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Review Article

A Review on Toxins Mediated Neuro Diseases and Ameliorative Role of Certain Phytochemicals

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Abstract

According to an estimate, about 6.8 million people die every year as a result of neurological disorders. These disorders arise due to degeneration of nerve cells and disrupt normal brain functions impacting personal and professional behaviour like cognition, retention and neurological functions. Though there are many reasons attributed to the emergence of neurodegenerative diseases like genetic, environmental, age, physiological processes etc. The free radicals are formed in the body as a normal product of aerobic metabolism, but it can also be formed due to increased exposure of environmental toxins like heavy metals (aluminium, arsenic, copper, iron, manganese, zinc, cadmium, lead), pesticides (organochlorines, organophosphates), and chronic inflammations or certain disease conditions. If the turnover of free radicals is not maintained, they ultimately lead to initiation of several diseases such as the hepatic, renal, cardiac, neurodegenerative disorders and many more. Brain cells completely depend on oxygen and glucose for energy requirement the increased free radicals may disrupt this process making the individual susceptible to diseases. In this review we have discussed an update of various aspects of neurodegenerative diseases arising due to environment neurotoxins, intrinsic factors, and their amelioration.

INTRODUCTION

According to the World Health Organization (2007), the neurological disorders have affected millions of populations globally. The report says that one billion people suffer all over the world, 50 million suffer from epilepsy and 24 million from Alzheimer, depression, and dementias. This disease affects people in all countries irrespective of age, sex, education, or income. Neurodegenerative diseases arise slowly. In this case, the nerve cells or spinal cord does not respond to the stimulus or takes time for responding due to decrease in signal transduction. Gradually with time, the nerves degenerate and stop functioning (ataxia) or develop sensory dysfunction (dementia). Since these diseases are irreversible, there is no cure. Once the progression starts, it can only be delayed or slowed but cannot be reversed or stopped [1-5]. Alzheimer's is the most common of all neurodegenerative diseases affecting memory and cognition. In this, the plaques called amyloid plaques, and tau tangles are formed. These amyloid plaques are fragments of a transmembrane protein, 'amyloid precursor protein', which helps in neurons growth, survival and repair after injury [6]. Parkinson's disease arise due to loss of nerve cells of peripheral nervous system involved in coordination and muscle movement. Huntington's is due to the inheritance of mutated Huntington's gene (HTT) gene. This HTT gene is characterized by expansion of polyglutamine tract poly Q or CAG nucleotide triplet. These mutated genes form inclusion bodies in neurons damaging molecular motors and axonal transport [7]. Multiple sclerosis is an autoimmune disease resulting in loss of sensation, and mobility. Frontotemporal dementia affects person's behaviour, and speaking. Progressive supranuclear palsy is due to accumulation of tau proteins affecting movements and balance. Creutzfeldt Jacob is due to prions proteins affecting cognition and neuro behaviour.

It is a well-known fact that free radicals are formed in the body as a normal product of aerobic metabolism, but they can also be formed due to increased exposure of environmental toxins like heavy metals such as lead, arsenic, mercury etc and the xenobiotics such as pesticides. Other factors like lack of physical activity, intake of saturated fatty acids and refined sugars, chronic inflammations, and social factors all contribute to disease initiation causing death of neurons and normal brain functions. Brain cells completely depend on oxygen and glucose for energy. Any deviation from this would cause accumulation of free radicals, which decreases the energy supply to the brain [2]. Hence if the turnover of free radicals is not maintained, it

ultimately weakens the immune system leading to initiation of several diseases like hepatic, renal, cardiac, neurodegenerative diseases and many more [8,9]. This review presents an updated account of possible environmental toxins and internal factors responsible for development of neurodiseases. Further, the possible amelioration strategies of neurodiseases have also been discussed.

SOCIOECONOMIC IMPACT OF NEURODEGENERATIVE DISEASES

Poverty in childhood, lack of proper hygiene and education, unresolved health issues / disabilities and sometimes the physical abuses, tortures etc. all make the person to suffer from the neurological diseases [10]. Persons who suffer from non-communicable neurological diseases, need dependency which makes them feel inferior [11]. In a report it is stated that parents of children who have low income and education and low quality of life, all these make their children susceptible for higher incidence of epilepsy [12,13]. According to data of World Health Organization and World Federation of Neurological Disorders, inadequate funding, lack of specialist healthcare professionals and costs of treatments are major barriers to proper care and management of neurological disorders.

EXTERNAL FACTORS RESPONSIBLE FOR ONSET OF NEURO-DISEASES

The environmental toxins/stress have played major role in emergence of neurodiseases. Chronic exposure of atmospheric pollutants like heavy metals and pesticides, air pollution affects the blood brain barrier, and cognitive functions etc. The severity of disease depends upon dose and duration of exposure. In common heavy metals exposure resulted in increased amyloid plaque deposition in Alzheimer's and α-synuclein in Parkinsons.

1. Aluminium (Al): The most common use of Al now days is as food wrappers. Other uses are kitchen utensils, cables, duralamine, an alloy, which has 90% of Al. Its admissible daily intake (ADI) is 1 mg/kg of body weight. It interferes with the metabolism of the neurotransmitter i.e. acetylcholine. It may result into iron deposition on myelin sheaths, increased amyloid plaque proteins, and enhanced oxidative stress [14-16].

2. Arsenic (As): It is primarily used as an insecticide / herbicide, and hence present in the atmosphere. It dissolves in rain contaminating the ground water. It's As^{+3} arsenite form is more toxic than As^{+5} form [17]. It is very much like phosphate and can replace it in few biological functions [18]. Astrocytic cells are the main brain energy metabolic cells. Arsenic interferes with astrocytic metabolism causing decreased glycolysis and CNS impairments [19-20].

3. Copper (Cu): It is used in making electrical appliances, wires, copper plating and copper utensils. Increased levels of it causes increased ROS, DNA damage, amyloid plaques deposition in Alzheimer. Abnormal prion proteins PrP^{Sc} have higher affinity for Cu making it resistant to ubiquinol degradation [21].

4. Iron (Fe): Excess Fe deposition in a developing brain due to haemolysis may lead to immature blood brain barrier formation and neuron damage or neurodegeneration with brain iron accumulation (NBIA) [22-23].

5. Manganese (Mn): The main exposure is through food containing Mn. In the environment, it reaches from mining and welding industries. High content of Mn causes the development of Parkinsonism, which is like Parkinsons characterized by lethargies, convulsions, and psychosis [24].

6. Zinc (Zn): Excess Zn interferes with iron and copper absorption causing apoptosis by unregulated activity of enzymes and antioxidants. Ischemia, retarded mental and physical development all are due to high Zn [25].

7. Cadmium (Cd): The Cd is a known carcinogen, used in batteries, and alloys. People working in mines or smokers are more often exposed to its adverse effects. It damages the blood brain barrier (BBB) permeability, promotes DNA damage, oxidation and apoptosis [26].

8. Lead (Pb): The primary source of Pb exposure are batteries and automobile exhaust. It impairs the cognitive functions. According to a study, it stimulates microglia resulting in over production of nitric oxide synthase, interleukin 1 β and tumour necrosis factor causing onset of neurodiseases [27-29].

9. Pesticides: The chemicals are mainly used as a disinfectant and crop protection from insects. Organochlorines inhibit the γ-amino butyric acid (GABA) by blocking GABA receptors. They alter Na-Ca channel and transporters causing neurotoxicity [30]. Organophosphates inhibit AChE activity irreversibly resulting in convulsions tremors and death [31].

INTRINSIC FACTORS RESPONSIBLE FOR NEUROTOXIC STIMULATION

The major risk factors responsible for neurotoxic stimulation are aging, DNA damage, mitochondrial dysfunction, protein misfolding, neuroinflammation, excitotoxicity, extrinsic / intrinsic apoptosis or both and defects in the removal pathways of misfolded proteins via ubiquitin proteosomes [32]. Theses uncontrolled and misfolded proteins in the endoplasmic reticulum and cytosol often work as a precursor for neuro pathologies:

Anatomical differences

It is due to changes in size and shape of neurons, glial cells including astrocytes and microglia. In strokes or formation of amyloid plaques in brain cell, it deforms the structure of the

cell. Endothelial cells surrounding glial cells of brain are less permeable to macrophages, hence weak defence system in brain.

Reduction in the level of Dopamine

In Parkinson's synthesis of catecholamines neurotransmitter, the level of 'dopamine' decreases which sends message to the brain for movement, resulting in shaking hands, legs, and which slowly worsens over the period. The precursor amino acid for dopamine is tyrosine and when tyrosine conversion to L-dopa is blocked, dopamine is decreased. The exposure to pesticides such as dieldrin and benomyl has been reported to cause dopamine degeneration and inhibits elimination of dihydroxyphenyl aldehyde a toxic compound of dopamine metabolism [33-35].

Oxidation of myelin sheath by free radical species

The myelin sheath of nerve cells acts as insulator and protects neurons. It is made up of unsaturated fatty acids and protein. Uncontrolled free radicals' production causes oxidation of lipids, proteins, DNA leading to by-products formations like alcohols, aldehydes, cholesterol oxides, peroxides, ketones which are toxic and weaken our immune system [36]. Deposition of iron on myelin sheaths due to breaking or non-continuity in mitochondrial respiratory chain activates immune system. The activated immune system leads to crossing of blood brain barrier (BBB) by immune cells like T cells, B cells, and macrophages and attacking myelin sheaths. This initiates responses like neuroinflammation, demyelination, loss of grey matter and neuronal cell death [37-39].

Calcium and reactive oxygen species (ROS)

Calcium as an important second messenger interacts with the metalloenzymes leading to ROS production [40, 41]. Both calcium and ROS are interdependent. Though, calcium signalling is regulated by ROS production, calcium signalling is crucial for ROS generation [42]. Thus, increased calcium can cause increased ROS. This crosstalk initiates the pathogenesis of several neurodegenerative diseases and neuronal cells death [43-45].

Excitotoxicity mediated neurodiseases

It is due to over production of glutamate receptors where neurotransmitters show neurotoxic effects. The N-methyl-D aspartate receptors (NMDARs) are a group of three ionotropic glutamate receptors, which may cause increased calcium level, and hence increased ROS resulting into occurrence of the CNS diseases [46]. The glutamate antagonists such as memantine inhibit binding of these receptors with glutamate and hence decrease levels of calcium and ROS [47].

ROLE OF ANTIOXIDANTS IN AMELIORATION OF NEUROLOGICAL DISEASES

Antioxidants are known to sequester metal ions causing oxidative stress in neurons, thereby halting the disease escalating to neurons. They act as a defence system to neutralize the free radicals mediated acute or chronic adverse effects. The antioxidants (enzymatic and non-enzymatic) work synergistically to combat the effects of the free radical species [48,49].

The role of antioxidants is summarised as following: (i) 17β estradiol, an estrogen, is synthesized in the brain by steroids to protect the neurons; (ii) N acetyl cysteine (NAC) is a glutathione precursor, acts as an antioxidant, and anti-inflammatory agent in neuro-diseases and in mucolytic therapy. NAC increases the levels of cysteine and glutathione working as a scavenger of ROS and free radicals. It also restricts the release of cytokines in immune cell proliferation [50]. NAC may help in glutamatergic neurotransmission controlling neuropsychiatric diseases [51,52]. (iii) The resveratrol is a type of natural phenol produced by plants in response to injury or attack by pathogens. It is present in the skin of grapes, berries and fruits [53]. It decreases oxidative stress, cholinergic neurotransmission, neuronal apoptosis and helps in clearance of amyloid plaque protein [54]. (iv) Carotenoids inhibit apoptosis and ROS mediated mitochondrial dysfunction. They control transcription factors such as Nrf2, and NF-κB regulating apoptosis [55]. (v) Lycopene prevents loss of antiapoptotic proteins i.e. Bcl-2 and Bcl-xL, and inhibits pro-apoptotic proteins like Bax [56]. β-carotene inhibits lipids peroxidation and its lower levels are associated with traumatic brain injury [57]. (vi) Astaxanthin prevents brain oedema, via the NF-κB pathway. It inhibits Na^+-K^+-$2Cl^-$ co-transporter-1 (NKCC1), thus reducing the disruption of BBB and acting as neuroprotector [58].

(vii) Lutein protects neurons from apoptotic death by preventing loss of Bcl-2 and Bcl-xL, and accumulation of Bax. It also prevents ganglionic cells from excess glutamate receptors supressing apoptosis [59]. (viii) Fucoxanthin activates PI3K/Akt pathway promoting Nrf2 translocation during neurotoxic stimulation [60]. (ix) Omega fatty acids are divided into two categories omega-3 and omega-6 fatty acids. Omega-3 fatty acids comprise α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Omega-6 consist of linoleic acid (LA) and arachidonic acid (ARA). Among these DHA consisting of 90% of omega 3 fatty acid is responsible for maintaining cellular key processes such as release of neurotransmitters, gene expression, myelination, neuroinflammation and neuronal growth [61,62]. (x) Vitamin E (Tocopherols) plays an important role in central and peripheral nervous system. Its deficiency often leads to ataxia, dysarthria and neuromuscular disorders [63]. It inhibits glutamate induced apoptosis and protects against cerebral ischemia [64,65]. They neutralize unstable lipid peroxyl radicals generated from PUFA. Mutation in the α-Tocopherol transfer protein encoded by gene TPPA develops spinocerebellar ataxia (lack of fine motor control), areflexia, loss of proprioception and finally death [66]. (xi) Melatonin, an amphiphilic substance, secreted by the pineal gland [67] is a known antioxidant, and anti-inflammatory agent inhibiting synthesis of prooxidants while promoting that of antioxidant enzymes. As an anti-inflammatory agent, it inhibits cyclooxygenase-2 and blocks the binding of nuclear factor κB to DNA, thus, reducing the expression of the inducible nitric oxide synthase resulting in decreased synthesis of proinflammatory signals [68].

Table 1: Plants, their phytochemicals and effects on neurodiseases

S. No.	Scientific name	Family	Part used	Common name	Active compound	Effect
1	*Withania somnifera*	Solanaceae	Root	Ashwagandha	Withanolide A, withanoside lV, Vl	Regeneration of neuronal axons and sendrites, reconstruction of post/ pre neuronal axons, anti-stress
2	*Bacopa monnieri*	Plantaginaceae	Leaf	Brahmi	brahmine, herpestine, saponins (bacosides A, A3, and B and bacopasaponin A to F), D -mannitol, betulinic acid, β-sitosterol, and stigmasterols	Neuroprotective, restores activities of cholinergic enzymes, improved cognitive functions
3	*Centella asiatica*	Umbelliferae (Apiceae)	Whole part	Indian pennywort	Triterpenoids, volatile fatty acids, glycosides, flavonoids, alkaloids, and tannins, asiaticoside	Inhibiting overactivation of p38 MAPK pathway acting as anti-inflammatory,
4	Mucuna pruriens	Fabaceae	Whole plant	velvet bean	L-dopa and hallucinogenic tryptamines, and anti-nutritional factors (phenols and tannins)	L-dopa act as dopamine precursor, can cross blood brain barrier restoring neurotransmission
5	***Papaver somniferum***	Papaveraceae	Latex capsule seeds	Oppium poppy	Phenanthrenes (thebaine morphine, codeine, and sanguinarine)	Supress the brain (pain killers), enhance mood acting on special neurons
6	Loranthus longifolia	Loranthaceae	Leafs		alkaloids, flavonoids, tannins, terpenoids, reducing sugars, carbohydrates and cardiac glycosides in aqueous extract	Neuroprotection, anxiety, depression
7	Aconitum	Ranunculaceae	tubers	aconite, monkshood, wolfsbane, leopard's bane, devil's helmet or blue rocket	Aconitine, mesaconitine	Neuronal disorders, pain, inflammation
8	***Panax ginseng***	Araliliaceae	roots and rhizomes	Asian ginseng, Chinese ginseng, Japanese gingseng or Korean ginseng	Ginsenosides (Rg1), ginseng polysaccharides, ginseng polypeptides, panaxosides	Antidepressant by enhancement of the BDNF-TrkB signalling pathway, increase acetylcholine levels, anti-depression, anti-Alzheimer's disease, anti-Parkinson's disease and protect neurons
9	*Hyoscyamus niger*	Solanaceae	leaves	henbane, black henbane, or stinking nightshade	Hyoscyamine, scopolamine, and tropane alkaloids	blocks the function of acetylcholine in the brain and antagonizes the muscarinic receptors
10	***Embilica officinalis***	Euphorbiaceae	Root	Amla	Gallic acid, ascorbic acid, ellagic acid, rutin, quercetin, and catechol, tannins, epigallocatechin-3-gallat and polyphenols	Neuroprotection, Sleep disorders, sedatives, Anxiety, epilepsy,
11	***Valeriana officinalis***	Caprifoliaceae	fruit	Garden heliotrope	actinidine, chatinine, shyanthine, valerianine, and valerine	increased GABA receptors, prevents excitotoxicity, neuronal death
12	***Ferula asafoetida***	Apiaceae	Rhizome, tap root	Stinking gum	ferulic acid, umbel-liferone, asaresinotannols, farnesiferols A, B, and C, glucose, galactose, l-arabinose, rhamnose, and glucuronic acid and volatile oil (3-17%) consisting of disulfides (2-butyl propenyl disulfide) with monoterpenes (α- and β-pinene, etc.), free ferulic acid, valeric acid, and traces of vanillin	Sedative, anti-oxidant
13	***Datura metel***	Solanaceae	Seeds, leafs	Datura	tropane alkaloids, tannins, flavonoids, saponins and withanolides	Neuro protection, convulsions
14	***Avena sativa***	Poaceae	Seed	Oat	*β*-glucans *β*-glucan, avenanthramides, tocols, sterols, and avenacosides	increased synthesis of brain growth factors (neurotrophins and the vasodilatory molecule nitric oxide, which play a pivotal role in cerebral blood flow regulation) modulation of neurotransmission and inhibition of the enzymes such as MAO-B and AChE, which catalyse the oxidation or hydrolysis of numerous neurotransmitters
15	***Annona squamosa***	Annonaceae	Seeds,bark, leaves	Sugar apple	diterpenoid alkaloid atisine, oxophoebine, reticuline, isocorydine, methylcorydaldine and, flavonoid quercetin-3-O-glucoside	anti-inflammatory effect through reduction NF-κβ and attenuated apoptotic on neural cells through reduction of caspase 3
16	***Acoros calamus***	Acoraceae	Leaves, rhizome	sweet flag, sway or muskrat root	Phenylpropanoids (asarone and eugenol), sterols, triterpene glycosides, triterpenoid saponins, sesquiterpenoids, monoterpenes, and alkaloids	Neuroprotection, enhanced memory power

17	*Evolvulus alsinoides*	Convolvulaceae	dwarf morning-glory and slender dwarf morning-glory	Whole plant	Scopoletin, umbelliferone, scopolin and 2-methyl-1,2,3,4-butanetetrol	Improves spatial memory formation, inhibit AChE
18	***Rosmarinus officinalis***	Lamiaceae	rosemary	leaves	Rosmarinic acid, camphor, caffeic acid, ursolic acid, betulinic acid, carnosic acid, and carnosol	Decreased lipid peroxidation in cerebral tissues in ischemic patients
29	***Aegle marmelos***	Rutaceae	Bael fruit	Leaves, bark, roots, fruit, seedss	marmenol, marmin, marmelosin, marmelide, psoralen, alloimperatorin, rutaretin, scopoletin, aegelin, marmelin, fagarine, anhydromarmelin, limonene, â-phellandrene, betulinic acid, marmesin, imperatorin, marmelosin, luvangentin and auroptene	Decreased oxidation, neuroprotection
20	***Rauwolfia serpentine***	Apocynaceae	Indian snakeroot, devil pepper, or serpentine wood		alkaloids of the indole alkaloid (ajmaline, ajmalicine, reserpine, serpentine), and others	mental diseases, schizophrenia bipolar disorder, epilepsy seizures, insomnia, sleep problems

PHYTOCHEMICALS AS THERAPEUTICS AGAINST NEURODEGENERATIVE DISEASES

The Ayurvedic treatments are safe with no side effects. The plant based bioactive molecules help maintain balance among vata, pitta and kapha doshas. In ayurveda, treatment of neurological disorders is called vata vyadhi in which brain tissues dries due to lack of nourishment. Vata vyadhi further has 4 categories (i) Kevala vata (Vata alone), (ii) Samsarga (Vata with Pitta and Kapha), (iii) Avarana (entrapment by other Dosha / Dhatu / Mala), and (iv) Dhatu Kshaya Janya (neurodegenerative). Medicinal plants like *Withania somnifera, Bacopa monnieri, Centella asiatica, Mucuna pruriens, Papaver somniferum, Loranthus longifolia*, *Aconitum, Cassia occidentalis, Panax ginseng, Hyoscyamus niger, Valeriana, Embilica officinalis, Ferula asafoetida, Datura metel, Avena sativa, Annona squamosa, Acoros calamus, Evolvulus alsinoides, Rosmarinus officinalis, Aegle marmelos,* and *Rauwolfia serpentine* are in use since ancient times for neurological treatment [69-101]. In addition to these, ginger, turmeric, black pepper in diets can also help to reduces the imbalances in vatta, pitta and kapha doshas. The panch karma massage, yoga helps to improves circulation, flexibility, and relieving stress. In the Table 1, a brief description of plants, their phytochemicals and effects on neuro diseases is given.

CONCLUSION

The neurological diseases are like a stigma for a person suffering from it and to the family as well. The society needs to be made aware for no any behavioural discrimination with them. There are many reasons for neuro related problems, but the impact of the disease gets increased by several folds when he or she starts feeling alienated in the society. In order to overcome stigma and discrimination, the awareness among the people about various aspects of such diseases is required. There is an urgent need of carrying out extensive research in this direction, especially about early diagnosis, and effective treatment involving plant based bioactive compounds in addition to the regular therapeutics for the neurological disorders.

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