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Neurodegenerative Diseases: Metals as a susceptible factor and its herbal therapy

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Abstract
Neurodegenerative disease is a wide expression where the compilation of circumstances mainly affects neurons, which is a basic unit of the nervous system. Neurons are of utmost importance for brain function, however, like other cells of the body, they do not reproduce or replace once damaged. Neurodegenerative disease is a progressive disease which affects movement and mental functions, affecting approximately 30 million individuals worldwide. Alzheimer's, Parkinson's, Huntington's and amyotrophic lateral sclerosis diseases are examples of this condition. These diseases are characterized by separate etiologies with distinct morphological and pathophysiological features. There are many evidences that suggest that these disorders arise by multi-factorial conditions such as oxidative stress, mitochondrial dysfunction, and/or exposure to metal toxicity and pesticides. The role of metals in neurodegenerative diseases has been widely considered as an underlying cause and, several studies pinpoint the toxic effects of metals. Metals are elements of air, water, and ecosystem. Although metals are vital components, however excessive accumulation of this element causes detrimental effects such as aluminum has been controversially invoked as an aggravating factor or cofactor in Alzheimer's disease as well as in other neurodegenerative diseases, Manganese exposure can play an important role in causing parkinsonian disturbances, possibly enhancing physiological aging of brain in conjunction with genetic predisposition. In this review, we explore the effects of metals in two of the most common neurodegenerative diseases, Alzheimer's and Parkinson's disease and clinical effects of synthetic drugs and herbal medicines for these neurodegenerative diseases.

Keywords: neurodegenerative disease, metal accumulation, Alzheimer's disease, Parkinson's disease

1. Introduction

1.1 Neurodegenerative diseases

Neurodegenerative disease is a term that indicates a range of conditions which primarily affect the neurons in the human brain. Neurons normally don't reproduce or replace themselves, so when they become damaged or die, they cannot be replaced by the body. Neurodegenerative diseases are incurable and enervating conditions that result in progressive degeneration and/or of nerve cells. This causes problems with movement (called ataxias), or mental functioning (called dementias) [1].

Most of the neurodegenerative diseases are rare and have been found to be caused by purely genetic factors while some of the cases in this group of diseases stem from unknown causes. Cases are often divided into "genetic," those stemming from purely inherited factors or sporadic, and those caused by unknown factors, including environmental exposures. Most cases are now thought to arise from a combination of genetic risk factors and environmental influences [2].

Different neurodegenerative diseases are Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). A common feature of virtually all neurodegenerative diseases is that the consequences are often devastating, with severe mental and physical effects [2]. There are evidences that suggests that these neurodegenerative diseases may also arise due to exposure to metal toxicity [3].

Metals are present in water, air and a variety of ecosystems since they are component of earth's crust and are involved in various physiological processes, such as oxygen transport, electron transport, protein modification, neurotransmitter synthesis, immune responses, etc [4]. Although metals are important for animals and plants, but in trace amounts. Excessive metal levels accumulate in various organs, including brain which may cause various detrimental intracellular events such as oxidative stress, mitochondrial dysfunction, DNA fragmentation, protein mis folding, endoplasmic reticulum (ER) stress, and activation of apoptosis [5]. These effects may alter neurotransmission and lead to neuro degeneration, which is visible as cognitive problems, movement disorders, and learning and memory dysfunction.

2. Alzheimer's disease

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. [6]

Alzheimer's disease is named after Dr. Alois Alzheimer, who noticed changes in the brain tissue of a woman who had died of an unusual mental illness whose symptoms included memory loss, language problems, and unpredictable behavior. After she died, he examined her brain and found many abnormal clumps (which are now called amyloid plaques) and tangled bundles of fibers (which are now called neurofibrillary tangles) [6].

The hallmark pathology of Alzheimer's disease is the accumulation of amyloid plaques between neurons in the

brain [7] and the abnormal accumulations of a protein called tau inside the neurons called neurofibrillary tangles [8].
The causes of Alzheimer's are usually thought to be a combination of genetic, lifestyle, and environmental factors [6].

2.1 Drug treatment
The Food and Drug Administration (FDA) has approved two types of drugs specifically to treat symptoms of Alzheimer's disease.

- Cholinesterase inhibitors (example: Donepezil, Rivastigmine, Galantamine) [9]
- Memantine [9]

2.2 Herbal treatment
Synthetic drugs for human brain disorders are usually expensive, and sometimes show serious and unavoidable side effects. Therefore, the herbal drugs are chosen over synthetic drugs for a range of human brain disorders.

2.2.1 Curcuma longa
Synonyms: Indian saffron, Curcuma, Turmeric, Haldi [10].
Biological source: Turmeric consists of dried, as well as, fresh rhizomes of the plant known as Curcuma longa, belonging to family Zingiberaceae [10].
Chemical constituents: Curcumin, is believed to be the principal pharmacological agent [10].

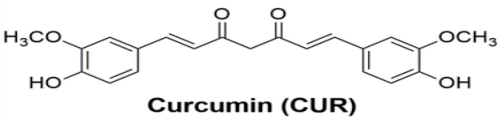


Fig 1

Mode of action
Clinical researches suggest that curcumin is active in AD as an antioxidant, anti-inflammatory therapeutic agent that improves the cognitive functions [11]. Clinical studies also suggest that curcumin could be useful in reversing neuro degeneration stemming from Aβ production [12], preventing β-amyloid protein formation [13], decreasing beta-amyloid plaques, inhibiting Aβ accumulation [14].

2.2.2 Brahmi
Synonym: Bacopa [10]
Biological source: It consists of the fresh leaves and the stems of the plant known as Bacopa moniera (herpestismoniera), belonging to family Scrophulariaceae.
Chemical constituents
Brahmi is found to contain the alkaloids brahmine, herpestine and the mixture of 3 other alkaloids. It contains saponins, namely bacosides A and B. additionally it also contains betulic acid, stigmasterol, monnierin and hersaponin [10].

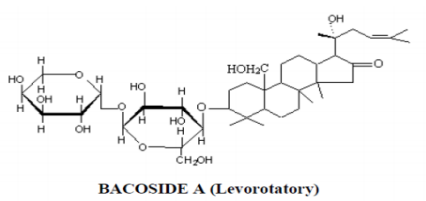


Fig 2

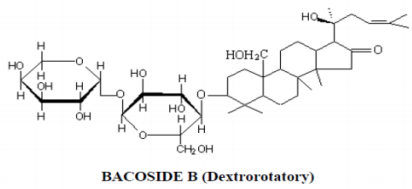


Fig 3

Mode of action
Traditional medicine has used B. monnieri for improving memory and cognitive function [15]. Many studies related to neuropharmacological effects and cognitive functions of B. monnieri extracts have been conducted extensively [16]. In the hippocampus, B. monnieri increase protein kinase activity, which provides a nootropic action (cognitive functions) [17]. In an animal Alzheimer model, rats fed with B. monnieri extract showed decreased cholinergic degeneration and exhibited cognition-enhancing effect [18].

2.2.3 Ginger
Synonyms: Zingber, Zingiberis, Sunthi [10]
Biological source: Ginger consists of whole or cut, dried scrapped or unscrapped rhizomes of *Zingiberofficinale*, family Zingiberaceae [10].
Chemical constituents: Ginger consists of volatile oil (1-4 percent), fat (10 percent), fibre (5 percent), starch (40-60 percent). Ginger oil is constituted of monoterpene hydrocarbons, sesquiterpene hydrocarbons, oxygenated mono and sesquiterpenes, and phenyl propanoids. Sesquiterpene hydrocarbon content of all types of ginger oil from different countries is found to be same and includes α-zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene and α-curcumene. Aroma and flavour are the main characters of ginger. Aroma is due to fragrant principles of volatile oil while the flavour, pungency and pharmacological actionsare exerted by phenolic ketones of oleo-resin. Phenolic ketones of oleo-resin include gingerols like zingerone, paradols, gingediols, shogaols, and hexahydrocurcumin and o-methyl ethers of these compounds [10].

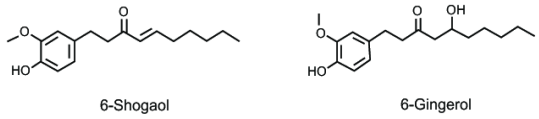
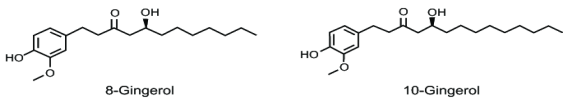


Fig 3



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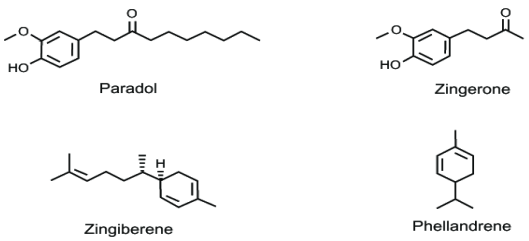


Fig 5

Mode of action

In vitro assays have shown the Acetylcholinesterase inhibitory activity of *Z.* officinaleis. Inhibiting the Acetylcholinesterase enzyme increases acetylcholine levels in synapses, augments the activity of cholinergic pathways, and enhances cognitive functions in AD patients. Furthermore, Z. officinaleis can inhibit lipid peroxidation and provide the protective effect against AD [19].

2.2.4 Panax ginseng

Synonyms: Ninjin, Pannag, Panax [10].

Biological source: Ginseng is the dried root of various species of Panax like P. ginseng (Korean ginseng), P. japonica (Japanese ginseng), P. notoginseng (Chinese ginseng) and P. quinquefolium (American ginseng), belonging to family Araliaceae [10].

Chemical constituents: Ginseng contains a mixture of several saponin glycosides, belonging to triterpenoid group. They are grouped as follows:

1. Ginsenosides;
2. Panaxosides; and
3. Chikusetsusaponin [10]

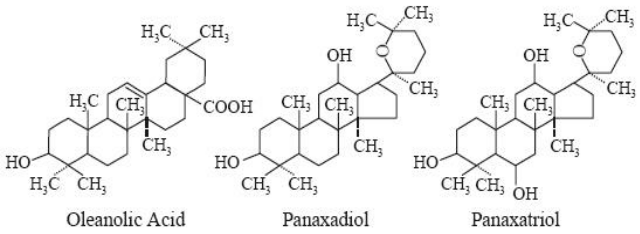


Fig 6

Mode of action

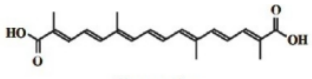
Several studies have shown that ginsenosides from ginseng can inhibit inflammatory mechanisms in the brain. They are especially protective against beta amyloid, the inflammatory microscopic substance that accumulates in specific areas of brains affected by Alzheimer's. Ginseng extracts also inhibit immunoexcitotoxic activation of microglia, an important factor in preventing the destructive process of Alzheimer's disease [20].

2.2.5 Crocus sativus

Synonyms: Saffron, hay saffron, kesar [10].

Biological source: Crocus consists of dried stigmas and upper parts of styles of plant known as Crocus sativus, family Iridaceae [10].

Chemical constituents: Saffron contains red colouring matter known as Crocin and crocetin, bitter principle picrocrocin and traces of volatile oil [10].



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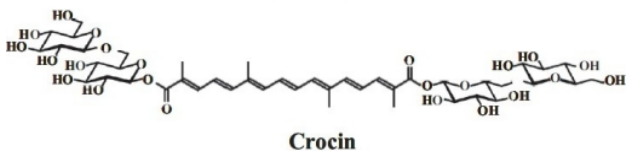

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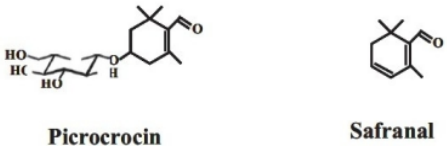


Fig 9

Mode of action

Various studies concluded that Crocus sativus was effective in treating mild-to-moderate Alzheimer's disease due to its "antioxidant and anti amyloidgenic" abilities, thus being able to inhibit the aggregation and deposition of the beta-amyloid plaques [21]. Saffron is also reported to be beneficial in moderating acetylcholinesterase.

2.3. Metals and Alzheimer's disease

The exact cause of Alzheimer's disease is still not known. However, metals are thought to be a susceptible factor for Alzheimer's disease.

Small amounts of certain metals, such as zinc, copper, and iron, are necessary for our bodies to function properly. These are referred to as biometals. Other metals like aluminum are not needed for survival but can be tolerated by the body in low doses. Abnormally high concentrations of these metals may lead to neurotoxic effects.

2.3.1 Aluminum in the etiology of Alzheimer's disease

Aluminum (Al) is exuberantly distributed in our environment, and compounds containing Al have been used in manufacturing (e.g., clays, glasses, and alum) for centuries. Although Al is one of the most common elements in the biosphere, the amounts taken up into living cells are very small. Hence, some authors regard Al as the root cause of AD [22].

During the 1960s and 1970s, aluminum came into view as a possible suspect in causing Alzheimer's disease. This suspicion led to concerns about everyday exposure to aluminum through sources such as cooking pots, foil, beverage cans, etc [23].

Aluminum was the first metal that was proposed as a possible cause for Alzheimer's disease. The hypothesis that aluminum is a risk factor in the development of β-amyloid plaques and neurofibrillary tangles (NFT) and dementia in Alzheimer's disease is based on studies by Wisniewski *et al*, Klatzo *et al.* and terry & Pena in 1965 that showed that injection of experimental animals with Al compounds induces the formation of NFT [24].

2.3.2 Zinc, copper, and iron

The bio metals zinc, copper, and iron play a variety of important roles in the brain, including cell signaling and neuroplasticity. However, excessive levels of these metals may be harmful for our health. In cell cultures, physiological concentrations of zinc, iron and copper can promote the formation of β-amyloid plaques [25]. In addition, all three of these bio metals can accelerate the formation of neurofibrillary tangles, another toxic protein found in Alzheimer's disease. Copper and iron are also believed to contribute to oxidative stress [26]. Oxidative stress is a chemical process involving free oxygen radicals that gradually leads to cell damage and aging.

2.3.3 Lead

Lead (Pb) is a non-essential heavy metal and a abundantly

present pollutant in the ecosystem. Pb exposure leads to oxidative stress, mitochondrial dysfunction and changes to the Golgi apparatus [27]. The main goal of Pb-induced toxicity is the nervous system, and children are particularly sensitive to Pb intoxication. The hippocampus is the primary region of Pb aggregation, although the metal may also aggregate in several other brain regions [28]. It has been recorded that Pb exposure results in deficiency in intelligence, memory, executive functioning and attention, processing speed, language, emotion and motor skills [29]. Workers with occupational exposure to Pb have shown impairment of verbal memory and visual memory performance, lower decision-making speed, deficiency in visuomotor coordination, and increased interpersonal conflict.

2.3.4 Cadmium

Cadmium can enter the peripheral and central neurons from the nasal mucosa or the olfactory bulb, which damages permeability of the BBB [30]. Miners, welders, smokers, and workers in battery production are at a danger of high Cd exposure [30]. Chronic exposure to Cd may severely interfere with normal function of the nervous system, and infants and children are more susceptible than adults [30]. Cd is a possible etiological factor of neurodegenerative diseases, including AD [31] and PD [32]. Jiang *et al.* found that Cadmium accelerates self-aggregation of Alzheimer's tau peptide R3 [31].

2.3.5 Other Metals

Though the metals described above have been the focus of Alzheimer's metal lobiology research, it's possible that others could be involved as well. A small number of studies have drawn connections between Alzheimer's and cobalt, and manganese, among others [32].

3. Parkinson's disease

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system [33]. It is the most common muscular functioning disorder and is the second most common neurodegenerative disorder after Alzheimer's disease (AD). The important features of Parkinson's disease are akinesia, muscular rigidity, postural instability, loss of associated movements and tremor. The hallmark pathology of PD remains the loss of dopamine neurons in the substantia nigra And the occurrence of cytoplasmic inclusions known as Lewy bodies in surviving neurons [34]. The exact cause of Parkinson's disease is not yet known, but it is considered to be potentiated by the interaction of environmental and genetic factors.

Parkinson's disease is named after the English doctor James Parkinson, who published the first detailed description in "An Essay on the Shaking Palsy", in 1817 [35].

In 2015, PD affected 6.2 million people and resulted in about 117,400 deaths globally [36]. Parkinson's disease typically occurs in people over the age of 60 [37]. When it is seen in people before the age of 50, it is called young-onset PD [38].

Symptoms of Parkinson's disease include tremor, slowed movement (bradykinesia), rigid muscles, impaired posture and balance, loss of automatic movements, speech changes, writing changes [39]. A PD diagnosis is based on evidence of at least two out of three specific signs and symptoms: tremor, slowed mobility (bradykinesia) and stiffness (rigidity) [40].

Types of Parkinsonism

1. **Primary/idiopathic Parkinsonism [41]:** As the name suggests the cause of the disease is unknown. Over the years the dopaminergic neurons degenerate due to H_2O_2 and free radicals such as O_2^- (superoxide) and $OONO^-$
2. **Secondary/Drug Induced Parkinsonism [41]:** There is no degeneration of dopamine as seen in the above case, but the decrease in dopamine is drug induced.

3.1 Drug treatment [41]

The drugs used in the treatment of Parkinsonism can be classified as:

1. **Those that increases the dopaminergic activity:**
   - Precursors of dopamine: levodopa (1-dopa).
   - Drugs that inhibit dopamine metabolism
     (a) MAO-B inhibitors: Selegiline.
     (b) COMT inhibitors: Tolcapone, Entacapone.
   - Drugs that release dopamine: Amantadine.
   - Dopamine receptor agonists: Bromocriptine, Lysuride, Ropinirole.
2. **Those that suppress the cholinergic activity**
   Atropine and atropine substitutes such as benzhexol, procyclidine; and antihistaminics with anticholinergic properties.
   - Levodopa is a "universal antiparkinsonian drug.

3.2 Herbal treatment

Synthetic drugs for human brain disorders are usually expensive, and sometimes show serious and unavoidable side effects. Therefore, the herbal drugs are chosen over synthetic drugs for a range of human brain disorders.

3.2.1 Curcuma longa

Synonyms: Indian saffron, Curcuma, Turmeric, Haldi [10].

Biological source: Turmeric consists of dried, as well as, fresh rhizomes of the plant known as Curcuma longa, belonging to family Zingiberaceae [10].

Chemical constituents: Curcumin, is believed to be the principal pharmacological agent [10].

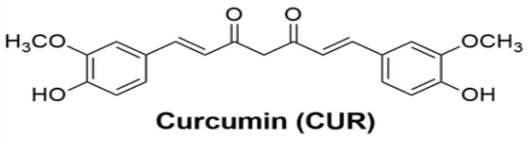


Fig 10

Mode of action

Curcumin showed neuroprotective properties in an animal model of Parkinson's disease; the beneficial effect was due to its antioxidant capabilities and its ability to penetrate the brain [42]. The c-Jun N-terminal kinase (JNK) signalling pathway is involved in dopaminergic neuronal degeneration, which is in turn associated with Parkinson's. Curcumin prevents dopaminergic neuronal death through inhibition of the JNK pathway, and thereby offers a neuroprotective effect that may be beneficial for Parkinson's disease [43].

3.2.2 Jatamansi

Synonym: Nard, Indian spike nard [10].

Biological source: Jatamansi consists of dried rhizomes of

Nardostachys jatamansi, belonging to family Valerianaceae [10].

Chemical constituents: Jatamansi contains 1-2 percent of pale yellow volatile oil, resin, sugar, starch and bitter principle, an alcohol and its isovaleric ester. It also contains jatamansic acid and ketones jatamansone and nardostachone [10].

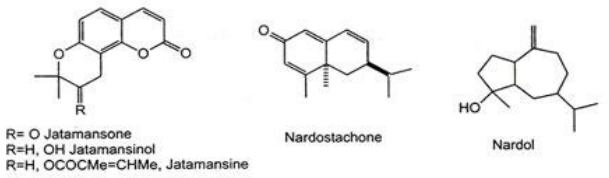


Fig 11

Mode of action

Jatamansi is beneficial for people suffering from neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. Oxidative stress plays a critical role in the development of Parkinson's disease and the antioxidant property of jatamansi helps counter this. According to an animal study, treatment with an extract of Jatamansi slowed down neuronal injury in rats. It also reduced problems with muscular coordination and locomotor activity induced by a drug that mimicked the effects of Parkinson's [44].

3.2.3 Ginkgo biloba

Synonyms: Maiden hair tree, Kew tree. [10]

Biological source: The dried leaves of Ginkgo biloba Linn, the only living member of family Ginkgoaceae. [10]

Chemical constituents: Active ingredients of ginkgo leaf are various flavanol glycosides, which mainly include flavonol, mono-, di- and triglycosides of kaempferol, quercetin and isorhamnetin [10].

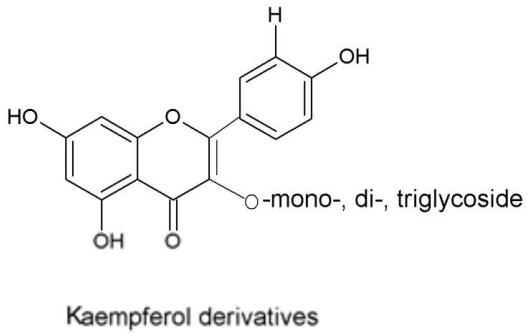
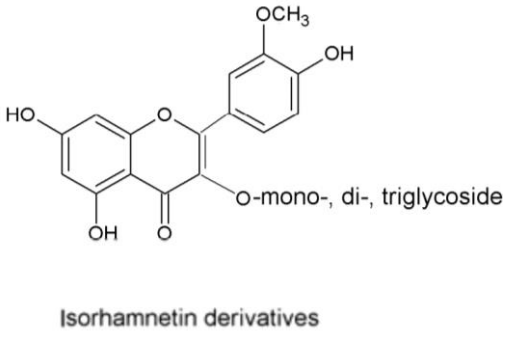


Fig 12



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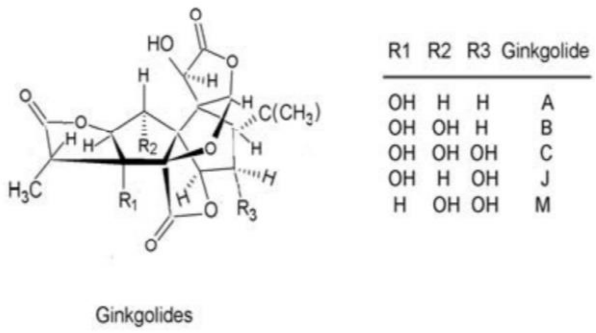

Fig 14

Mode of action

The main mechanism of action of Ginkgo biloba leaf extracts is inhibition of enzyme monoamine oxidase. This enzyme is responsible for the metabolism of dopamine and formation of free radicals which damages dopaminergic neurons [45]. Inhibition of monoamine oxidase, by standardized Gingko extracts, is said to have a neurorestorative effect in Parkinson's disease [46]. It restores dopamine levels. Gingko extracts can also halt progression in Parkinson's disease by reducing alpha-synuclein accumulation and regulating dopamine activity [47].

3.2.4 Mucuna pruriens

Synonym: Velvet bean, Atmagupta, Kaunch, Kawach and Cowhage [10].

Biological source: Mucuna pruriens is a tropical legume native to Africa and tropical Asia and widely naturalized and cultivated. It belongs to family Fabaceae [10].

Chemical constituents: The seeds of the plant contain L-DOPA, with trace amounts of serotonin, nicotine, and bufotenine [10].

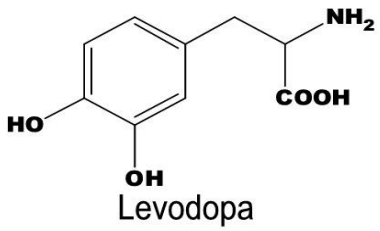

Fig 15

Mode of action

Mucuna pruriens has been used to remedy the symptoms of Parkinson's disease. It is a natural source of L-dopa, a dopamine precursor. In animal models, L-dopa obtained from Mucuna pruriens produced better results than synthetic levodopa [48]. Compared with synthetic levodopa, Mucuna pruriens produces a unique interaction within the brain that may protect against treatment-induced dyskinesia [49].

3.2.5 Ashwagandha

Synonym: Withania root, Asgandh, winter cherry [10].

Biological source: It consists of dried roots and stem bases of Withania somnifera, belonging to family Solanaceae [10].

Chemical constituents: The main constituents of ashwagandha are alkaloids and steroidal lactones. Among the various alkaloids, withanine is the main constituent [10].

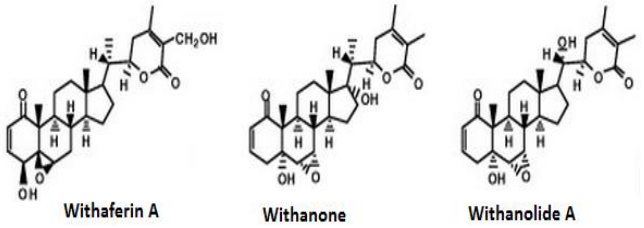

Fig 16

Mode of action

Withania somnifera, a 4000-year-old traditional herbal medicine of India, do have optimistic effects on neural growth and locomotor function. The anti-parkinsonian effects of Withania somnifera extract was evaluated in 6-Hydroxydopamine (6-OHDA) induced Parkinsonian rats. Treatment with Withania somnifera extract reversed some of the symptoms of Parkinsons disease such as significantly decreased striatal dopamine (DA) level [50].

3.3 Metals and Parkinson's disease

Some metals with neurotoxic effects have been associated with secondary Parkinsonism. Manganese was one of the major elements associated with Parkinsonism. Many metals such as mercury, copper, and others can be released from metal body implants such as dental restorations, phagocyted by blood macrophages, and transported into the brain. Upon apoptosis, the metal debris is released in the brain and can be taken up by brain macrophages, such as neuro-melanocytes. Neuro-melanocytes are one of the cell types which are involved in the synthesis of dopamine in the substantia nigra. Therefore, ingested metal debris could impair the viability of neuro-melanocytes and thus dopamine production. Several epidemiological studies have shown a significant association between PD and long-term exposure to metals such as mercury, lead, manganese, copper, iron, aluminum, bismuth, titanium and zinc. The main sources of metal exposure are occupational exposure, environmental pollution, contaminated seafood, medications, and dental metals restorations such as amalgam fillings, etc

3.3.1 Manganese

Mn is a nutrient necessary for biological processes within the human body [51]. Low concentrations of manganese are essential to the body. However, exposure to high levels of manganese may be toxic. Consumption of food is the primary route for entrance into the body. Manganese can be inhaled as well, and this serves as an occupational hazard for those who work in welding and mining industries [52].

Excess accumulation of manganese (Mn) in the brain results in a neurological syndrome with cognitive, psychiatric, and movement abnormalities. The highest concentrations of Mn in the brain are achieved in the basal ganglia, which may bring about a form of Parkinsonism known as manganism. [53] Mn is elevated in dopaminergic neurons of the substantia nigra, providing a possible basis for the motor deficiency observed in manganism [54].

The mechanism of manganese neurotoxicity is decay of the globus pallidum mediated by interruption of the mitochondria initiating both apoptosis and cell death via formation of highly reactive oxygen species. [55] In rats, early low-level exposure to manganese was associated with higher levels of astrocytosis in the striatum as well as motor and cognitive impairment later in life, supporting manganese as a potent neurotoxicant [56].

There is extensive use of Mn-based pesticides, both in industrialized and in developing countries. In addition, the adoption of an organometallic compound such as methyl-cyclopentadienyl manganese tricarbonyl ($CH_3C_5H_4Mn(CO)_3$), as a lead substitute in gasoline could become an additional important source of environmental exposure [57].

Since Mn elimination from the CNS requires a long time, neurotoxic effects may occur later in life, increasing the prevalence of Parkinsonian disturbances in elderly individuals. Therefore, the problem of Mn neurotoxicity is becoming of great concern because of several factors [57].

3.3.2 Mercury

Parkinson's disease onset has been widely linked with exposure to elevated levels of mercury. Mercury targets areas of the brain which are not able to detoxify mercury [58]. Even at the lowest levels, inorganic mercury causes neuro degeneration within minutes of exposure.

Detectable blood mercury levels were six times more frequent in individuals with PD than in healthy controls [59]. In another study, higher blood Hg levels were seen in PD patients compared to controls, and mercury exposure was associated with an 8-fold increase in the risk of developing PD [60].

After being occupationally exposed to mercury in a chlorine factory for 30 years, a patient developed Parkinsonism [61]. A 47-year-old dentist with parkinsonism was found to be intoxicated with mercury. Following chelation treatment, he regained health [62]. In dentists and dental assistants who are occupationally exposed to mercury from dental amalgam, an elevated mortality of PD has been described [63]. Among several professions, dentists were the most common among PD patients [64].

In industrialized countries, dental amalgams are the single largest source of mercury exposure [65]. For the general population, amalgam fillings also are the primary source of mercury in the CNS [66].

Mercury is neurotoxic in every chemical form and appears to be of importance in the development of PD. Metals such as iron, copper, and lead do exert a synergistic effect when in combination with mercury. Taken together, mercury, as well as other metals, may contribute to the development of PD.

3.3.3 Other Metals

Upon analysis of brain tissues from PD patients elevated levels of aluminum, iron, and zinc were found in the substantia nigra compared to controls [67]. In the substantia nigra of PD patients, the accumulation of iron was twice as much compared to controls [68]. This was confirmed in other studies. Thus, high levels of trivalent iron were found in Lewy bodies and dopaminergic neurons of the substantia nigra of PD patients. Substantia nigra neurons contain neuromelanin that can bind to iron and produce free radicals that in turn initiate lipid peroxidation and cell death. Iron also promotes auto-oxidation of dopamine in substantia nigra neurons, releasing additional free radicals.

4. Conclusion

Metals play an important role in our daily life as they are widely involved in numerous enzymatic activities; however,

excessive amounts in the human body usually result in neurotoxicity. Once metals have accumulated in the nervous system, oxidative stress, mitochondrial dysfunction, and protein mis folding are the most common deficits associated with metal-induced toxicity. Once injured, neurons must spend greater energy to synthesize neurotransmitters and maintain homeostasis. The increased burden along with the neurotoxicity may lead to neuronal death. Industrial development increases the risk of heavy metal exposure through production and consumption of commercial products containing metal compounds. Occupational and environmental exposure to the metals reviewed above has been suggested as a possible cause of neurodegenerative disorders. Genetic factors cannot always be controlled, but if all the responsible environmental factors could be identified, they could be counteracted, even if they cannot be eliminated completely.

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