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SHORT REVIEW

A Review Study on Herbal Nutraceuticals: A Leading Edge in the Treatment of Neurological Disorders with the Help of Medicinal Plants

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Abstract

Neurodegenerative diseases are characterized by the loss and death of neurons with their structure and functions and this is causing a great burden on society at present time. The degeneration of neurons is caused due to a variety of factors which may be genetic, environmental, oxidative stress and many more. The scientific articles regarding neurodegenerative disorders, their classification, and mechanism of action are pooled from different scientific databases. We have used preferred reporting items for systemic reviewing of articles to filter those which are highly relevant and counter the information at present: neurodegenerative disorders, medicinal plants, herbal plants from neurodegeneration, and herbal nutraceuticals as summarized. As per the side effects caused by the use of synthetic drugs for the treatment of various neurological disorders, to reduce their efficacy, it was found the new advancement of herbal nutraceuticals has created havoc and has been reported to possess neuroprotective effects with minimized side effects. Medicinal plants for neuro-degenerative diseases have been documented to cure a variety of neurological disorders and their effects over synthetic drugs by the advancing use of herbal nutraceuticals. This review will provide the role of herbal nutraceuticals and medicinal plants in curing neurodegenerative diseases in the present era.

Keywords: *Ayurveda*, Herbal Nutraceuticals, Medicinal Plants, Neurodegenerative Disorders

Abbreviations

Central Nervous System (CNS), Global Burden of Disease (GBD), Tension-Type Headache (TTH), Alzheimer's Disease (AD), Parkinson's Disease (PD), Pentylene Tetrazole (PTZ), EEG (Electroencephalogram)

1. Introduction

The nervous system is a multiplex network which helps an organism interact with the environment. Many sensory points help in the detection of environmental stimuli and the motor component then shows control over the skeletal, cardiac and other smooth muscles along with controls the glandular secretions which are coordinated in a complete system for proper motor responses to the stimuli which further receive, stores and process the information as seen in Figure 1. The nervous system is made up of broad neural networks as signalling in these circuits causes thinking, feeling, language, memory and all the sensation functions[1]. It is known that neurons are the basic functional unit of the nervous system and they function as it receives, integrates and then transmits the information to the other cells of the body[2]. At the time of childhood, the neural stem cells make many neurons which further reduces in adulthood[3].

The most intricate organ is the human Central Nervous System (CNS) which determines awareness. All of our behaviour, from the most fundamental needs like breathing to the support of our ideas and feelings, is underpinned by its activity[4]. Brain affects a large

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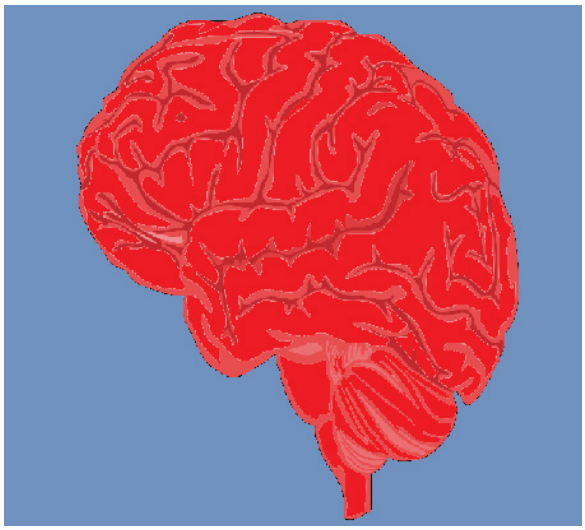

Figure 1. Human brain.

section of the population, affects people of all ages, and is common in industrialized and emerging nations. Additionally, compared to other disease groups, these illnesses have the highest global health, economic and social capital burden[5].

1.2 Neurological Disorders: A Burden on Healthcare

The burden of neurological disorders is a major significant in global health. According to the most recent estimates, the neurological conditions included in the Global Burden of Disease (GBD) Study—are Alzheimer's, dementia, Parkinson's disease, multiple sclerosis, epilepsy and many more. Dementia, epilepsy, migraines, and stroke are among the top 50 causes of disability-adjusted life years, even though this appears to be a modest total percentage. The burden of this disease is considered to increase in the lower and middle-income countries in the next decade[6].

The word neurological disorders is used to describe the conditions of CNS as it results from physical injury to the brain, and spinal cord in the form it affects the central as well as peripheral nervous system. Neurological disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease, Stroke, migraine and other disorders[7].

Different intracellular and extracellular changes can be seen in neurodegenerative illnesses. Any polypeptide that fails to fold properly is sent to its breakdown processes, known as autophagy or the ubiquitin-proteasome system[8] since translational and posttranslational modification mechanisms are extremely complicated and sophisticated.

1.3 Various Factors Which Lead to the Development of Neurological Disorders

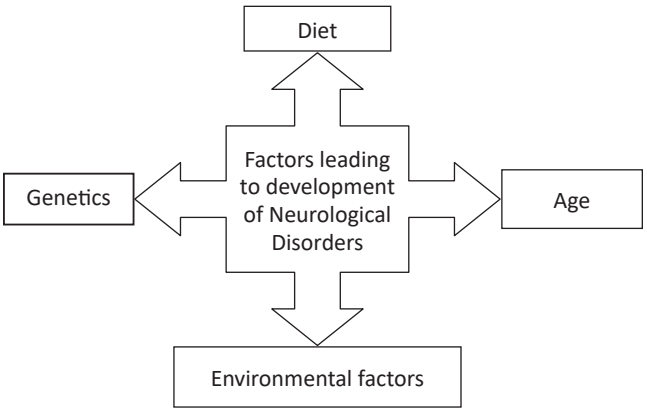

Figure 2. Different factors leading to neurodegenerative diseases.

1.4 Diet

The Western diet, sometimes known as the Standard American Diet, consists of foods that have undergone extensive processing and refinement. As a result, a variety of health issues including obesity, diabetes, cardiovascular disease, and many other illnesses become major health risks. The mechanism which depends on the use for its treatment in certain neurodegenerative diseases is considered a better source of energy which reduces the generation of free radicals, increasing the mitochondrial biogenesis pathway and making use of the ability of ketones by bypassing the defect in complex I activity found in some neuronal disorders. The mechanism which depends on the use for the treatment of specific types of neurodegenerative diseases is found as diet being the major energy source lowers the production of free radicals, increases in mitochondrial biogenesis pathway, utilizing ketone capacity to work in defecting complex I activity[9] (Figure 2).

1.5 Age

In developing countries, early exposure to unhealthy conditions brought on by poverty, such as infections, malnutrition, and prenatal stress, may have a significant impact on ageing and shorten life expectancy[10] (Figure 2).

1.6 Environmental Factors

Due to their capacity to interfere with brain functioning, environmental pollutants such as heavy metals, and pesticides are known to been linked to the development of Parkinson's disease and Alzheimer's disease. The compounds such as Asbestos, Pb, MeHg, Cd, and other toxic heavy metals have all been linked to neurotoxicity, which in turn causes neurodegenerative diseases[11] (Figure 2).

2. Predomination of Neurodegenerative Disorders: Enhanced due to Dysfunction of Specific Neuron Population

A disorder called dementia is, a syndrome of chronic nature of neurons caused due to many disorders of the brain and led by disturbances of many efficient cortical functions that include memory learning, and judgment process which is a social burden. The disease Alzheimer's is a pathological state of the CNS which is related to Alzheimer's disease as marked by neurofibrillary tangles, disarrangement of neurotransmitters in the neuronal regions and beta-amyloid plaques combined all are related to different inflammatory mechanisms. As seen the major risk factor associated with Alzheimer's disease is the increase in the age factor[12].

Epilepsy is a neuronal disorder as known as "provoked epileptic symptomatic seizures" which might occur due to brain injury. This disorder affects the regions of muscles and senses and if both of them are combined then it will lead to total loss of consciousness[13].

Parkinson's disease is a multiple neurological disorder that progresses to tremors, stiffness of muscles, difficulty in walking, balance and coordination dysfunction. The stimuli responsible for it are genetic as well as non-genetic. Age is a major risk factor for this disorder[14].

2.1 Mechanism of Neurodegenerative Disorders

This disorder affects a large area of the population in millions across the world and is linked to the accumulation of insoluble protein aggregates and the mechanism of this aggregation is from beta-amalyoid that is based upon the mechanism of neurodegeneration as seen in Figure 3.

The mechanism is as follows:

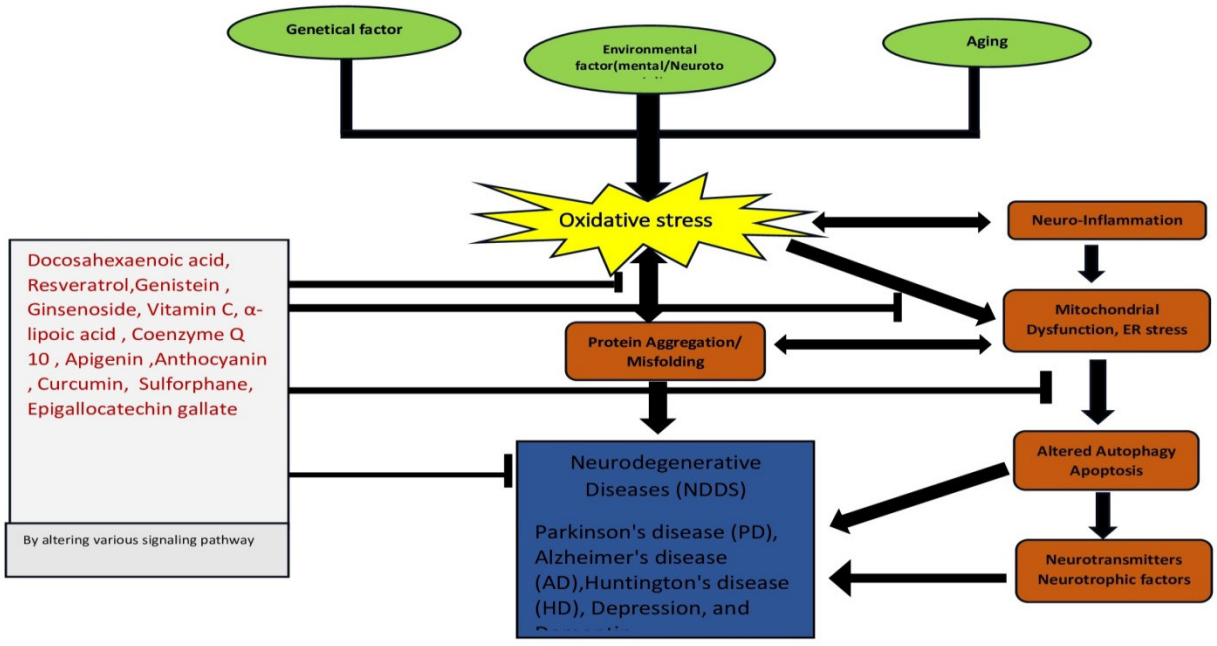

Figure 3. The mechanism leading to the formation of neurodegenerative diseases.

2.1.1 Molecular Mechanism

This occurs due to the misfolding of different neuro degenerated proteins and this disformed degradation leads to deposition in the brain regions and leads to symptoms such as amyloid-beta, tau for AD, and prion proteins for prion diseases.

2.1.2 Cellular Mechanism

The L-glutamate leads to cause of acute excitotoxicity in the regions of the brain which leads to long-term neurodegenerative processes and causes chronic neurodegenerative disorders[15].

Oxidative stress impairs the bioenergetics capacity of the nervous system and this is responsible for the pathogenesis of different kinds of neurodegenerative disorders[16].

3. Current Trends in Medicinal Plants and Herbs in Treating Neurological Disorders

Natural products originating from plants are known to be associated with use as traditional medicines for thousands of years around the whole globe. There are many varieties of plants that are used for medical treatment in different cultures and by them many new drugs are discovered through the use of herbal sources[17].

3.1 *Ayurveda*: Indian System of Medicine

The implementation of herbal medicines round back from the earliest times of human history. There are proofs of herbs which are being used for the treatment of different diseases and to rejuvenate the body system in all ancient civilizations that is Indian, Egyptian, Chinese and Greek as well as Romans. Plants are the main body of medicines and contain the majestic power of healing[18].

The term *Ayurveda* is "science of life", which is believed to be the world's oldest health care system and indigenous to India. As of all the alternative medicines in the world it is considered to be a more recognized and highly practiced discipline in other disciplines of alternative medicines. In the practice of *Ayurveda*, the substances are of natural origin which is originated from plants and their parts and are further used in the form of medicines in single or combined form. The reliance on Ayurvedic medicines is that the disease is due to disturbances or imbalances in the human body and certain mental elements reduce the resistance of the body to many diseases. If all the imbalances are corrected or defined the defence mechanism of the body is enhanced due to these herbal formulations which results in changes in lifestyle, diet and the resistance of the body in eliminating the diseases[19].

3.2 Some of the Ayurvedic Ways of Treating Neurodegenerative Disease

As through all the disciplines of *Ayurveda*, the Rasayana tantra is used as a treatment in improving longevity and memory, youthful appearance and helps in maintaining physical strength[20].

3.3 Neuro-therapeutic Benefits of Medicinal Plants

The literature finds that the identification of many herbs has shown great protective effects for neurodegenerative disorders. The authors summarized the details based on the mechanism and effects of the medicinal plants.

3.4 *Withania somnifera*

The plant Ashwagandha and its supplements help in improving functions of the brain, and memory and enhance the ability to perform different tasks (Figure 4). There are many animal studies done which suggest that this plant helps in reducing the problems of memory and brain functions which are caused due to injury or certain diseases. This plant promotes anti-oxidant activity which helps in protecting nerve cells from very harmful free radicals[21].

The plant inhibits haloperidol or reserpine-induced catalepsy and provides an efficient approach to treating Parkinson's disease. Due to this the antiparkinson effect of this plant along with its extracts has shown advanced antioxidant, antiperoxidative and free radical scavenging properties[22].

The intake of ashwagandha root extract is known to reduce jerks and clonus by approx. 70% with the dose of 100mg/kg and reduction in severity of Pentylene tetrazole (PTZ)-induced convulsions which was evidenced from the patterns of EEG waves. The root extract of the plant showed reduced severity in motor seizures as induced by electrical stimulation in the right

Figure 4. *Withania somnifera* plant.

basilateral amygdaliod nuclear complex by bipolar electrodes. The protective effect of this plant extract in convulsions has shown involvement in Gaba Amino Butyric Acid-ergic mediation[23].

The plant has strong aphrodisiac, sedative, revitalizing, and life-extension effects. Additionally, Medhya Rasayana, which translates to "that which promotes learning and a good memory", as seen in Figure 5 is employed as a general tonic to boost vitality and treat geriatric issues[24].

3.5 *Azadirachta indica*

The plant "Neem" is known as a storehouse of many therapeutic molecules; therefore it is known as a "Pharmaceutical Wonder". It is found that around 300 Phytochemicals have been isolated from neem which has diverse chemical properties and complex structures. The main phytochemicals present are glycoproteins, triterpenes, limonoids, phenols, tannins, saponins, gallic acid and many other[25].

The plant has many diverse activities as a study was done which investigated that the plant has neuroprotective effects as the leaves against cisplatin-induced neurotoxicity further results showed the morphological work before and after the injection of Cisplatin implied well-preserved brain tissue, which reported there were no changes in biochemical parameters were seen with neem treated groups[26].

A study was done in which intake of neem leaf extract was given at a dose of 200mg/kg body weight which has shown diversified antidepressant action as seen in Figure 5. There are many bioactive components which are present in neem that are responsible for many health effects[27].

Further Biochemical analysis was done on leaf extracts which have shown a high intake of proline which is the current or present treatment used in many neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, Polycythemia[28].

3.6 *Bacopa monnieri*

The plant "Brahmi" is a very well-known plant having many medicinal properties in *Ayurveda* (Figure 6). This plant is commonly found in India and parts of Australia. It helps to rejuvenate the nerve cells and empowers the memory. It contains two saponins Bacoside A and B which are made up of Sapogenins-Bacogenins A1-A4, Betulic acid and many other alkaloids are present in it. In all of them, Bacoside A is found to improve the memory[29].

It also repairs the damaged neurons by increasing the kinase activity, synthesis of neurons, restoration of synaptic activity and transmission of nerve impulse[30].

It is an Ayurvedic herb, which has re-emerged as a course of treatment for many memory-related disorders. The medical potency of this plant is seen in India as well as in China based on its literature. Many chemical compounds can be isolated from Brahmi; actively it contains bacoside-A and bacoside-B. It also contains many other Phytochemicals such as alkaloids, glycosides, flavonoids, and saponins[31].

The plant contains active constituents which help in treating Parkinson's disease, a disorder in which loss of neurons takes place which produces dopamine in the

Figure 5. *Azadirachta indica* plant.

Figure 6. *Bacopa monnieri* plant.

region of substancia nigra and alpha-synclein protein that is accumulated in the inclusion bodies[32].

The plant shows anti-depressant action due to components such as Bacosides A and B bacopasaponin C, bacopasides I and II[33].

4. Traditional Herbs for Neuroprotection

Traditional herbs or medicinal drugs showed a positive effect on the functions of the brain that is known as Nootropics[34].

In the present time, there is a sudden increase in neurological disorders and severe side effects which is caused due to the long-term intake of synthetic drugs this has raised the attention of researchers towards the use of natural plants and resources. Many medicinal plants Ginkgo biloba, Panax ginseng, *Valeriana officinalis* and *Withania somnifera* are highly used in many traditional systems of therapy as they contain neuroprotective properties. The plant Ginkgo biloba has major use in the treatment of cerebral insufficiency which memory loss, absent minds, confusion, depression, anxiety, and dizziness[35].

There are more than 120 traditional medicines that are extensively used in the therapy of CNS disorders in Asian countries around the globe. According to the Indian system of medicine, there are the majority of plants that have cured neurodegenerative disorders[36].

Apart from medicinal plants and herbs, there is a more advanced way of preventing neurological disorders along with the regulation of brain physiology.

5. Medicinal Plants as Herbal Nutraceuticals

Although various medications can help with neuronal health, the main drawback is that long-term use of these medications is linked to several adverse side effects. As a result, the use of nutraceuticals which are advantageous, cost-effective, and have fewer or no side effects than pharmaceuticals is highly preferred. The founder of medicine Hippocrates once said let food be your medicine and medicine be your food[37].

Various separated nutrients, dietary supplements, herbal goods, and genetically modified "designer" foods are all examples of nutraceuticals. These foods can then be further processed to create items like cereals, soups, and beverages. These dietary supplements are thought to have an impact on the majority of therapeutic areas, such as the common cold and cough, digestive issues, the prevention of certain cancers, osteoporosis, arthritic, hypertension, cardiac diseases, pain relievers, depression, and sleeping disorders[38].

Certain Antioxidant nutraceuticals which contain turmeric, curcumin, lutein, and lycopene can be used to treat neuronal disorders such as dementia and AD[39].

Many pronounced nutraceuticals that helpful in treating AD as they contain many essential antioxidants that are used in the treatment of many chronic diseases caused due to oxidative stress that plays a major part in neurological disorders[40].

5.1 Nutraceuticals in Ameliorating Neurodegeneration

The neurodegenerative disorders mainly occur due to the misfolding of proteins[41] as such the abnormal misfolding of proteins Ƭau and amyloid-beta leads to the generation of Alzheimer's disease, traumatic brain injuries that can be induced by modification of Ƭau, transactive response binding protein-43 and A-beta proteins as such Ƭau and TDP-43 misfunctioning causes epilepsy and other dysfunctions[42].

In context to the therapeutic potential, the use of nutraceuticals is highly recommended which easily replaces synthetic drug ingredients such as donepezil, tacrine, rivastigmine, and galantamine as they work by inhibiting acetylcholinesterase enzyme; statins such as atorvastatin it works by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase; alpha-tocopherol, aspirin, ibuprofen and different other non-steroidal anti-inflammatory drugs, the compounds which show major side effects[43].

Further, this confirms that nutraceuticals show a one effective alternate area that can be used in the management of neurological disorders as they have an advantage in the prices, easily available with decreased side effects.

As we are involving nutraceuticals the major herbal nutraceuticals in the treatment of neurological disorders include bacoside A, bacoside B and brahmine where Bacoside A and B are saponin derivatives and brahmine is an alkaloid derivates that is obtained from the plant Brahmi (*Bacopa monnieri*). This plant has also the properties of a nootropic plant that is highly used in *Ayurveda* for its neurocognitive enhancing properties. They help the brain with oxidative stress, generation of free radicals, and poor antioxidant property[44].

6. Current Trends in Medicinal Plants Research and Neurodegenerative Disorders

The ethnopharmacological approach is distinct in natural product research because it draws upon the expertise of the social and cultural sciences. The book "Ethnopharmacological Search for Psychoactive Drugs" introduced the word "ethnopharmacology" for the first time in 1967. Because of their importance in native medical systems, medicinal plants are regarded as a part of traditional knowledge in many regions of the world. Many explorers, traders, missionaries, and other knowledgeable professionals in healing and customs have recorded the applications of medicinal plants; these descriptions form the foundation for ethnopharmacology-based medication development. Drug research has frequently started with this kind of knowledge. Natural Products (NP) have been utilized as remedies to treat a variety of ailments since ancient times. NP continue to play a significant role in the identification of new therapeutic leads and have demonstrated their worth as a source of therapeutic compounds in the past. A significant source of drug

discovery is the wide range of medicinal plants and their ethnomedical history. It has been investigated whether the Apiaceae plant *Centella asiatica* (L.) Urb. possesses neuroprotective and anti-inflammatory qualities. The plant uses its antioxidant qualities and mitochondria protection to achieve its effects.

7. Conclusion

There are many unwanted adverse effects associated with the use of synthetic drugs for curing various neurodegenerative disorders. To encompass these consequences of the disorders there is a profound use of medicinal plants to decrease the side effects. A variety of bioactive compounds are found in these herbs and medicinal plants which treat many neurodegenerative disorders that can be used in the form of nootropics. Further advances in the present era for the use of these medicinal plants occur in the form of herbal nutraceuticals that contain medicinal as well as health benefits that are highly used in the areas of *Ayurveda* for neuroenhancing properties.

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9. References

1. Simonato M, Bennett J, Boulis NM, Castro MG, Fink DJ, Goins WF, *et al.* Progress in gene therapy for neurological disorders. Nat Rev Neurol. 2013; 9(5):277-91. https://doi.org/10.1038/nrneurol.2013.56 PMid:23609618 PMCid:PMC3908892
2. van den Heuvel MP, Sporns O. Network hubs in the human brain. Trends in Cognitive Sciences. 2013; 17(12):683-96. https://doi.org/10.1016/j.tics.2013.09.012 PMid:24231140
3. Ganat YM, Silbereis J, Cave C, Ngu H, Anderson GM, Ohkubo Y, *et al.* Early postnatal astroglial cells produce multilineage precursors and neural stem cells *in vivo*. J Neurosci. 2006; 26(33):8609-21. https://doi.org/10.1523/JNEUROSCI.2532-06.2006 PMid:16914687 PMCid:PMC6674357
4. Kandel ER, Squire LR. Neuroscience: Breaking down scientific barriers to the study of brain and mind. Science. 2000; 290:1113-20. https://doi.org/10.1126/science.290.5494.1113 PMid:11185010
5. Nathan DG, Fontanarosa PB, Wilson JD: Opportunities for medical research in the 21st century. The Journal of the American Medical Association. 2001; 285:533-4. https://doi.org/10.1001/jama.285.5.533 PMid:11176853
6. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, *et al.* Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859):2197-223. https://doi.org/10.1016/S0140-6736(12)61689-4 PMid:23245608
7. Mattson MP. Apoptosis in neurodegenerative disorders. Nat Rev Cell Biol. 2000; 1(2):120-30. https://doi.org/10.1038/35040009 PMid:11253364
8. Hinge NS, Kathuria H, Pandey MM. Engineering of structural and functional properties of nanotherapeutics and nanodiagnostics for intranasal brain targeting in Alzheimer's. Appl Mater Today. 2022; 26. https://doi.org/10.1016/j.apmt.2021.101303
9. Paoli A, Bianco A, Damiani E, Bosco G. Ketogenic diet in neuromuscular and neurodegenerative diseases. BioMed Research International. 2014; 2014:1-10. https://doi.org/10.1155/2014/474296 PMid:25101284 PMCid:PMC4101992
10. Wong E, Cuervo AM. Autophagy gone awry in neurodegenerative diseases. Nat Neurosci. 2010; 13(7):805–11. https://doi.org/10.1038/nn.2575 PMid:20581817 PMCid:PMC4038747
11. Aizenman E, Mastroberardino PG. Metals and neurodegeneration. Neurobiol Dis. 2015; 81:1–3. https://doi.org/10.1016/j.nbd.2015.08.012 PMid:26542885 PMCid:PMC4793913
12. Rasool M, Malik A, Qureshi MS, Manan A, Pushparaj PN, Asif M, *et al.* Recent updates in the treatment of neurodegenerative disorders using natural compounds. evidence-based complementary and alternative medicine. 2014; 2014:1–7. https://doi.org/10.1155/2014/979730 PMid:24864161 PMCid:PMC4017872
13. Paoli A. Canato M. Toniolo L, Bargossi AM, Ner M, Alesso D, *et al.* The ketogenic diet: an underappreciated therapeutic option? La ClinicanTerapeutica. 2011; 162(5):e145-53.
14. Kouli A, Torsney KM, Kuan WL. Parkinson's disease: Etiology, neuropathology, and pathogenesis. Parkinson's Disease: Pathogenesis and Clinical Aspects. 2018; 1(1):3-26. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch1 PMid:30702842
15. Jellinger KA. Basic mechanisms of neurodegeneration: A critical update. J Cell Mol Med. 2010; 14(3). https://doi.org/10.1111/j.1582-4934.2010.01010.x PMid:20070435 PMCid:PMC3823450

16. Guo T, Zhang D, Zeng Y, Huang TY, Xu H, Zhao Y. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Mol Neurodegener. 2020; 15(1). https://doi.org/10.1186/s13024-020-00391-7 PMid:32677986 PMCid:PMC7364557
17. Liu Y, Yin H, Chen K. Platelet proteomics and its advanced application for research of blood stasis syndrome and activated blood circulation herbs of Chinese medicine. Sci China Life Sci. 2013; 56(11):1000–6. https://doi.org/10.1007/s11427-013-4551-8 PMid:24114444
18. Bakhru HK. Herbs that heal. Natural remedies for good health. New Delhi, India: Orient Paperbacks; 2001. p. 17.
19. Mook-Jung I, Shin JE, Yun SH, *et al*. Protective effects of asiaticoside derivatives against beta amyloid neurotoxicity. J Neurosci Res. 1999; 58:417-25.
20. Singh RH, Narsimhamurthy K, Singh G. Neuronutrient impact of Ayurvedic Rasayana therapy in brain aging. Biogerontology. 2008; 9:369-74. https://doi.org/10.1007/s10522-008-9185-z PMid:18931935
21. Kuboyama K, Thoda C, Komatsu K, Effects of Ashwagandha (Roots of *Withania somnifera*) on neurodegenerative diseases. Biol Pharm Bull. 2014; 37(6):892-97. https://doi.org/10.1248/bpb.b14-00022 PMid:24882401
22. Kumar A, Kulkarni SK, Effect of BR-16A (Mentat) a polyherbal formulation on drug-induced catalepsy in mice. Indian Journal of Experimental Biology. 2016; 44(1): 45-8.
23. Kulkarni SK, Sharma A, Verma A, Ticku MK. GABA receptor mediated anticonvulsant action of *Withania somnifera* root extract. Indian Drugs. 1993:305-312.
24. Nagashayana N, Sankarankutty P, Nampoothiri MR, *et al*. Association of L-DOPA with recovery following Ayurveda medication in Parkinson's disease. J Neurol Sci. 2000; 176(2):124-127.
25. Gupta SC, Prasad S, Tyagi AK, Kunnumakkara AB, Aggarwal BB. Neem (*Azadirachta indica*): An Indian traditional panacea with modern molecular basis. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2017; 34:14–20. https://doi.org/10.1016/j.phymed.2017.07.001 PMid:28899496
26. Moneim AA. Azadirachta indica attenuates cisplatin-induced neurotoxicity in rats. Indian J Pharmacol. 2014; 46(3). https://doi.org/10.4103/0253-7613.132182 PMid:24987180 PMCid:PMC4071710
27. Jaiswal AK, Bhattacharya SK, Acharya SB. Anxiolytic activity of *Azadirachta indica* leaf extract in rats. Indian Journal of Experimental Biology. 1994; 32(7):489-91.
28. Dash SP, Dixit S, Sahoo S. Phytochemical and biochemical characterizations from leaf extracts from *Azadirachta indica*: an important medicinal plant. Biochemistry and Analytical Biochemistry. 2017; 06(02). https://doi.org/10.4172/2161-1009.1000323
29. Russo A, Borrelli F. *Bacopa monniera*, a reputed nootropic plant: An overview. Phytomedicine. 2005; 12(4):305-17. https://doi.org/10.1016/j.phymed.2003.12.008 PMid:15898709
30. Singh H, Dhawan B. Neuropsychopharmacological effects of the Ayurvedic nootropic *Bacopa monniera* Linn. (Brahmi). Indian J Pharmacol. 1997; 29:S359-65.
31. Basu N, Rastogi R, Dhar ML. Chemical examination of *Bacopa monniera* Wettst Part IIIBacoside B. India J Chem. 1967; 5:84-95.
32. Feany MB, Bender WW. A Drosophila model of Parkinson's disease. Nature. 2000; 404(6776):394-8. https://doi.org/10.1038/35006074 PMid:10746727
33. Zhou Y, Shen YH, Zhang C, Su J, Liu RH, Zhang WD. *Triterpene saponins* from *Bacopa monnieri* and their antidepressant effects in two mice models. J Nat Prod. 2007; 70(4):652-5. https://doi.org/10.1021/np060470s PMid:17343408
34. Houghton PJ, Raman A. Laboratory handbook for fractionation of natural extracts. London: Chapman and Hall; 1998; p. 199. https://doi.org/10.1007/978-1-4615-5809-5
35. Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. Br J Pharmacol. 1992; 34(4):352-8. https://doi.org/10.1111/j.1365-2125.1992.tb05642.x PMid:1457269 PMCid:PMC1381419
36. Kumar GP, Khanum F. Neuroprotective potential of phytochemicals. Pharmacog Rev. 2012; 6(12): 81-90. https://doi.org/10.4103/0973-7847.99898 PMid: 23055633 PMCid: PMC3459459
37. Biesalaki HK. Nutraceuticals: The link between nutrition and medicine. In: Kramer K, Hoppe PP, Packer L, editors. Nutraceuticals in health and disease prevention. New York, Marcel Dekker Inc.; 2001. p. 1-26.
38. Das L, Bhaumik E, Raychaudhuri U, Chakraborty R. Role of nutraceuticals in human health. Journal of Food Science and Technology. 2011; 49(2):173-83. https://doi.org/10.1007/s13197-011-0269-4 PMid:23572839 PMCid:PMC3550857
39. Sachdeva V, Roy A, Bharadvaja N. Current prospects of nutraceuticals: A review. Curr Pharm Biotechnol. 2020; 21(10):884-96. https://doi.org/10.2174/1389201021666200130113441 PMid:32000642
40. Frisardi V, Panza F, Solfrizzi V, Seripa D, Pilotto A. Plasma lipid disturbances and cognitive decline. Journal of the American Geriatrics Society. 2010; 58(12):2429-30. https://doi.org/10.1111/j.1532-5415.2010.03164.x PMid:21143446
41. Colín-González AL, Ali SF, Túnez I, Santamaría A. On the antioxidant, neuroprotective and anti-inflammatory properties of S-allyl cysteine: An update. Neurochem Int. 2015; 89:83-91. https://doi.org/10.1016/j.neuint.2015.06.011 PMid:26122973
42. Grassi D, Ferri C, Desideri G. Brain protection and cognitive function: Cocoa flavonoids as nutraceuticals. Curr Pharm

Des. 2015; 22(2):145-51. https://doi.org/10.2174/1381612822666151112145730 PMid:26561075

43. Lenaz G. The mitochondrial production of reactive oxygen species: mechanisms and implications in human pathology. International Union of Biochemistry and Molecular Biology: Life. 2001; 52(3-5):159-64. https://doi.org/10.1080/15216540152845957 PMid:11798028

44. Manap ASA, Vijayabalan S, Madhavan P, Chia YY, Arya A, Wong EH, *et al*. *Bacopa monnieri*, a neuroprotective lead in Alzheimer disease: A review on its properties, mechanisms of action, and preclinical and clinical studies. Drug Target Insights. 2019; 13. https://doi.org/10.1177/1177392819866412 PMid:31391778 PMCid:PMC6669844