An overview on herbal approach for the management of neurological complications

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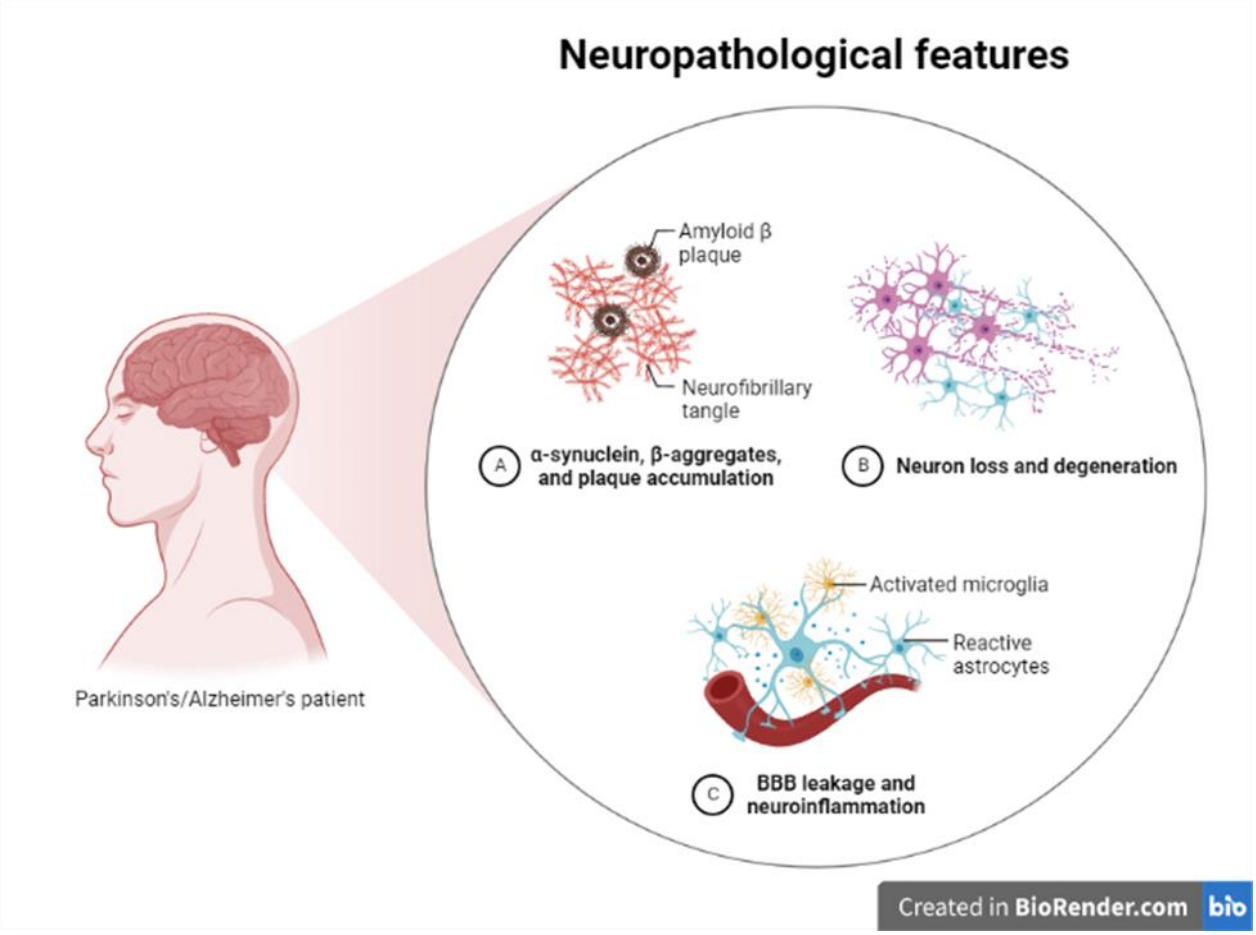
ABSTRACT:

If we see our today's society the high level of anxiety, psychological stress and defective life style with wrong routine are now one of the major causes of neurodegenerative diseases. Instead of stress, anxiety & defective lifestyle increasing age and heredity are also important contributors. Many researches have been done in this field & also there are many allopathic preparations available to treat these disorders, neurodegenerative diseases are a big burden for our society. Two of the main neurodegenerative disorders are Alzheimer's disease and Parkinson's disease that have a significant socioeconomic impact. As we know that there is no any permanent treatment for these problems in allopathic system of medicine. These drugs can modify the symptoms but cannot provide the permanent cure. In other words, we can say that these agents don't work on the root cause of the problem. For many years, people have looked to natural herbs as a possible treatment for neurodegenerative diseases.

Key words: Oxidative stress, Neurodegeneration, Parkinson's disease, Neuroprotective, Apoptosis

1. INTRODUCTION:

In today's scenario many allopathic preparations are available to treat neurodegenerative disorders they can enhance the level of important biological amines in our brain and provides relief for example levodopa given in Parkinson's disease increases the level of dopamine. Chlorpromazine, haloperidol etc. are used to treat psychotic disorders. Similarly, imipramine, citalopram, sertraline etc. are used to treat depression and mental illness. Allopathic preparations are fast working agents but they also have their associated side effects. Now world is looking for herbal preparations with least side effects. As we know that neurodegenerative disorders are very common in today's society. Today's life style & stressful environment is also playing an important role. Overload of free radicals, lack of antioxidants & some genetic factors are also important key players. Many allopathic remedies are available but they have their own side effects. Many herbal drugs have a potential to treat the neurodegeneration without causing serious side effects. A large population is interested & continuously searching for such herbal remedies, but in absence of correct information they can't access the utility of these herbs. In neurodegenerative disorders there is degeneration of neurons or deficiency of neurotransmitters. Common herbs which help in neurodegeneration are Gooseberry, ginger, ocimum, turmeric, etc. Ginger & ocimum are potent acetyl cholinesterase inhibitors hence they improve learning & memory. These herbs are very helpful in dementia & Alzheimer's disease. There have been reports of numerous natural remedies, especially plant extracts, being utilised in conventional medicine for neuroprotective, memory-improving, and antiageing purposes. There are many examples of plants which have neuroprotective properties. For example, turmeric is an easily available plant if we consume raw turmeric then it is more beneficial for us. It prevents neuronal inflammation, and is an excellent antioxidant. Golden milk is the milk mixed with raw turmeric is a well-known drink full of many health benefits. Similarly ginger which is very easily available in our kitchen has a good neuroprotective property it promotes the function of acetylcholine which is responsible for learning and memory. The main objective of this review article is to give a short synopsis of a number of neurodegenerative disorders, the pathogenesis involved in the disease & their possible treatment with herbal drugs. [1]



1.1 Epidemiology of Neurological disorder

In India, the percentage of DALYs (disability-adjusted life years) attributable to non-communicable neurological illnesses doubled from 4 % in 1990 to 8 % in 2019, whereas the percentage attributable to neurological disorders brought on by injuries rose from 0.2 % to 0.6%. It is important to note that in the same time period, the contribution of communicable neurological illnesses fell from 4 to 1%. In India in 2019, stroke accounted for 37.9% of all DALYs associated with neurological disorders, followed by encephalitis (5.3%), cerebral palsy (5.7%), headache related issue's (17.5%), and epilepsy (11.3%). Crude DALY rates for certain neurological diseases in 2019 varied greatly amongst the states. In 2019, men were more likely than women to suffer from traumatic brain injuries and migraines, as well as multiple sclerosis. In children under the age of five, communicable diseases accounted for the majority of all DALYs associated neurological disorders, but in all other age groups, non-communicable neurological illnesses were the primary culprit. The main risk factors included high body mass index, high fasting plasma glucose, high dietary risks, and high systolic blood pressure.

Low birth weight, short gestation, and air pollution were the recognised risk factors for communicable illnesses, all of which had only minor contributions to DALYs.

The India State-Level disease Burden Initiative released the first comprehensive studies of the sickness burden brought on by neurological conditions and their tendency in each Indian state on July 14, 2021, in the Lancet Global Health. These neurological conditions include infectious and non-infectious as well as injury-related neurological conditions. Between 1990 and 2019, the share of non-communicable and injury-related neurological diseases more than doubled in India's overall disease burden, whereas the proportion of communicable neurological disorders decreased by 75%. In all other age groups, non-communicable neurological illnesses made the largest contribution; however, communicable diseases made up the majority of the load of neurological disorders in children under the age of five. Epilepsy, a variety of headache problems, and stroke are the leading causes of neurological ailments in India. Brain stroke caused approximately 699,000 deaths in India in 2019, accounting for 7.4% of all fatalities. Numerous neurological problems carry varying degrees of burden among the states, which has a big impact on the policies and initiatives designed to lessen this burden. Hypertension, hyperlipidemia, automobile fumes, exposure to heavy metals, psychological stress, bad eating habits can acts as a trigger agents in the pathogenesis of neuronal diseases. [2]

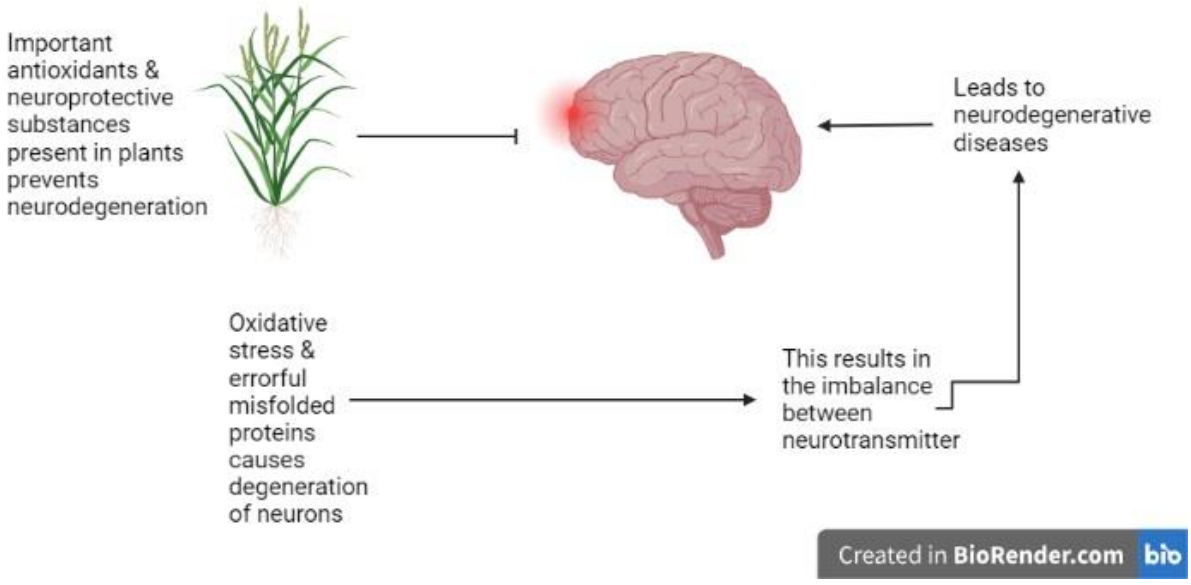


Diagram showing use of herbal remedies to treat neurological diseases

1.2 Common pathophysiological indicators of the death of neurons

1.2.1 Aggregation and Misfolding of Proteins

Proteins need to keep their three-dimensional structure in order to operate effectively in the biological system. Polypeptide chains arrange themselves into this three-dimensional form through a process called protein folding. The right three-dimensional structure of the protein, which is based on the amino acid sequence, is crucial to its optimal operation. However, mistakes in this complex, sequential process, known as protein misfolding, might cause the protein to adopt an aberrant structure. Misfolded proteins are unable to revert to their original structure, lose their normal activity, and in some cases turn harmful. As we age, misfolded conformation aggregates slowly build up because they can be produced spontaneously at low rates throughout life. We can observe the beta amyloid deposition in the brain of the patients suffering from neurodegenerative disease like Alzheimer's after death of the patient. The brain's amyloid deposits, which are formed by these aggregates, are identifiable and observable structures. Additionally, a mutation of some kind raises the possibility of protein misfolding, which occurs in genetic or familial cases of neurodegenerative disorders. [3]

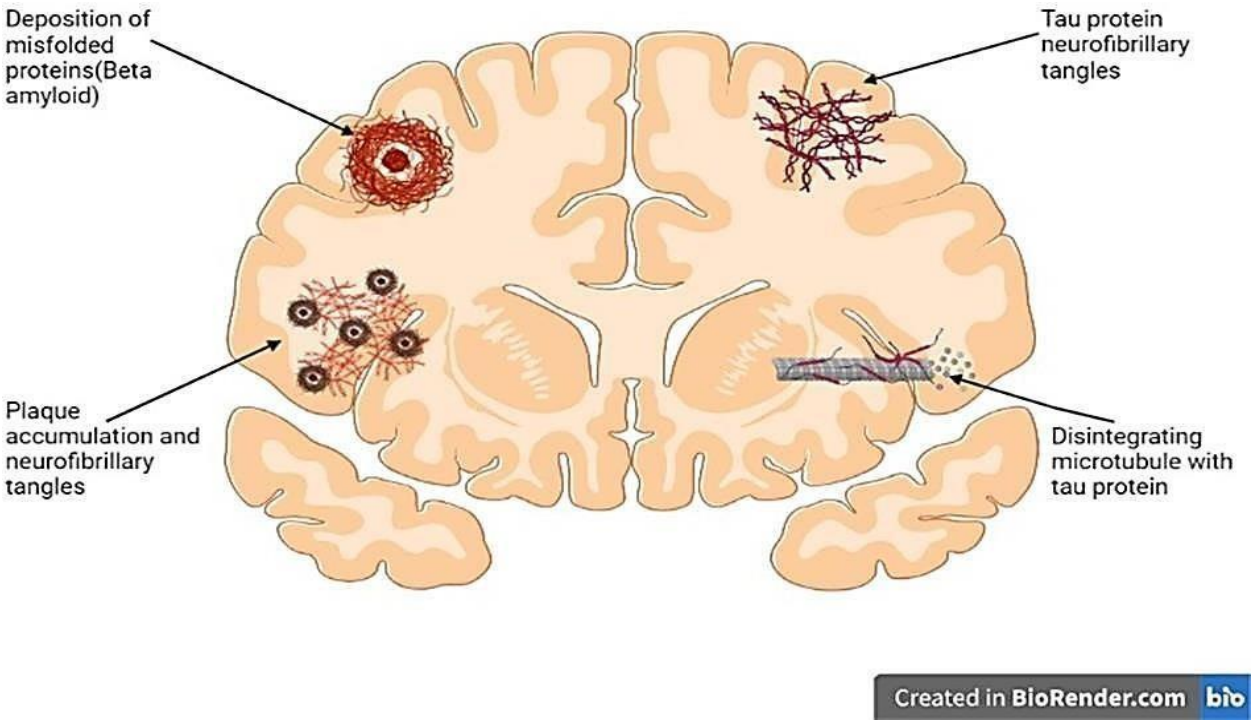


Diagram showing deposition of misfolded defective proteins in brain

1.2.2 Oxidative stress and neurodegenerative diseases

An imbalance between oxidants and antioxidants in a biological system leads to oxidative stress. This imbalance is due to excess of free radicals and deficiency of strong cellular antioxidants. It is also understood that oxidative stress has a significant pathogenic role in various neurodegenerative disorders. Excess of oxidants causes malfunctioning of mitochondria, due to which cellular energy production decreases which is also related with the cell injury. Due to mitochondrial damage, ATP production in the cell decreases & it affects the normal functioning of sodium potassium pumps of the cell. Numerous neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, have been linked to the advancement of oxidative stress. As we know that lipids are very necessary for the normal cellular architecture and functioning, damage to lipids, proteins, and DNA due to process of oxidation are responsible for many neuronal complications. Through a number of various methods, including the deactivation of crucial functions or the up regulation of harmful cascades, this damage can cause cell death.

If we take example of nervous tissue it leads to neurodegeneration. Proteomic and oxidative stress investigations of HD-related human brain tissues show that oxidative stress and damage to certain important macromolecules are responsible for the pathogenesis of neuronal diseases. [4]

1.2.3 Mitochondrial malfunction & neuroinflammation in neurodegeneration

Many researches are in support that poor energy metabolism and oxidative damage is linked to Alzheimer's disease. Neuroinflammation is also a characteristic feature of patients suffering from Alzheimer’s disease. The post-mortem analysis of the brain of the patients has proven this concept. In addition to other changes, Alzheimer's disease brains exhibit an average 50% loss in mitochondrial RNA content, which is expected to lower oxidative phosphorylation. Numerous biochemical, genetic, and clinical aspects of sporadic Alzheimer's disease could be explained by the mitochondrial cascade hypothesis, which has recently undergone an upgrade. In the Alzheimer's brain, a significant rise in oxidative damage to mitochondrial DNA may result in aberrant mitochondrial dynamics and malfunction, which ultimately harm cholinergic neurons. Deposition of defective beta amyloid protein helps in the development of transition pore in the mitochondria of the cell. When there is any change in the normal physiology of the mitochondria due to various noxious stimuli these pores open and important solutes go outside from the mitochondria. In transgenic models of Alzheimer's disease, amyloid beta (Aβ) induced mitochondrial dysfunction occurs early and sets off the pathogenesis of AD. [5]

1.2.4 Increased rate of apoptosis & neuroinflammation in neurodegeneration

Both physically and pathologically, apoptosis occurs in the neurons. It happens naturally as a homeostatic mechanism to maintain cell population during the developmental process and is essential for the growth and maturity of the nervous system. DNA fragmentation, proteolysis, shrinkage of the cell and an increase in calcium in the cytosol are related to apoptosis.

There is increased rate of apoptosis is observed in neurodegenerative diseases, brain samples of the patients after death are analysed and approves the theory. According to the type and intensity of the stress, neurons can die in a variety of ways. The nature, timing, and precise reasons of neuronal destruction in NDDs, as well as their connections to fundamental processes, are still up for debate. Programmed cell death (apoptosis) is divided into three main categories based on various morphologic criteria and biochemical characteristics: apoptosis, autophagy, and necrosis. Common morphological changes that occur in apoptosis due to activation of caspase are reduction in cell size, breakdown of genetic material and increased phagocytosis by adjacent cells. Neuroinflammation is an important feature of the neurodegenerative disorders. Due to activity of microglia and astrocyte cells which are the macrophages of the brain tissue. Neuroinflammation typically occurs as a result of CNS damage, infection, toxins, or autoimmune. While transient neuroinflammatory signaling is protective during development and tissue repair after injury, chronic neuroinflammation is linked to the progression of neurodegenerative diseases. Microglia, the CNS's resident immune cells, are principally responsible internalize misfolded proteins to aid their clearance, however in neurodegenerative disease states, this process is deregulated, resulting in for pathological neuroinflammation linked with dementia. [6]

Some common neurodegenerative disorders

1. Alzheimer’s disease

Alzheimer's disease is a common neurodegenerative disease (AD). It is an untreatable disease of cognition and behaviour that impairs social and professional activities and is also the main reason for older people being institutionalised. Alzheimer's disease is a brain condition that gradually impairs thinking and memory abilities as well as the capacity to perform daily routine of the life for example the patient forgets that what the use of toothbrush is. The majority of patients with the disease initially experience symptoms in their mid-60s. Sometimes it is observed that in some individual’s symptoms of Alzheimer’s disease start between 35-60 years. The most common cause of dementia in older peoples is Alzheimer’s disease. In the initial phase of the disease only memory related issues are observed. When the disease is in advanced stage there are personality changes, slight depression and reduced sensory & motor functions. AD often begins at the age of 65, and the risk from this age increases by 50% every five years. As a result, it has been hypothesised that the risk of AD increases to 20–40% for those who live into their eighties, depending on a number of variables like population dynamics and geography. As the world's population ages and the economy grows, the number of people with NDs and the associated dementia increases. There has been a major increase in scientific interest in the search for novel therapeutic agents for the prevention of such type of these diseases Neurofibrillary tangles and senile plaques are the two main lesions formed by the pathophysiological alterations in Alzheimer's disease. Accumulation of hyper phosphorylated tau protein is responsible for the formation of neurofibrillary tangles. Production of senile plaques inside the brain is due to accumulation of defective proteins called beta amyloid. According to studies the initiation of Alzheimer’s disease takes place by the excess of free radicals, neuroinflammation & deposition of defective proteins in the form of beta amyloid all these events collectively cause neurotoxicity.

It is now clear that the impairment of learning & memory activities in the Alzheimer's disease is due to abnormalities in the cholinergic system which is due to deposition of defective abnormal proteins inside the brain.[7]

2. Parkinson's disease

A complex neuronal disease is named after its discoverer James Parkinson. The disease is characterized by continuous tremors, rigidity or inflexibility; decreased movements which are hypokinesia, sialorrhea that is excessive salivation, due to excess of acetylcholine, expression less face, and disturbed handwriting. Also, there is postural instability and postural hypotension, little depression insomnia and behavioral changes are also present in many patients. If we consider the pathogenesis of the Parkinson's disease then we find this conclusion that is oxidative stress due to excessive free radical generation and deposition of misfolded proteins inside the brain are the root cause behind the problem. There is malfunctioning of mitochondrial dysfunction and we know that the mitochondria are very necessary cell organelle. If we see the present scenario then we find that still no any medicine has been discovered that can abolish the root cause of the disease. Antioxidants like polyphenols, curcumin and glutathione can improve the condition by reducing the free radical load. If we talk about the levodopa then we can conclude that it can only provide the symptomatic relief with a number of side effects.[8] The Parkinson's disease is also an age-related neurodegenerative disease, and it has serious effects on quality of life as well as financial costs associated with patient care. About 1% of people over the age of sixty have PD, which is mostly a mobility issue as opposed to Alzheimer's in which primarily learning & memory is impaired. Rigidity, hypokinesia, uncoordinated gait, bent posture, sialorrhea, hypomimia, micrographia, is some of its characteristic symptoms. In Parkinson's disease there is degeneration of dopaminergic neurons in the substantia nigra corpus striatum region of the brain. The disease is associated with non-motor disorders like dementia because neurodegeneration is not just confined to the basal ganglia. It has long been known that PD and neuronal cell oxidative damage are related. For instance, it has been demonstrated that the autoxidative breakdown of dopamine due to presence of oxidants is also responsible for the depletion of dopamine in the brain. [9]

3. Motor neuron disease

An adult-onset neurodegenerative condition called motor neuron disease (MND) causes respiratory, bulbar, and limb muscles to gradually weaken. Respiratory failure is the most frequent cause of death, which often happens three to five years later. The disease begins in the mid age of the life. Increasing age, male sex, and the inheritance of a genetic vulnerability are the risk factors in the development of the MND, while other factors like exercise are still being studied. Ninety % of motor disease's disease cases are episodic. Inheritance is used for the balance. Motor neuron disease in families is typically autosomal dominant. Super oxide dismutase is an antioxidant enzyme present in the brain & mutation in the gene which codes for this enzyme is responsible for the development of this disease in approx. 20% patients. [10]

Three different disease types—amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA), and primary lateral sclerosis—are called collectively as motor neuron disease. Amyotrophic lateral sclerosis, affects upper and lower motor neurons, and is the most prevalent. Although certain upper motor neuron symptoms may appear later in the disease, progressive muscular atrophy is mostly a lower motor neuron disease. The rarest MND variant is primary lateral sclerosis (PLS). A variant of ALS known as progressive bulbar palsy, which primarily affects Lower motor neurons. Patients with progressive bulbar palsy initially only experience speech and swallowing difficulties due to muscle weakness. The diagnosis of MND is done clinically in the absence of a conclusive diagnostic test. Consideration of other diagnosis should be given to weakness that is abnormal or out of proportion to wasting. [11]

4. Huntington's disease

This is a neurodegenerative disease which occurs due to mutation in the huntingtin gene. The gene is responsible for the expression of HTT protein. Making of the protein huntingtin is guided by the HTT gene. Although its precise function is uncertain, this protein appears to be crucial for normal prenatal development and appears to play a significant role in brain nerve cells. Many bodily tissues contain huntingtin, but the brain is where it is most active. [12] This protein may participate in signalling process of the cell, movement of some substances in the cell, binding of certain proteins, and protects the cell against apoptosis or cell death. Certain studies suggest that it helps to restore the damaged genetic material (DNA). Huntington's disease is due to an abnormality in this gene & that anomaly is the repeats of the base pairs that are cytosine, adenine & guanine called CAG nucleotide. The nucleotides cytosine, adenine, and guanine are repeated several times in a row in this section. In the huntingtin gene the CAG section is an average repeated 20 times. [13] In the European population this anomaly in Huntington's gene is much higher as compared to the population of East Asia. Mutation in huntingtin gene is responsible for neuronal dysfunction and loss at the cellular level via a number of mechanisms, including the impairment of protein homeostasis, transcription, and cellular functions. The mutant protein also shows cellular toxicity. As we know that no any pharmacological treatment is available in the world that can treat the disease or make improvement in the symptoms. Only non-pharmacological treatments like patient counselling or other supportive ways can improve the quality of life to a little extent. As compared to past few decades now we can understand the pathological and macroscopic changes that take place in patient's brain. Scientists are in continuous search of new lead molecules to treat this serious disease. As we know that the disease is due to mutation in the huntingtin gene the most appropriate option of the treatment is to make changes in the mutant gene by antisense codon treatment method. Scientists from whole world are continuously trying for this. [14]

Table:1 Important neuroprotective plant's their constituents & neuroprotective mechanism.

S. No	Plant name	Chemical constituents	Neuroprotective mechanism
1	*Curcuma longa*	Curcumin	Protects against synaptic dysfunction. Curcumin has antidepressant properties through controlling serotonin and dopamine release. The level of neurotrophic factors like brain derived neurotrophic factor is increased by curcumin. (Kulkarni et al., 2010).
2	*Ginkgo biloba*	Bilobolide,Ginkgolide, Kaemferal, Quercetin, Stigmasterol	Prevents neuronal atrophy and cell death in hippocampus Acts as a free radical scavenger, Protects neurons against oxidative damage and apoptosis due to ageing process, cerebral ischemia, and neurodegenerative diseases. Prevents beta amyloid deposition in the brain. (Brondino N et al.,2018)
3	*Zingiber officinalis*	Gingerol, Shogaol, Zingerone	Increases the level of acetylcholine in brain. Acts as blood thinner, lowers cholesterol, antioxidant and anti-inflammatory in nature. (Summya et al., 2016)
4	*Ilex Paraguariensis*	Chlorogenic acid, caffeine, theophylline, theobromine, quercetin	Useful in dementia. Cause inhibition of AChE. Antiepileptic (Pamela M. Bortoli et al.,2018)
5	*Centella asiatica*	Asiticoside, centeloside, Madecassoside, Asiatic acid	Brain tonic, antianxiety in nature, used as memory enhancer neuroprotective, prevent beta amyloid plaque formation in brain, reduces oxidative stress & dopamine neurotoxicity in Parkinson's disease. (Mahmud Tareq et al.,2012)
6	*Glycyrrhiza glabra*	Glycyrrhizin, glabridin	Improves learning & memory. Malonyl dialdehyde which is harmful for brain is lowered by glabridin, while levels of two endogenous antioxidants, superoxide dismutase and reduced glutathione, were

			increased. Decreases apoptosis in neurons. (Xue-QingYu et al., 2007)
7	*Acorus calamus*	Asarone	Sedative, improves memory power & intellect. At a dosage of 200 g/mL, the plant shows the property of acetylcholinesterase enzyme inhibition (Pulok kumar et al., 2008)
8	*Emblica officinalis*	Vitamin-c, phyllembin	Improves acetylcholine levels, memory enhancer. Acts as powerful antioxidant (Ramakrishna.V et al., 2014)
9	*Corydalis ternata*	Protropene	Anticholinesterase, anti- amnesic Inhibits acetylcholinesterase activity and amyloid- aggregation, which are important dementia indicators, are inhibited by coptisine and berberine. (Yu Jin Kim et al., 2017)
10	*Uncaria rhyncophylla*	Rhyncophylline, Corynoxine	Prevents ischemia induced neuronal loss It has been demonstrated that Uncaria rhynchophylla is efficient at preventing the production of A fibrils, performing A fibril disassembly, and inhibiting antiacetylcholinesterase. (Yan-Fang Xian et al., 2012)
11	*Bacoppa* monnieri	Bacoside A, Bacoside B, Beta sitostrol,Cucurbitacin	The plant is anti-oxidant, neuroprotective, inhibits acetylcholinesterase and activates choline acetyltransferase, decreases amyloid, increases cerebral blood flow, and modifies neurotransmitters like acetylcholine, 5-HT, and dopamine. (Sebastian Aguiar et al., 2013)
12	*Panax ginseng*	Ginsenoside Rg1, Ginsenoside Rb1, Dammarane, Ginsenoside Rd, Panaxatriol	Neuroprotective, Prevents neuronal inflammation & beta amyloid aggregation in the brain. Potent antioxidant (Jing Li et al., 2021)
13	*Crocus sativus*	Carotenoids, α-crocetin and glycoside crocin and picrocrocin, the aglyconesafranal the antioxidant carotenoids lycopene, zeaxanthin and vitamin B_2.	Crocin prevents beta amyloid deposition & acts as antioxidant,reduces oxidative stress (John.W.Finley et al., 2017)
14	*Terminalia chebula*	Chebulic acid,chebulinic acid,galic acid,elagic acid	Antioxidative reduces free radicals, prevents beta amyloid deposition in brain

			(Mohamed Asik Raj Mohamed et al., 2017)
15	*Calendulla officinalis*	Flavonoids, triterpenoids, essential oils.	Antioxidant prevents oxidative damage of neurons (Ali Esmail Al-Snafi 2021)
16	*Coriandrum sativum*	Linalool, geraniol, borneol, myristyl aldehyde etc.	Antianxiety agent, potentiate the action of GABA (Jun Sakurai et al., 2019)
17	*Cyperus rotundus*	α-Cyperone, myrtenol caryophyllene oxide and β-pinene	Prevents oxidative stress & acetylcholinesterase activity (Chatchada Sutalangka et al., 2017)
18	*Dalbergia sissoo*	Dalberginone, dalbergin, phenylchromine, dalbergichromine etc.	Prevents beta amyloid deposition & oxidative stress (Shikha Raheja et al., 2021)
19	*Tinosporia cardiofolia*	Tinosporide, tinosporine, giloinsterol, betasitosterol etc.	Prevents degeneration of neurons Induced by glutamate (A.Sharma 2018)
20	*Andrographis paniculata*	Andrographolide,14deoxyandrographolide Neoandrographolide, andrograpanin, isoandrographolide	The plant shows anti-inflammatory activity in neurodegenerative disorders. (Li Tao et al., 2018)
21	*Nigella sativa*	Thymoquinone, carvacrol, ecosadienoic acid, myristic acid etc.	Improves learning and memory by reducing acetylcholinesterase enzyme activity and oxidative stress. (Md.Reza Khajdair et al., 2019)
22	*Ferula assafoetida*	Ferulic acid, coumarin, sesquiterpene, glucuronic acid etc.	Acetylcholinesterase and monoamine oxidase B (MAO-B) are inhibited. Antiepileptic in nature. (Md.Reza Khajdair et al., 2019)
23	*Salvia officinalis*	Caryophyllene, Eucalyptol, borneol, etc.	Inhibit acetylcholine esterase in brain, improves cognitive performance, anti-inflammatory (Marcello Irti et al., 2010)
24	*Coffea arabica*	Caffeine (methylxanthine)	Methylxanthines, which function as adenosine-receptor antagonists and adenosine $A2_A$ receptor antagonists, may

			help to postpone or prevent the beginning of AD. (Marcello Irti et al., 2010)
25	*Ocimum sanctum*	Oleanolic acid, Ursolic acid, Eugenol, Carvacrol, Rosemarinic acid Linalool, beta sitosterol & βcaryophyllene	Helpful in epilepsy because it facilitates GABAergic neurotransmission, Prevents AChE hence improves acetylcholine. (Mohamed Ali Sayed et al., 2021)

Biomolecules helpful in the management of neurodegeneration

1. Polyphenols

These are well known antioxidants that protect our body from oxidative stress. It is proved from different studies that a naturally occurring polyphenol, resveratrol is a powerful antioxidant. Resveratrol shows its antioxidant action by reducing the amount of free radicals & highly reactive superoxide ions which harms the human brain. In a similar manner, quercetin has demonstrated defence against oxidative stress and associated diseases. Quercetin participates in numerous signalling pathways to lessen oxidative stress and display pharmacological effects in a range of cell and disease types. [15] Several studies have found that drinking green tea, which is high in polyphenols, and its main ingredient, epigallocatechin-3-gallate (EGCG), can reduce oxidative stress. In diverse disease models, other polyphenols such puerarin, baicalin, and phlorizin also reduced oxidative stress. Now we have significant clinical evidences that polyphenols are potential antioxidants as well as neuroprotective. Polyphenols decreases atheroma formation & neuroinflammation it also controls the high level of low-density lipoproteins. Fruit extracts with high polyphenol content have been demonstrated to inhibit ROS and free radicals. Bilberry juice high in polyphenols can be used as potent antioxidant and anti-inflammatory. An extensive clinical investigation found that consuming polyphenols in diet, improves memory and slow down the ageing process of the brain. Consumption of polyphenols reduces the risk of Alzheimer's disease as it reduces plasma homocysteine which is a risk factor for the development of AD pathogenesis. [16] In conclusion, polyphenols are potent antioxidants and are neuroprotective in nature. By using polyphenols, we can reduce the risk of neurodegenerative diseases in our society.

2. Flavonoids

Flavonoids are diverse plant pigments, present in a wide range of foods, including fruits, green vegetables, dry fruits, and many natural drinks. They are commonly present in human diet and have a variety of biological effects, as anti-inflammatory, anti-cancer, and anti-viral properties. Flavonoids might be one of the safest non-immunogenic chemicals. Flavonoids are very small chemical molecules that are easily absorbed by the human body for a long time. [17] Recent molecular techniques of investigations enable us in the identification of particular flavonoids having many biological features with good pharmacological effect on humans. The ability of flavonoids to modify neuronal activity and to prevent neurodegeneration has recently attracted a lot of attention.

Studies on animal and human dietary supplementation with flavonoid-rich plant or food extracts have revealed benefits in cognition function, which may be due to the protection of susceptible neurons, the enhancement of current neuronal function, or the stimulation of neuronal regeneration. [18]. Their capacity for neuroprotection has been established in models of oxidative stress and amyloid beta-induced neuronal death. Ginkgo biloba extract which is rich in flavonoids is a good neuroprotective agent. Individual flavonoids, like the citrus flavanone tangeretin, have also been shown to maintain the nigro-striatal working after 6-hydroxydopamine administration, indicating that they may act as potential neuroprotective agents against Parkinson's disease. Additionally, flavonoids might improve memory, shield against age-related cognitive deficits, and even reverse some age-related reductions. Flavonoids & other polyphenols have an ability to maintain the signaling process of the central nervous system. They also have an ability to prevent neuroinflammation. [19] Flavonoids are significant constituents of fruits, green vegetables, and beverages like wine, tea, chocolate, and fruit juices. Three carbon atoms connect the two aromatic rings that make up the most common structure of flavonoids to create an oxygenated heterocyclic ring. [20] According to a recent study a plant *Adenium obesum* which is of Apocynaceae family & rich in flavonoids is also neuroprotective in nature and helpful in the treatment of Parkinsons disease and depression.

3. Terpenoids

Terpenoids are flammable substances that give plants and flowers their aroma. They are widely dispersed in higher plants like eucalyptus, citrus, and conifers as well as in the leaves and fruits of those plants. Terpenes are the substances that were derived from terpentine, a volatile liquid obtained from pine trees.[21] Terpenoids are abundantly found in a variety of creatures, including plants, animals, marine organisms, fungus, sedimentary rocks, and oils that are frequently referred to as "terpenes." Terpenoids are a vast class of chemicals with a wide range of powerful biological functions, including the creation of biological membranes, signal transduction in biological system, anti-inflammatory, potent antioxidant etc.

Terpenoids and their semi-synthetic derivatives could be effective in neuroprotective treatments for a variety of neurological and cognitive disorders. After long research it can be concluded that they are an efficient neuroprotective agent. Some best examples are ginsenosides, ursolic acid oleanolic acid, cerastrol, asiatic acid, erythrodiol, which can be used to treat neuroinflammation and oxidative stress. Many others, such as lupeol, rosemarinic acid, resveratrol, betulinic acid, maslinic acid, uvaol, tormentic acid, and erythrodiol, have also gained attention recently. These substances can appear as free substances, conjugates, or saponins and are found in higher plants, including popular food and nonedible plants. These terpenoids have been used as an efficient & very safe drugs to enhance learning, memory & cognitive function in traditional medicine for many years and are very useful to combat with Alzheimer’s and other neurological diseases. Plants, bacteria, fungi, animals, marine life, sedimentary rocks and oils are just a few of the many different types of organisms that contain terpenoids. These molecules, sometimes referred to as "terpenes," are biosynthesized natural chemicals with a range of structural traits.

These chemicals are present in higher plants, including edible and non-edible species, and can take the form of free substances, conjugates, or saponins. These terpenoids have been used for a very long time in conventional medicine to boost up the memory. They have different structures and functions, which has stimulated research into their commercial application and highlighted their value as additional treatments for psychiatric illnesses.[22] Terpenoids can cross the blood brain barrier to show their neuroprotective Effects. The BBB maintains the balance of the central nervous system and stop unwanted substances to go inside the brain. Ginkgo and skullcap are some important plants having terpenoid and have very good neuroprotective properties. Their chemical makeup may reflect how they behave biologically. The popular herbal drug ginseng, also known as Panax ginseng, may have neuroprotective properties. The primary terpenoid in ginseng, ginsenoside Rb1, has been discovered as one of the plant's most potent active ingredients [23]. Ginsenoside Rg1 has been shown to have protective effects on BBB. Ginkgo biloba is a well-liked herbal remedy having anti-inflammatory, antioxidant, and good for vascular system. Ginkgo is widely known for its neuroprotective qualities reduce cerebral oedema after brain injury [24].

4. Alkaloids

A large class of naturally occurring substances called alkaloids typically comprise oxygen, nitrogen, carbon, and hydrogen. Alkaloids may have an impact on the central nervous system (CNS), which includes the brain and spinal cords nerve cells, which regulate several direct bodily processes and behaviour. They may also have an impact on the autonomic nervous system, which controls respiration, heartbeat, circulation, and internal organ function. The hallucinating substance Lysergic acid diethylamide and the fungal alkaloids ergine and psilocybin are also an example of alkaloids. These alkaloids could obstruct or conflict with serotonin's function in the brain. The principal mechanism of action of ergot alkaloids was formerly believed to be their notable effects on blood flow.

Tropane alkaloids like atropine, hyoscyamine present in Datura plant has an effect on the central nervous. A powerful analgesic and narcotic, alkaloid like morphine is obtained from the plant *Papaver somniferum*. Gamma amino butyric acid levels rise in the brain's synapses as a result when morphine's binds with its opioid receptors in the brain. Vinpocetine is a highly effective vasodilator that is an alkaloid derived from plant *Vinca minor*. [25] The effects of hypoxia and ischemia may be mitigated by the use of vinpocetine because it improves cerebral circulation & glucose uptake from neuronal cells. The plants like *Narcissus tazetta*, Galanthus *nivalis*, and *Leucojum aestivum* naturally contain galantamine which is an alkaloid. Galantamine is a drug used to treat amnesia & it improves the memory power. The medication can also activate nicotinic receptors to improve cognition and memory. It is a member of the pharmacological class known as cholinesterase inhibitors. [26]

5. Fatty acids

Polyunsaturated fatty acids and monounsaturated fatty acids have a therapeutic role in the neuroprotection & maintenance of cognitive ability in humans. The majority of research has been on the nuts containing n23 and n26 omega-3 and omega- 6 polyunsaturated fatty acids.

Numerous studies have demonstrated that n23 fatty acid-deficient diets will decrease cognitive performance. In order for neurons to communicate with other cells, they need to have normal anchor receptors, ion channels, and the ability to release and reabsorb unmetabolized neurotransmitters. These requirements are all dependent on the structure of the cell. The neuronal membrane's fatty acid content affects these characteristics. While essential fatty acids have been proven to promote membrane integrity, it has been shown that the fatty acid composition of neuronal membranes diminishes with age. In addition to affecting the biophysical properties of membranes, PUFAs which are present in the form of phospholipids in neuronal membranes can directly participate in neuronal signalling to promote overall neuronal health & function.[27]

6. Some other chemical substances which are neuroprotective in nature

Sulforaphane

Cruciferous vegetables like cauliflower are very rich in a neuroprotective substance known as sulforaphane (SFN). In cruciferous plants there is present a chemical called glucoraphanin which acts as an initial molecule in the synthesis of sulforaphane. Sulforaphane's potential to lessen the incidence of different cancers and the harm caused by various types of oxidative stress has been the subject of extensive research. However, SFN has very potent antioxidant and anti-inflammatory properties that enable it to significantly reduce cytotoxicity in the nervous system, with seemingly very little of its own toxicity within the therapeutic range. Although there haven't been many human studies on the protective effects of SFN on the nervous system, they do exist. Many researches are in support that numerous prevalent, disabling disorders of the central nervous system, such as Alzheimer's disease, Parkinson's disease, epilepsy, stroke, and others, may be treated with SFN supplementation. Sulforaphane has been shown in numerous studies to have neuroprotective benefits in animal models of both acute and chronic neurodegenerative diseases. Sulforaphane treatment in a rodent stroke model decreased brain damage and brain swelling. Because Sulforaphane possess good antioxidant properties it prevents damage of dopamine secreting neurons. It also reduces the harm of neuronal mitochondria from various oxidative stresses. [28]

Hypericin and pseudo hypericin

Hypericin and pseudo hypericin, two naphthodianthrones, are the main constituents of the plant *Hypericum perforatum*. Both hypericin and pseudo hypericin have antidepressant properties. It is also an antioxidant & anti-inflammatory. [29]

Honey

Honey is a natural & marvellous sweet substance produced by honey bees. From ancient time it is well established that honey has a great medicinal value. It acts as a good antioxidant, antimicrobial & anti-inflammatory agent. Honey is very rich in antioxidant compounds like flavonoids & phenols, many vitamins.

Additionally, the synergistic impact of various bioactive substances in honey may potentially be a factor in honey's ability to protect against neurodegeneration. [30] Various important constituents, of honey such as polyphenols, possess neuroprotective effects by lowering oxidative stress and reducing neuroinflammation. Honey is a good memory enhancer and prevents the process of neurodegeneration. It also prevents apoptosis in the neuronal cells & maintains the integrity of neurons. It also protects the brain from ischemia caused by under perfusion of brain tissues. Honey has a protective role on the hippocampus of the brain that's why honey can improves learning and memory. In short, we can say that honey is a very rich in antioxidants, important vitamins, minerals hence it is a very potent neuroprotective agent. [31]

Resveratrol

Resveratrol is a potent antioxidant & anti-inflammatory agent and is helpful in the management of various diseases. It can combat with many neurological diseases like Parkinson's & Alzheimer's disease. Resveratrol can overcome the problem of cerebral ischemia as in case of ischemic stroke which can cause irreversible cell injury to neurons. It has a protective effect in neurological diseases. Resveratrol supplementation over an extended period of time may help protect against cognitive decline and oxidative stress brought on by streptozotocin intra-cerebroventricular injection. It has been demonstrated that resveratrol prevents the development and growth of amyloid fibrils and weakens already formed amyloid fibrils. Resveratrol may also lessen amyloid secretion from several cell lines. Resveratrol was demonstrated to lessen neurodegeneration in the hippocampus and prevent cognitive impairment and beta amyloid deposition which is an important feature of Alzheimer's disease. Red grapes contain a significant amount of the phytochemical resveratrol, which has antioxidant properties. Recent research has however demonstrated that resveratrol enters the brain quickly after peripheral treatment and can save nerve cells in the central nervous system from ischemic & hypoxic cell injury. Resveratrol supplementation prevents harm of ischemic stroke to spinal cord & brain. It can protect neurons against nitric oxide induced oxidative damage. Similar to this, resveratrol shields the dopaminergic neurons in the midbrain from oxidative and metabolic stress. [32]

Garlic

Since ancient times, garlic has been utilised all over the world for its numerous health advantages. Garlic and its preparations help in reducing the risk of cardiovascular diseases, stroke, and malignancies. Recent studies are beginning to show that garlic and its compounds have positive impacts on neuronal functions. More than a thousand studies have been published in the last ten years alone on the health advantages of garlic. Based on its powerful and diverse effects, it is regarded as one of the finest meals for illness prevention. The risk factors involve in neuronal insufficiency are raised cholesterol, hypertension, increased aggregation of platelets.

Garlic has a role in fighting with these situations.[33] Garlic preparations also reduces the raised level of protein homocysteine which is harmful for our body as it damages arteries and promotes blood clotting hence is a risk factor for cardiovascular disorders. These risk factors have a significant impact on atherosclerosis, which causes both cardiovascular and cerebrovascular disease. The hypolipidemic and anti-platelet properties of garlic are its best-known benefits. Garlic is a good antioxidant and reduces oxidative stress which is one of the etiological factors involved in the neurodegenerative disorders. As we know that numerous neurodegenerative cascades start due to an excess of free radicals weather it is due to psychological stress or due a disturbance in the metabolic pathways of the body. Garlic is a well-known antioxidant and is the killer of oxidative stress. S-Allyl cysteine is an important chemical constituent present in the garlic which acts as a neuroprotective agent and prevents the deposition of misfolded erroneous proteins which are called beta amyloid in our brain. Aged (old) garlic extract has the potential to improve human health. The most prevalent element in old garlic extract is SAC, an organosulfur molecule that is water soluble. S-allyl cysteine has been shown in studies to have neuroprotective properties against neurodegeneration and neuroinflammation. [34]

Rosehip

In all the rose flowers below the petals a slight spherical structure is present which contains the seed of rose and is known as rose hip. Rose hip is a good antioxidant & very rich in vitamin C. Other constituents are ellagic acid, quercetin, catechins, lycopene & beta carotene. Now a day many antiarthritic preparations contain rosehip because it prevents the degeneration of cartilages and acts as a lubricant for the joints. It is also helpful in the management of cancer, diabetes & hyperlipidaemia. As we know that hyperlipidaemia may be responsible for many types of cerebral ischemic strokes because hyperlipidaemia promotes the condition of atherosclerosis. Many studies suggest that rose hip is helpful in the management of neurodegenerative diseases. It prevent the accumulation of defective proteins in the brain hence also provides protection from Alzheimer's disease. It also has anticonvulsant properties. It is an excellent oxidant hence inhibits oxidative stress thus protect & support neurons. [35]

Summary & conclusion: Because the costs of modern pharmaceuticals are out of their price range, the population is in search of least costly and effective herbal products. Peoples have their belief in the traditional ayurvedic preparations from ancient time because they are very effective with least side effects. It will be erroneous to say that herbal preparations have no any side effect. They also have but very less as compared to allopathic drugs. Peoples are in continuous search of effective herbal preparations but due to lack of knowledge and less knowledgeable persons of this field they cannot access them. Herbal preparations have a wide range of biologically active chemicals that show their tremendous pharmacological actions in a smoother and multifunctional way. They have additional benefits like boost up of energy, can modulate our immune system. Many pharmaceutical industries in our country are serving our society by preparing the suitable dosage form of herbal drug like syrups, tablets, ointment, creams etc.

In this review we have discussed a few neurological diseases, which are prevalent in our society, major reasons contributing to aetiology of the diseases, and some concrete examples of neuroprotective plant & chemicals used in many traditional medical systems. It may be said that herbs are the most promising & effective class of medications for treating neurological issues.

Conflict of interest:

There is no conflict of interest in this work, according to the authors.

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