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Review Article

Nutraceuticals: An inspiring therapy for lifestyle diseases

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Abstract

Among natural sources, majorly we consider plant-based phytochemicals to offer safe and long-lasting effects. Phytochemicals or secondary metabolites are the extract obtained from herbal plants that serve as an excellent venture for their utilization as formulation. Different nutraceuticals (herbal formulations) have always been a part of the world. Everyone around the world could use these supplements for their benefit. Since the end of the eighth century and the beginning of the nineteenth century, the concept of using products has improved. Nutraceutical food supplement plays an essential role for humans to stay healthy and gets all the important nutrients used for the body's basic metabolism and further prevent all kinds of illnesses. The present review highlights the potential of nutraceuticals against various types of leading life-threatening disorders such as diabetes, obesity, asthma, cardiac conditions, arthritis, cancer, etc. This review focuses on the nutraceuticals that help manage certain many life-threatening disorders.

Keywords: Phytoconstituents; nutraceuticals; food supplements; life-threatening disorder

Introduction

'**Nutraceuticals**', a term given by Dr Stephen De Felice in 1989, became a newly accepted word in Oxford Dictionary. The term '**Nutraceutical**' is made by two words: "nutrire," i.e., "to nourish," and "pharmaceutical," which means "to cure." [1]. Nutraceuticals are biologically active substances that may be considered food or a part of food with nutritional benefits to human health in treating various diseases. Most diseases, such as obesity, diabetes, cardiac issues and so on, occur due to imbalanced diet and living style. Nutraceuticals are crucial in disease prevention as they promote good health [2]. India has been an abundant source of medicinal plant species, but traditional communities have used only a limited number of plant species for treating different diseases. Herbs and herbals are plant-derived products with no woody tissues and can be modified in many ways depending on individual purposes. For processing, the herbs are generally subjected to drying; however, excessive heating may reduce the activity potential of herbal products. Since ancient times, herbs have constituted a rich concentration of antioxidants and have been employed for flavouring and aroma. Most plant constituents, such as carotenoids, lycopene, catechins, polyphenols, etc., are well-known in nutraceuticals for disease management [3].

Many research studies have been done extensively on herbs and spices to observe their antioxidant and antimicrobial potential to establish their beneficial effects on humans. Herbs and spices contain many bio-actives, including flavonoids, alkaloids, tannins, phenolic diterpenes and related compounds, sulphur-containing compounds etc. Many plants/herbs have been used for medicinal purposes at home and are also available as marketed formulations. For instance, herbs such as *Allium sativum* (garlic) extracts, *Ocimum basilicum* (Tulsi), *Aloe barbadensis M.* (aloe vera) gel, *Zingiber officinale* (ginger) root, *Tinospora cordifolia (Giloy)*, etc. have been known for excellent health benefits in reducing cholesterol, boosting immunity, anti-ulcer, wound healing, antimicrobial and antioxidant activities.

Despite the disparity in scientific evidence, the consumption of herbs has tremendously increased globally based on the health benefits reported by various studies [4].

Based on various reports, it is suggested that taking any food and nutritional supplements derived from herbs, roots, vegetables, fruits etc., improves health by reducing adverse results such as inflammation, radical scavenging features etc., during any infections in the body, thereby boosting the immune system. Eventually, using nutraceuticals can offer adjuvant therapeutic and prophylactic assistance to manage a wide variety of disorders. For example, Parsley contains flavonoids and shows diuretic and antipyretic action [5]. The reasons for the transition to nutraceuticals may be as follows [6,7].

- Consumers are becoming more worried about healthcare costs.
- Nutraceuticals are used by people disappointed with pharmaceutical agents to maintain well-being and avoid chronic disease.
- According to healthcare specialists, our excessively processed food supply, which originates from crops farmed with chemical fertilizers, pesticides, herbicides, and sometimes genetically engineered seeds, lacks the nutrients required for optimal health.
- People are more inclined to believe in preventing the disease.
- Individuals are suffering from long-time illnesses for which allopathic medicine has failed to provide a cure.
- Nutraceuticals are readily available and less expensive than pharmaceuticals, and they do not place an undue financial burden on their consumers because they are either food or parts." Instead of "Patients who are struggling financially.

Phytochemicals have a large apparent volume of dispersion and can cause organ accumulation. These herbals have recently been employed to make nutraceuticals that offer a supplementary regimen to the treatment therapy for better patient compliance and lesser side effects than synthetic preparations [8,9]. The importance of nutraceuticals and their application as cardioprotective, hepatoprotective, antiepileptic, anti-inflammatory and many more for managing life-threatening diseases have been reported. Since various kinds of literature are available on similar lines, this review mainly discussed the fundamentals of nutraceuticals. It highlighted some essential facts about the therapeutic use of nutraceuticals as complementary medicine to conventional therapies allowing dose reduction and minimizing adverse effects [10-15].

Mechanism of action of nutraceuticals

Herbal phytochemicals used in nutraceuticals show their therapeutic action by various mechanisms, including suppressing the over-expression of proteins, enzymes, amino acids, and hormones. These phytoconstituents starts the generation of protection enzyme. Also, these are quickly taken by normal tissue and taken after being of occurring naturally. Nutraceuticals are effective in disease management such as cancer, obesity, arthritis, etc. Moreover, it strengthens the body's defence mechanism and refines the immune response towards diseases [16,17]. Figure 1 represents several mechanisms of actions of nutraceuticals in disease management.

Classifications of nutraceuticals

The impact of nutraceuticals became more relevant as the current generation is more focused on approaches to preventive healthcare. There is much misunderstanding about words like "nutraceuticals," "functional foods," "dietary supplements," "designer foods," "medical foods," "pharmafoods," and "phytochemicals," among others. Their substitutable use by diverse entities on diverse events indicates that it tends to have a thin dividing line [18]. Nutraceuticals can be developed as solid dosage forms like capsules, tablets, and liquid formulations. It can be divided into a dietary fibre, probiotics, prebiotics, polyunsaturated fatty acids, antioxidants and other natural foods. Based on various characteristics, nutraceuticals can be categorized based on a natural food source, chemical

nature, mechanism of action and traditional and non-traditional nutraceuticals. Here, the categorization is done as traditional and non-traditional nutraceuticals [19].

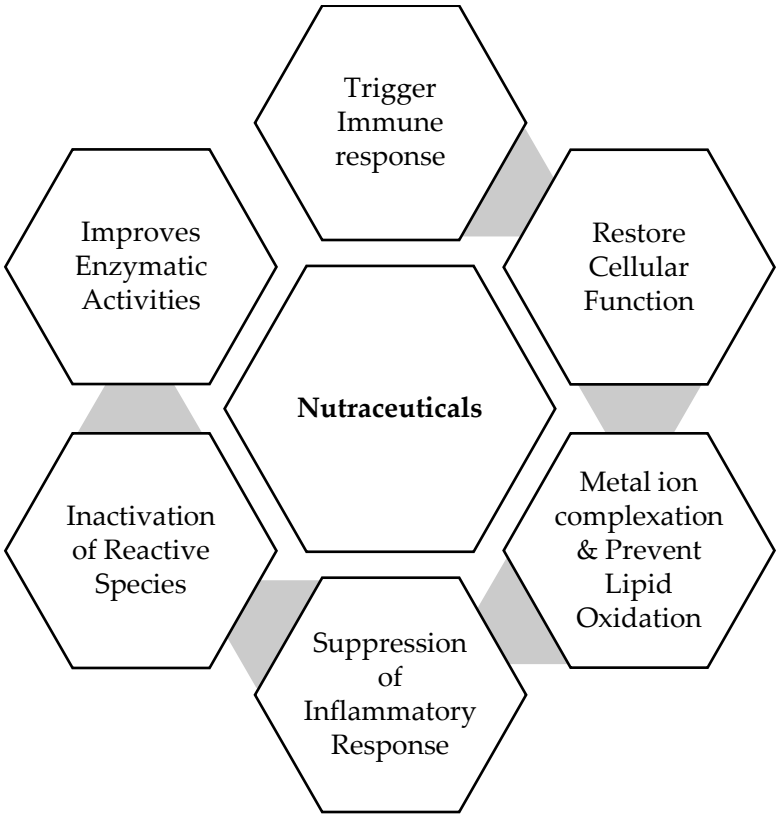

Figure 1. Several mechanisms of actions of nutraceuticals in disease management.

Traditional nutraceuticals

These include natural foods with potential health benefits. These are substances that have been derived directly from natural resources without modifying the food in any way. Vegetables, fruits, grains, dairy, meat, dairy products, and other foods may be included. For example, nutrient-dense foods like the lycopene found in tomatoes. Traditional nutraceuticals positively impact health by boosting immunity and lowering the risk of life-threatening disorders, including cancer and heart disease. For instance, the secondary metabolite flavonoid, which is rich in antioxidant characteristics and aids in suppressing tumours, lowers the risk of heart attacks and kidney-related problems. Chemical components (nutrients including vitamins, amino acids, minerals, etc.), probiotic bacteria, and enzymes are additional categories for both traditional food and nutraceuticals [20]. The following is a description of each functional category of nutraceuticals:

Dietary -fibre

Nondigestible carbohydrates and lignin, found naturally in plants, make up dietary fibre. Functional fibre is a type of nondigestible carbohydrate with physiological benefits for the body. Adult men should consume 38 gm of fibre per day, while adult women should consume 25 gm per day, according to the Dietary Reference Intake (DRI). There was insufficient information to identify an optimal upper consumption level for dietary or functional fibre [21].

Pro-biotics

Probiotics are live bacteria and yeasts that are good for your health, especially your digestive system. Bacteria are commonly associated with the transmission of diseases. On the other hand, your body is teeming with excellent and dangerous microorganisms. Probiotics are sometimes called "good" or

"useful" bacteria since they maintain your gut health. Probiotic Microorganism based preparations generally contain live microorganisms which improve an individual's health upon adequate consumption. Regularly consuming these products makes the intestine more friendly and promotes the body process like healthy digestion, absorption of specific nutrients and metabolism by removing toxic flora from the intestine—for example, appropriate consumption of *Bacillus bulgaris*.

Moreover, the antimicrobial property generally aids the altering impact on microflora resulting in better retention of supplements within the body tissues. Probiotics are beneficial in conditions like lactose intolerance as they initiate the formation of the related enzyme (ß-galactosidase), which helps in hydrolysing lactose into its sugar components. The few available probiotics are Milk (*Lactococcus lactis*), Yoghurt (*Streptococcus thermophilus*), and gastrointestinal tract (*Lactobacillus johnsonii*) [22].

Nutraceutical enzymes

Enzymes are proteins produced by cells inside a body that helps in regulating various metabolic pathways and act as a biocatalyst. Nowadays, enzyme supplements for treatment are much considered for managing several rare diseases like Hunter Syndrome, Gaucher disease, Pompe disease and Fabry disease. However, microbial sources are preferred over plant and animal sources for enzyme production due to the enzyme effect and cost effect. Nutraceutical microorganisms are food supplemented with bioengineered crops to augment the nutrients and their overall effect. For example, broccoli and rice are rich in vitamins and β-carotene. A few examples of enzymes obtained from microbial sources are Invertase, *Lactase,* and *Pectinase,* obtained from plant cell walls [23].

Pre-biotics

Prebiotics are chemicals that promote the growth or activity of beneficial microorganisms (such as bacteria and fungi). In concept, however, it is a broader phrase that can refer to various body parts. Prebiotics, like probiotics, are conceptually transitional between foods and medications as a functional dietary component. They usually face an intermediate level of regulatory scrutiny, depending on the country, especially regarding health claims. Prebiotics are all fibre, but not all fibre is prebiotic [24,25].

Poly-unsaturated fatty acids

The first double C-bound position of polyunsaturated fatty acids (PUFAs) differs between omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids. Needed fatty acids are two PUFAs that the human body cannot generate yet are required for physiological health. As a result, they have to be obtained through dietary means. One is linoleic acid, which belongs to the n-6 family [25].

Anti-oxidants

Free radical damage to cells is thought to have a significant part in the ageing process and disease progression. Antioxidants are the body's first line of defence against free radical damage and are crucial for overall health and happiness. Free radicals can be stabilised or deactivated by antioxidants before they harm cells. Antioxidants are essential for cellular and systemic health and well-being [25,26].

Poly-phenols

They are phytochemical compounds found naturally in plant-based food like fruits, vegetables, whole grains, cereals, tea, and coffee; more than 8000 polyphenolic compounds have been identified in whole plant foods, including phenolic acids, flavonoids, stilbenes. These chemicals are secondary metabolites produced by plants to protect them from UV radiation, oxidants, and infections [26].

Spices

Since the dawn of time, spices have played a crucial role in the culinary art of flavouring food. They are aromatic vegetable parts more for flavouring food than for supplying nutrition. They may be left whole, shattered, or ground up. Spices play a significant role in the economy of the producing nation because they are used extensively as pesticides in native medicines, pharmaceuticals, Nutraceuticals,

aroma therapy, beverages, perfumes, dental preparations, cosmetics, and other products in addition to flavouring and seasoning [26,27].

Dietary-supplements

It is a liquid or capsule-based item which have nutrients extracted from foods which have been concentrated. Vitamins, herbs or other botanicals, enzymes, glandular, and metabolites are all "dietary ingredients" in these products. Dietary products can only be used to help the body's primary function but not to treat any disorder or illness, except for some of the well-defined exceptions that achieve this goal by utilising nutraceuticals' ability to detoxify our body and restore proper digestion and eating habits [28].

Functional-food

They are "food or any food product that, in addition to the usual nutrients it provides, can give a benefit to health." They are designed to make it possible for consumers to eat nutrient-dense foods in their natural state as opposed to consuming liquid or capsule-based nutritional supplements. Nutrification is the process of adding nutrients to functional foods [28,29].

Medicinal food

Under the supervision of a health practitioner, this food should be consumed or administered internally for the precise dietary treatment of a condition with a specific nutrient requirement. Food that does not include any ingredients that promote disease or contain a nutrient the body cannot naturally produce due to a specific disease state is defined by medical evaluation based on accepted scientific principles [29].

Non-traditional nutraceuticals

Nutraceuticals or food products belonging to this category are synthesized artificially with the help of biotechnology to add bioactive to the products for enhancing food properties and human health. For example, cereals infused with minerals and vitamins and rice enriched with β-carotene contain a provitamin A bioactive, which boosts antioxidant activity. Based on the processing method, non-traditional nutraceuticals may be arranged into fortified nutraceuticals and recombinant nutraceuticals.

Fortified nutraceuticals

These constitute food or nutraceutical products prepared from agricultural breeding or adding compatible nutrients to main components to improve their overall health value. For instance, fortified orange juice can improve glycaemic control if calcium is added to food products like orange juice. A few fortified examples are minerals added to cereals, flour fortified with iron, calcium and folic acid, and orange juice fortified with calcium cholecalciferol fortified milk are generally used for managing vitamin D deficiency.

Recombinant nutraceuticals

These foods and nutraceuticals are produced by using biotechnology and genetic recombination. The crops are genetically modified to produce products containing recombinant compounds and proteins, making them more beneficial to health, for example, golden rice, golden mustard, iron rice, multivitamin corn and gold kiwi fruit. Gold kiwi fruit consists of a recombinant gene that helps increase ascorbic acid levels and carotenoid and lutein to improve immunity. Also, it is considered a rich source of potassium, vitamin and fibre. In addition, food products such as cheese, bread, yoghurt and many other energy-providing foods are produced with the help of biotechnology [30,31].

Nutraceuticals over pharmaceuticals in disease management

The term ‘Nutraceuticals’ is well understood & widely accepted; however, it does not have any standard definition. The ideal definition is ‘food or a component of food (including beverages) that has

medical or health benefits, such as disease prevention or therapy. Many natural nutraceuticals offer preventive benefits for various conditions in rising markets, including cardiovascular disorders, diabetes, obesity, allergies, and cancer [32]. Ayurveda, since ever, relies on strategies to inculcate the use of phytochemical extractives, alone or in combinations, in many immunostimulants and other disease ailments. Nutraceuticals containing poly herbals constituents are beneficial to the body in regulating internal processes. Phytochemicals have been proven to be effective in accelerating the production of protective enzymes as well as inhibiting the over-expressed proteins, enzymes, hormones etc., and, in this way, boosting immunity instead of affecting healthy cells (to certain concentrations) [33]. Nutraceuticals used for the treatment or prevention of different diseases are mentioned below.

Cardio-vascular disorders

Supplements like dietary fibres, Anti-oxidants, Omega-3, vitamins, and minerals are used to prevent and treatment of Cardiovascular disorders. Polyphenol found in grapes protects from arterial disorders. Onion, grapes, apples, and cherries have flavonoids that can inhibit the ACE and give strength to the capillary, which are used as an oxygen and another nutrient carrier for every cell of the body. Rice bran improves cardiovascular health by lowering serum cholesterol levels, lowering the level of LDL and increasing the level of HDL [32].

Diet-related disorders

Diet-related diseases are on the rise in Western countries, owing to the increased availability of high-calorie foods. Obesity, diabetes, and neurodegeneration are all important diet-related diseases, with low-grade inflammation as a shared pathogenic denominator [34].

Heart-attack and lung-cancer

In addition to its fiber, corn also contains a lot of folates, which benefits heart health. It is predicted that consuming the recommended daily amount of folate will reduce the occurrence of heart attacks by 10%. Corn also contains cryptoxanthin, a naturally occurring carotenoid pigment. Regular use of cryptoxanthin has been proven to reduce the incidence of lung cancer by 27% [35].

Diabetes

People with diabetes may benefit from the ethyl esters found in N-3 fatty acids. Docosahexaenoic acid plays a role in neuro visual development and insulin resistance. Diabetic neuropathy can be treated with lipoic acid, an antioxidant. The dietary fiber psyllium has been used to treat diabetes and reduce lipid levels in hyperlipidemia [36].

Obesity

As a worldwide epidemic, obesity can be defined as excessive body fat. Heart disease, coronary artery disease, high blood pressure, high cholesterol, respiratory illness, osteoarthritis, cancer, and infertility are all well-known risk factors [35,36].

Cancer

Flavonoids that inhibit estrogen-producing enzymes prevent estrogen-related malignancies. “Phytoestrogens” (hormonal activity) can be used to prevent a wide range of breast or prostate cancer. Curcumin from curry and soya flavones in soy foods have cancer-fighting qualities. Lycopene is found in high concentrations in the skin, testes, adrenals, and prostate, where it fights cancer [37,38].

Anti-inflammatory activity

Curcumin (diferuloylmethane) is an anti-carcinogenic, anti-oxidative, and anti-inflammatory polyphenol found in turmeric. Spinach, cucumber, turmeric rhizomes, and beet-root have an antitumor effect. Gamma linolenic acid is a fatty acid found in green leafy vegetables, almonds, and vegetable oils

such as evening primrose oil and blackcurrant seed oil that is used to alleviate inflammation and auto-immune diseases [38].

Alzheimer's disease

β - carotene, lycopene, and turmerin may protect against some diseases by counteracting the harmful effects of oxidative stress, mitochondrial malfunction, and different types of brain degeneration [38].

Parkinson's disease

The disease can be prevented by adding Vitamin E to the diet. Although exploratory studies have shown some promising benefits with nutritional supplements, it is essential to note that there is not enough scientific data to recommend them for Parkinson's disease right now. Patients should be aware that over-the-counter medications have side effects, can combine with different medications, and are expensive [39].

Osteo-arthritis

Osteoarthritis is the most frequent type of arthritis in the U.S., a crippling joint illness affecting approximately twenty-one million people. Joint discomfort caused by osteoarthritis and other joint problems may cause people to become less active, resulting in an imbalance in energy and gaining weight. Weight gain can aggravate existing problems by putting additional strain on joints. Nutraceuticals have both nutritional & pharmacological qualities, & they tend to modulate gene expression and Nitrous oxide and Prostaglandin E2 generation, which could explain their anti-inflammatory effects [39,40].

Adrenal-dysfunction

Adaptogenic products are non-synthetic plants which can normalize physiology; they can affect the basic functionality of the human body; they merely have a minor effect on regular bodily functioning, encouraging non-specific stress resistance. Examples are *Ocimum Eleutherococcus senticosus*, Ginkgo biloba etc. [41] Table 1 represents the nutraceutical used for different medical conditions and their natural origin.

Table 1. Various nutraceuticals in different disorders with natural origin.

Disease	Nutraceuticals	Source	Reference
Cardiovascular health	Co-q-10	Soyabeans, olive oils	[42]
	Melatonin	Bone marrow, Pineal, Glands	
	Dha	Fish oil	
	Reservatrol	Grapes, Red wine	
	Caretonoids	Carrot, Sweet Potato	
	Catechin	Tea extracts.	
Joint health	Glucosamine	Found in Ligaments, tendons , cartilages,	[43]
	Chondroitin	Proteoglycans of articular cartilage	
Eye health	Dha	Linseed (flax oil), Fish oil.	[43]
	Pycnogeal	Barley	
	Loteins	Spinach	
Diabetes	Green tea	Plant Camellia Sinensis	[43]
	Resveratrol	Red Wine, Grapes	
	Cinnamon supplements	Cinnamon extracts	
Obesity	Bottle guard	Plants	[43]
	Black gram	Plants	
	Green tea	Plants	
	Vitamin c	Supplements, Citric fruits	
	Fenugreek	Spices	
Cancer prevention	Dha	Flax seeds, Fish oil	[44]
	Resveratrol	Red Wine, Grapes	
	Lycopene	Tomato	

In addition, many plant-origin phytochemicals show proven activity in different disease conditions such as Allergy, inflammation, cardiovascular disease, obesity, skin care and cancer prevention etc. Many phytochemicals have been investigated as treatment options which show potential effects in desired dose [45]. Tables 2 [46-48] and Table 3 [23,49] represent a few examples of reported phytochemicals, their actions in various disorders, and a few examples of commercially available nutraceutical products, respectively.

Table 2. Some herbs & plants are listed with their therapeutic effects and doses.

Plants	Therapeutic properties	Dosage aprrox.
Allium sativum. L (Garlic)	Antimicrobial, hypolipidemic, antioxidant Antineoplastic, antithrombotic, antiatherogenic effects.	Cloves: 2-5 gm fresh; 0.4-1.2 gm dried powder
Citrus aurantium. L (Bitter Orange)	Stimulates the of CNS, assistance in weight loss	Fruit: 60-120 mg
Cissus quadrangularis Linn (Hadjora)	Anti-inflammatory, anti-obesity, analgesic, antibiotic, antimicrobial, hypoglycemic.	Stem: 100-500 mg
Coleus forskohlii	Treating disorders such as glaucoma, heart failure, bronchial asthma.	Root: 50-300 mg
Commiphora muklul Engl. (Indian Belellium tree)	Hypolipidemic, anti-inflammatory, antitumor.	Resin: 50-100 mg
Coriandrum sativum L. (Coriander)	Hypogylcemic, hypolipidemic, hypotenstive.	Leaf: 5 mg
Costus igneus. Nak (Fiery spiral ginger)	Diurectic , hypotensive, hypoglycemic.	Leaf: 5000 mg
Cyperus Rotundus L. (Nutgrass)	Anti-inflammatory, antidiabetic, hypocholesterolemic.	Leaf: 1-3 gm
Foeniculum vulgare. Mill (Fennel seeds)	Antispasmodic, secretolytic, secretomor, antibacterial.	Seeds: 1-7 gm
Garcinia Cambogia (Malabar Tamarind)	Anti-obesity, Anti-inflammatory, antiulcer.	Fruits: 200-500 mg
Glycyrrhiza glabra Linne (Licrorice)	Anti-inflammatory, antiulcer, anti-depressive.,	Root: 2-4 gm
Piper nigrum. L (black pepper)	Anti-inflammatory, antioxidant, analgesic.	Seeds: 2-5 gm
Phyllanthus embilica. L (Amla)	Anabolic, antibacterial, antipyretic, antiviral, antioxidant.	Seeds: 3-6 gm
Vitis vinifers. L (Grape)	Anti-inflammatory, antithrombotic, cardioprotective effects.	Seed extract 100-500 mg

Table 3. Examples of few commercially available nutraceutical products.

Product	Category	Manufacturer
Proteinex®	Protein supplement	Pfizer Ltd., Mumbai, India
Omega woman	Immunity booster	Wassen, Surrey, U.K.
Calcirol D-3	Calcium supplement	Cadilla Healthcare Ltd. Ahemdabad, India
Chyawanprash	Immunity booster	Dabur India Ltd.
GRD	Nutritional supplement	Zydus Cadila Ltd., Ahemdabad, India

Future prospects of nutraceuticals

Finding a new molecule is more complex, costly and riskier than already available drug molecules. Also, synthetic drugs' side effects and ineffectiveness have emerged in need to establish nutraceutical products as a supplementary alternative therapy. In the last two decades, there has been a rapid increase in nutraceutical use due to increased public awareness of health-related issues. Nutraceuticals help manage severe health conditions by providing sufficient nutrients to the body upon consumption, improving overall health and preventing diseases. Numerous pharmaceutical firms are endeavouring to produce nutraceuticals due to the immense and rapidly rising demand. Anti-arthritic, cold and cough, sleeping conditions, digestion, avoidance of some diseases, osteoporosis, blood pressure, cholesterol management, pain relievers, depression, and diabetes are medical conditions managed by nutraceuticals. Nutraceutical consumers believe that nutraceuticals or dietary supplements are much safer than those synthetic compounds. However, it is equally important to understand that their presumption could be wrong, and medical diagnosis is required to prescribe conventional medicines

for critical conditions. Recently, treatment with nutraceuticals for managing health has been considered prophylactic in many diseases. For instance, carnitine and flaxseed oil are prescribed for managing cardiac conditions and antioxidants such as green tea and soy products are for cancer prevention. Several manufacturing units are launching new nutraceutical products into the market for its expansion point. Many companies have introduced nutraceuticals to the market such as Novartis launched "functional food", Dean farms launched "Columbus healthier eggs" (rich in fatty acids) in 1988, and Allied Bakeries launched burgeon bread in 1997 which contains soy and flaxseed and also enriched with natural plant estrogen to treat menopausal symptoms [19]. Recently, government financial support for clinical investigations of herbal and nutraceuticals has been increased to strengthen the research to establish a vital piece of evidence towards the use, effectivity, quality and safety of nutraceuticals against certain life-threatening disorders.

Conclusion

This review paper provides information on nutraceuticals that can potentially cure different diseases. Nutraceuticals have demonstrated their ability to provide health advantages and disease prevention and should be consumed following their acceptable recommended consumption. In today's environment, where everyone is taking medicines independently, they play a critical part in therapeutic growth. However, the growth is contingent on maintaining quality, purity, safety, and efficacy. Not only formulation but the constituents play tremendous roles in treating the ailments alone or in combination with other natural constituents and chemotherapeutic agents. All this proves to be a significant milestone in treating severe conditions in unique ways.

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Declaration of interest

The authors declare no conflict of interest.

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