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REVIEW ARTICLE: NOVEL NUTRACEUTICALS

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ABSTRACT

A nutraceutical is an essential food component which included in a diet provides nutritional and pharmaceutical benefits. Nutraceutical provides extra health benefits, in prevention and promotion of health due to adverse effects of drugs, consumers are adding dietary food supplements. A nutraceutical is a substance that is considered as a food or its part which, in addition to its normal nutritional value provides health benefits including the prevention of disease or promotion of health. Due to adverse effects of drugs, consumers are preferring food supplements to improve health. This brought revolution worldwide in the field of nutraceuticals. Nutraceuticals provide extra health benefits, in addition to the basic nutritional value found in foods. As nanotechnology provides "a new dimension" accompanied with new or modified properties conferred to many current materials, it is widely used for the production of a new generation of drug formulations, and it is also used in the food industry and even in various types of nutritional supplements. These nano formulations of supplements are being prepared especially with the purpose to improve bio-availability, protect active ingredients against degradation, or reduce side effects.

KEYWORDS: Nutraceuticals, Health, Disease, Nano formulations.

INTRODUCTION

The famous Hippocrates' quote (400 BC), "Let food be thy medicine and medicine be thy food", represents that there has been a great interest in herbal products since decades. There are many historical civilizations, such as ancient India, Egyptian, Greek, Roman and others that used herbal products and plants in treating and preventing diseases.[1]

Nutraceutical is derived from the amalgamation of terms nutrition and pharmaceutical and was coined by Stephen De Felice in 1989. He defined Nutraceuticals as, "a food (or part of a food) that provides medical or health benefit including the prevention and/or treatment of a disease". Nutraceuticals are known as bioactive substances that are present in common food or botanical-based sources that can be delivered in the form of dietary supplements or functional food, supplying beneficial effects in addition to the nutritional essential components. These are a piece of food or nourishment which offer wholesome and drug benefits, that is, offer supplements to the body, give obstruction against a few infections and furthermore help in relieving of certain sicknesses.[2]

With the presence of side effects induced by some pharmaceutical drugs and the emergence of antimicrobial resistance, nutraceutical compounds have gained attention as an alternative therapeutic and preventive approach along with the advantages of being more affordable and available. Several studies have significantly shown the beneficial effects of nutraceutical ingredients on immune system functions. Such functions include enhancing the infection response mechanism, boosting immunomodulatory activity, and contributing to reducing the impacts of autoimmune disorders and hypersensitivity. Nutraceutical have also been shown to exert lipid-lowering, anti-inflammatory, anti-cancer and antioxidant activity.[3]

The most common type of nutraceutical products are dietary supplements. A dietary supplement is a liquid or capsule version of nutrients found in foods and is taken as an additional supplement to the daily diet. Amino acids, vitamins, minerals, botanicals and herbs are all forms of dietary supplements. Amino acids help to build muscle and improve muscle function. Vitamin B6 and B12 along with folic acid plays an important role in prevention of cardiovascular disease. Vitamin D strengthens bones and prevents osteoporosis and reduces certain types of cancers. Minerals such as calcium also strengthen bones and helps in prevention of osteoporosis.

The reasons for shift towards nutraceuticals are[3,4]

1. Increasing numbers of consumers, concerned about healthcare costs.
2. Dissatisfied with pharmaceutical agents in promoting health, are turning to nutraceuticals to improve their health and prevent chronic disease.
3. Health care provider recognize the fact that our heavily processed food supply, coming from crops grown with chemical fertilizers, pesticides, herbicides, and often genetically modified seeds, lacks sufficient nutrients necessary for optimum Health.

4. People believing more in prevention than a cure.
5. People who have chronic diseases and have found no solution in allopathic medicines.
6. Economically challenged patients.

Classification of nutraceuticals[5]

The food sources used as nutraceuticals are all natural and can be categorized as

1. Dietary Fiber
2. Probiotics
3. Prebiotics
4. Polyunsaturated fatty acids
5. Antioxidant vitamin
6. Polyphenols
7. Spices

I. Dietary supplements

Dietary supplements, such as the vitamins, protein, fats, carbohydrates supplements are typically sold in the form of pill, tablet, capsule or in liquid form. A dietary supplement is a product that contains nutrients derived from food products that are concentrated in liquid or capsule form. In the US, the Dietary Supplement Health and Education Act (DSHEA) of 1994 defined the term: "A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet.[3]

The "dietary ingredients" in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandular, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, soft gels, gel caps, liquids, or powders.

Dietary supplements do not have to be approved by the U. S. Food and Drug Administration (FDA) before marketing, but companies must register their manufacturing facilities with the FDA.

A dietary substance is referred to product such as certified antibiotic, accepted new drug, or permitted /licensed biological substance that was marketed as dietary supplement. With a few well-defined exceptions, dietary supplements may only be marketed to support the structure or function of the body, and may not claim to treat a disease or condition, and must include a

label that says: "These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." it achieves this goal by using efficacy of such nutraceuticals in detoxifying the body, avoiding vitamin and mineral deficiencies, and restoring healthy digestion and dietary habit.[6]

II. Probiotic microorganisms

Probiotic are live microbes that can be present in different types of products, including foods, drugs, dietary supplements. Lactobacillus species & Saccharomyces cerevisiae and E. coli & Bacillus species are also used as probiotic. Lactic acid bacteria including Lactobacillus species, which are used for fermentation of food. The fermentation of food improves in the taste profile and lowers the pH which prevents contamination from pathogens.

They have an antimicrobial effect through modifying the microflora, preventing adhesion of pathogens to the intestinal epithelium, competing for nutrients necessary for pathogen survival, producing an antitoxin effect and reversing some of the consequences of infection on the intestinal epithelium, such as secretory changes and neutrophil migration. Probiotics can cure lactose intolerance by the production of the specific enzyme (ß-galactosidase) that can hydrolyze the offending lactose into its component sugars.[7]

In the selection for probiotics, one should consider safety, functional and technological aspects as follows show a potential health benefit.

- Probiotics should have human origin.
- Commonly gram-positive organism.
- Can survival after passage through acid and bile.
- Can adherence to the human intestinal cells and grow in the gut.
- Can show antagonist action against pathogenic or carcinogenic bacteria.
- Clinically proven documented beneficial health effects.[7,8]

List of Bacteria and their beneficial effects[7,8,9,10]

Name of bacteria	**Action**
L. rhamnosus (High tolerance to bile salts, surviving in less than favorable environments)	• Reduction of viral-associated pulmonary damage • Prevention and reduction of severity of atopic dermatitis in children • Reduction of risk for developing allergic

	disease • Anti-diabetic potential • Prevention of necrotizing enterocolitis in newborns • Prevention or treatment of bacterial vaginosis • Aid in weight loss of obese women • Treatment of acute gastroenteritis in children • Reduction of risk for rhinovirus infections in preterm infants • Protection of human colonic muscle from lipopolysaccharide-induced damage • Produces lactic acid in the large intestine.
L. lactis	• Treatment of antibiotic-associated diarrhoea • Adhesion to vaginal epithelial cells • Production of bacteriocins I as lacticins, nisin A, lactococcins • Modulation of brain activity • Wide spectrum of bactericidal and fungicidal action to the pathogens like activity against *C. difficile* • Use for cytokine delivery • Formation of acetaldehyde, diacetyl, acetoin, and 2-3 butylene-glycol during fermentation which lead to typical flavour in cheese. • Can able to degrade methionine to methonethiol, dimethyledisulphide • (DMDS), citrate and dimethyltrisulphide (DMTS) • Utilize in formulation of animal food products
E. faecium	• Treatment of antibiotic-associated diarrhoea • Decreased duration of acute diarrhoea from gastroenteritis • Prevent infection by Salmonella enteric ssp. • Stimulate animal growth, reduce coliform counts by the production of antimicrobial metabolites and therefore utilize in formulation of animal food products • Production of bacteriocin-like inhibitory substances which show antimicrobial activity against Gram(+) bacteria.
E. coli	• Treatment of functional constipation in adults • Treatment of inflammatory bowel disease, gastrointestinal disorders • Pro-inflammatory potential • Reduction of Salmonella enterica

	Typhimurium intestinal colonization by iron competition • Promote immune, digestive (produce various digestive enzymes), reproductive health

Prebiotics

Prebiotics are dietary substances i.e. non-starch polysaccharides and oligosaccharides, poorly digested by human enzymes. They nurture a selected group of micro-organisms living in the gut. They favour the growth of beneficial bacteria over the harmful ones.

Commonly known prebiotics are

- Oligofructose
- Insulin
- Lactulose
- Breast milk oligosaccharides
- Galacto-oligosaccharides[11]

"Prebiotics" are a more recent addition to our vocabulary and are substances which when consumed are not digested by us. Instead, they act as a nutrient source for the good probiotic bacteria. This encourages the probiotic bacteria to grow in a favorable environment, which in turn reduces the chances that harmful microorganisms may start to grow in our digestive tract. Insulin is a prebiotic that has been widely used in processed foods. Essentially, it is a type of fiber obtained from the roots of plants such as chicory, Jerusalem artichoke, and even dandelions.[6,7]

Polyunsaturated fatty acids

The group of poly-unsaturated fatty acids (PUFAs) is divided into two groups: omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA), differing in the position where the first double C-bound is located. Two PUFAs are called essential fatty acids since they cannot be synthesized in the human body and are vital for physiological integrity. Therefore, they must be obtained from the diet. One is linoleic acid (LA) and belongs to the n-6 family. The other one is α-linolenic acid (LNA) belonging to the n-3 family. These essential parent compounds can be converted in the human body to long chain (LC) fatty acid but humans cannot interconvert n-3 and n-6 fatty acids.LA and ALA occur in almost all dietary fats and attain major proportions in most vegetable oils. ALA is primarily present in plants, seeds, nuts.[12]

Antioxidants

Damage to cells caused by free radicals is believed to play a central role in the aging process and in disease progression. Antioxidants are our first line of defense against free radical damage, and are critical for maintaining optimum health and wellbeing. Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called "free radicals." Free radicals are capable of attacking the healthy cells of the body, causing them to lose their structure and function. Antioxidants are capable of stabilizing, or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being.[13]

Spices

Spices are a group of esoteric food adjuncts that have been in use for thousands of years to enhance the quality of foods, the quantity and variety consumed in tropical countries is particularly extensive. These spice ingredients impart characteristic flavor, odour, or piquancy and color to foods. Some spices, like fenugreek, can also modify the texture of food. It is a common experience that their distinct aroma stimulates the appetite. Not only are spices used as flavorings and seasonings, but many are also used in perfumery, cosmetics, and toiletries. In addition, several spices have long been recognized to possess medicinal properties such as tonic, carminative, stomachic antispasmodic, and anthelminthic. Although these observations are largely empirical, these undoubtedly efficacious attributes have earned them pharmacological applications in the indigenous system of medicine not only in India, but in other countries as well.[14]

Medicinal properties of some spices[14]

Spice	Medicinal properties
Coriander (Coriandrum sativum)	Anti-dyspeptic, flavorant
Cumin (Cuminum cyminum)	Antispasmodic, carminative, digestive stimulant.
Fenugreek (Trigonella Foenumgraecum)	Diuretic, emmenagogue, emollient, useful in heart disease
Garlic (Allium sativum)	Anti-dyspeptic, anti-flatulent, for ear infection, duodenal ulcers, as rubefacient in skin diseases
Ginger (Zingiber officinale)	Sialogogue, useful in diseases of heart and blood
Onion (Allium cepa)	Diuretic, emmenagogue, expectorant, for bleeding piles
Pepper (Piper nigrum)	Antipyretic, Rubefacient
Red pepper (Capsicum annuum)	Anti-inflammatory, for pain relief (rheumatism/neuralgia) Useful in indigestion, rubefacient
Turmeric (Curcuma longa)	Anti-inflammatory, diuretic, laxative, good for affections of the liver, jaundice, diseases of blood.

Novel nutraceuticals[6]

Nanotechnology is a rapidly growing field that ensures the development of materials with new dimensions, new drug, novel properties, and a wider range of applications. U.S. National Nanotechnology Initiative defines nanoparticles (NPs) in the range of 1–100 nm. According to the Recommendation on the definition of a nanomaterial adopted by the European Commission, the term "nanomaterial" means "a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm. In specific cases and were warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%".

However, in pharmacy, particles of 10–500 nm have been used, rarely up to 700 nm. From the aspect of passage through vessels, the inside diameter of which is in the range from 25 mm (aorta) to 5 μm (capillaries), the ideal size of NPs should be <300 nm to ensure efficient transport for targeted distribution of drugs. Nutraceuticals formulations are hampered by many obstacles that negatively affect their efficacy. Many natural active ingredients suffer from low solubility, poor permeability, fast metabolism, short half-life and others. For instance, curcumin has low solubility, poor oral bioavailability, limited tissue distribution, short half-life and rapid metabolism. Additionally, Epigallocatechin Gallate (EGCG) is a bioactive compound in green tea that has a vasculo-protective effect through its antioxidative and hypolipidemic effects. However, EGCG uses are limited because of its fast degradation in the gut and low solubility. These kinds of challenges that jeopardize the nutraceuticals existence push scientists and formulators to use different novel systems to maximize nutraceuticals safety and efficacy.[15,16]

1. Nanoparticles

Nanoparticle is a particle that has three nanoscale dimensions, which range approximately from 1 to 100 nanometer (nm). The new synthesized nanoparticles have completely different electrical, mechanical, physical and chemical properties. Nanotechnology has gained extensive popularity in the field of drug delivery system. Nowadays, nanotechnology has been extensively applied in the field of Nutraceutical.

Semyonov et al.[17] enhanced the bio availability and solubility of genistein by loading it into enzymatic ally developed dextran nanoparticles. Genistein is isoflavone and it has antioxidant and anti-inflammatory properties.

Wei et al.[17] designed nanoparticles, which were loaded with Chinese yams, radix astragal, rhizoma anemarrhenae, chicken's gizzard membranes -, radix puerariae, raw gypsum, rhizoma alismatis and/or others to treat or prevent many diseases, such as diabetes, heart diseases and others.

2. Nanospheres and Nano capsules

Both nanospheres and nano capsules are polymeric nanoparticles, which have a diameter with less than 1 μm. Nano capsule has a vesicular structure which is surrounded by a polymeric membrane. The active ingredient is encapsulated into nano capsule. Nanospheres have a dispersed polymeric matrix, in which active ingredient is dispersed.

Hu et al[19] made a polymeric nanoparticle and conjugated it with chitosan. This system was loaded by curcumin to be used as antioxidant. Moreover, Hu et al. characterized this polymeric system via Fourier-Transform Infrared spectroscopy (FTIR) and proton Nuclear Magnetic Resonance (1 H NMR) analysis. The particle size and Poly-Disperse Index (PDI) were measured via Dynamic Light Scattering (DLS). Finally, zeta potential and the morphology of nanoparticles were determined via laser doppler microelectrophoresis and Transition Electron Microscopy (TEM).[18]

3. Metal nanoparticles

Metals, such as silver (Ag), iron (Fe), zinc oxide (Zn O), titanium oxide (TiO2), are prepared in the nano size range. Metal nanoparticles have many advantages, including relatively large surface area, good bio compatibility and good catalytic activity. Furthermore, superior selectivity, metal nanoparticles are usually isolable, dispersible and reusable catalysts.[21] Metal nanoparticles can be applied as metal or metal-oxide, such as nano-Ag, nano-Zn O, nano-Cu and nano-TiO2. Each has its specific dimensions, homogeneousness and aggregative properties. These different characteristics influence the compound’s biological activity and toxicity.[20]

Otunola et al.[22] conducted a study to analyze silver nanoparticles (Ag NPs) biological activity (antimicrobial and antioxidant activity) in three different herbal species namely;

garlic, ginger and cayenne pepper. Each active ingredient was encapsulated into Ag NPs. These metallic nanoparticles had spherical shapes and average sizes of 3- 6 nm, 3-22 nm and 3-18 nm for garlic, ginger and cayenne pepper, respectively. It was concluded that Ag Nps exhibited more potent antibacterial activity against two gram-negative and two gram-positive bacterial strains. Additionally, 1,1 diphenyl 2 picrylhydrazyl (DPPH) and 2,2 Azino bis (3 ethylbenzthiazoline 6 sulfonic acid) (ABTS) assays showed that Ag Np's had better antioxidant activity.

4. Lipid-Based carriers

Nano capsules based on lipid formulations having larger surface area than micronized carriers can more effectively enhance solubility, bioavailability, and controlled release of nano encapsulated phenolic compounds and could be successfully applied in functional foods. For example, the physical stability of β-Car nano capsules (>300 nm) showed only minor changes during storage, suggesting that they could be used in functional beverages and foods as well as nutraceutical products.[23]

Richard et al[24] formulated pegylated or cationic liposomes or niosomes to encapsulate the active ingredients into. It was claimed that the natural components were parts of natural plants, such as coffee bean, aloe vera, hazelnut oil, almond oil and others. Furthermore, Richard and his team claimed that their system had many uses such as rejuvenation of stratum corneum and epi-dermis, treatment of acne and anti-wrinkles. The morphology and size of vesicles were evaluated by TEM. Lastly, particle size, PDI and zeta potential were measured via DLS.

5. Lipid based carriers[25]

Liposomes: Liposome is traditional lipid-based carrier. It was prepared for the first time by Alec D Bangham in 1965. Liposomes are spherical vesicles that consist of a lipid bilayer membrane and an aqueous cavity. The coinage of liposome was originated from two Greek terms namely; lipid (fat) and soma (body). liposomes are able to protect active ingredients against enzymatic degradation. Moreover, they are flexible, biocompatible and non-toxic carriers. They have the merits of dual drug delivery by loading drugs with different physicochemical properties in their core and lipid bilayer. For hydrophobic drugs, liposomes improve their solubility, stability and bioavailability.

Gao et al[26] loaded natural ingredients into liposomal system. Moreover, it was claimed that the system could also be formulated in the form of sustained released tablets, gel powder, lotion and other dosage form. The natural ingredients were crocin, crocetin, green tea extract, curcumin, resveratrol, panax ginseng extract, α-lipoic and/or L-carnitine. The synthesized formulation was used in treating cancer and improving health. In another patent, Underwood et al. prepared nanoparticles of whole fruits (black chokeberries, cherries, plums, blueberries, pomegranates, raspberries, cranberries and/or black elderberries) and encapsulated them into emulsion and/or liposome. It was claimed that the prepared formulation was used in decreasing symptoms of arthritic pain, diabetes, gout and others.

6. Solid Lipid Nanoparticles (SLNs) and Nanostructure Lipid Carriers (NLCs)

SLNs and NLCs have been introduced into the delivery systems since 1990 as substitutes of traditional liposomes, polymeric nanoparticles and emulsions.

1. Solid lipid nanoparticles

Solid Lipid Nanoparticles (SLNs) have spherical structure and nano-ranged size (around 40 to 1000 nm). SLNs consist of surfactant (0.1 to 30 % w/w) and solid fat (0.5 to 5%). They are solid at body and ambient temperature. Furthermore, particle size, stability and drug loading depend on type of lipid and surfactant. SLNs are considerably suitable for both hydrophilic and lipophilic drugs. However, the drug loading capacity depends on drug lipophilicity. Moreover, system instability during storage and high-water content have been reported as disadvantages.

α-Lipoic acid is a natural antioxidant that is utilized in antiaging topical preparation. It has low irritation effect compared to other antiaging agents. Additionally, α-lipoic is useful for treating delicate areas (area around the eye). α-lipoic acid suffers from chemical degradation, which leads to bad odor in topical preparations.

Souto et al[27] solved such problem by incorporating α-lipoic acid into SLNs. Moreover, loaded α-lipoic acid showed higher occlusive effect. Hence, the system increased skin hydration and protection against UV irradiation.

Nanostructure Lipid Carriers (NLCs)

Nanostructure Lipid Carriers (NLCs) are considered a modification of SLNs. The main modification is that the lipids of NLCs are a mixture of both solid and liquid oils. Therefore,

NLCs enhance stability and drug loading. NLCs were introduced in 1999 to overcome SLNs drawbacks, such as low drug loading capacity and instability (Drug expulsion).

Resveratrol is a naturally occurring anticancer agent. However, resveratrol suffers from photo sensitivity, low solubility and oral bioavailability.

Neves et al[28] utilized SLNs and NLCs to encapsulate resveratrol. Both systems enhanced trans-resveratrol protection against photo-degradation. Furthermore, NLCs succeeded to improve resveratrol encapsulation. Additionally, NLCs prevented its rapid crystallization and release in GIT. Clearly, both system enhanced resveratrol oral bio availability for cancer treatment.

CONCLUSION

Nutraceutical provide the health benefits and has the capacity to prevent the diseases and also to diagnosis the diseases. Nutraceutical present in the various food and it has to be taken in the balanced diet, mainly it acts as a self-medication which exhibits the therapeutic efficacy. Nutraceutical have proven efficacy in numerous health diseases, including cancer, inflammatory, cholesterol, rheumatism, diabetes, and other chronic diseases. The use of scientifically and medically approved nutraceutical can definitely improve health and prevent certain diseases, and some have exhibited the same efficacy as that of conventional pharmaceuticals. The consumption of food products with such dietary supplements/nutraceuticals can be easily used in practice when an appropriate stability of the active ingredient in the formulation could be guaranteed at least until the date of consumption (expiration date). For these purposes, nano-formulations of active compounds prepared using biodegradable nature- or semisynthetic-based nanocarriers, such as polymeric matrices, micelles, liposomes, nano-emulsions, solid lipid NPs, nanostructured lipid carriers, or appropriate inorganic matrices are especially favorable, securing not only enhanced stability but also frequently controlled release of nutrients.Generally, nutraceutical have lower incidences of side effects, adverse effects, and drug interactions as compared to both complementary medicines and conventional pharmaceuticals. However, risk beneficent uses of nutraceutical have not yet been documented. Hence, it can be concluded that various chemical constituents from natural sources can be obtained and prepared into various optimized, safe, stable formulations for the treatment and diagnosis of diseases.

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