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Review for Role of Nutraceuticals in Neurodegenerative Diseases

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Abstract

The neurodegenerative disorder NDDs includes Parkinson's Disease (PD), Alzheimer's Disease (AD), Huntington's Disease (HD), prion disease; Motor Neuron Disease (MND) characterized by intense memory loss enough to interfere with social and occupational execution. It is the most general form of dementia, affecting more than 20 million people worldwide. Posed lifestyle changes are associated with drastically increased risk of chronic illness and diseases, posing a substantial healthcare and financial burden to society globally. The treatments of neurodegenerative disorder are through cholinesterase inhibitors or NMDA-receptor antagonists, while doubts remain about the therapeutic efficacy of these nutraceutical product such as fruits, vegetables, grains, meat, fish, eggs, minerals, carbohydrates, Flavonoids, Carotenoids, Crocin, Cyanidin, Luteolin, Quercetin and Kaempferol, Withanine, Asiatic Acid, Bhilavanol A and Bhilavanol B, vitamin B3, vitamin B9 or folate, vitamin B12, vitamin B6, vitamin D, vitamin E, and vitamin C, Omega-3 Fatty Acid Molecules, N-acetyl Cysteine, S-adenosyl Methionine, L-Tryptophan/5-HTP, Zinc and amino acid-based compounds, as the origin for every nutraceutical is different depending on the natural source and this phytochemical have been used in the treatments neurodegenerative diseases. The demand of nutraceuticals is widely increasing to combat neurological interventions. An association between food habits and the 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 disorders and nutraceutical therapy in the prevention of disease.

Keywords: Neurodegenerative disorder; Phytochemistry; Food supplements

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Introduction

Neurological aliments include wide array of chronic diseases comprising highly complicated etiology [1]. Neurodegenerative Disorders (NDDs) are heterogeneous group of various chronic debilitating condition or diseases which, affects the Peripheral or Central Nervous System (PNS and CNS). The major NDDs includes Parkinson's Disease (PD), Alzheimer's Disease (AD), Huntington's Disease (HD), prion disease, Motor Neuron Disease (MND) is mainly caused due to lowered neuronal counts (decreased neural progenitor cells; NPCs) or loss of neuronal integrity (protein tangle/aggregation) as well as lack of communication (decreased neurotransmitters) which eventually results in loss of cognitive (memory impairment), sensory and, motor functions. NDDs like PD, AD and, HD can result in dementia and depression and thus contribute to elevated mortality and morbidity, (disabilities) which pose an enormous economic burden [2-5].

Also, NDDs are highly connected to aging, and hence the prevalence rate is higher in older people than young owing to decline or altered hormone secretion, enhanced oxidative stress, and, neuro-inflammation. However, the in-depth mechanism of PD, AD and, HD are yet to fully explored (hence it's incurable till date). Moreover, the brain is highly prone to oxidative stress owing to high fatty acid content (especially polyunsaturated fatty acids, which contributes to 10% of total dry brain weight), high oxygen consumption and redox signaling (about 20% basal oxygen for ATP production), low antioxidant content with higher neurotransmitter auto-oxidation [6].

Alzheimer's Disease (AD) is regarded as one of the hallmark outcomes of an aging brain, and it is characterized by sequential loss of memory and changes in brain mass. In the advanced stage of the disease, a patient hardly recognizes the family members and fellow beings. Alzheimer's disease represents one of the major contributors to the development of dementia, which is characterized by the formation of amyloid plaques and neurofibrillary tangles in brain tissues. In the recent past, several efforts pertaining to drug discovery have been made to interfere with the development and progression of Alzheimer's disease. In brief, 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 [7].

Nutraceuticals

Nutraceuticals are the combination of pharmaceutical and nutrition, which was first coined by Stephen L DeFelice. Nutraceuticals refer to any food particles (whole) or a part of the food (purified food product) which renders health or medical benefits including, the prevention and treatment of disease [8,9]. Nevertheless, recently nutraceuticals are redefined as a food product or its secondary metabolites that could deliver health benefits (to prevent or treat diseases) in the clinical setting [10,11]. Numerous studies have indicated the neuroprotective effect of nutraceuticals (complementary medicine) against various NDDs *via* regulating energy metabolism, neuro-oxidative stress, neuroinflammation and enhance neurogenesis (improve NPCs proliferation, growth factor, neurotrophies) through various signaling pathways [12,13].

It epitomizes the holistic method of treatment and promotes equilibrium in various dimensions of human existence and unification of the body, mind, and soul. There are several formulations that have claimed to slow down the age-related mental illnesses, and in general, enhance memory retention and improve cognitive behaviors. Some of the key bioactive molecules that serve as potential ingredients of nutraceuticals are obtained from native plants such as Turmeric (*Curcuma longa*), Tea (*Camilla sinensis*), Gingko (*Ginkgo biloba*), Cinnamon (*Cinnamomum zeylanicum*), Black pepper (*Piper nigrum* L.)**,** Ginger *(Zingiber officinale),* etc. The efficiency and efficacy of these plants, which have been tested for the last 2000 years, show the richness of the ancient and ethnic Indian traditional knowledge. The American Nutraceutical Association defines nutraceutical is food or its product possessing health-benefitting properties. They range from dietary nutrient supplements to genetically designed foods, herbal products, beverages, soups, vegetables, fruits, and processed foods, like cereals, etc. [14,15].

However, only few nutraceuticals are effective in clinical setting which, complicate the right choice of nutraceuticals for the management of NDDs and its related symptoms. Therefore, this mini-review was intended to compile all popular (major) nutraceuticals against which, might be effective against various NDDs especially PD, AD, HD and, prion disease as well as depression (sequential effect of NDDs) with special reference to clinical trials and its proposed brief mechanism (including in vitro and animal studies). Hence, this contribution would aid common people to choose better nutraceuticals to combat various NDDs along with standard neuroprotective agents and modified lifestyle pattern. The nutraceuticals chosen for this mini-review were obtained from several databases (search engine) including, Google Scholar, Web of Science, Scopus, PubMed, Science Direct. Using a combination of various keywords such as "neuroprotection, anti-neurotoxicity, nutraceuticals, complementary medicine" in a clinical setting (clinical trials) as well as a cell line or in-vitro and animal studies (pre-clinical studies) were also included but only for explaining the proposed brief neuroprotective mechanism. Thus, the author's clear intention is to include only effective neuroprotective nutraceuticals (positive impact) against various neurodegenerative conditions in a clinical setting for better understating (mechanism) and recommendation (treatment/ prevention). Antioxidant, anti-obesity, anti-cancer, anti-diabetic, anti-microbial as well as neuroprotective and cardioprotective properties [16,17].

Nutraceuticals and its Categories

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

Phytochemistry of food-based nutraceuticals

This category includes food products obtained directly from nature without any change in their original constituent form. These include fruits, vegetables, grains, meat, fish, eggs, and dairy that provide several benefits beyond basic nutrition [18,19]. 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. The planting of nutrients can be used in preventing brittle bones, uplifting hemoglobin, and strengthening muscle power and neuronal transmission. Fatty acids and its compounds enhance brain functioning and aid a decrease in cholesterol present in the arteries, tending to show its hypolipidemic effects [20,21].

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 [22,23]. Nutraceuticals can also be classified based on the secondary metabolites they possess, such as fatty acids, carbohydrates, Flavonoids, Carotenoids, Crocin, Cyanidin, Luteolin, Quercetin and Kaempferol, Withanine, Asiatic Acid, Bhilavanol A and Bhilavanol B, vitamin B3, vitamin B9 or folate, vitamin B12, vitamin B6, vitamin D, vitamin E, and vitamin C, Omega-3 Fatty Acid Molecules, N-acetyl Cysteine , S-adenosyl Methionine, L-Tryptophan/5-HTP, Vitamin D, Zinc and amino acid-based

compounds, as the origin for every nutraceutical is different depending on the natural source and this phytochemical are mostly useful in neuro-degenerative diseases [24].

Tannin-containing compounds, such as lavender, help in releasing stress and lowering blood pressure. 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. Terpenoid-containing compounds, such as peppermint and menthol, are used in respiratory conditions. Many other commonly used herbs, such as *Aloe vera*, possesses anti-inflammatory and dilating properties, hence it is used in wound healing; ephedra possess bronchodilator and vasoconstriction effects, hence it is used for bronchospasms [25]. 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 [26-28].

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 [29]. 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 [30]. They have also been studied for their efficacy in neurological interventions, such as depression [31]. They also include enzymes and glandular extracts, and can be consumed in all dosage forms, including capsules, powders, tablets, 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 plants 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 healthier 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 in the market for consumption in raw forms [26-28, 32].

Nutraceuticals used in Alzheimer's disease

Alzheimer's Disease (AD), also known as Senile Dementia of the Alzheimer Type (SDAT) or the primary degenerative dementia of the Alzheimer's type (PDDAT), is the most common form of memory loss as mentioned by Linseman in his article published in 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 [33]. The process of ageing 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 [34].

Additionally, researchers suggest that the prevention of AD is not as complex as assumed. The consumption of food products and herbal plants that are rich in phytoconstituents are Flavonoids include catechin, epicatechin, epigallocatechin, quercetin, kaempferol and epigallocatechin gallate. The main resources of flavonoids include fruits, vegetables, and drinks, such as wine, tea, cocoa and also the major carotenoids present in humans include lutein, zeaxanthin, lycopene, and β-cryptoxanthin, including α and β carotenes. Crocin, Cyanidin obtained from cranberries, strawberries and polyunsaturated fatty acids and saturated and trans-fatty acids tends to suppress neurodegeneration while foods rich in trans-fat can enhance neurodegeneration [35]. These are a group of commonly found polyphenolic compounds mainly extracted from the human diet. 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 [36,37]. Some of the compounds beneficial in AD.

Nutraceuticals used 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 drastic depletion of Dopamine (DA). Factors, such as oxidative stress, depletion of antioxidants, damage to mitochondria, etc., contribute to neurodegeneration leading to PD [38]. Anti-Parkinson's diseases provide symptomatic relief by supplementing dopamine and preventing symptoms of motor abnormalities and gait, and providing neuroprotection [39]. Therefore, a wide range of drug molecules are 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.

Oxidative stress and damage free radicals in association with the dysfunction of mitochondria this condition will be used in Nutrients include Fish oil, Coenzyme Q10, lycopene and herbal phytochemical include ginsenosides, vincamine, vinpocetine, EGCG and synthetic are mitoapocynin and mito Q these compounds leads to compromised cellular metabolism and energy homeostasis, thereby impacting the functioning of the brain, and leading to neurodegenerative disorders, including PD.

Endocrine reticulum stress pathway misfolding and aggregation of proteins this condition will be used in Nutrients are several vitamins, including vitamin B3, vitamin B9 or folate, vitamin B12, vitamin B6, vitamin D, vitamin E, and vitamin C, beta carotene, Coenzyme Q10 and herbal phytochemical include crocin, rosmarinic acid, baicalin, gallic acid can be used in Parkinson's disease [40].

Neuroinflammation that condition will be used in Nutrients include W-3 polysaturated and herbal phytochemical include curcumin, silymarin, asiatic acid, quercetin, extracts of mucuna pruriens useful in neurodegeneration and onset of Parkinson's disease [39-42]. 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 least toxic to humans. With this as the principle, 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 [41,42].

Nutraceuticals used 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 a 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. In depression condition will be used in Nutraceuticals such as, folic acid, omega-3 fatty acids, Omega-3 Fatty Acid Molecules, N-acetyl Cysteine, S-adenosyl Methionine, L-Tryptophan/5-HTP, vitamin D and zinc and several other essential macro and micronutrients, can trigger the functioning of the brain and have evidently shown results in the management as an adjunctive therapy of depression [43-45].

Nutraceuticals used 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. They are mainly employed as an adjunctive therapy and sometimes as a monotherapy in patients who are in dire need of psychotic care. 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 thereby improving the efficacy of psychiatric medicines and ameliorating their side effects [46-49].

The commonly used nutraceuticals in psychosis include omega-3 fatty acids and vitamins, including vitamin B3, vitamin B9 or folate, vitamin B12, vitamin B6, vitamin D, vitamin E, and vitamin C can be used in psychotic disorders and 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. The latter include Eicosatetraenoic Acid (EPA) and Docosahexaenoic Acid (DHA) [50]. All of them are important components of the phospholipid cell membrane and are essential for 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 microinflammatory and oxidative stress. They modulate the functioning of mitochondria, which are the main source of oxidative stress [51].

Nutraceuticals used in neurodegenerative disorders

Neurodegenerative disorders mainly develop by protein misfolding. 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, trans active response (deoxyribonucleic 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. 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 [52-55]. These misfolded proteins further stimulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, which causes the production of inflammatory cytokines (such as tumor necrosis factor-α (TNF-α), interleukins-1β (IL-1β), etc.), and leading to the activation of destructive molecules (like cyclooxygenase (COX-2), 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 [56-58].

Additionally, further inflammatory misfolded proteins change the signaling of GSK3β with the simultaneously provoked inflammatory cytokines, which leads to hyperphosphorylation of tau proteins, and causes an increased synthesis of cholesterol. Furthermore, it also results in the formation of lipid raft, harboring misprocessing and misfolding of proteins due to the promotion of enzymes, thereby setting up a vicious cycle. 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 [59-61]. Nutraceuticals, when used for their therapeutic potential, can easily replace synthetic drug for marketed ingredients, such as donepezil,

galantamine, rivastigmine, and tacrine, 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 other Cyclooxygenase (COX) inhibitors under the category of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); etc., bur these synthetic drugs compounds various side effects. Hence, the nutraceuticals are most useful therapy and effective alternative in the management of neurological disorders due to their affordable prices and availability and very less side effects [62,63].

Conclusion

Generally, there is significant evidence supporting a role of the ACH in Neurodegenerative disorders. As cholinergic function is essential for short-term memory, the cholinergic insufficiency in Neurodegenerative disorders was also believed to be dependable for much of the short-term memory deficit. 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 evidently described in various studies.

The experimental research on various plants products for therapeutic efficacy of these nutraceutical product such as fruits, vegetables, grains, meat, fish, eggs, minerals, carbohydrates, Flavonoids, Carotenoids, Crocin, Cyanidin, Luteolin, Quercetin and Kaempferol, Withanine, Asiatic Acid, Bhilavanol A and Bhilavanol B, vitamin B3, vitamin B9 or folate, vitamin B12, vitamin B6, vitamin D, vitamin E, and vitamin C, Omega-3 Fatty Acid Molecules, N-acetyl Cysteine , S-adenosyl Methionine, L-Tryptophan/5-HTP, Zinc and amino acid-based compounds, as the origin for every nutraceutical is different depending on the natural source and this phytochemical has provided new directions for the affordable treatment of neurodegenerative diseases in this era of many public health system crises. 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, Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD).

References

1. Williams, Robert J, KP Mohanakumar, Beart PM (2016) Neuro-nutraceuticals: Further insights into their promise for brain health. Neurochem Int 1-3.
2. Farkhondeh T, Yazdi HS, Samarghandian S (2019) The protective effects of green tea catechins in the management of neurodegenerative diseases: a review. Curr drug discov technol 16: 57-65.
3. Adefegha SA (2018) Functional foods and nutraceuticals as dietary intervention in chronic diseases; novel perspectives for health promotion and disease prevention. J Diet Suppl 15: 977-1009.
4. Agnihotri A, Aruoma OI (2020) Alzheimer's disease and Parkinson's disease: a nutritional toxicology perspective of the impact of oxidative stress, mitochondrial dysfunction, nutrigenomics and environmental chemicals. J Am Coll Nutr 39: 16-27.
5. Wimo A, Jönsson L, Bond J, Prince M, Winblad B, et al. (2013) The worldwide economic impact of dementia. Alzheimer's Dement 9: 1-1.
6. Cobley JN, Fiorello ML, Bailey DM (2018) 13 reasons why the brain is susceptible to oxidative stress. Redox biol 15: 490-503.
7. Gupta C, Prakash D (2015) Nutraceuticals for geriatrics. J tradit complement med 5: 5-14.
8. Venkatakrishnan K, Chiu HF, Wang CK (2019) Popular functional foods and herbs for the management of type-2-diabetes mellitus: a comprehensive review with special reference to clinical trials and its proposed mechanism. J Funct Foods 57:425-438.
9. Chiu HF, Shen YC, Venkatakrishnan K, Wang CK (2018) Popular functional foods and nutraceuticals with lipid lowering activity and in relation to cardiovascular disease, dyslipidemia, and related complications: an overview. J Food Bioact 2:16-27.
10. Daliu P, Santini A, Novellino E (2018) A decade of nutraceutical patents: Where are we now in 2018? Expert opin ther pat 28: 875-882.
11. Santini A, Novellino E (2018) Nutraceuticals-shedding light on the grey area between pharmaceuticals and food. Expert Rev Clin Pharmacol 11: 545-547.
12. Pandareesh MD, Kandikattu HK, Razack S, Amruta N, Choudhari R, et al. (2018) Nutrition and nutraceuticals in neuroinflammatory and brain metabolic stress: implications for neurodegenerative disorders CNS Neurol. Disord.-Drug Targets (Former. Curr. Drug Targets-CNS Neurol. Disord.)17: 680-688.
13. Dadhania PV, Trivedi PP, Vikram A, Nand Tripathi D (2016) Nutraceuticals against neurodegeneration: A mechanistic insight. Curr Neuropharmacol 14: 627-640.
14. Prakash V, Boekel (2010) Nutraceuticals: Possible future ingredients and food safety aspects. In Ensuring Global Food Safety; Academic Press: Cambridge, MA, USA 333-338.
15. Venkatakrishnan K, Chiu HF, Wang CK (2019) Extensive review of popular functional foods and nutraceuticals against obesity and its related complications with a special focus on randomized clinical trials. Food Funct 10: 2313-2329.
16. Mantzorou M, Pavlidou E, Vasios G, Tsagalioti E, Giaginis C (2018) Effects of curcumin consumption on human chronic diseases: A narrative review of the most recent clinical data. Phytother Res 32: 957-975.
17. Perrone L, Squillaro T, Napolitano F, Terracciano C, Sampaolo S, Melone MA (2019) The autophagy signaling pathway: A potential multifunctional therapeutic target of curcumin in neurological and neuromuscular diseases. Nutrition 11: 1881.
18. Bhaskarachary K (2016) Traditional Foods, Functional Foods and Nutraceuticals. Proc. Indian Natl Sci Acad 82: 1565-1577.
19. Bhat ZF, Bhat H (2011) Milk and Dairy Products as Functional Foods: A Review. Int J Dairy Sci 6: 1-12.

20. Ramalingum N, Mahomoodally MF (2014) The therapeutic potential of medicinal foods. Adv Pharmacol Sci 354264.

21. Prakash V, Boekel (2010) Nutraceuticals: Possible future ingredients and food safety aspects. In Ensuring Global Food Safety. Academic Press: Cambridge, MA, USA333-338.

22. Dohrmann DD, Putnik P, Bursac Kova cevic D, Simal Gandara J, Lorenzo JM, (2019) Mediterranean and Argentinean Diets and Their Potential Roles in Neurodegenerative Diseases. Food Res Int 120: 464-477.

23. Barba FJ, Putnik P, Kovacevic DB (2020) AgriFood Industry Strategies for Healthy Diets and Sustainability: New Challenges in Nutrition and Public Health; Press A Ed, MPS Limited Chennai India: Tamil Nadu, India.

24. Chintale Ashwini G, Kadam Vaishali S, Sakhare Ram S, Birajdar Ganesh O, Nalwad Digambar (2013) N. Role of nutraceuticals in various diseases: A comprehensive review. Int J Res Pharm Chem 3: 290-299.

25. Williams RJ, Mohanakumar KP, Beart PM Neuro-nutraceuticals: Further insights into their promise for brain health. Neurochem Int 95: 1-3.

26. Putnik P, Gabric D, Roohinejad S, Barba FJ, Granato D et al. (2019). Bioavailability and food production of organosulfur compounds from edible Allium species. In Innovative Thermal and Non-Thermal Processing, Bioaccessibility and Bioavailability of Nutrients and Bioactive Compounds; Francisco J, Barba, JMAS, Giancarlo Cravotto J, Lorenzo M, Eds, Woodhead Publishing: Cambridge, UK, 293-308.

27. Putnik P, Gabric D, Roohinejad S, Barba FJ, Granato D, et al. (2019) An Overview of Organosulfur Compounds From Allium Spp.: From Processing and Preservation to Evaluation of Their Bioavailability, Antimicrobial, and Anti-Inflammatory Properties. Food Chem 276: 680-691.

28. Poojary MM, Putnik P, Bursac Kovacevic D, Barba FJ, Lorenzo JM et al. (2017) Shpigelman, A. Stability and extraction of bioactive sulfur compounds from Allium genus processed by traditional and innovative technologies. J Food Compost Anal 61: 28-39.

29. Montesano D, Rocchetti G, Putnik P, Lucini L (2018) Bioactive profile of pumpkin: An overview on terpenoids and their health-promoting properties. Curr. Opin. Food Sci. 22: 81-87.

30. Pillitteri JL, Shiffman S, Rohay JM, Harkins AM, Burton SL et al. (2008) Use of Dietary Supplements for Weight Loss in the United States: Results of a National Survey. Obesity 16: 790-796.

31. Rao TS, Asha MR, Ramesh BN, Rao KS (2008) Understanding Nutrition, Depression and Mental Illnesses. Indian J. Psychiatry 50: 77-82.

32. Tapal A, Kaul Tiku P (2019) Nutritional and Nutraceutical Improvement by Enzymatic Modification of Food Proteins. In Enzymes in Food Biotechnology; Kuddus M, Ed, Academic Press: Cambridge, MA, USA 471-481.

33. Frisardi V, Panza F, Solfrizzi V, Seripa D, Pilotto A (2010) Plasma lipid disturbances and cognitive decline. J Am Geriatr Soc 58: 2429-2430.

34. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A et al. (2001) Oxidative Damage is the Earliest Event in Alzheimer Disease. J Neuropathol Exp Neurol 60: 759-767.

35. Dohrmann DD, Putnik P, Bursac Kovacevic D, Simal Gandara J, Lorenzo et al. (2019) Japanese, Mediterranean and Argentinean Diets and Their Potential Roles in Neurodegenerative Diseases. Food Res. Int. 120: 464-477.

36. Sawmiller D, Li S, Shahaduzzaman M, Smith AJ, Obregon D, et al. (2014) Luteolin Reduces Alzheimer's Disease Pathologies Induced by Traumatic Brain Injury. Int J Mol Sci 15: 895-904.

37. Wang H, Wang H, Cheng H, Che Z (2016) Ameliorating Effect of Luteolin on Memory Impairment in an Alzheimer's Disease Model. Mol Med Rep 13: 4215-4220.

38. Mythr R, Kumar A, Mms B (2015) Nutraceuticals and Other Natural Products in Parkinson's Disease Therapy: Focus on Clinical Applications. In Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease; Academic Press: Cambridge, MA, USA 421-431.

39. Mandel S, Grunblatt E, Riederer P, Gerlach M, Levites Y, et al. (2003) Neuroprotective strategies in Parkinson's disease: An update on progress. CNS Drugs 17: 729-762.

40. Tatton W, Chalmers Redman R, Brown D, Tatton N (2003) Apoptosis in Parkinson's disease: Signals for neuronal degradation. Ann Neurol 53: S61-S70.

41. Jenner P, Olanow CW (1996) Oxidative stress and the pathogenesis of Parkinson's disease. Neurology 47: 161S-170S.

42. Henchcliffe C, Beal MF (2008) Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. Nat Clin Pract Neurol 4: 600-609.

43. Lama A, Pirozzi C, Avagliano C, Annunziata C, Mollica MP, et al. (2020) Nutraceuticals: An integrative approach to starve Parkinson's disease. Brain Behav. Immun Health 2: 100037.

44. Ceskova E, Silhan P (2018) Novel treatment options in depression and psychosis. Neuropsychiatr. Dis Treat 14: 741.

45. Van der Burg KP, Cribb L, Firth J, Karmacoska D, Sarris J (2019) Nutrient and genetic biomarkers of nutraceutical treatment response in mood and psychotic disorders: A systematic review. Nutr Neurosci 1-17.

46. Balanzá-Martínez V (2017) Nutritional supplements in psychotic disorders. Actas Esp Psiquiatr 45: 16-25.

47. Davis J, Moylan S, Harvey B.H, Maes M, Berk M. (2014) Neuroprogression in schizophrenia: Pathways underpinning clinical staging and therapeutic corollaries. Aust N Z J Psychiatry 48: 512-529.

48. Howes OD, Kapur, S (2009) The dopamine hypothesis of schizophrenia: Version III—The final common pathway. Schizophr Bull 35: 549-562.

49. Savitz AJ, Xu H, Gopal S, Nuamah I, Ravenstijn P, et al. (2016) Efficacy and Safety of Paliperidone Palmitate 3-Month Formulation for Patients with Schizophrenia: A Randomized, Multicenter, Double-Blind, Noninferiority Study. Int J Neuropsychopharmacol 19.

50. Brown HE, Roffman JL (2016) Emerging treatments in schizophrenia: Highlights from recent supplementation and prevention trials. Harv Rev Psychiatry 24: e1-e7.

51. Sarris J, Logan AC, Akbaraly TN, Amminger GP, Balanza Martínez V, et al. (2015) Nutritional medicine as mainstream in psychiatry. Lancet Psychiatry 2: 271-274.

52. Colín-González AL, Ali SF, Túnez I Santamaría A (2015) On the antioxidant, neuroprotective and anti-inflammatory properties of S-allyl cysteine: An update. Neurochem Int 89: 83-91.

53. Grassi D, Ferri C, Desideri G (2016) Brain protection and cognitive function: Cocoa flavonoids as nutraceuticals. Curr Pharm Des 22: 145-151.

54. Johnston GA (2015) Flavonoid nutraceuticals and ionotropic

receptors for the inhibitory neurotransmitter GABA. Neurochem Int 89: 120-125.

55. Saldanha SN, Tollefsbol TO (2012) The Role of Nutraceuticals in Chemoprevention and Chemotherapy and Their Clinical Outcomes. J Oncol 192-464.

56. Chauhan NB, Mehla J (2015) Ameliorative Effects of Nutraceuticals in Neurological Disorders. In Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease; Elsevier: Amsterdam, The Netherlands 245-260.

57. Asadi Shekaari M, Kalantaripour TP, Nejad FA, Namazian E, Eslami A (2012) The anticonvulsant and neuroprotective effects of walnuts on the neurons of rat brain cortex. Avicenna J Med Biotechnol 4: 155.

58. Kelsey NA, Wilkins HM, Linseman DA (2004) Nutraceutical antioxidants as novel neuroprotective agents. Molecules 15: 7792-7814.

59. Barber SC, Mead RJ, Shaw PJ (2006) Oxidative stress in ALS: A mechanism of neurodegeneration and a therapeutic target. Biochim. Biophys Acta Mol Basis Dis 1762: 1051-1067.

60. Gonsette R (2008) Neurodegeneration in multiple sclerosis: The role of oxidative stress and excitotoxicity. J Neurol Sci 274: 48-53.

61. Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443: 787-795.

62. Lenaz G (2001) The Mitochondrial Production of Reactive Oxygen Species: Mechanisms and Implications in Human Pathology. IUBMB life 52: 159-164.

63. Ott M, Gogvadze V, Orrenius S, Zhivotovsky B (2007) Mitochondria, oxidative stress and cell death: Apoptosis 12: 913-922.