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Therapeutic Approaches of Nutraceuticals in Neurological Disorders: A Review

Vipul Kumar[1], Harsh Gupta[2], Anamika[3] and Roshan Kumar[4]

[1]Research Scholar, Department of Pharmacy, Guru Nanak College of Pharmaceutical Sciences, Dehradun-248007, Uttarakhand, INDIA.

[2]Research Scholar, Department of Pharmacy, Guru Nanak College of Pharmaceutical Sciences, Dehradun-248007, Uttarakhand, INDIA.

[3]Assistant Professor, Department of Pharmacy, Shree Dev Bhoomi Institute of Education Science and Technology (SDBIT), Dehradun, INDIA.

[4]Assistant Professor, Department of Pharmacy, Shree Dev Bhoomi Institute of Education Science and Technology (SDBIT), Dehradun, INDIA.

[4]Corresponding Author: rjroshan244@gmail.com

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ABSTRACT

A big problem in healthcare around the world is neurological illnesses. There is a huge healthcare and financial burden on society worldwide due to the dramatically increased risk of chronic sickness and diseases linked with posed lifestyle changes. Fine treatment for sick illnesses with few known adverse effects is the goal of research. A number of functional food studies have been launched in the last few decades in an effort to identify meals with enhanced therapeutic activity and reduced adverse effects. As a result, research into nutraceutical therapy for illness prevention and various extraction procedures for disorders has been underway. Progressive memory loss characterises Alzheimer's disease (AD), a neurodegenerative disorder. The pharmaceutical options available today are expensive, come with unwanted side effects, and are in short supply. Scientists and researchers have noticed that nutraceuticals have a big impact. The anti-Alzheimer's efficacy of nutraceuticals was examined in a number of clinical and preclinical investigations. The study of new therapeutic targets, such as the pathophysiological mechanisms and unique cascades, has resulted from the growing understanding of the AD pathogenesis. Therefore, the most effective and well-known nutraceuticals will be showcased in the present development, together with brief mechanisms involving antioxidants, autophagy control, anti-inflammatory, mitochondrial homeostasis, and more. Nutraceuticals have real-world impacts, and getting your hands on phytochemicals and other vital bioactive ingredients from therapeutically active foods is a top priority. Because of this, the term "functional foods" has been muddied and replaced with similar ones such as "pharmafoods," "medifoods," "vita foods," or "medicinal foods." Nutraceuticals are in high demand to counteract neurological interventions, and there is an urgent need to stick to healthy options. Nutraceuticals may play a preventative role in neurological therapies due to the demonstrated correlation between dietary patterns and lifestyle factors and neurodegeneration. Examining high-quality clinical trials is the focus of the present study, which touches on several important neurological topics. In light of nutraceuticals' promise as multi-targeted therapy for Alzheimer's disease, it is critical to assess them as promising lead molecules for the development of new drugs. Prospective studies should, according to the authors' understanding, take into account blood-brain barrier permeability alteration, bioavailability, and features of randomised clinical trials.

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

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I. INTRODUCTION

According to Williams et al. (2016), neurological disorders encompass a broad range of long-term conditions with intricate causes. Problems with the brain or nerves could be the result of a nutrient-poor diet. More than 10 million people experience neurological problems every year, and that number is projected to increase. As a result of neurodegenerative processes, brain functionality declines with age; therefore, cellular and molecular targets are being sought after that could lead to improved brain functioning (Williams et al. 2015). In Western countries, approximately 3.1% of the population between the ages of 70 and 79 is thought to be susceptible to neurodegenerative illnesses, whereas in India, the corresponding disease incidence is 0.7%. The fundamental reason for the variation is that various ingredients necessitate distinct eating habits and ways of life. People have relied on spices and natural remedies for many ailments from the beginning of time, and these have had impressive benefits (BungÎu and Popa 2015). There has been a rebirth in the study of nutrition and human health thanks to scientific and technological advancements, which have opened the door to the discovery and use of various phytochemicals from both plants and non-plant sources that have medicinal qualities. This has created opportunities for the development of new dietary substances. Because of this breakthrough, a new word has emerged: nutraceuticals. It is derived from the merging of the nutrition and pharmaceutical industries. In 1989, Dr. Stephen De Felice came up with the term "nutraceutical" (Altaf et al. 2019). Nutraceuticals are defined by the American Nutraceutical Association as foods or their derivatives that have health-promoting characteristics. Supplemental nutritional foods, herbal remedies, drinks, soups, produce, fruits, and processed foods (cereals, etc.) are all part of this category (Van Boekel 2022). To far, more than a thousand more probiotic chemicals have been discovered, with vitamins, minerals, and amino acids making up the bulk of nutraceuticals. The earliest known examples of the medicinal and curative potential of foodstuffs come from the Sumerians, Chinese, and Indians (a claim that has been backed up by Ayurveda for five thousand years) (Orlando 2018). Nutraceuticals, in a nutshell, are functional foods that have well-documented health advantages beyond those associated with their nutritional content. The use of nutraceuticals shows promise as a method for managing a number of long-term conditions, including neurological problems. It was written by Gupta and Prakash in 2015. Nutraceutical research is devoted to studying compounds derived from traditional medications and their potential benefits in suffering chronic and degenerative diseases (Abdel-Daim et al. 2019). A number of restrictions, such as low bioavailability, brain permeability, metabolism, etc., limit the therapeutic impacts that nutraceuticals may have (Brown et al. 2009). When added to some pharmaceuticals, nutraceuticals can increase their therapeutic benefits through enhancing re-uptake of blocked monoamines and other pathways, leading to remarkable neurological effects (Van Der Burg et al. 2021). Nutraceuticals may have an important role in brain health and neurological diseases, as this review demonstrates. Throughout the prehistoric period, people all across the globe relied on plants as a remedy for a wide range of illnesses. Alternative medicine, including phytotherapy, ethnopharmacology, herbalism, and pharmacy, can be traced historically as leading to nutraceuticals (Georgiou et al. 2011). Medicinal plants, minerals, animals, and vegetables all had a role in the therapy's development, which included both magical and instinctual elements. Philosophers held that food had a role in both public and personal health before the idea of nutraceuticals emerged. Throughout history, from the time of Hippocrates (460-377 BC), or about 2000 years ago, to the advent of modern medicine, people have understood that people's diets have a significant impact on the prevalence of many diseases (Kidd 2012).To expedite research in the biomedical field, the educational foundation known as the New York Foundation for Innovation in Medicine coined the word "nutraceuticals" in 1989 (Kuhnau 1976). The most advantageous recipients of traditional Asian knowledge were the Europeans (Chanda et al. 2019). A modern drug development process that includes clinical trials was initiated in response to the need for chemists to play an active part in ensuring the safe and effective use of medications (Menon and Spudich 2010). According to González-Sarrías et al. (2013), the healing techniques included in the Unani, Ayurveda (including Sushruta, Samhita, and Charaka), Ashtavaidya, and Siddha medical systems are well-known in Indian history. There is a plethora of nutrients and food items that have not yet been studied, but which could have beneficial biological effects (Yapijakis 2009). Currently, the nutraceutical market is booming, with present-day food industry (Andlauer and Fürst, 2002), which is a $30 billion market expanding at a 5% yearly pace (Chauhan and Mehla, 2015). In light of what is now known about nutraceuticals, nutritionists, food technologists, doctors, and food chemists face a formidable issue (Peterson et al. 2017). The findings of clinical trials conducted on both humans and animals confirm the drug's therapeutic properties, which are essential steps in the pharmaceutical development process (Granato et al. 2020). Scientific evidence has emerged that certain food molecules can protect against lifestyle-related diseases, despite the lack of prior evidence suggesting any such effects (Bagchi and Sreejayan 2016). A good diet is even more important, and nutraceuticals can help you live longer, among other benefits (Champagne et al. 2018). Their popularity in preventing neurological illness conditions is due to the fact that they not only help with medical ailments but also with proven psychological advantages (Casey et al. 2010). For

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Volume-3 Issue-2 || April 2024 || PP. 261-281

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lifestyle-related illnesses, nutrient-rich diets are more commonly used, especially by the elderly, because they are less likely to be associated with negative side effects (Nicastro et al. 2015). The purpose of this publication is to educate readers about the potential of nutraceuticals for the treatment of neurodegenerative and psychotic diseases. Specifically, it will focus on practical, readily available components that have demonstrated neuroprotective properties. Nutraceuticals may have an important role in brain health and neurological diseases, as this review demonstrates.

II. METHODOLOGY

A comprehensive literature study on the use of nutraceuticals in neurological illnesses was conducted prior to the commencement of the review article. For a comprehensive grasp of the subject and to assess the currently used psychoactive and neuroprotective nutraceuticals, research and review articles were evaluated and read extensively from a variety of scientific databases and search engines, including Pubmed, Medline, Science Direct, Google scholar, Scopus, the Cochrane library, etc. Article writing commenced following the completion of the literature review. About two months passed before the review article was finally finished.

III. NUTRACEUTICALS

Foods and other products that have health-promoting properties are called nutraceuticals according to the American Nutraceutical Association. Vitamin supplements, herbal remedies, GMOs, fruits, drinks, veggies, soups, and processed foods like cereals are all part of this category. There are more than a thousand different types of nutraceuticals, but the most popular ones include vitamins, minerals, and amino acids. Keservani et al. (2010) states that no probiotic compounds have been discovered up to this point. In addition to the Sumerians, Egyptians, and Chinese, the Indians are one of the earliest civilizations to have recorded the effective use of food products in medicine and the treatment of illness (Jamshidi-Kia et al. 2017). This is a truth that Ayurveda has upheld for more than five thousand years. An increasingly important and challenging area of research is the study of nutraceuticals. Dietary changes centred on nutrient-dense foods have recently gained popularity as a means for consumers to maintain good health and ward off potential health problems. Nutraceuticals are substances that have their origins in plants and animals. De Felice defined nutraceuticals as "foods or food components that, when consumed, contribute to a healthy lifestyle by aiding in the prevention and treatment of disease" (Prakash and van Boekel 2010). Nutraceuticals include carbs, vitamins, fibres, and other nutrients. Dietary availability determines the classification of nutraceuticals into typical and non-typical types. Dietary foods that have been around for a long time are considered traditional foods. As an example, there are supplements called probiotics that are made from microorganisms. Probiotics, which include live bacteria like Lactobacillus and Bifidobacteria, can help prevent stomach problems. Recent studies have also demonstrated that they can prevent children from developing allergies. Both nutrients and herbals are examples of traditional nutraceuticals; they are sourced from plants. According to Gul et al. (2016), non-traditional nutraceuticals include recombinant agents and fortified foods. The first group consists of nutrient-dense foods like fruits and vegetables, and the second group consists of biotech-made, high-calorie foods. Primary and secondary metabolites are the two main classes of active chemicals that plants generate during metabolic activities. The byproducts of primary metabolism include carbs, vitamins, amino acids, and fatty acids. Chemicals produced mainly as a defence mechanism against naturally occurring infections are known as secondary metabolism products. These molecules are commonly known as secondary metabolites or phytochemicals. The extraction of secondary metabolites from plants is accomplished using several methods. An assortment of functional ingredients compose the finished product. This is the case with extracts from plants that have medical uses that date back centuries. Another component of traditional nutraceuticals are nutraceutical enzymes. Enzymes produced by our species are useful chemicals that are now used to treat lysosomal storage diseases like as Gaucher, Pompe, and Fabry (Poddar et al. 2019). Chemical composition allows for the categorization of secondary metabolites such as phenols, tannins, saponins, carotenoids, and flavonoids. The chemical structural diversity of these molecules suggests that they may serve a variety of biological purposes. Multiple studies have shown that it has antioxidant, cardioprotective, anticancer, antiidiabetic, anti-inflammatory, anti-aging, and neuroprotective properties. In addition, scientists can study many action mechanisms affecting different metabolic pathways that may be involved in the development of different diseases due to the diversity of their chemical composition. The function of food in maintaining good health is widely recognised. According to Pandareesh et al. (2018), ippocrates once said, "Let thy food be thy medicine, and medicine is thy food," emphasising the need of a balanced diet in preventing sickness. New evidence supports this claim, and a plethora of studies are currently investigating the potential therapeutic and preventative uses of individual compounds or combinations of compounds for a wide range of medical conditions. For instance, millions of people experience the consequences of Alzheimer's disease, and the disease's incidence is expected to grow dramatically, so many specialists are worried about it (Frank et al. 2020).

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IV. NUTRACEUTICALS AND ITS CATEGORIES

Preventing symptoms of moderate diseases to very dangerous malignancies is the goal of nutraceuticals, which are part of the category of nonspecific biological therapies. Their neuroprotective role is widely recognised and emphasised. The following criteria can be used to classify them:

4.1 Food-Based Nutraceuticals or Traditional Nutraceuticals

Foods that have been unaltered from their natural state and sourced directly from the earth fall under this category (Bhaskarachary et al. 2016). In addition to meeting nutritional needs, these foods also have other advantages, such as being rich in protein, fibre, and healthy fats (Bhat & Bhat 2011).

4.2 Nutrients

The metabolic pathways have long-established nutritional qualities in the main metabolites of substances such as minerals, fatty acids, vitamins, and amino acids. Neurological diseases can be effectively treated with the help of these nutrients when combined with plant and animal products (Elsebai et al. 2016). Preventing brittle bones, increasing haemoglobin, and bolstering muscle power and neural transmission are all possible with the application of nutrients in planting. In addition to improving cognitive function, fatty acids and their byproducts can lower arterial cholesterol levels, a phenomenon known as hypolipidemia (Ali et al., 2023).

4.3 Herbals or Extracts and Concentrates of Botanical Products

Mood and other lifestyle-related diseases can be effectively treated with a blend of herbs and nutrients (Dohrmann et al. 2019). Stress relief and reduced blood pressure are two benefits of tannin-containing plants like lavender (Barba et al. 2020). The antioxidant capacity of flavonoids, which include substances like parsley's psoralen, which also has carminative and diuretic qualities, has been demonstrated in clinical trials to reduce the risk of diabetes, cardiovascular disease, and renal abnormalities (Putnik et al. 2019a). Compounds containing terpenoids, such peppermint and menthol, are utilised for respiratory issues. Ephedra is utilised for bronchospasms because of its bronchodilator and vasoconstriction actions, and many other regularly used herbs, like aloe vera, have anti-inflammatory and dilating characteristics, which aid in wound healing (Putnik et al. 2019b). Garlic and ginger, two of the most popular spices, have anti-inflammatory and anti-cancer effects, help with hypertension, and promote immunity (Poojary et al. 2017). Nutraceuticals include both herbal remedies and the phytoconstituents found in them. Vegetables, for instance, include carotenoids, which have anticarcinogenic qualities and enhance immunity (Montesano et al. 2018). Foods that don't contain carotenoids, including chickpeas and soy beans, help flush out cholesterol. As a phenolic acid, curcumin, derived from turmeric, one of the most ubiquitous household spices, has the has the most potent antioxidant and anti-inflammatory effects. According to Pillitteri et al. (2008), dietary supplements, particularly those containing antioxidant-rich foods like ginger, cumin, green tea, etc., have demonstrated encouraging results in terms of weight loss. Their effectiveness in neurological treatments, including those for depression, has also been investigated (Rao et al. 2008).

4.4 Probiotic Microorganisms

The renowned scientist Metchnikoff first used the word "probiotic." In terms of the physiology of the stomach and intestines, they are quite beneficial. They help eliminate harmful bacteria from the digestive tract and have antibiotic characteristics. According to Gosálbez and Ramón (2015), a well-balanced diet promotes physical and mental wellness. The use of probiotics in the treatment of gastrointestinal diseases has been revolutionary. These findings have led to the introduction of probiotics for use as dietary supplements, including probiotic drinks and pills. So, contemporary probiotics assert their efficacy in treating a wide range of diseases and disorders, from diarrhoea to neurological disorders like Alzheimer's and depression. Since there is a dearth of published data on the safety of probiotics, there is an urgent need to investigate them. The advantages and disadvantages of probiotics are not easily distinguished. Zucko et al. (2020) found that probiotics had a moderate therapeutic impact in cases when individuals with impaired immune systems were at high risk of infection. It is believed that medicines based on probiotics, prebiotics, and synbiotics can modulate gut flora to decrease neuroinflammation (Li et al. 2020). The composition of the microbiota can be affected by diet, which in turn affects the function of the gut-brain axis. Cognitive impairment, behavioural problems, and diminished brain volume are all associated with gut dysbiosis in the aged (Castelli et al. 2021). The aggregation of Aβ, neuroinflammation, oxidative stress, and insulin resistance can be caused by gut dysbiosis, which could add to the cause of Alzheimer's disease (Castelli et al. 2021). Probiotics, such as Lactobacillus, have been shown in clinical trials to aid in immunomodulation and decrease IL -8 and other proinflammatory markers. Bifidobacterium breve A1 enhanced blood BDNF levels and memory (Pluta et al. 2020). In their role as prebiotics, fibre components promote the growth of beneficial bacteria and probiotics. Several prebiotics, including oligosaccharides and inulin, have anti-AD properties due to their ability to regulate inflammation and neurotransmitters. After being given prebiotics, AD rats showed a multitude of signalling pathways, including PI3K-Akt and PPAR. Combinations of probiotics and prebiotics are known as synbiotics. Memory and general cognitive function were enhanced in Alzheimer's patients when given kefir-fermented milk as

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Volume-3 Issue-2 || April 2024 || PP. 261-281

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a synbiotic (Pereira et al., 2021). Proinflammatory cytokines such TNF- α, IL-8, and IL12p70 were decreased following treatment with the synbiotic. Serum levels of NO rose after kefir administration, but levels of O2, H2O2, and ONOO- /OH-decreased substantially. Mitochondrial membrane potential was restored by kefir therapy. In addition to its other advantages, this synbiotic therapy reduced PARP-1 cleavage (Pluta et al. 2020).

4.5 Nutraceutical Enzymes

Cells manufacture enzymes and biocatalysts, which are structures made of protein. Their primary application is in the treatment of gastrointestinal disorders including GERD, constipation, diarrhoea, etc., because they speed up metabolic processes. The benefits of enzyme supplements on brain health are minimal, although there have been recent therapeutic successes in treating uncommon conditions including Gaucher disease and Hunter syndrome. Because they may be made from either plants or animals, they are quite cheap. There are many benefits to using nutraceuticals that are found in food. Garlic, ginger, turmeric, dairy products, carotenoids, and other food-based nutraceuticals are far healthier and may supply all the necessary nutrients for our body. You can find them in most grocery stores, and they help keep serious health problems like diabetes and cancer from getting worse. Prioritising one's mental health means making healthy eating choices, which may be the most enticing neuroprotective strategy. But there are also some drawbacks to them. When it comes to nutraceuticals derived from food, the biggest concern is how safe they are. Before releasing functional foods to the public in their raw form, there must be urgent research on their safety. Unless ingested in a limited quantity, all substances are poisonous. A diet with strong anticarcinogen properties might clearly also have other beneficial effects, such as harmful to the heart. According to Tapal and Tiku (2019), it is recommended to administer the desired dose.

4.6 Non-Traditional Nutraceuticals

Agriculturally derived foodstuffs and nutrients are a part of this category; examples include vitamin-and mineral-enriched cereals, orange juice fortified with calcium, and so on (Singh and Sinha 2012). Researchers in the field of cultural science have made significant strides in improving the nutritional value of crops through the development of new methods and the modification of existing ones (Sapkale et al. 2012).

V. NUTRACEUTICALS IN AMELIORATING NEURODEGENERATION

The main cause of neurodegenerative diseases is protein misfolding, according to Colín-González et al. (2015). Grassi et al. (2016) found that abnormal misfolding of the proteins ʃau and amyloid-β (Aβ) causes Alzheimer's disease to progress. Modifying τau, transactive response (deoxyribose nucleic acid) (TAR DNA) binding protein-43 (TDP-43), and Aβ proteins can induce traumatic brain injury. Misfunctioning of τau and TDP-43 can afterwards lead to epilepsy and other tauopathies. According to Johnston (2015), protein Aβ in down syndrome and α-synuclein in Parkinson's disease primarily trigger a series of harmful molecular and cellular events that lead to more deterioration. According to Saldanha and Tollefsbol (2012), inflammatory cytokines like TNF-α and IL-1β are produced when these misfolded proteins boost the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-β). In a study conducted by Asadi-Shekaari et al. (2012), it was found that the release of reactive oxygen species (ROS) and glutamate-induced oxidative damage activate harmful molecules such as cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS). These actions contribute to mitochondrial dysfunction and toxicity, as highlighted by Kelsey et al. (2010). In addition, the signalling of GSK3β is further disrupted by the misfolded proteins when inflammatory cytokines are stimulated at the same time. This results in the hyperphosphorylation of τau proteins and an increase in cholesterol synthesis. In addition, it promotes the production of enzymes, which leads to misprocessing and misfolding of proteins, which in turn causes lipid rafts to form, creating a vicious cycle (Barber et al. 2006). Misfolded proteins are a vicious cycle that begins with enzyme promotion (Gonsette 2008). Additionally, cholinergic functions, extracellular signal-regulated kinase (ERK), cyclic adenosine monophosphate (cAMP) response-element binding signalling (CREB), and protein kinase A/protein kinase B (PKB/PKA) are all dysregulated by misfolded proteins, which in turn causes synaptic degradation and cognitive function defects (Lin and Beal 2006). As a kind of supplement treatment, nutraceuticals have the potential to alter the cellular and molecular cascade, which in turn can prevent neurodegeneration by focusing on misfolded proteins on nearly every level. Research has shown that nutraceuticals. The study conducted by Ghabaee et al. (2010) found that the drug effectively reduced hypercholesterolemia and inflammation while simultaneously improving the cholinergic system through the inhibition of acetylcholinesterase. When utilised for their therapeutic purposes, nutraceuticals can readily substitute synthetic drug ingredients. This includes acetylcholinesterase inhibitors (donepezil, tacrine, rivastigmine, and galantamine) and statins (rosuvastatin and atorvastatin) that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Additionally, alpha-tocopherol or vitamin E, aspirin, ibuprofen, and other NSAIDs that are cyclooxygenase (COX) inhibitors, etc., because these substances have obvious negative consequences (Lenaz 2001). Because of their low cost, wide availability, and lack of side effects, nutraceuticals provide a comprehensive and successful alternative to

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Volume-3 Issue-2 || April 2024 || PP. 261-281

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traditional methods of treating neurological illnesses (Ott et al. 2007). Figure 1 provides a concise representation of the pathophysiology of misfolded proteins that cause neurodegeneration.

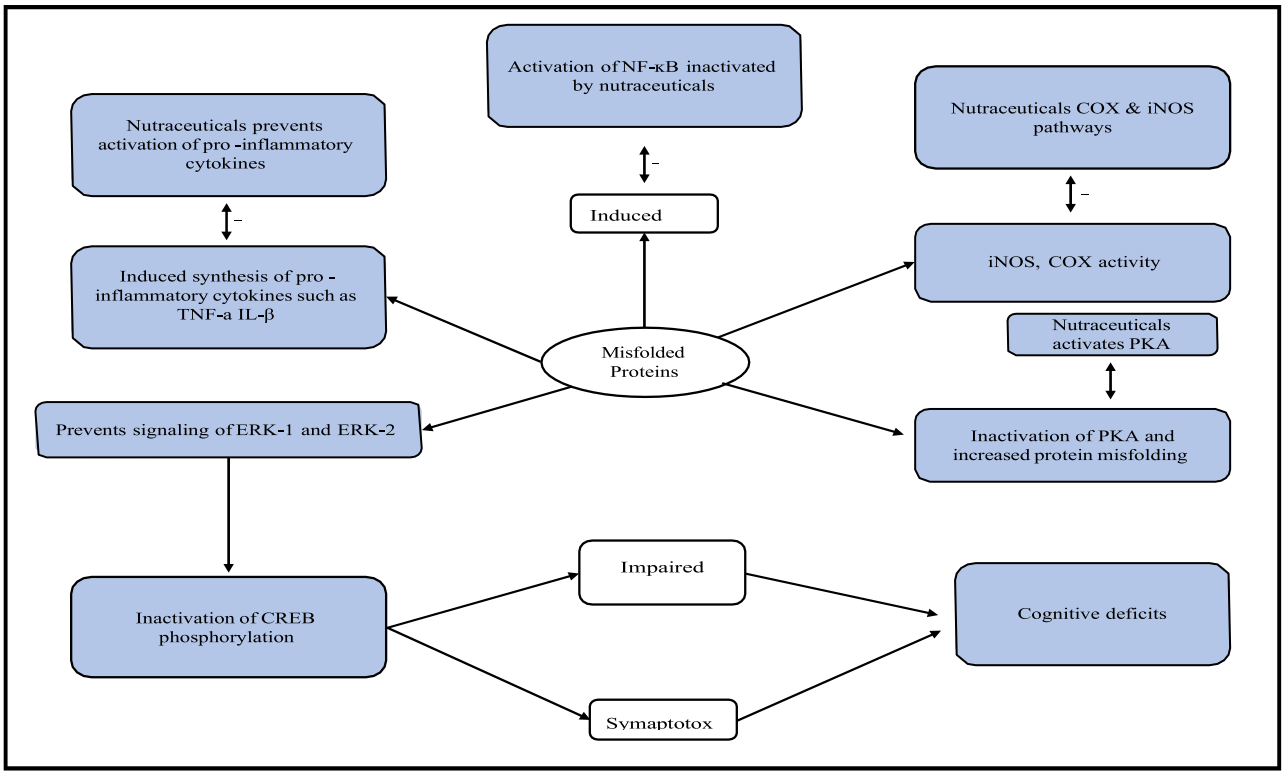

Figure 1. Summarized pathogenesis of misfolded proteins and neurodegeneration mediated upon their activation

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).

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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).

VI. 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.

VI.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	(Wang et al. 2013)

ISSN: 2583-4053
Volume-3 Issue-2 || April 2024 || PP. 261-281
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			spatial learning and memory	
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)

ISSN: 2583-4053
Volume-3 Issue-2 || April 2024 || PP. 261-281
https://doi.org/10.55544/jrasb.3.2.43

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,	In a placebo-controlled, double-blind, balanced, crossover study including 20 young, healthy	(Martín-Moreno et al. 2012)

ISSN: 2583-4053
Volume-3 Issue-2 || April 2024 || PP. 261-281
https://doi.org/10.55544/jrasb.3.2.43

		and crossover design of 20 young, healthy people	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)	
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.).

VII. 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.

VII.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

ISSN: 2583-4053

Volume-3 Issue-2 || April 2024 || PP. 261-281

https://doi.org/10.55544/jrasb.3.2.43

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).

VII.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

ISSN: 2583-4053

Volume-3 Issue-2 || April 2024 || PP. 261-281

https://doi.org/10.55544/jrasb.3.2.43

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.

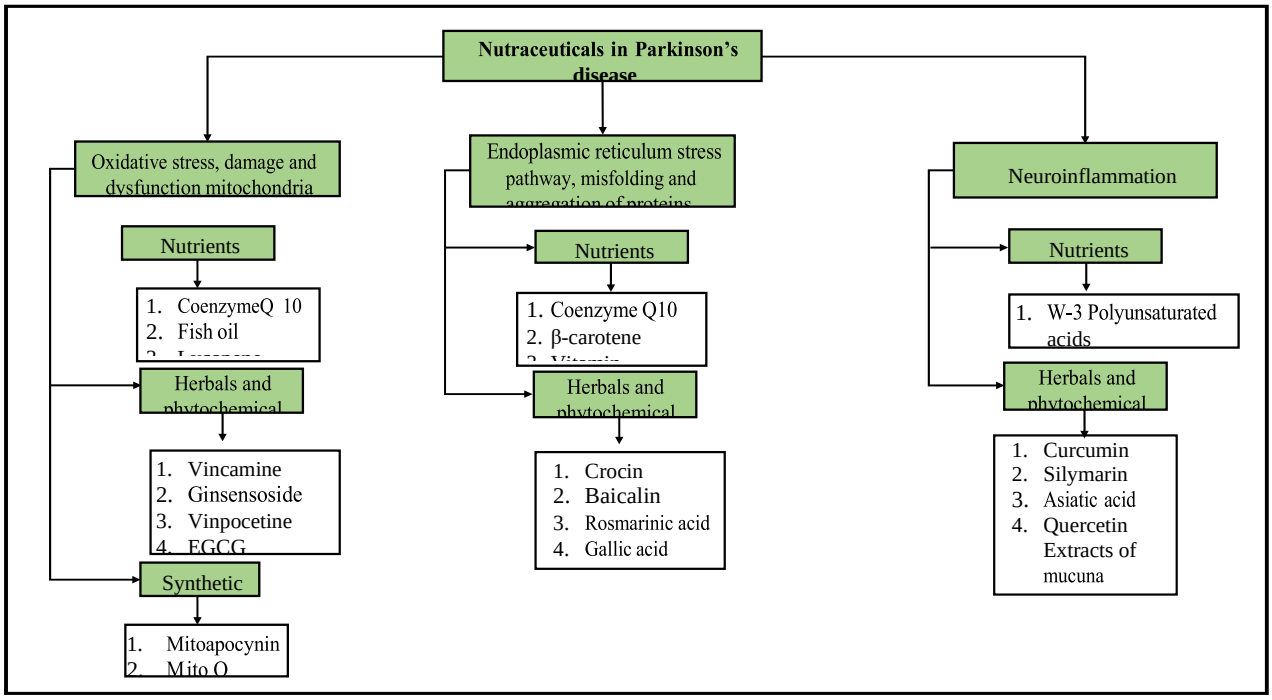

Figure 2: Nutraceuticals in Parkinson's disease act by three pathways 1. By preventing oxidative stress, which leads to the protection of mitochondria from further damage and dysfunction and ultimately maintains energy homeostasis and cellular metabolism; 2. Activation of misfolded proteins and their 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).

VIII. 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)

ISSN: 2583-4053
Volume-3 Issue-2 || April 2024 || PP. 261-281
https://doi.org/10.55544/jrasb.3.2.43

Table 5: 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).

IX. 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

ISSN: 2583-4053
Volume-3 Issue-2 || April 2024 || PP. 261-281
https://doi.org/10.55544/jrasb.3.2.43

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 6: 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)

X. 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

ISSN: 2583-4053
Volume-3 Issue-2 || April 2024 || PP. 261-281
https://doi.org/10.55544/jrasb.3.2.43

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.

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