THERAPEUTIC APPROACHES OF NUTRACEUTICALS IN THE PREVENTION OF NEUROLOGICAL DISORDERS

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Abstract

Neurological diseases are one of the major healthcare issues worldwide. Posed lifestyle changes are associated with a drastically increased risk of chronic illness and diseases, posing a substantial healthcare and financial burden to society globally. Researchers aim to provide fine treatment for ailing disorders with minimal exposed side effects. In recent decades, several studies on functional foods have been initiated to obtain foods that have fewer side effects and increased therapeutic activity. Hence, an attempt has been made to unravel several extraction techniques

disorders and nutraceutical therapy in the prevention of disease. Alzheimer's disease (AD) is a neurological illness that causes memory loss over time. Currently, available pharmaceutical medicines and products are limited, and they have side effects at a higher price. Researchers and scientists have observed significant effects of nutraceuticals. Various preclinical and clinical studies were investigated for the Anti- Alzheimer's activity of nutraceuticals. The increasing ability of the pathogenesis of AD has led to the analysis of novel therapeutic targets, including the pathophysiological mechanisms and distinct cascades. So, current improvement will show the most adequate and prominent nutraceuticals and suggested concise mechanisms involving autophagy regulation, anti- inflammatory, antioxidant, mitochondrial homeostasis, and others. The effects of nutraceuticals cannot be ignored; it is important to acquire essential bioactive compounds or phytochemicals from therapeutically active food products. This has led to the conception of the term functional foods being meddled with other similar terms like "pharmafoods," "medifoods", "vita foods", or "medicinal foods". With a dire need to adhere to healthy options, the demand for nutraceuticals is widely increasing to combat neurological interventions. An association between food habits and individual lifestyle with neurodegeneration has been manifested, thereby proposing the role of nutraceuticals as prophylactic treatment for neurological interventions.

The current review covers some of the major neurological to investigate high- quality clinical trials. Given the potential of nutraceuticals to battle**.** AD as multi- targeted therapies, it's vital to evaluate them as viable lead compounds for drug discovery and development. To the best of the authors 'knowledge, modification of blood-brain barrier permeability, bioavailability, and aspects of randomized clinical trials should be considered in prospective investigations.

Keywords: neurological disorders; nutraceuticals; herbal therapeutics; food supplements; neurodegeneration, flavonoid, nutraceuticals, oxidative stress, probiotics

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DOI: - 10.48047/ecb/2023.12.si5a.038

1 INTRODUCTION

Neurological ailments include a wide array of chronic diseases comprising a highly complicated etiology (Williams et al. 2016). A nutrient-deficient diet may lead to disturbances in the central or peripheral nervous system. Globally, more than 10 million people suffer from neurological disorders annually, which is expected to rise. Brain functioning tends to deteriorate with aging due to neurodegenerative processes, hence leading to the identification of cellular and molecular targets that ultimately leverage better functioning of the brain (Williams et al. 2015). About 3.1% of the population in Western countries aged between 70-79 years are considered prone to neurodegenerative diseases while the incidence of disease in individuals of similar age groups in India is 0.7%. The difference is mainly due to varying lifestyles and food habits depending upon the consumption of different ingredients. Since immemorial times, people have been dependent upon spices and natural products for curing different ailments, which have shown remarkable results (Bungãu and Popa 2015). The advancement in science and technology has led to the investigation and utilization of several phytochemicals with therapeutic properties from both plant and non-plant sources, leading to a renaissance in the research of nutrition and human health, thereby creating opportunities for the advancement of novel dietary substances. With this innovation arises a new term called nutraceuticals, which comes from the combination of nutrition and pharmaceutical. The term nutraceutical was coined by Dr. Stephen De Felice in the year 1989 (Altaf et al. 2019). The American Nutraceutical Association defines nutraceuticals as a food or its product possessing health-benefiting properties. They range from dietary nutrient supplements to genetically designed foods, herbal products, beverages, soups, vegetables, fruits, and processed foods, like cereals, etc (Van Boekel 2022).

Nutraceuticals are mainly represented by vitamins, minerals, and amino acids, and over 1000 other probiotic compounds have been identified to date. The most ancient civilizations that presented evidence of the effective use of food products in medicine and ailing diseases include Indians, a fact even supported by Ayurveda for 5000 years; Chinese; Egyptians; and Sumerians (Orlando 2018). In brief, a nutraceutical can be defined as a functional food exerting established health benefits apart from its nutritional properties. Evidence reveals that nutraceuticals are emerging as a promising strategy in the management of several chronic diseases, including neurological disorders (Gupta and Prakash 2015). The focus of ongoing research in the field of nutraceuticals is the investigation of molecules that are isolated from traditional medicines and how they can be helpful in debilitating and degenerative pathologies (Abdel-Daim et al. 2019). Amidst the potential benefits of nutraceuticals, they still pose certain limitations, such as poor bioavailability, poor brain permeability, metabolism, etc. thereby challenging their beneficial effects (Brown et al. 2009).

Nutraceuticals in adjunction can strengthen the therapeutic effects of certain medications when used in adjunction by the augmentation of several pathways, such as enhanced re-uptake of inhibited monoamines, thereby providing exceptional neurobiological effects (Van Der Burg et al. 2021). The current review highlights the potential role of nutraceuticals in brain health and neurological disorders. Plants served as a treatment source for various diseases throughout the prehistoric era all over the world. The path to nutraceuticals can be traced historically by establishing links between alternative medicine, including herbalism, apothecary, ethnopharmacology, and phytotherapy (Georgiou et al. 2011). The therapy evolved from vegetables, animals, mineral-sourced compounds, and medicinal plants, constituting both instinctive and magical components. Before the concept of nutraceuticals originated, philosophers believed in the concept of diet in the public as well as individual health. From the era of Hippocrates (460-377 BC), i.e., 2000 years back, to the rising phase of modern medicine, it was recognized that the difference in diseases depends upon the food consumed in society (Kidd 2012).

In the year 1989, the New York Foundation for Innovation in Medicine, an educational foundation, came up with the term “nutraceuticals” to promote research rapidly in the biomedical sector (Kuhnau 1976). The Europeans acquired traditional knowledge from Asian countries and benefited the most (Chanda et al. 2019). The rational use of medicines urged the role of pharmacists and the discovery of principles in drug action with the simultaneous development of modern drug development with clinical trials (Menon and Spudich 2010). The Indian history, including the Unani, Ayurveda (including Sushruta, Samhita, and Charaka), Ashtavaidya, and Siddha systems of medicines, is renowned for possessing the art of healing procedures (González-Sarrías et al. 2013). There is an abundance of unexplored food products and nutrients that possess valuable biological activities (Yapijakis 2009). At present, the nutraceutical industry is the rapidly establishing segment of today's food market (Andlauer and Fürst 2002), with a 30 billion US dollar market growing annually at a rate of 5% per annum (Chauhan and Mehla 2015). The current stand on nutraceuticals and the knowledge accumulated about it poses a great challenge for nutritionists, food technologists, physicians, and food chemists (Peterson et al. 2017). In the process of pharmaceutical development, clinical testing on animals and humans is a must and the results obtained verify the therapeutic effects of the drug (Granato et al. 2020). While no established methods for verification of the therapeutic effects of nutritional foods were indicated in the past, in recent times, it has been scientifically proven that food compounds can prevent lifestyle-related disorders (Bagchi and Sreejayan 2016).

Nutraceuticals offer several advantages, including an increased significance of a healthy diet and aiding a longer life (Champagne et al. 2018). Apart from its beneficial effects on medical conditions, it also assists with proven psychological benefits; hence, they are the most popular in preventing neurological disease conditions (Casey et al. 2010). Due to the lesser perceived side effects, more populations, mainly the elderly, tend to adhere more towards nutrient-rich foods for lifestyle-related disorders (Nicastro et al. 2015). The aim and scope of the manuscript are to raise the awareness of the readers about the use of nutraceuticals in the management of neurodegenerative and psychotic disorders through the use of ingredients that are easily available and tend to show proven neuroprotective effects. The current review highlights the potential role of nutraceuticals in brain health and neurological disorders.

2 METHODOLOGY

Before commencing the review article, a deep literature survey on nutraceuticals in neurological disorders was performed. Research and review articles from various search engines and scientific databases, such as Pubmed, Medline, Science Direct, Google scholar, Scopus, Cochrane library, etc., were assessed and thoroughly read for a deep understanding of the topic and to evaluate the currently employed psychoactive and neuroprotective nutraceuticals. After the literature survey, the article writing was initiated. The total time for the completion of the review article was approximately 2 months.

3 NUTRACEUTICALS

The American Nutraceutical Association defines nutraceuticals as food or product with health-promoting characteristics. They include dietary vitamin supplements, genetically modified foods, herbal goods, fruits, beverages, vegetables, soups, and processed meals such as cereals. Vitamins, minerals, and amino acids are among the most common nutraceuticals, although there are over 1000 more. Until now, no probiotic substances have been found (Keservani et al. 2010).

Indians are among the most ancient cultures to have provided evidence of the efficient use of food products in medicine and the treatment of sickness, a fact Ayurveda has maintained for over 5000 years; Sumerians, Egyptians, and Chinese (Jamshidi-Kia et al. 2017). The study of nutraceuticals is a tough topic that is steadily gaining prominence. Consumers' eating habits have prompted them to embrace new dietary patterns based on nutrient- rich foods to stay healthy and avoid the danger of future negative health outcomes. Nutraceuticals are compounds derived from animals and plants. The term nutraceutical is a combination of the words "nutrition" and "pharmaceutical," and it refers to foods or food components, such as carbohydrates, vitamins, fibers, and other nutrients, that when consumed, contribute to a healthy lifestyle by aiding in the prevention and treatment of disease, as defined by De Felice in 1995 (Prakash and van Boekel 2010). Nutraceuticals are divided into traditional and atypical categories based on dietary availability. Traditional foods are those that contain nutritional value by nature. Probiotics, for example, are microorganism- derived supplements. Lactobacillus and Bifidobacteria, two types of live bacteria included in probiotics, protect against gastrointestinal disorders. They have also been shown to protect against the development of allergies in children in recent studies Traditional nutraceuticals include nutrients and herbals, both of which are derived from plants. Fortified and recombinant agents are examples of non- traditional nutraceuticals (Gul et al. 2016). The first category includes foods high in nutrients such as vitamins and minerals, while the second category includes foods that have been made using biotechnology techniques and are high in energy Plants produce two active molecules throughout their metabolic processes: primary and secondary metabolites. Vitamins, amino acids, fatty acids, and carbohydrates are the nutrients produced during primary metabolism. On the other hand, secondary metabolism products are chemicals that are primarily created as a defense against natural pathogens.

Secondary metabolites or phytochemicals are the common names for these compounds. Different approaches are used to extract secondary metabolites from plants. The final product is made up of a variety of active components. This is the situation with botanical extracts, which have long been used for medicinal value. Traditional nutraceuticals include nutraceutical enzymes as well. Our organism's enzymes are valuable compounds now employed to treat lysosomal storage disorders like Fabry, Pompe, and Gaucher disease (Poddar et al. 2019). Phenols, flavonoids, tannins, saponins, carotenoids, and other secondary metabolites are categorized according to their chemical composition. These compounds are expected to have a wide range of biological functions due to their chemical structural variety.

Antioxidant, cardioprotective, anticancer, antidiabetic, anti- inflammatory, anti- aging, and neuroprotective actions have been demonstrated in numerous research. Furthermore, the diversity of their chemical composition allows researchers to investigate several modes of action that affect various metabolic pathways implicated in the etiology of various disorders Food is regarded to have an important role in sustaining good health. Hippocrates remarked, ‘Let thy food be thy medicine, and medicine is thy food,’ stressing the significance of a healthy diet in illness prevention (Pandareesh et al. 2018). Current research backs up this assertion, and many studies are now focusing on the preventive and curative effects of single compounds or combinations of compounds in treating various diseases. For example, many experts are concerned about Alzheimer's disease because millions of individuals suffer from its effects, and its incidence is predicted to climb significantly (Frank et al. 2020).

4 NUTRACEUTICALS AND ITS CATEGORIES

Nutraceuticals fall under nonspecific biological therapies and are used in the prevention of symptoms of mild disorders to highly toxic malignancies. Their role as neuroprotective is well-pronounced and highly acknowledged. They can be categorized considering the following criteria:

4.1 Food-Based Nutraceuticals or Traditional Nutraceuticals

This category includes food products obtained directly from nature without any change in their original constituent form (Bhaskarachary et al. 2016). These include fruits, vegetables, grains, meat, fish, eggs, and dairy which provide several benefits beyond basic nutrition (Bhat and Bhat 2011).

4.1.1 Nutrients

The primary metabolites of substances like minerals, fatty acids, vitamins, and amino acids possess well-established nutritional properties in the metabolic pathways. These nutrients in combination with animal and plant products have several benefits in curing neurological disorders (Elsebai et al. 2016). The planting of nutrients can be used in preventing brittle bones, uplifting hemoglobin, and strengthening muscle power and neuronal transmission. Fatty acids and their compounds enhance brain functioning and aid a decrease in cholesterol present in the arteries, tending to show its hypolipidemic effects (Ali et al. 2023).

4.1.2 Herbals or Extracts and Concentrates of Botanical Products

The combination of nutrients and herbals poses an excellent impact on lifestyle-related disorders, including mental health (Dohrmann et al. 2019). Tannin-containing compounds, such as lavender, help in releasing stress and lowering blood pressure (Barba et al. 2020). Flavonoids have been clinically proven to prevent diabetes, cardiovascular disorders, and kidney abnormalities based on their antioxidant potential, containing compounds, such as psoralen, which is obtained from parsley and also possess carminative and diuretic properties (Putnik et al. 2019a).

Terpenoid-containing compounds, such as peppermint and menthol, are used in respiratory conditions. Many other commonly used herbs, such as aloe vera, possess anti-inflammatory and dilating properties, hence it is used in wound healing; ephedra possesses bronchodilator and vasoconstriction effects, hence it is used for bronchospasms (Putnik et al. 2019b). The most commonly used food ingredients, garlic, and ginger, possess anti-inflammatory and chemotherapeutic properties, are used in hypertension, and are a strong immunity booster (Poojary et al. 2017). Not only herbal products but also the phytoconstituents they possess can also be categorized under nutraceuticals, for example, vegetables contain carotenoids, which boost immunity, mainly killer cells, and possess anticarcinogenic properties (Montesano et al. 2018). Non-carotenoid foods, such as chickpeas and soya beans, aid in the removal of cholesterol. Curcumin obtained from turmeric, one of the most common ingredients in the kitchen, can be classified under phenolic acids and possesses the highest antioxidant activity, and acts as an anti-inflammatory. Dietary supplements, mainly antioxidant-rich foods, such as green tea, ginger, cumin, etc., have shown promising effects in weight loss (Pillitteri et al. 2008). They have also been studied for their efficacy in neurological interventions, such as depression (Rao et al. 2008). They also include enzymes and glandular extracts and can be consumed in all dosage forms, including capsules, powders, tablets, etc.

4.1.3 Probiotic Microorganisms

The term probiotic was coined by the famous scientist Metchnikoff. They are highly advantageous concerning gastric and intestinal physiology. They possess antibiotic properties and aid in the removal of toxic flora from the gut. A healthy diet leads to a healthy brain and body (Gosálbez and Ramón 2015). The consumption of probiotics has been a breakthrough in the management of gastrointestinal disorders. After these results, probiotics have also been initiated for their consumption as supplements in the form of capsules and probiotic beverages.

Thus, modern-day probiotics claim to be effective in all health conditions from diarrhea to neurological conditions, such as depression and Alzheimer’s, and are challenged for their therapeutic effects. There is a great need to explore probiotics, as published research on their safety is lacking. It is difficult to differentiate the benefits of probiotics from their contraindications. In instances with a high risk of infection in patients with compromised immune systems, the probiotics may be moderately effective therapeutically (Zucko et al. 2020).

Probiotics, prebiotics, and synbiotics- based therapies are thought to be a doorway for modulating gut flora in neuroinflammation suppression (Li et al. 2020). Diet can alter the microbiota composition, which impacts the gut-brain axis' function. Gut dysbiosis is linked to cognitive decline, behavioral issues, and shrinking brain capacity in the elderly (Castelli et al. 2021).

Gut dysbiosis may contribute to the etiology of Alzheimer's disease by causing Aβ aggregation, neuroinflammation, oxidative stress, and insulin resistance (Castelli et al. 2021). According to clinical trials, probiotics like Lactobacillus can help immunomodulation and reduce proinflammatory indicators like IL-8.

Blood BDNF levels and cognition were improved by Bifidobacterium breve A1 (Pluta et al. 2020). Fiber components act as prebiotics, assisting probiotics and bacteria in their growth. Because of their capacity to balance inflammation and neurotransmitters, oligosaccharides and inulin are examples of prebiotics with anti- AD benefits. Following prebiotic administration in AD rodents, numerous signaling pathways, such as PI3K- Akt and PPAR, were mediated. Synbiotics are a combination of probiotics and prebiotics. (Pereira et al. 2021) found that using kefir- fermented milk as a synbiotic improved memory and overall cognitive function in Alzheimer's patients. After treatment with the synbiotic, proinflammatory cytokines such as TNF- α, IL- 8, and IL12p70 were reduced. Following kefir treatment, serum levels of O2, H2O2, and ONOO- /OH- decreased significantly, while NO levels increased. Kefir treatment helped to restore mitochondrial membrane potential. Another benefit of this synbiotic treatment was a decrease in the cleavage of PARP- 1 (Pluta et al. 2020).

4.1.4 Nutraceutical Enzymes

Enzymes or biocatalysts are protein structures and are synthesized by cells. They cause metabolic processes to occur faster and are mainly beneficial in medical problems related to the gastrointestinal tract, such as gastroesophageal reflux disease, constipation, diarrhea, etc. Enzyme supplements provide the least advantages in neurological health, but recently, some therapies have been procured to cure rare disorders, such as Hunter syndrome, Gaucher disease, etc.

They are highly economical as they are obtained from both plant and animal sources. A large number of advantages are offered upon the consumption of food-based nutraceuticals. Nutraceuticals obtained from foods, such as garlic, ginger, turmeric, dairy products, carotenoids, etc., are much heathier and can provide all the essential nutrients required by our body. They are easily available in grocery stores and prevent the exacerbation of severe life-related disorders, such as diabetes, and even cancers.

Having good mental health is a priority, and a good diet can be the most appealing option for neuroprotection. However, they pose certain disadvantages too. The most stressed drawback of food-based nutraceuticals is their safety. There is still a dire need to explore functional foods for their safety before they are released into the market for consumption in raw forms. All substances are poison unless consumed in a finite amount. It is evident that a food that is highly active as an anticarcinogen can simultaneously act as a cardiotoxic. Thus, administration of the desired dose is recommended (Tapal and Tiku 2019).

4.2 Non-Traditional Nutraceuticals

These include foods obtained from the breeding of agricultural products and nutrients, such as orange juice fortified with calcium, vitamins, and minerals in cereals, etc (Singh and Sinha 2012). Cultural scientists have successfully invented techniques and have changed the nutritional content of crops, and more research is being carried out to improve the quality of nutrition in crops (Sapkale et al. 2012).

4.2.1 Fortified Nutraceuticals

These are the type of nutraceuticals that are designed from breeding at the agricultural level by enhancing nutrients (Ottaway 2008), such as minerals in cereals, increasing calcium, folic acid, and iron in flour, making milk fortified with cholecalciferol for the treatment of vitamin D deficiency, etc (Street 2015).

4.2.2 Recombinant Nutraceuticals

Nutraceuticals obtained from the application of biotechnology in food products are called recombinant nutraceuticals. These nutraceuticals are among the most commonly used category, including the extraction of nutrients from certain food products, like dairy products, cheese, and bread, to extract the enzyme that is therapeutically beneficial if used at optimum levels (Nwosu and Ubaoji 2020).

Non-traditional nutraceuticals have emerged to boost a larger extract of nutrients in already existing food supplements and aim to provide more benefits in the same volume of food consumption. It offers several advantages and is a blessing in the era of sedentary lifestyles, yet it poses certain threats. The production of nutraceuticals still lacks regulations by the Food and Drug Administration (FDA) (Administration 1995). Many companies synthesize non-traditional nutraceuticals of poor quality to obtain larger profits and margins.

Additionally, the bioavailability of enhanced nutrients is not monitored and is generally poor in various scenarios. The testing of nutraceuticals is not as controlled as pharmaceuticals, clearly indicating no defined regulations.

4.3 Based on the Mechanism of Action

Based on the therapeutic properties possessed, nutraceuticals have been further classified into antibacterial, antifungal, antioxidants, anti-inflammatory, and antiobesity categories to distinguish their role and assess their uses.

Food-borne infections are the cause of a wide number of deaths due to infection. Many bioactive compounds have been used as a potent antibacterial therapy in the management of infectious disorders, such as carsonic acid (terpenoids), quercetin (polyphenols), etc. They are obtained from a wide number of fruits and vegetables (Gutiérrez-del-Río et al. 2018).

Traditional foods have been consumed for many years for their therapeutic activity as an anticancer, antidiabetic, etc. Various studies have led to the formation of medicinal mushrooms as a good candidate for antifungal therapy with the least side effects. These mushrooms are widely popular all over Asia (Giavasis 2014). Nutraceuticals have been used in various inflammatory disorders, including rheumatoid arthritis, because of their anti-inflammatory action (Al-Okbi 2014). Foods rich in antioxidants, carotenoids, and tocopherols possess higher anti-inflammatory activity.

Nutraceuticals are renowned for their free radical scavenging properties and antioxidant action. This antioxidant activity leads to its role in the management of other related disorders, such as obesity (Cornelli 2009). As discussed above, consuming anything in excess acts as a poison. The consumption of nutraceuticals based on their mechanism of action is highly supportive. Consuming any compound for its therapeutic activity tends to decrease the chances of evident toxic traits associated with it and benefits the person for the desired diseased condition. Additionally, it leads to monitored administration of nutraceuticals and prevents any toxic effects associated with high doses.

4.4 Based on the Chemical Nature of the Products

Nutraceuticals can also be classified based on the secondary metabolites they possess, such as fatty acids, carbohydrates, and amino acid-based compounds, as the origin of every nutraceutical is different depending on the natural source (Chintale Ashwini et al. 2013).

Most commonly used nutraceuticals as adjunctive therapy in different neurological disorders are classified as it is presented in Figure 1.

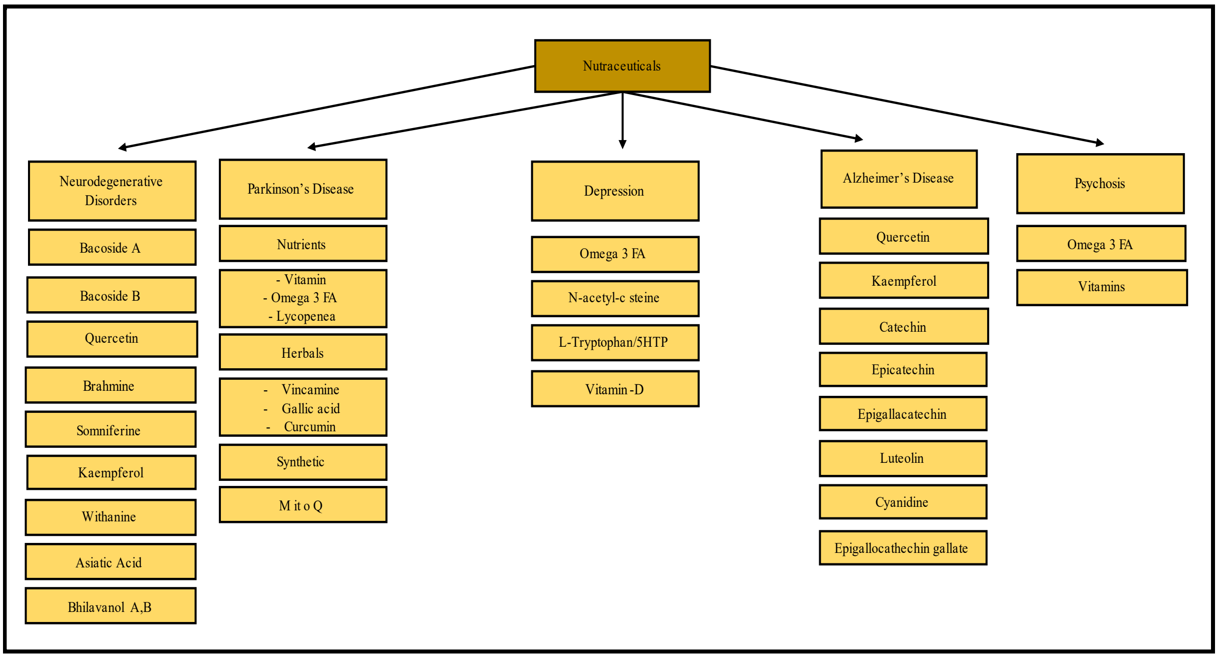

Figure 1. Some of the most commonly used nutraceuticals can be employed as adjunctive therapy in the management of neurological degeneration, Parkinson's disease, depression, Alzheimer's disease, and psychosis simultaneously (Williams et al. 2015)

The chemical nature of the compound defines the activity it is associated with. Consuming nutraceuticals based on their chemical nature can enhance the therapeutic activity and minimize the risks of toxic actions that can be experienced. However, the results are not as expected. The functioning of every individual is different, and some active compounds tend to react with host molecules and produce toxic traits.

5 NUTRACEUTICALS IN AMELIORATING NEURODEGENERATION

Neurodegenerative disorders mainly develop by protein misfolding (Colín-González et al. 2015). Abnormal misfolding of the proteins τau and amyloid-β (Aβ) leads to the progression of Alzheimer's disease; traumatic brain injury can be induced by modifying τau, transactive response (deoxyribose nucleic acid) (TAR DNA) binding protein-43 (TDP-43), and Aβ proteins; while τau and TDP-43 misfunctioning can subsequently induce epilepsy and various other tauopathies (Grassi et al. 2016). The cytotoxic cascade of molecular and cellular events is mainly induced by protein Aβ in down syndrome, and α-synuclein in Parkinson's disease, leading to detrimental consequences and further degeneration (Johnston 2015).

These misfolded proteins further stimulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) activation (Saldanha and Tollefsbol 2012), which causes the production of inflammatory cytokines (such as tumor necrosis factor- α) (TNF-α), interleukins-1β (IL-1β), etc.) (Asadi-Shekaari et al. 2012), and leading to the activation of destructive molecules (like cyclooxygenase (COX-2), and inducible nitric oxide synthase (iNOS); the actions mentioned are the results of reactive oxygen species (ROS) release and glutamate-induced oxidative damage, causing the dysfunction of mitochondria and toxicity (Kelsey et al. 2010). Additionally, the misfolded proteins further dysregulate the signaling of GSK3β with simultaneously provoked inflammatory cytokines, which leads to hyperphosphorylation of τau proteins and causes an increased synthesis of cholesterol. Furthermore, it also results in the formation of lipid rafts, harboring misprocessing and misfolding of proteins due to the promotion of enzymes, thereby setting up a vicious cycle (Barber et al. 2006).

Moreover, misfolded proteins are due to the promotion of enzymes, thereby setting up a vicious cycle (Gonsette 2008). Moreover, misfolded proteins dysregulate various signaling pathways-such as extracellular signal-regulated kinase (ERK), cyclic adenosine monophosphate (cAMP) response-element binding signaling (CREB), and protein kinase A/protein kinase B (PKB/PKA), and cholinergic functions, leading to defects in cognitive functions and degradation of the synaptic process (Lin and Beal 2006). Nutraceuticals can tend to modify the cellular and molecular cascade and can lead to the prevention of neurodegeneration by targeting proteins that are misfolded practically at all levels and act as supplementation therapy. It has been found that nutraceuticals have antioxidant, antihypercholesterolemia, and anti-inflammatory effects with simultaneous production of the enhanced cholinergic system due to acetylcholinesterase inhibition (Ghabaee et al. 2010). Nutraceuticals, when used for their therapeutic potential, can easily replace synthetic drug ingredients, such as donepezil, tacrine, rivastigmine, and galantamine, which act by inhibiting acetylcholinesterase enzyme; statins like rosuvastatin and atorvastatin, which act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase; alpha-tocopherol or vitamin E; aspirin, ibuprofen, and another cyclooxygenase (COX) inhibitors under the category of non-steroidal anti-inflammatory drugs (NSAIDs); etc., as these compounds possess evident side effects (Lenaz 2001). Hence, nutraceuticals offer an all-in-one effective alternative in the management of neurological disorders due to their affordable prices and availability and decreased side effects (Ott et al. 2007). The pathogenesis of misfolded proteins that mediate neurodegeneration is briefly represented in Figure 2.

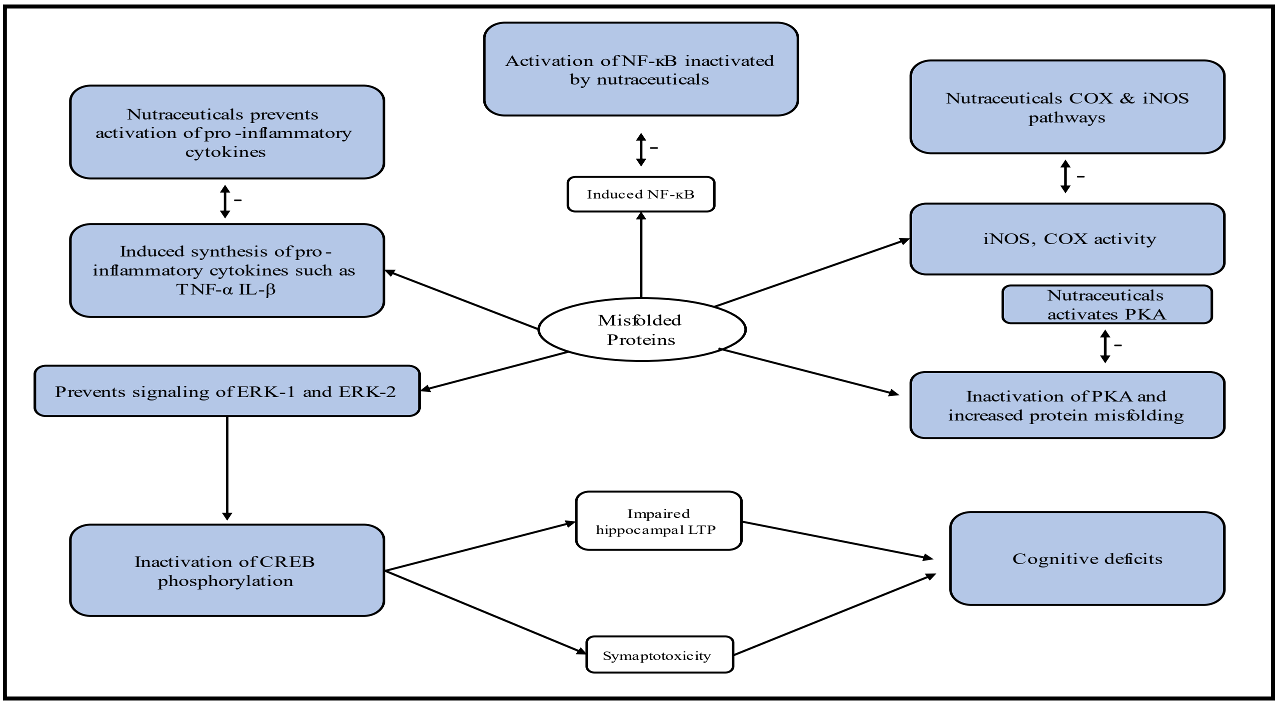

Figure 2. Summarized pathogenesis of misfolded proteins and neurodegeneration mediated upon their activation. The misfolded proteins lead to the activation of a cascade of inflammatory proteins, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX), and activation of interleukins and inflammatory cytokines, which leads to inflammation and further neurodegeneration. Inhibition of these cascade proteins by active nutraceuticals tends to provide neuroprotective action.

The main nutraceuticals in neurological disorders include bacoside A, bacoside B, and brahmine (as they were classified in Figure 1). Bacoside A and bacoside B are saponin derivatives, while brahmine is an alkaloid derivative, which is obtained from Brahmi (*Bacopa monnieri)*. It is a renowned nootropic plant, which has been used in Ayurveda for its neurocognitive-enhancing properties. The human brain is highly susceptible to neurodegeneration due to an increase in oxidative stress and the generation of free radicals due to a high metabolic rate; poor antioxidant activity of catalase, glutathione peroxidase, and other free radical scavenging enzymes; and the presence of unsaturated fatty acids in the membranes of cells (Abdul Manap et al. 2019). The plant is a proven antioxidant. Through various studies, it has been established that the protein amino group side chains, after the reaction with d-galactose, lead to the generation of amadori products that result in advanced glycation end products (AEGs). The glycated products lead to a 50-fold increased production of free radicals than non-glycated products, ensuring oxidative stress. Administration of phytoconstituents, mainly bacosides A and B and brahmine, significantly decreased the number of AEGs and prevented aluminum-mediated neurotoxicity in the cerebral cortex region of the brain and is effective in the prevention of neurodegeneration (Zhu et al. 2007).

5.1 Quercetin and Kaempferol

The generation of free radicals in the brain leads to the inhibition of amyloid β1-42 proteins and their aggregation and also leads to fibril destabilization. Quercetin and kaempferol have been proven to decrease the levels of free radicals remarkably (Bungau et al. 2019). They also prevent the activation of NF-kB, which further prevents the activation of proinflammatory cytokines, mainly interleukins. It is among the most commonly explored phytoconstituents, mainly obtained from the leaf extract of *Gingko biloba*, in the prevention and cure of cognitive disorders (Pallavi and Kumar 2018). They are also highly effective in improving the circulation of blood in the brain and preventing the progression of Alzheimer's disease (Purza et al. 2019).

5.2 Within

Withanine is the chief steroidal alkaloid obtained from ashwagandha, also known as Indian ginseng, which has been used for its memory-boosting and neurocognitive-enhancing properties for more than 2500 years. It possesses high antioxidant potential and can be used to improve oxidative stress-mediated neurodegeneration. The methanolic extract of ashwagandha root exhibits memory-boosting action and inhibits the enzyme acetylcholinesterase, which is of great significance in neurodegeneration as it indirectly facilitates the transmission of cholinergic neurons and is highly recommended in the treatment and management of Alzheimer's disease (Sivasankarapillai et al. 2020). The levels of catecholamines, including serotonin, are also augmented besides the antioxidant activity by maintaining the levels of antioxidant enzymes, mainly glutathione, and catalase. Withanine inhibits the activation of nitric oxide, which further reverses oxidative stress, and presents remarkable neuroprotective effects. Somniferine, also obtained from ashwagandha, is also widely used for its neuroprotection and memory-enhancing effects.

5.3 Asiatic Acid

Gotu kola has been used for its memory-enhancing properties in Ayurveda and also aids in improving learning. Its principal phytoconstituent, namely asiatic acid, is chiefly responsible for neuroprotective actions. It acts by decreasing the levels of malondialdehyde while simultaneously increasing glutathione. Malondialdehyde is a by-product formed post-peroxidation of lipids which acts as an utmost important marker for the detection of free radicals of oxidative stress-mediated neurodegeneration. Asiatic acid increases the levels of free radical scavenging enzymes, such as glutathione, and augments its antioxidant medication protection against neurodegeneration (Pallavi and Kumar 2018).

5.4 Bhilavanol A and Bhilavanol B

Bhilavanol A and flavanol B, which are chiefly obtained from bhallaatak, inhibit the activation of acetylcholinesterase and are highly effective against stress-mediated neurodegeneration. Ingredients of the Mediterranean diet, such as coffee, extra virgin olive oil, walnuts, etc., also improve memory and are highly beneficial. The phenolic compounds extracted from plants are highly emphasized as they possess maximum therapeutic benefits (Pallavi and Kumar 2018).

6 NUTRACEUTICALS IN ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD), also known as senile dementia of the Alzheimer's type (SDAT) or the primary degenerative dementia of the Alzheimer's type (PDDAT), is the most common form of memory loss (Linseman, 2009). Pronounced nutraceuticals that are helpful in the management of AD include super essential antioxidants, which can be employed in the treatment of all chronic diseases due to oxidative stress, which exhibits a crucial part in neurological disorders, including AD (Frisardi et al. 2010).

The process of aging and lack of intake of dietary antioxidants accelerates oxidative stress causing disease progression and stimulation. Various studies have reported an association between the intake of higher amounts of dietary antioxidants and diminished risk in patients with AD, which is highly imperative as disease prevention is considerably cooler than treating it (Raoufi et al. 2023). Additionally, researchers suggest that the prevention of AD is not as complex as assumed. The consumption of food products that are rich in polyunsaturated fatty acids and saturated and trans fatty acids tends to suppress neurodegeneration while foods rich in trans-fat can enhance neurodegeneration. The use of antioxidants for treatment is a hopeful option for slowing the progression and advancement of diseases (Puentes-Díaz et al. 2023). Some of the compounds beneficial in AD are described in Sections 5.1-5.5.

6.1 Flavonoids

The main employed flavonoids in neurogenerative disorders, mainly Alzheimer's, include catechin, epicatechin, epigallocatechin, and epigallocatechin gallate. These are a group of commonly found polyphenolic compounds mainly extracted from the human diet. The main resources of flavonoids include fruits, vegetables, and drinks, such as wine, tea, and cocoa. Flavonoids and their metabolic products possess neurological-modulating actions and have been studied to interact with the neuronal-glial signaling pathway, which is mainly involved in the survival and functioning of neurons (Haș et al. 2023). The cerebral flow of blood is also modulated by the upregulated activity of antioxidant proteins and enzymes, which causes synaptic plasticity and repair of neuronal functions by inhibiting the process of neuropathology in the brain mainly associated with AD (Romero-Márquez et al. 2023).

Table 1 Preclinical studies on flavonoids for the treatment of Alzheimer's diseases

Sr. no.	Name of nutraceuticals	The model used in the study	Effect/study	References
1	Genistein	Rats	In hippocampal CA1 neurons, genistein boosted phosphorylation/ activation of eNOS, which activated Nrf2/Keap1 and its downstream antioxidant protein, heme oxygenase (HO)-1, and improved spatial learning and memory	(Wang et al. 2013)
2	Naringin	Rats	Naringin improved cognitive impairments and reduced oxide- nitrosative stress and cytokine release caused by the mitochondrial malfunction	(Sachdeva and Chopra 2015)
3	Naringenin	Rats	Naringenin increased passive avoidance and radial arm maze performance; reduced hippocampus malondialdehyde; did not affect nitrite and superoxide dismutase activity; and reduced apoptosis	(Ghofrani et al. 2015)
4	Curcumin	Rats	Curcumin reduced oxidized proteins and interleukin- 1beta, GFAP, insoluble beta- amyloid, soluble Aβ, and plaque load in astrocytic cells. However, the membrane fraction's amyloid precursor (APP) levels were not lowered; Microgliosis was reduced in neuronal layers but not in plaques	(Lim et al. 2001)
5	Lycopene	Rats	Lycopene improved mitochondrial morphological changes, cytochrome c release after activating the mitochondrial permeability transition pores; improved mitochondrial complex activities and restored ATP levels in A- treated neurons; and prevented mitochondrial DNA damage and improved mitochondrial transcription factor Aβ protein levels	(Qu et al. 2016)
6	Crocetin	Rats	Crocetin decreased pro- inflammatory cytokines in plasma while increasing anti-inflammatory cytokines blocked NF- kB activation and P53 expression in the hippocampus, decreased Aβin several brain regions, and improved learning and memory impairments	(Zhang et al. 2018)
7	Huperzine A	Rats	Huperzine A reduced the iron overload-induced decrease in neuronal cell viability, lowered ROS, raised ATP, and prevented the labile iron pool level from rising	(Xiao et al. 2002)
8	Berberine	HEK293 Cell line	Berberine reduced tau hyperphosphorylation at Ser198/199/202, Ser396, Ser404, Thr205, and Thr231; restored protein phosphates 2A activity and reversed GSK- 3β activation; and reversed both malondialdehyde and superoxide dismutase activity	(Yu et al. 2011)
9	Kaempferol	Rats	Kaempferol improved spatial learning and memory, increased superoxide dismutase and glutathione levels in the brain, and decreased tumor necrosis factor and malondialdehyde levels.	(Kouhestani et al. 2018)
10	Crocin	Rats	Crocin increased spatial memory indicators while decreasing the Bax/Bcl- 2 ratios and cleaved the Caspase- 3 levels. Crocin did not affect Beclin- 1 or the LC3- II/LC3- I ratio	(Asadi et al. 2015)

Table 2 Clinical studies on flavonoids for the treatment of Alzheimer's diseases

Sr.no.	Name of nutraceuticals	The model used in the study	Effect/study	References
1	30 mg/day for 22 weeks, Crocus sativus (saffron), Oral	Phase 2 double-blind clinical trial in mild- to moderate Alzheimer's disease patients	Crocus sativus was well- tolerated and lessened the severity of the symptoms	(Akhondzadeh et al. 2010)
2	Capsules containing Docosahexaenoic acid and eicosapentaenoic acid	Phase 1 of a 33- participant double-blind clinical trial	Patients given omega- 3 had lower levels of EPA, docosapentaenoic acid (DPA n- 3, DHA, and fatty acids (n- FA) than that given placebo. Compared with the control group, AA, docosatetraenoic acid, and the n- 6 /n- 3 FAs ratio were lower; inflammatory indicators were unaffected	(Freund Levi et al. 2014)
3	2.152-mg docosahexaenoic acid every day for 6 months	Phase 2/Phase 3 randomized placebo-controlled clinical trial with 33 participants	Docosahexaenoic Acid treatment showed a 28% increase in CSF DHA and a 43% increase in CSF EPA; Increased CSF EPA was three times larger in nonAPOE4 carriers than in APOE4 carriers; there was no change in brain volume or cognitive scores	(Arellanes et al. 2020)
4	Over 90 days, milk was fermented with kefir grains as a nutritional supplement	Patients with Alzheimer's disease who have cognitive abnormalities are studied in an uncontrolled clinical trial	Memory, visual-spatial/abstraction skills, and executive/language abilities all increased dramatically; absolute/relative reductions in several cytokine indicators of inflammation and oxidative stress markers (O2- , H2O2, and ONOO, by 30%, respectively); increase in NO bioavailability (100%)	(Pereira et al. 2021)

6.2 Carotenoids

About 700 diverse members of the carotenoid family have been identified to date, 40 of which are found in human tissues and blood. The major carotenoids present in humans include lutein, zeaxanthin, lycopene, and β-cryptoxanthin, including α and β carotenes. The antioxidant activity of carotenoids can be identified based on their chemical structure setting. They are fat-soluble pigments and can mainly be extracted from fruits and vegetables that are orange, deep-yellow, and red. Astaxanthin, a seafood-derived carotenoid, has been extensively studied for its anti-inflammatory and antioxidant potential *in vivo* and *in vitro* animal models, and its microcirculatory protective functions and mitochondrial protective functions have been identified, suggesting it is a potent neuroprotective compound. Patients with severe or moderate AD lack major carotenoids, such as lutein and beta carotene, compared with patients with mild AD (Gowthaman et al. 2023).

Table 3 Preclinical studies on carotenoids for the treatment of Alzheimer's diseases

Sr.no.	Name of nutraceuticals	The model used in the study	Effect/study	References
1	Ginsenoside	Mice	Ginsenoside Rg1 lowers Aβ accumulation and enhances cognitive function in a transgenic mouse model by stimulating the protein kinase A/cAMP response element-binding protein signaling pathway	(Fang et al. 2012)
2	Ginkgolide A & B	Rat	Ginkgolides A and B protect neuronal cells against synaptic injury, as demonstrated by the loss of presynaptic, synaptic marker synaptophysin, and enhance neuronal survival in the face of Aβ- induced toxicity. & Ginkgolide B protects hippocampal neurons against Aβ-induced apoptosis by increasing the synthesis of brain-derived neurotrophic factors and lowering apoptotic cell death in hemorrhagic rat brains	(Xiao et al. 2010)
3	Cannabidiol	Mouse	In a mouse model of AD induced by intrahippocampal injection of Aβ (1-42), CBD's neuroprotective qualities were confirmed by a decrease in glial- activated proinflammatory mediators	(Esposito et al. 2006a)
4	Synthetic cannabinoids (JWH- 133, HU- 210, WIN55,212– 2	Rat	In rats given A, the activation of microglia and the generation of cytokines was reduced. As a result, these synthetic medicines ameliorate cognitive impairment by lowering the reduction in neural marker levels	(Martín-Moreno et al. 2012)

Table 4 Clinical studies on carotenoids for the treatment of Alzheimer's diseases

Sr.no.	Name of nutraceuticals	The model used in the study	Effect/study	References
1	Ginsenoside	Double-blind, placebo-controlled, and crossover design of 20 young, healthy people	In a placebo-controlled, double-blind, balanced, crossover study including 20 young, healthy participants who were given a single dose of 200, 400, or 600 mg ginseng extract, the advantages of ginseng extract in terms of improved cognitive function was the largest (Quality of memory)	(Martín-Moreno et al. 2012)
2	Cannabidiol	Double-blind controlled	By inhibiting glycogen synthase kinase- 3, an enzyme that generates tau hyperphosphorylation in Alzheimer's patients, CBD medication decreases tau hyperphosphorylation, one of the disease's clinical manifestations	(Esposito et al. 2006b)

6.3 Crocin

Crocin is a chief phytoconstituent obtained from saffron (Crocus sativus). It has been used for ages for its antispasmodic, neurine sedative, gingival sedative, expectorant, stimulant, and carminative properties. Saffron has been proven to act in the prevention of epilepsy, depression, and inflammatory disorders. Crocin is also known to improve learning and enhance memory based on its long-term potential being blocked by ethanol, and hence, it is used in neurodegenerative disorders, such as AD. Crocin tends to improve cognition by ADAS-Cog and CDR-SD-mediated enzymes in patients with mild to moderate AD. Through various studies it has been concluded that crocin can significantly alter the levels of oxidative markers in the region of the hippocampus and abolish the deleterious effects on learning and memory due to chronic stress (Gowthaman et al. 2023).

6.4 Cyanidin

The other major compounds include cyanidin (anthocyanidins), which is mainly obtained from cranberries, strawberries, etc., and exert potent anti-inflammatory and neuroprotective action by suppressing the activation of proinflammatory cytokines and ultimately brain cell damage. The main role can be attributed to the inhibition of phospholipase A2, which is chiefly involved in the signaling of proinflammatory cytokines and oxidative stress parameters, the inhibition of which presents remarkable neuroprotection (Ciric et al. 2023).

6.5 Luteolin

Luteolin and apigenin are flavones, which possess remarkable neuroprotective activity. The principal sources of these flavone-containing compounds include rosemary, parsley, and celery (Tao et al. 2023). These phytoconstituents possess remarkable pharmacological benefits, mainly the ability to protect DNA against hydrogen peroxide-mediated toxicity, further preventing inflammation and cell damage in Alzheimer's (Suyal et al.).

7 NUTRACEUTICALS IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurological disease with impaired dopaminergic neurons in the substantia nigra par compacta region of the brain, leading to a drastic depletion of dopamine (DA). Factors, such as oxidative stress, depletion of antioxidants, damage to mitochondria, etc., contribute to neurodegeneration leading to PD (Gowthaman et al. 2023). Anti-Parkinson's diseases provide symptomatic relief by supplementing dopamine and preventing symptoms of motor abnormalities and gait, and providing neuroprotection (Gowthaman et al. 2023). Therefore, a wide range of drug molecules is implemented, which act by the activation of several pathways of the prevalent pharmacotherapy. Abundant studies on vitamins and their supplementation in animals and clinical studies have been performed, which depicted mixed outcomes in managing the symptoms of PD; therefore, there is a need for more research and established evidence on their effects on PD.

Several vitamins, including vitamin B3, vitamin B9 or folate, vitamin B12, vitamin B6, vitamin D, vitamin E, and vitamin C, can be used in Parkinson's disease (Hu et al.). The anti-Parkinson drugs currently employed prevent disease progression by providing symptomatic relief only. The main challenge lies in recognizing the ideal lead molecule, which, besides targeting multiple pathways and curing disease, is also the least toxic to humans (García-Fernández et al. 2023). With this as the principal, a wide number of herbal and natural products have been studied clinically for use in PD to evaluate and clarify if such herbal molecules can be implemented as an independent or adjunctive therapy in disease management (Alharthy et al. 2023).

It is tough to retrospectively study the effect of a herbal drug, food product, or supplement in a large population due to the high levels of variance and unreliability of results based on patients' statements and contributing lifestyle patterns. Thus, these challenges during clinical trials on synthesized herbal products restrict the emergence of the identified lead molecule in the market (Leong et al. 2023). Natural products exert favorable effects on PD by blunting the different pathologic pathways inducing it, like oxidative stress, dysfunction of mitochondria, neuroinflammation, and apoptosis.

7.1 Targeting the Dysfunction of Mitochondria and Oxidative Stress

Uninhibited oxidative stress and free radicals in association with the dysfunction of mitochondria lead to compromised cellular metabolism and energy homeostasis, thereby impacting the functioning of the brain, and leading to neurodegenerative disorders, including PD. However, it is not clear if the dysfunction of mitochondria is a consequence or cause of neurodegeneration. The mutations in mitochondrial DNA in dopaminergic neurons and defective chains in the respiratory system in patients with PD have been hypothesized as the mechanism that induces mitochondrial dysfunction.

The mitochondria in cells regulate the supply of ATP and calcium to release stored neurotransmitters into the synaptic cleft and depolarizing neurons, hence protecting cells by fission and fusion. The role of α-Syn was demonstrated in the morphological maintenance of mitochondria and enhanced efficiency of ATP synthase. The aggregates of α-Syn lead to compromised functioning of bioenergetic mitochondria and upregulate the generation of reactive oxygen species, which causes an unbalance between the oxidative status and death of primary neurons in rats.

Neuromelanin (Nm), a crucial pigment present in dopaminergic neurons, is highly protective against oxidative stress. Nm can easily chelate multiple ions, including iron and zinc, to maintain balance in the redox system. Surplus iron concentrations have a significant role in the pathology of PD as abundant iron stores and Nm levels can aggravate neurotoxic events, which trigger autooxidation of DA and leads to neuroinflammation. The components of food besides nutraceuticals have been successfully shown to prevent or delay the progression of the disease by preserving the functioning of mitochondria, further strengthening its role as a major pathological mechanism in PD (Ali et al. 2023). There are several nutrients, phytochemicals, or synthetic compounds that can act and prevent disease progression by preventing mitochondrial dysfunction (Montgomery et al. 2023).

Amongst nutritional supplementation, coenzyme Q10 (CoQ10) and fish oil can be used efficiently in PD management as they are the key components of the electron transport chain and are actively involved in the production of ATP, counteracting 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-mediated neurotoxicity and blocking the transfer of electrons between complex 1 and other complexes. Apart from this, polyphenols also possess multidimensional features to counteract the pathology of PD as they can easily surpass the blood-brain barrier and present favorable actions by improving motor and gait abnormalities in patients by protecting dopaminergic neurons and limiting free radicals. Lycopene, as initially studied, is a lipid-soluble acyclic carotenoid obtained from red-colored fruits and vegetables, mainly tomatoes, which exerts an antioxidant effect and has presented neuroprotective action in a study conducted on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (MPTP)-induced mice, and has been shown to enhance the levels of dopamine (DA) in the striatum region. The therapeutic effects of lycopene are dedicated to its antioxidant activity accompanied by neurobehavioral deficits and an increase in the activity of superoxide dismutase (SOD) and nicotinamide adenine dinucleotide (reduced form) (NADH) dehydrogenase at the striatal level besides increased glutathione and decreased malonaldehyde concentrations.

Fish oil is highly rich in omega-3 fatty acids, such as eicosapentaenoic and docosahexaenoic acids, thereby showing neuroprotective effects by multiple pathways. EGCG or epigallocatechin-3 gallate is one of the most prevalent polyphenols obtained from Camellia sinensis and has successfully shown neuroprotective activities due to its ability to surpass the blood-brain barrier (BBB). The catechol-like structure of EGCG is responsible for the radical scavenging activity and iron chelation property of the phytoconstituent. It substantially improved motor functions in diseased patients and decreased neurotoxicity by enhancing DA levels in the striatal region of the brain. Ginseng and its derivatives, ginsenosides, demonstrated neuroprotective activity in several studies on PD. The antioxidant activity of ginsenoside is related to its ability to manage the levels of glutathione and the reactive oxygen species-mediated NF-kB pathway, and regulation of the transport of iron and related proteins, thereby causing depleted stores of iron in the nigral region of the brain. Vincamine, an alkaloid obtained from the vinca plant, has proven anti-PD activity via different mechanisms of action. It possesses vasodilation activity and causes muscle relaxation of the capillaries in neurons, causing an increased flow of nutrients and glucose to the brain with a parallel increase in ATP generation through the Krebs cycle.

Oxidative stress and iron are also targeted by vincamine to improve the production of DA and lessen the neuronal damage produced. Hence, the role of vincamine and its derivatives, vinpocetine, can be summarized in the management of PD by reducing the synthesis of ROS and iron-chelating molecules. Another synthetic compound, namely mito Q, is also used in the management of PD. The structure of mito Q comprises a lipophilic cation called triphenylphosphine, which is the chief constituent responsible for its antioxidant activity and maintains the functioning of the respiratory chain. A natural antioxidant compound named apocynin is being investigated for its PD-protective activity (Leong et al. 2023).

7.2 Endoplasmic Reticulum (ER) Stress Pathway and Protein Misfolding and Aggregation

Abnormally misfolded proteins evoke stress in the ER and lead to unfolded protein responses (UPRs), which further cause ER-mediated aggregation and degradation of proteins and autophagy. The principal aim of therapies that act by targeting this mechanism is to prevent the aggregation of proteins and the formation of misfolded proteins (Ali et al. 2023). The inability to clear aggregated proteins or remove damaged organelles can cause apoptosis or cell death and lead to neurodegeneration. Vitamins are the most commonly used nutrients in patients with PD. However, hydrophobic antioxidants, such as vitamin A, beta carotene, and CoQ10, also possess anti-fibrillogenic properties. Vitamin A promptly inhibits the deposition of intracellular α-Syn in vivo. Crocin is another phytoconstituent that possesses neuroprotective properties in several central nervous systems (CNS) disorders, which can be ventured through successive results obtained from in vivo and in vitro studies. This carotenoid decreases the expression of CHOP and binding immunoglobulin protein (BIP)/Grp78 and inhibits the activation of various factors responsible for apoptosis, including proapoptotic factor caspase 12 PC12 cells, after exposure to MPP.

Bicalein is a flavonoid isolated from the roots of Scutellaria baicalensis georgi, a plant obtained from Iran. This compound significantly prevents fibrillation and neurotoxicity by pausing the formation of an oligomer of α-Syn. This flavone tends to induce autophagy, decrease inflammation and inflammatory cytokines, and inhibit apoptosis, thereby restoring the levels of DA in an MPP-induced model in mice. Resveratrol represents a potent pharmaceutical compound due to its solubility and stability. It increases metabolic turnover and enhances the microflora in the gut but possesses low BBB permeability, hence it can compromise the bioavailability of polyphenol compounds in the brain (Gowthaman et al. 2023).

Nutraceuticals having action in Parkinson's disease are summarized in Figure 3.

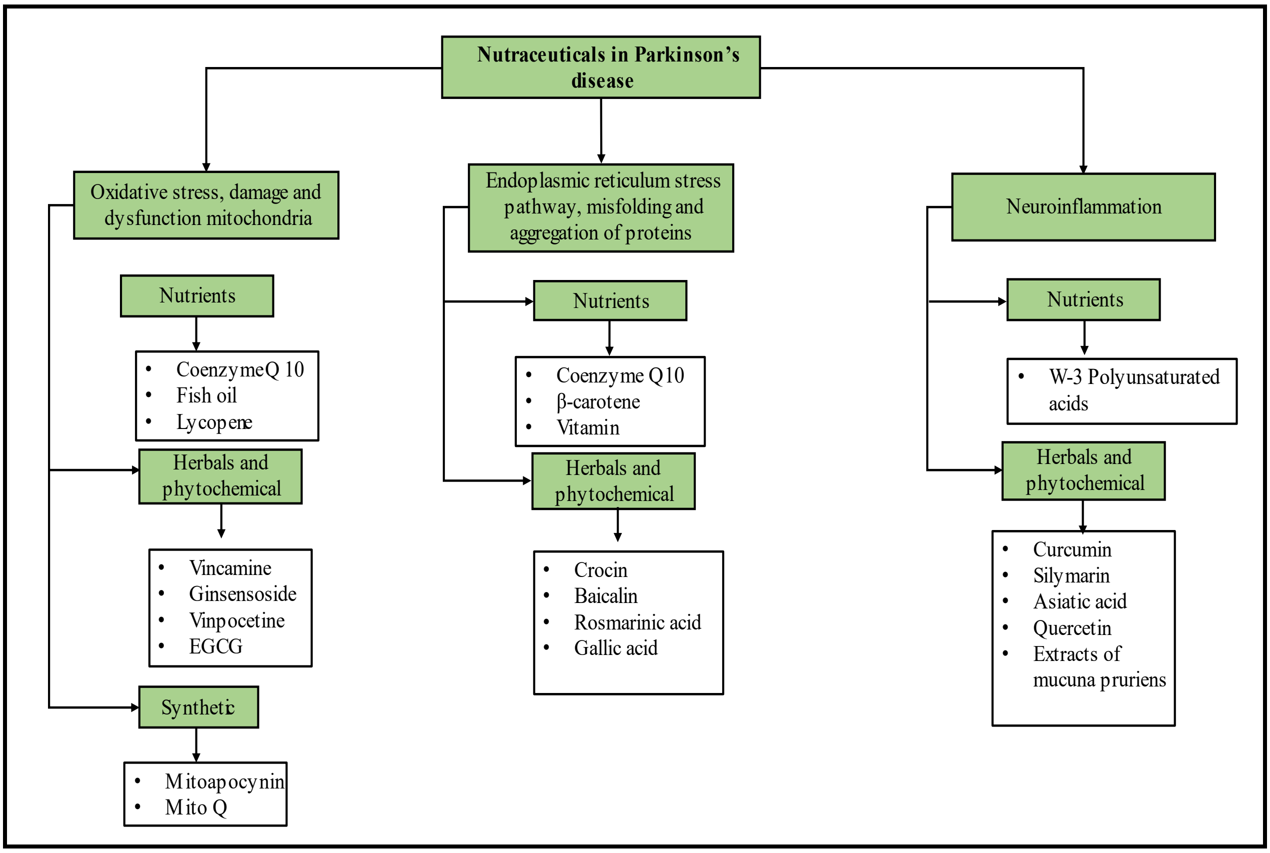

Figure 3. Nutraceuticals in Parkinson's disease act by three pathways 1. By preventing oxidative stress, which leads to the protection of mitochondria from further damage and dysfunction and ultimately maintains energy homeostasis and cellular metabolism; 2. Activation of misfolded proteins and their aggregation induces stress in the endoplasmic reticulum (ER), which further causes autophagy and degradation of neuronal proteins. 3. Inflammation in neuronal cells is the main cause of neurodegeneration and the onset of Parkinson's disease (Alharthy et al. 2023).

8 NUTRACEUTICALS IN DEPRESSION

Depression is a mental disorder, which is mainly characterized by a sad or depressed mood combined with a decreased interest in any social activity, leading to an impaired routine. Its prevalence is about 15% with an annual incidence of 7%. It poses a huge burden on society with an increased cost of life quality as a depressed person is less productive and is at higher mortality risk. Omega-3 fatty acids and folic acid have generally been effective for unipolar depression, particularly as an adjunctive therapy, with increasing evidence for its efficacy as a monotherapy. The nutrients obtained from dietary products are critical for proper brain functioning as a relationship between the quality of food and brain health and mood has been identified and studied, leading to the application of nutraceuticals as supplements (Ceskova and Silhan 2018). A whole-grain diet rich in nutrients, such as zinc, folic acid, omega-3 fatty acids, and several other essential macro and micro nutrients, can trigger the functioning of the brain and has shown results in the management of depression (Kris-Etherton et al. 2021).

The mechanisms of action of some nutraceuticals in depression are presented in Table 1.

Table 1. Some of the commonly employed nutraceuticals in the management of depression as adjunctive therapy, which thereby presents a curative approach (Ceskova and Silhan 2018).

Table 1. Some of the commonly employed nutraceuticals in the management of depression as adjunctive therapy, which thereby presents a curative approach (Ceskova and Silhan 2018).

Compound	Mechanism of Action	References
Omega-3 Fatty Acid Molecules	They act by inhibiting the reuptake of monoamines during neurological transmission and benefit neurotransmission by increasing the fluidity in the membranes of cells. These molecules decrease inflammatory mediators and their synthesis, enhancing neurogenesis and preventing depressive episodes.	(Fodor et al. 2018)
N-acetyl Cysteine	It mainly comprises anti-inflammatory and antioxidant activities which lead to the replenishment of glutathione levels and enhances neurogenesis. It also protects the individual against mitochondrial toxicity and modulates the glutamate pathway thereby preventing depression.	(Makkar et al. 2020)
S-adenosyl Methionine	It mainly influences the production and biotransformation of neurotransmitters as it is an important methyl donor of methyl groups. It also decreases the secretion of prolactin and increases the conversion of phosphatidylcholine.	(Hiemke et al. 2011)
L-Tryptophan/5-HTP	Tryptophan is required for conversion into serotonin in the presence of B6 and magnesium to actively form 5-HTP through intermediate processes. The augmentation of tryptophan with a range of antidepressants is effective in increasing effect. It is used in concert with a range of antidepressants, protein deficient, or in patients with dysregulated serotonergic pathways.	(Sarris 2017)
Vitamin D	Vitamin D is a 'neurosteroid' compound that acts as a ligand for receptors that are present in the hypothalamus, substantia nigra, and prefrontal cortex region of the brain. It chiefly regulates the genetic expression leading to the coding of protein tyrosine hydroxylase.	(Eyles et al. 2013)
Zinc	Zinc is the most predominant trace element found in the hippocampus, amygdala, and neocortex regions of the brain. It mainly leads to the amplification of neurogenesis in hippocampal regions by increasing BNDF. The activity of glutamate and NMDA receptors is also modified.	(Wenstrup et al. 1990)

Apart from the nutraceuticals mentioned above, Hypericum perforatum, commonly known as St. John's Wort, has also been studied for its remarkable antidepressant activity. The plant is a highly rich source of flavanol glycosides, including major components, such as rutin, quercetin, hypericin, and hyperforin. The plant acts as an antidepressant by inhibiting the enzyme monoamine oxidase (MAO). Carbon dioxide (CO2) extracts enriched with hyperforin and ad-hyperforin inhibited the re-uptake of neurotransmitters, such as norepinephrine, serotonin, and dopamine, and showed antidepressant effects (Butterweck and Schmidt 2007).

9 NUTRACEUTICALS IN PSYCHOTIC DISORDERS

Nutraceuticals, besides the functional roles studied, also play a key role in the management of mood disorders and psychotic disorders, such as schizophrenia and bipolar disorder (Cloutier et al. 2016). They are mainly employed as adjunctive therapy and sometimes as a monotherapy in patients who are in dire need of psychotic care (Martínez-Cengotitabengoa and González-Pinto 2017). Nutraceuticals strongly amplify the therapeutic efficacy of the medications employed by strengthening the neuroprotection by enhancing the inhibited re-uptake of monoamines and showing neurobiological effects (Davis et al. 2014), thereby improving the efficacy of psychiatric medicines (Howes and Kapur 2009). The commonly used nutraceuticals in psychosis include omega-3 fatty acids and vitamins. There are two main types of polyunsaturated fatty acids in the human body: Those of the omega-6 series, such as arachidonic acid (AA), obtained from linoleic acid, and those of the omega-3 series, obtained as alpha-linolenic acid (Savitz et al. 2016). The latter include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Brown and Roffman 2016). All of them are important components of the phospholipid cell membrane and are essential for the survival of the human body. However, as the body cannot synthesize them, they must be obtained through the diet. On the molecular level, omega-3 EPA and DHA have properties that are of interest in psychotic disorders. They improve dopaminergic and serotoninergic neurotransmission.

They decrease micro inflammatory and oxidative stress. They modulate the functioning of mitochondria, which are the main source of oxidative stress (Sarris et al. 2015). Additionally, they protect against toxicity due to apoptosis and regulate gene expression of brain-derived neurotrophic factor (BDNF) (Pilakka-Kanthikeel et al. 2013). Vitamins are organic compounds that the human body cannot synthesize in adequate amounts, so they need to be obtained through the diet. The efficacy of interventions with vitamins in schizophrenia has been reviewed recently and ameliorating their side effects (Arroll et al. 2014).

Table 2 summarizes the most relevant information regarding the commonly used nutraceuticals in various neurological aliments.

Table 2. Summary of the nutraceuticals discussed in the current review with their mode of action and specific disease activity.

Disease	Mechanism of Action and Commonly Used Nutraceuticals	References
Neurodegenerative Disorders	Neurodegenerative disorders are mainly developed by protein misfolding. Nutraceuticals mainly prevent misfolding of proteins by inhibiting the activation and synthesis of proinflammatory cytokines and associated pathways. Examples: bacoside A, bacoside B, brahmine, quercetin, kaempferol, withanine, somniferine, asiatic acid, bhilavanol A, and B.	(Lama et al. 2020)
Alzheimer's Disease	AD is mainly associated with an increase in oxidative stress and free radicals. Nutraceuticals typically antioxidant in nature are mostly employed in the management of this disease. Examples: flavonoids (fruits, vegetables, tea, wine, coffee); carotenoids (lutein, zeaxanthin, lycopene, β-cryptoxanthin including α and β carotenes); anthocyanidins (cyanidin); flavones (luteolin, apigenin).	(Lama et al. 2020)
Parkinson's Disease	The uninhibited oxidative stress and free radicals in association with abnormally misfolded proteins, neuroinflammation, and dysfunctional mitochondria lead to compromised cellular metabolism and energy thereby impacting the functioning of the brain and leading to neurodegenerative disorders including PD. Examples: Vitamin A, Omega-3 fatty acids, lycopene, vincamine, gallic acid, curcumin, Mito Q.	(Lama et al. 2020)
Depression	Nutraceuticals that act by inhibiting the reuptake of monoamines possess anti-inflammatory and antioxidant properties which are well suited for the management of depression. Examples: Omega-3 fatty acids, folic acid, S-adenosyl methionine, zinc, N-acetyl cysteine, L-Tryptophan/5-HTP, Vitamin-D.	(Lama et al. 2020)
Psychosis	Nutraceuticals that can improve neurotransmission in dopaminergic serotoninergic neurons can be employed in the management of psychosis. These mainly include all types of vitamins and omega-3 fatty acids.	(Lama et al. 2020)

CONCLUSION

Nature has provided us with valuable herbal molecules with high potential in the cure and prevention of life-threatening diseases and lifestyle-related disorders, including neurodegeneration. The role played by phytonutrients in dealing with neurodegeneration and preventing cognition has been described in various studies. The curative effects of nutraceuticals can be attributed to their neuroprotective, anti-inflammatory, antioxidant, hypolipidemic, and healing properties, which target different ligands and receptors to enhance protein synthesis, which ultimately leads to neuroprotection. The folding of proteins and their degradation can be inhibited, leading to a healthy nervous system. The experimental research on plant products has provided new directions for the affordable treatment of neurodegenerative diseases in this era of many public health system crises.

A changing lifestyle has deteriorated the body's defense mechanism to scavenge free oxygen radicals by suppressing antioxidants, resulting in overloaded oxidative stress. Increasing age also tends to decrease levels of antioxidants in our body, thus attracting chronic illnesses in humans. Therefore, for years, the focus has been placed on targeting a variety of nutraceuticals for their therapeutic properties. Products containing antioxidants, such as vitamins, intrinsically act by scavenging free radicals and stimulating the synthesis of antioxidants in the body. The current review highlights the merits and demerits of nutraceutical therapy and its susceptibility to preventing disease progression in neurological disorders. Though nutraceuticals have been shown to exhibit remarkable properties, the response varies from person to person. Consuming them in acceptable and recommended dosages promotes good neurological health and keeps diseases at bay; hence, they are the best options for curing lifestyle-related mental disorders, like depression.

Advancements in molecular diagnostic and fundamentals have implemented particular usefulness for drug evaluation. An excess of experimental knowledge occurs regarding the effect of nutraceuticals on AD. Various preclinical and clinical studies have been performed on nutraceuticals. In addition, various substitute inhibits and enhance some pathophysiological levels associated with AD. Nutraceuticals are easily available and have fewer side effects with cost- effective advantages. However, further investigations and clinical trials are required to encourage its effect on disease. Evaluating more targeted neuroprotective nutraceuticals is anticipated by associating convenient bridging and amalgamating the crucial pharmacophoric action, which may accelerate the significant drugs for Alzheimer's disease.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Funding: No funding.

Acknowledgments: The authors like to thank Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, India for providing the basic facilities for the completion of the present article.

Conflicts of Interest: The authors declare no conflict of interest.

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