. Nutraceuticals exist as various types and may range from herbal products to isolated nutrient diets and may go up to existing genetically modified foods{37,38,39]. Plant foods such as vegetables, whole grains and vitamins are rich in dietary phytochemicals. Dietary supplements are consumed as such, or as isolated active ingredients. These phytochemicals are immensely diverse and these include carotenoids[40], phenolic[41], alkaloids[42],organosulfur[43] and nitrogen containing compounds[44]. However, these products may not be substantiated by scientific data on their safety, efficacy and effect on health and/or pathological conditions. In the pharmaceutical industry, it is mandatory to do clinical tests on animals or in vitro for the verification of a compound's effects. On the contrary, in nutrition, there was no such method in the past for the verification of effects of foods in preventing or treating diseases. In recent years, however, the food composition has been scientifically tested and verified as people are becoming more and more aware of health-related issues and how food can directly or indirectly be responsible for maintaining proper health and preventing diseases[45,46].

- NUTRACEUTICALS IN VARIOUS DISEASES

Nutraceuticals help enhance health, wellbeing and modulating immunity, thus preventing and treating various diseases and health issues (in chart) There are a variety of diseases that can be treated with the help of nutraceuticals which are discussed below:




Nutraceuticals and Dietary supplement in various Diseases

- Nutraceuticals in Cardiovascular Diseases

Among all other diseases, cardiovascular diseases reveal significant risk-related factors acquiescent to Nutraceuticals intervention [47]. There is significant evidence indicating that Nutraceuticals can be used in cardiovascular diseases [48,49]. Cardiovascular diseases (CVDs) mainly affect the blood vessels and the functioning of the heart. CVDs are one of biggest causes of mortality, as they account for about 30% of deaths all over the world annually [50]. Dietary supplements have been proven to be beneficial in risk management and prevention of cardiovascular diseases and can be classified broadly into the ones used in the treatment of arrhythmias [51], Congestive heart failure [52], angina [53], hypertension [54] and hyperlipidemias [55,56]. Some of the Nutraceuticals and dietary supplements that are used for the treatment and prevention of CVDs are discussed below.

1. Allicin and Alliin

Ischemic heart disease and atherosclerosis are associated with elevated levels of plasma triglycerides and blood-cholesterol are associated with. *Allium sativum* is antihyperlipidemic in nature and it exerts its effects by the elimination of cholesterol and its end-products in high amounts in the feces and by decreasing the cholesterol synthesis endogenously [57]. This helps in producing more favorable ratio of HDL and LDL. Allicin and alliin can effect cholesterol levels, if these can be protected by gastric acids. Garlic supplementation on serum cholesterol was assessed using thirteen placebo-controlled trials concerning 781 patients. Garlic also has some inherent antihypertensive effect, apart from being antihyperlipidemic [58,59].

2. Omega-3Fatty Acids

Omega-3 fatty acidsare derived from marine sources and are called polyunsaturated fatty acids (PUFAs). Docosahexaenoic acid (DHA) and Marine omega-3 eicosapentaenoic acid (EPA) plays a critical role in the treatment and prevention of cardiovascular diseases. In one study, it has been reported that intake of fish oil supplements reduced mortality rate by 29% for over a period of 2 years in the diet and reinfarction trial (DART), which was a randomized trial involving 2033 men post-myocardial infarction. Consumption of fish oil led to a noteworthy reduction in unexpected demises by 45%, cardiovascular diseases deceased by 30% and a 20% decrease in overall mortality. According to the recent clinical trial studies, it has been found that the risk of cardiac arrhythmias is decreased with the help of omega-3 fatty acids, and they also improve the health of the patients suffering from plaque formation caused by atherosclerosis. Omega-3 fatty acids enhance the electrical-stability of heart cells, thereby extending its relative refractory period and helping treat arrhythmias [60,61].

3. Soy Isoflavones

Soy proteins and soy isoflavones are important nutrients with potentially medicinal benefits such as antihyperlipidemic, antihypertensive, anti-hyperglycemic, antioxidant, anticancer, anti- inflammatory, anti-obesity and neuroprotective activities that support the biological plausibility for observational associations. It is evident from clinical study reports that consumption of soy protein reduces serum cholesterol levels in humans [62]. In addition, USFDA has evidenced that 25g of soy proteins or isoflavone per day intake showed a lowering of blood pressure in postmenopausal women. Moreover, soy proteins exert favorable effects on the serum lipid concentrations, especially in hypercholesterolemic patients. In a study, subjects fed with a diet low in saturated fat leads to the decrease in risk of coronary heart disease. Soy isoflavone had no effects on the lipid profiles [63]. Further a study reported significant reduction of the ratio of LDL to HDL after intake of new soy products, having high levels of isoflavones, cotyledon soy fiber and soy phospholipids (Abaco and Abalon) [64].

4. Proteins, Peptides and Amino Acids

Hypertension is associated with cardiovascular diseases. ACE (angiotensin converting enzyme) inhibitors have been a chief line of therapy to treat the condition, but these drugs lead to side effects such as hypotension, elevated levels of potassium, impaired renal function, coughing and skin rashes [65]. Natural, ACE inhibitors are found in casein and whey protein derived from milk. It is also evidenced from animal studies that these milk-derived proteins exert antihypertensive effects. The same has been reported in clinical studies where a statistically significant hypotensive effect has been observed [66].

5. Antioxidant Vitamins

Antioxidants have been used as potential supplements in chronic diseases such as cardiovascular diseases and cancer. They reduce LDL-cholesterol oxidation by counteracting the damaging effects of free radicals. Vegetables, fruits, fish and fixed oils contain antioxidant vitamins in large volumes, which works by preventing the formation of oxygen free radicals or by entrapping them. It has been evidenced in some epidemiologic studies of CHD patients on a diet of large quantities of antioxidants that they result in fewer incidences of morbidity and mortality. Supplements having antioxidant vitamins C and E help in preventing CHD. However, supplementation with ß-carotene can produce adverse effects and, thus, is not recommended. The National Health and Nutrition Examination Survey-I cohort study observed that risk of CHDs decreases in vitamin C intake, which was found in the observation of over 10 years in American men and women of age group of 25– ears, in which subjects were randomized with diverse combinations of 10 nutritional supplements for over five years [67].

6. Phytosterols

Phytosterols are structurally similar to cholesterol. They tend to compete for absorption through the small intestine. These are found naturally in vegetable oils, seeds, nuts, grains, wood pulp, etc. [68]. Intake of phytosterols led to increased hepatic uptake of LDL, reduced blood LDL levels, and reduced absorption of cholesterol. Studies have indicated up to 15% reduction in LDL levels by intake of plant sterols [69]. Plant sterols are derived from natural grains such as soy, sunflower and corns. Various studies evidenced that the consumption of 2–3 g/day of plant sterols/stanols tend to reduce LDL cholesterol levels up to 20%; although, there is substantial variation amongst individuals [70].

- Nutraceuticals in Cancer Chemo- and Radiotherapy

Radiotherapy and chemotherapy are conventional therapies for cancer therapy but have serious side effects and various complications (e.g., pain, fatigue, diarrhea, vomiting, nausea and hair loss) [71,72]. There are some cancers that are highly resistant to chemo- and radiotherapy and, because of this, systemic cytotoxic chemotherapy and radiotherapy are not very operative at cultivating patient subsistence [73,74]. In this situation, various combination therapies overlay an efficient means to treat cancer. Likewise, there are a variety of plants and natural supplements that are observed to reduce side effects of radiotherapy and chemotherapy. Thus, these should be used in the combination with radio- or chemotherapy for the reduction of side-effects and to augment treatment effectiveness. Proliferation of cells leading to cancer results in the need to treat, and the nutraceutical industry is evolving to treat the needs of the consumers. The evolution of the nutraceutical industry can be recognized as it has now reached disease prevention after it started from health promotion. A plethora of currently used herbs and phytochemicals are safe pharmacologically and have been proven to be potent nutraceuticals in suppressing tumor progression, alleviating the disadvantages of radio- and chemotherapy and increasing the sensitivity of these therapies [75,76]. Caponio and his team evaluated the effects of the phenolic compounds found in Aglianico Grape pomace (GP) on colorectal cancer cell lines at varying stages of development after subjecting them to an in vitro digesting model. Aglianico GP extract was found to have strong effects on cell proliferation and apoptosis, as well as on other cellular processes. A substantial upregulation of Bax, as well as the Bax/Bcl-2 ratio and caspase-3, was observed in both HT29 and SW480 cells. UHPLC-DAD analysis revealed that anthocyanins, phenolic acids, and flavonoids were the primary components responsible for the elevated (total phenolic content) TPC and antioxidant activity in the Aglianico GP digested extract [77]. In

2021, Zhang and his co-workers studied the combined effect of chrysin and apigenin by suppressing the activity of P38-MAPK/AKT pathway in colorectal cancer. Apigenin and chrysin, both at 25 µM, substantially inhibited clone number, migration and invasion, while increasing apoptosis in both colorectal cancer (CRC) cell lines. Additionally, chrysin and apigenin significantly suppressed p-P38 and p-AKT. Anisomycin, a P38 agonist, effectively mitigated the tumor-inhibiting action of apigenin and chrysin. Together, apigenin (25 µM) and chrysin (25 µM) had a synergistic impact in limiting the proliferation and metastasis of CRC cells by suppressing the P38-MAPK/AKT pathway [78].

1. Curcumin (Diferuloyl-Methane) from Turmeric (Curcuma Longa)

Curcumin has been classified as a commanding nutraceutical for cancer treatment. Pre-clinical studies with curcumin suggest that it inhibits carcinogenesis in different types of cancers, such as pancreatic, colorectal, prostate, gastric and hepatic cancer; in addition, it has been able to suppress it at every step, that is, angiogenesis, metastasis and proliferation. It is much more effective when it is in combination with the chemo- and radiotherapies for cancer treatment [79].

2. Ginger

Ginger is an anti mutagenic, antioxidant and anti-inflammatory nutraceutical and is known to diminish the side effects of radio and chemotherapy. It is these properties of ginger that provide helpful radio-protector activity. A reported loss in the doses of morphine in cancer patients is seen with the help of Ginsenoside Rf and Ginseng and its polysaccharides are helpful in reducing the side effects of cancer treatment therapies, which has reported to cause a 50% less risk in the recurrence of cancer [80].

3. Genistein

Genisteinis a potent isoflavone and has promising anti- carcinogenic properties. In vitro studies have shown that there are a few components that exert their antitumor effects only at higher concentrations that are not possible to achieve at normal dietary consumption [81]. Thus, it is difficult to achieve the desired effect at the tumor site, which leads us into thinking that the mode of delivery is a very important factor that needs to be considered in in-vivo studies and clinical trials. For a therapy to be formulated, the non-toxicity of the natural components is a very important factor. Nevertheless, it has been found that some compounds are more potent if administered early in life and Genistein is one of them [82].

- Nutraceuticals for Skin Treatment

The skin is known to be the body‘s largest organ and it offers protection against all sorts of microorganisms, ultraviolet radiations and chemicals also participating in sensitivity. As a result of having a major role in protecting the body, skin may face alterations, such as immune dysfunction, photo-aging and inflammation, which may result in harm on human health [83]. A

potential strategy of delaying or diminish pre-mature ageing of the skin and alleviation of skin-related disorders can be found with the help of nutraceuticals. These nutraceuticals can be bioactive peptides, bioactive polysaccharides, botanical extracts, carotenoids, etc. Supplementation with these products in several human trials has evidenced fewer signs of ageing and also protection against UV-radiation ageing [84].

1. Bio-Active Peptides

Peptide moieties are the combination of two or more amino acids and are short sized with low molecular weight (<3 kDa), and some may perform important biological actions thatare termed bioactive peptides. Bioactive peptides have been isolated from a wide variety of dietary proteins, including plant and animal. Eggs, milk (casein and whey), and meat proteins are the most common sources of animal protein. Soy, oat, pulses (chickpea, bean, pea and lentil), canola, wheat, flaxseed and hemp seed are common plant sources for bioactive peptides [107]. Peptides that are used for cosmetic purposes are usually derived from collagen and typically serve as nutraceutical formulations because of their increased bioavailability and solubility [85]. It has typically been observed in a controlled study of VERISOL®, which contains bioactive collagen peptide (BCP). In this study VERISOL® and a placebo were given to subjects for 8 weeks and skin wrinkles were measured before the treatment and after 8 weeks. It was observed that BCP promoted a significant decrease in the eye-wrinkle volume in comparison to placebo after a period of 8 weeks of treatment. Not only this, BCP intake showed an increase in the content of elastin and procollagen type1 along with an increase in the fibrillin content. Thus, this treatment reduced wrinkles and has encouraging effects on skin matrix synthesis [109]. Peptan F and porcine origin Peptan P are some other nutraceuticals of fish origin containing collagen peptides used to slow aging by effectively maintaining the moisture content within skin layers. Recently, a study indicated improved skin properties without risk of oxidative damage by use of a nutraceutical product Celergen®, proving it a safe and effective supplement. This nutraceutical is based on a marine collagen peptide derived from deep sea fish, grape skin, coenzyme Q10 and leutonin [86,87].

2. Bio-Active Polysaccharides

These are sugar-based polymers that have the energy storage and structural functions. They are present in life forms such as plants, fungi, animals and prokaryote organisms having diverse monosaccharide combinations, physicochemical properties and structures. The most useful of them for the nutraceutical formulations is the Glycosaminoglycans from the marine origin. The basic unit of these are- an un-branched disaccharide (repeating) unit of amino sugar called *N*-acetylglucosamine or *N*-acetylgalactosamine and an uronic acid called glucuronic or iduronic acid [88,89]. A human trial of the formulations containing these was conducted using Imedeen® DermOne®, these contain some protein fractions as well along with the glycosaminoglycans and served as dietary supplements for skin care. In addition to the protein the supplement contained zinc gluconate and vitamin C which are relevant for skin care. In the trial conducted, 10 women were treated with an amount of 500 mg of Imedeen® for a period of 90 days. Parameters evaluated were, dryness, brittleness of hair and nails, wrinkles and mottles. It was seen that after 90 days, all these signs were improved, and observations established skin thickness and elasticity [83].

3. Bio-Active Botanical Extracts

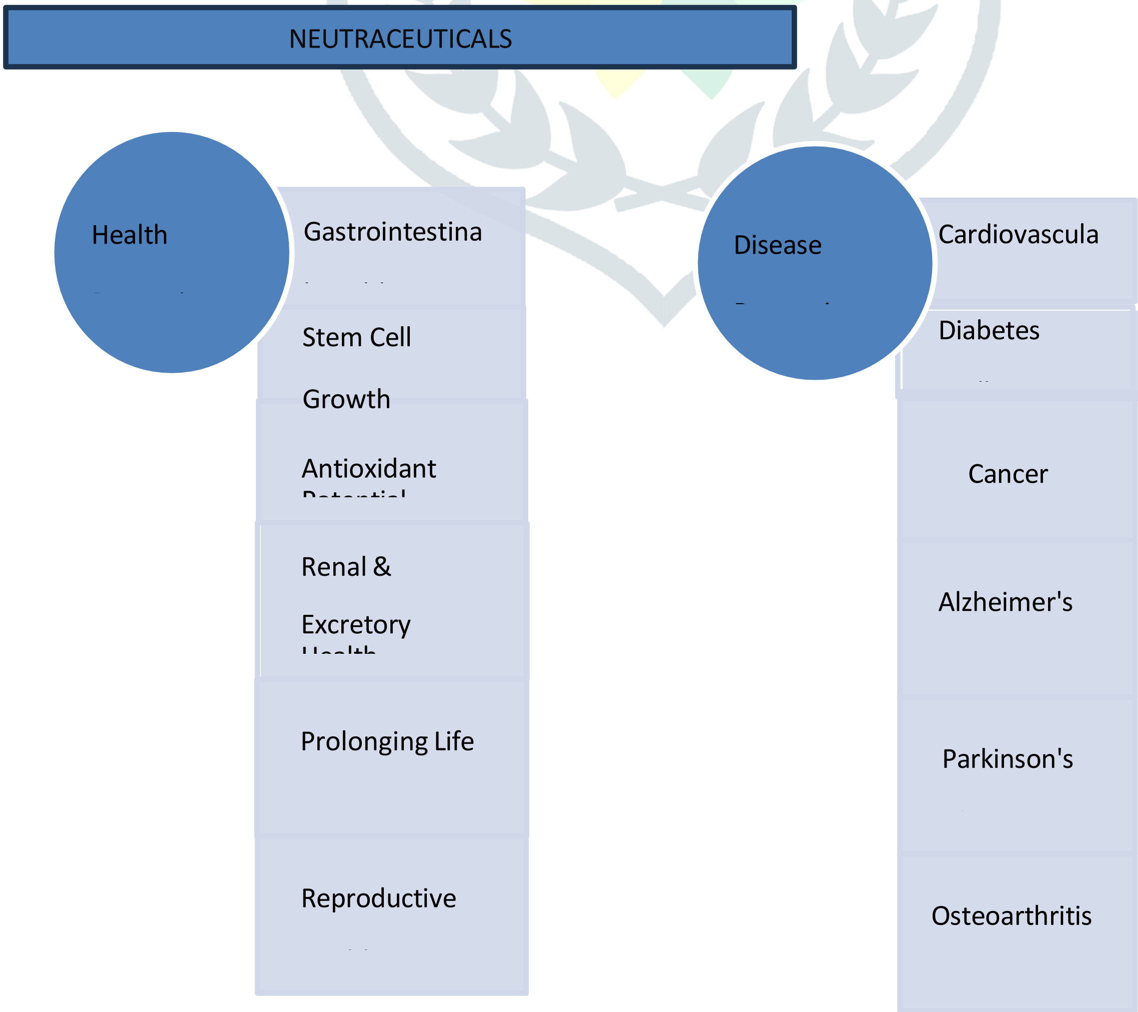
These extracts are multifaceted mixtures of various compounds having diverse structures and origin. Since long times they are being used and reviewed. Polyphenols are one of the key natural compounds with cosmetic applications with a plethora of families and structures. These are plant-based micronutrients available from diet. These are beneficial as support therapy in the prevention of diseases and also improved the outcome of diseases. Various polyphenols have significantly different bioavailability and the most abundant polyphenols in our diet possess the maximum concentration of active metabolites in target tissues. Their composition and proportion vary depending on the procedure of extraction and families [92]. Pycnogenol® is a formulation being made with the help of these and is rich in catechins, flavonoids and procyanidins (B1, B2, B3, B7 C1 and C2), also, they contain phenolic acids such asferulic acid and caffeic acids. It is also confirmed to have several effects such as cholesterol lowering and cardiovascular benefits because of its antidiabetic, anti- inflammatory and antioxidant properties [93,94,95].

4. Carotenoids

These are naturally occurring pigments found in algae, photo- synthetic bacteria and various plants. These have linear tetra terpenoid structure. These are found in natural sources such as fruits, vegetables etc. α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene are the most commonly used dietary carotenoids [96]. These carotenoids are used for skin health such as anti-ageing and photo protection of skin. The probiotics and carotenoids are reported for decreasing the skin damage due to UV-exposure and also in modulating early skin biomarkers of UV effects. A Carotenoid mixture supplement of α-carotene, β- carotene and lutein are proved effective in photo protection. Similarly, a mixture of beta-carotene, lutein and lycopene carotenoids is reported for protection against erythema. The vitamin C and E is studied for the photoprotective effect and found to effective in skin health care [97]. Vitamin C is a hydrophilic vitamin, commonly taken in large doses via consuming various food products with the intent of inhibiting the formation of carcinogenic nitrous metabolites. It acts as a cofactor for the synthesis of collagen fibers and inhibits the biosynthesis of elastin in fibroblasts thereby preventing its accumulation, which is highly present in photo-damaged skin. In combination with vitamin E, it acts synergistically working with its mechanism of transformation. Vitamin E is the main lipophilic antioxidant and is found in the form of tocopherols. It binds with peroxyl radicals, thereby preventing lipid peroxidation of polyunsaturated fatty acids. In addition, its use for preventing photodamage, sunburn, atopic dermatitis, etc., is clearly evidenced [98,99].

- Nutraceuticals as Specialized Medical Products

According to the legal basis, dietary foods and enhancements for distinct medical purposes are specialized medical products. These dietary supplements should be regulated according to the regulatory agencies such as ‗European Food Safety Authority' and the ‗U.S. Food and Drug Administration', in addition to numerous national protocols issued most often by the ‗Ministry of Agriculture' and/or ‗Ministry of Health' of various countries around the world [100]. Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms. Figure 3 shows a flow chart indicating role of nutraceuticals in health promotion and disease prevention. Various nutraceuticals in health promotion are summarized in Table 2 [101,102,103].



Role of Nutraceuticals in health promotion and disease prevention.

Table 4 :- Nutraceuticals with health benefits.

| **Nutraceuticals / Dietary Supplements** | **Nutrients** | **Health Benefits** |
|---|---|---|
| **ter Soluble Vitamins** | Vitamin C<br>Vitamin B1<br>Vitamin B2<br>Vitamin B3<br>Vitamin B6<br>Vitamin B12<br>Folic Acid<br>Pantothenic Acid | Wound Healing, Anti-Oxidant.<br>Carbohydrate metabolism, Neurological Function.<br>Energy Metabolism, Nerve Function.<br>Brain Function.<br>Convert Proteins to energy.<br>Formation of RBC‘s, Formation of genetic material of cells.<br>Intraneuronal synthesis of Acetylcholine.<br>Synthesis of Cholesterol, Steroids and Fatty Acids. |
| **at Soluble Vitamins** | Vitamin A Vitamin D<br>Vitamin E<br>Vitamin K | Cancer, Skin disorder, Healthy vision Antioxidant. Absorption of calcium, Formation of bones and teeth. Boost immune system, Antioxidant.<br>Blood clotting. |
| | Calcium | Maintaining bone strength, blood clotting. |

| | | |
|---|---|---|
| **Minerals** | Iron | Oxygen transport, Energy production. |
| | Magnesium | Healthy nerve and muscle function and bone function. |
| | Phosphorus | Phosphorylation process, Genetic material |
| | Copper | Heart functioning, Iron absorption. |
| | Iodine | Functioning of thyroid gland. |
| | Chromium | Diabetes |

| | | |
|---|---|---|
| | Selenium | Antioxidant |
| | Zinc | Sperm production, wound healing. |
| **Herbals** | Aloe vera | Anti-inflammatory, Wound healing. |
| | Evening Primrose oil | Treatment of atopic eczema |
| | Garlic | Anti-bacterial, Anti-fungal |
| | Ginseng | Carminative, Anti-emetic |
| | Green tea | Adaptogen |

CHALLENGES AND FORMULATIONS

A quality Nutraceuticals formulation with physical and chemical stability, adequate safety, technological feasibility and still cost effective entails many challenges. When compared with drug molecules that are well defined chemical entities, botanicals are complex ingredients containing multiple chemical constituents and usually several classes of compounds are present in a single product. Most of these botanicals are susceptible to heat, light, oxygen, alkaline pH and elevated humidity. These are usually having poor flow, bulk density and variable particle size distribution. Thus, successful development of nutraceutical formulation requires knowledge of the fundamental aspects of the physicochemical properties of the different types of ingredients, the use of adequate techniques of manufacturing, selection of the right excipients and the addition of suitable manufacturing overages based on critical stability studies [104,105]. Here, emphasis is given on:

1. Challenges with various dosage forms;
2. Approaches to deal with formulation challenges;
3. Excipients selection.

- Challenges in the Formulation of Nutraceuticals and Dietary Supplement

While formulating nutraceuticals, the poor aqueous solubility, high melting point of nutraceuticals and chemical instability of active constituents pose difficulties. For example, omega-3 fatty acids, carotenoids, oil soluble vitamins, curcumin possess high nutritional value but are poorly soluble. Therefore, the possible approach is to formulate these as novel delivery systems. These novel delivery systems make them costly. Thus, efforts are needed to make these formulations cost effective [106]. Another challenge in formulating nutraceuticals is their high melting point. For example, phytosterols, fatty alcohols and carotenoids all have high melting points that may cause instability to formulation. Therefore, the possible approach is to prepare solid dispersion/dissolve in suitable grade solvent and introduce in food as suspended nanocrystals. However, the challenge is again that it leads to deteriorated stability and shelf life, disagreeable appearance, and obnoxious odor and mouthfeel, which affect market value and customer demand. Therefore, there is need to develop cost-effective technologies [107,108,109]. Chemical instability is another challenge. For example, omega-3 fatty acid rich oils, such as fish oils, flaxseed oil, cod liver oils; carotenoids; lycopene or curcumin all have stability issues. The extent of the chemical degradation is completely dependent on the composition of the bioactive product, the environmental conditions such as temperature, pH, pressure, etc., or the presence of metals or other such oxidation-promoting agents. For such compounds, the development of nanoscale products is essential to protect them from degradation [110,111,112,113,114,115,116]. Further, in the case of the development of probiotics, special, selective bacterial strains are necessary. A current challenge is the selection of the proper strain followed by their incorporation in foods. Application of any mismatching bacterial or toxic cultures, in addition to their negligent handling, can cause disastrous consequences. Apart from these challenges, other considerations are solid dosage formulation and process design for drug products and nutrition products that are similar, but the purpose and regulatory requirements may differ [117,118]. Finally, there is a challenge in the formulation of nutraceuticals and dietary supplement dosage forms that are suitable for different groups of the aging population, especially older adults and children. This is because this group of people has limitations in solid dosage from (tablets or capsules) swallowing (dysphagia). Therefore, advanced dosage forms such as orodispersible tablets, fast dissolving films and easy-swallowing gels, which are normally used in pharmaceutical applications, have to be considered in nutraceutical and dietary supplement administration [119,120,121].

- Approaches to Deal with Formulation Challenges

One of the most widely used approaches is isolation or preparation of concentrates of nutraceuticals from natural sources. It is advantageous as most of herbal nutraceuticals are to be administered in a large dose per daily serving. Further, multiple ―active ingredients‖ are present in different sources. There is significant variation in active ingredient compression and flow characteristics within one dosage form. There are large variations in heat and moisture sensitivity of ingredients within one formula. Significant stability challenges are there with multiple opportunities for interaction. Different extraction processes involve microwave-assisted extraction, counter current extraction, maceration, percolation and Soxhlet extraction. Natural bioactive compounds are plant extracts; herbal concentrates; fruit, vegetable and specialty concentrates; and fungal and microbial materials, which are included in feedstock to produce concentrates (bio- fermentation process). Concentrates may include excipients used in production (such as spray dried carriers) [122,123]. Another promising approach is modification in delivery systems. Novel Drug Delivery Systems have been used to modify the properties of various compounds to produce new generations of drug compounds. They also play a role in the food industry and in various kinds of nutritional supplements. Various formulations of supplements prepared by nanotechnology, called nano formulations, that have increased bioavailability, reduced side effects and protect the active ingredients against the process of degradation, have been reported [146,147]. The polyphenols obtained as Nutraceuticals in the form of dietary sources have proved greatly advantageous in improving diseased symptoms as observed in preclinical and clinical studies. One of the most commonly encountered disadvantages is its lower bioavailability due to the lesser gastrointestinal absorption in the upper tract attributable to hydrophobicity, presence in the polymeric or glycosylated form in foods, and they bound tightly with the food matrices. All these factors lead to the minimum bio-accessibility of polyphenols inside the body. Therefore, food processing-based research and development techniques along with nano formulations, enzymatic treatment, probiotics combination therapies, among others, have proved advantageous to overcome this challenge [124,125]

- Liposomes and Nano emulsions

Liposomes and Nano emulsions are also termed as bilayer phospholipid vesicles and possess greater potential for the industry of Nutraceuticals as they can simultaneously encapsulate both hydrophilic and lipophilic materials. This ensures a synergistic effect and is also helpful in the protection of bioactive compounds that are highly sensitive, ensuring enhanced bioavailability, sustainable release and storage stability. As the nanoliposomes have unique properties, they can be effectively used in operative prevention against diseases and also for health promotion. One of the latest examples is lipid-based nanocarriers, nanophytosomes, which help in enabling the delivery of botanical nutraceuticals. They have the potential to be used in various food products for the design of novel functional beverages and food products. A study indicates increased chemical and physical stability of rutin when rutin complexes were formed in the form of phytosomes. These phytosome complexes of rutin were formed with the help of phosphatidylcholine (PC) with the molar ratio of (rutin: PC) being (1:3) with a particle size of less than one hundred nm and 99% encapsulation efficiency, as it was able to mask the undesirable properties of rutin. These were termed as phytosomes, phosphatidylcholine (PC)—rutin complexes [126,127].

- Lipid-Based Carriers

Lipid formulations in the form of nanocapsules, micronized carries are potential candidates to be used to effectively enhance the controlled release, solubility and bioavailability of phenolic compounds. As an example, β-Car nanocapsules (>300 nm), due to their physical stability showed only negligible variations during storage, which suggested that they can be widely used as functional foods and beverages along with being nutraceutical products [128,129].

- Polysaccharide Matrices

These are the kind of matrices that have numerous enzymatic exposures that guarantee degradation at specific points in the large and small intestine. When being used as a nanoparticle coating, they can effectively retard the nonspecific release of bioactive components encapsulated within until the coating is exposed in the intended environment where it was intended to be released. These coated nanoparticles can potentially be used to target various diverse organs of the GI tract to help improve the oral bioavailability [128,130].

- Excipient Selection

Next, the approach to deal with formulation challenges of nutraceuticals is modification in formulation parameters by appropriate selection of excipients. For nutrition, the final formula must be robust to accommodate the variable physical characteristics of natural ingredients in a complex formula. Materials and manufacturer must meet internal quality and safety, specifications and performance requirements. One formulation‘s functionality can be another formulation‘s dysfunctionality. Excipient functionality can only be properly assessed in the context of a particular formulation and manufacturing process. For natural product formulation, excipient functionality in a particular formula is heavily influenced by the complex combination of multiple active ingredient characteristics. Occasionally, seemingly equivalent excipients are not equivalent in functionality [132].

CHALLENGES

Drug interactions may be described as the situation when the activity of one active constituent is affected due to presence of other constituents. It may be food–drug interaction or drug–drug interaction. The pharmacological response may alleviate, lessen or induce side effects [133,134].

1) Garlic (alicin) exhibits a hypotensive property and a hypocholesterolemic effect, acts as an anti-inflammatory agent and possess anti-bacterial as well as anti-fungal properties. When it is administered with anticoagulants (such as warfarin), it may lead to increased bleeding. With hypoglycemic drugs, such asinsulin or glipizide, it may cause hypoglycemia. With protease inhibitors (such as indinavir or saquinavir), garlic decreases their blood levels and effectiveness [135,136].
2) Ginger is commonly used to treat various types of stomach problems—such as, to expel gas, formotion sickness, diarrhea, nausea (anti-emetic) and loss of appetite. It is also used in pain relief from arthritis, menstrual pain, upper respiratory tract infections—coughs and bronchitis. Ginger taken with anticoagulants may lead to risk of bleeding. If ingested with hypoglycemic drugs, such as insulin or glipizide, it may cause hypoglycemia. When co- administered with calcium channel blockers, ginger might reduce further or cause an irregular heartbeat [137,138].

3) Green tea (polyphenols) improves mental alertness and thinking. It is also used to treat a plethora of other medical conditions, including Crohn‘s disease, Parkinson‘s disease, cardiovascular disease, diabetes, hypotension, chronic fatigue syndrome (CFS), tooth decay, kidney stones and skin conditions. Consuming green tea with stimulant medications could have dangerous consequences, such as elevated heart rate and blood pressure. Bortezomib (Velcade) may not be as effective against some cancers if used with green tea. Consuming green tea may reduce the effectiveness of warfarin [139,140].

4) The leaf extract of *Gingko biloba* is effective in the treatment of Alzheimer‘s disease and other forms of dementia, Raynaud‘s syndrome, peripheral vascular disease, vertigo and dizziness, premenstrual syndrome (PMS) and improving color vision in people with diabetes. Ginkgo, when administered with anticoagulants/with NSAIDs, it may increase the risk of bleeding. When administered with anticonvulsants, it may reduce the effectiveness in preventing seizures [141,142].

5) Licorice has been used for various digestive system complaints such as stomach ulcers, heartburn, colic and chronic gastritis. It is also used for sore throat, bronchitis and in treating infections caused by bacteria or viruses [143]. Licorice is also used in an herbal form called Shakuyaku-kanzo to increase fertility in women. It is also used to treat prostate cancer and the skin disorders such aseczema, in combination with other herbs. It may make antihypertensive drugs less effective, as it may increase salt and water retention. When taken with anti-arrhythmic drugs, it may decrease their efficacy as it may increase the risk of an abnormal heart rhythm. In some cases, it decreases the levels of potassium as it increases urine formation. In such cases, the risk of digoxin toxicity also increases, if patient is on digoxin [144,145,146].

- Safety and quality control of nutraceuticals

Nutraceuticals are taken as supplements by users, which are available as over-the-counter products. Therefore, their safety is of prime concern, else it may lead to lethal effects. The most commonly observed issues are contamination, adulteration (inadvertent or intentional) or misleading labels. Adulteration may be inadvertent adulteration or intentional adulteration. Inadvertent adulteration may exist due to different conditions. For example, during the different stages of plant growth, the formulation and manufacturing of nutraceuticals, or during storage, contamination with fertilizers, heavy metals, fertilizers or microbial agents may take place. Adulteration may also take place with synthetic drugs, substitute species, dust, pollens, insects, rodents, parasites, microbes, fungi, mold, toxins and heavy metals. Any of this type of contamination may lead to infections or even serious illnesses such as gastritis and associated complications, liver injury and even life-threatening conditions. Therefore, raw-material and finished-product quality control is required and may be determined by specifications outlined in certain monographs, along with stability of active compound(s) and microbiological control [147]. Serious harmful effects may result from the intentional adulteration in supplements or herbal remedies. It usually occurs with synthetic compounds, mostly undeclared. It usually occurs with the intentions of altering pharmacological response and earns economic benefits. The sourcing of nutraceuticals from plants is often very limited, and extract preparation is time- and cost-consuming [148,149]. Therefore, these adulterations are not allowed from regulatory authorities.

Some examples of adulterations are quoted in below sections.

1) Fenfluramine is another dug that was used as an adulterant in Chinese traditional medicines and found in many slimming preparations. It caused primary pulmonary hypertension and valvular heart disease. This drug was withdrawn from market in 1997 [150].

2) In some weight control programs using an orexigens, diuretics, stimulants and laxative agents, it has been demonstrated that these products contain adulterants as ephedrine, norephedrine, caffeine and furosemide [151].

3) Morphological substitute usage is another common example of adulteration that may cause serious health issues. For example, *Panax ginseng* (Araliaceae), also known as ―Asian or Korean ginseng‖, is used as traditional medicine. It has been found to be adulterated with roots of *Panax quinquefolius* L. (American ginseng) and *Eleutherococcus senticosusmaxim* (Siberian ginseng), which may cause health problem [152,153]. Another similar example is *Panax ginseng* being used as adulterant in roots of *Mandragora officinarum* L. (Solanaceae) because they are morphologically similar, but have completely different pharmacological effects and phytochemistry [154]. Further, roots of *Pfaffia panaculata* (Mart.) *Kuntze* (Amaranthaceae), also known as ―Brazilian ginseng or suma root‖, morphologically resembles *P. ginseng* roots, but the phytochemical content is different and, hence, pharmacological action is also different [155].

4) Some other examples of physical similarity between species include the flower *Anthemisnobilis* L. and the chamomile, *Matricaria chamomilla* L. (Asteraceae), both of which are listed in the European Pharmacopoeia as therapeutic plants, as well as several other species in the family Asteraceae, such as *Tanacetum parthenium* (L.) Sch. Bip., *Tanacetum cinerariifolium* (Trevir.) *Schultz Bip*., *Tripleurospermum callosum* (Boiss. et Heldr.) *E. Hossain*, *Bellis perennis* L.and *Leucanthemum vulgare* L. Furthermore, the pharmacological activity differs depending on the phytoconstituents [156,157].

5) One of the serious intentional adulterations is use of peanut skin extract in different grape products. Grape seed- containing drugs are said to have very high bioactive polyphenols content and used in prevention of cardiovascular and neurodegenerative disorders. The peanut skin is used as it is widely available, is a high- volume byproduct and is very cheap compared to grape products. However, it is a potential allergen, which may cause serious concerns when used as adulterant

LATEST PATENT ON NUTRACEUTICALS

| t Number | Title | Year | Reference |
|---|---|---|---|
| **CN102088995B** | The use of angiogenin and angiogenin agonist for treating diseases and disorders | 2016 | 165 |

| | | | |
|---|---|---|---|
| **US20210292265A1** | Chalcones and derivatives for use in medicaments and nutraceuticals | 2021 | 159 |
| **US20210113554A1** | Nutraceuticals Having Sustained Release for Improved Bioavailability and Method of Production | 2021 | 160 |
| **US20210290722A1** | Nutraceuticals supplement composition for regulating metabolism and anti- aging | 2021 | 161 |
| **US10981083B2** | PROCESS for fractionation and | 2021 | 162 |

| | | | |
|---|---|---|---|
| | extraction of herbal plant material to isolate extractives for pharmaceuticals and nutraceuticals. | | |
| **US20220040248A1** | Prevention of Neuroinflammation associated Memory Loss Using Nutraceutical Compositions | 2022 | 163 |
| **US11270791B2** | In silico methods for obtaining nutraceutical compositions | 2022 | 164 |

CONCLUSION

In conclusion nutraceutical therapy offers promising support for various health conditions, but there are challenges in formulating these products effectively. Therapeutic efficacy and formulation strategies in nutraceuticals involve challenges such as selecting the proper strain, solid dosage formulation, and addressing limitations in swallowing for different age groups like isolating nutraceuticals from natural sources and modifying delivery systems have been widely used, Novel formulations using nanotechnology have been reported to enhance bioavailability, reduce side effects and protect active ingredients against degradation. Various studies emphasize the potential of nutraceuticals as alternatives or complementary tools to modern medicine, highlighting their promise in health care and disease prevention. Strategies like oral delivery approaches with specific excipients aim to improve the solubility and stability of nutraceuticals, enhancing their efficacy.

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