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Herbal Medicines Used for Neurodegenerative Diseases

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Abstract: ***The development of new drugs for neurodegenerative disorders, very specifically to make them to reach the brain is complicated. The isolation of specific phytoconstituents from ethanopharmacologically important plants may lead to identification of novel neuroprotective agents or neurotonic agents. The least number of drugs currently available for the treatment of neurodegenerative disorders and their adverse drug reactions accelerates the need for exploitation of alternative molecules from plant sources.***

Keywords: neurodegeneration, Green tea leaves, Cruciferous vegetables, Gatrodia elata, Mucuna pruriens, Bacopa monnieri, Citrus fruits, Berries vulgaris, Cannabis leaf, Rosemarinus officinalis, herbal medicines

List of Abbreviations

ALS	Amyotrophic Lateral Sclerosis
PD	Parkinson's Disease
AD	Alzheimer's Disease
HD	Huntington's Disease
APP	Amyloid Precursor Protein
LRRK-2	Leucine-Rich Repeat Kinase-2
GBA	Glucocerebrosidase
BDNF	Brain-Derived Neurotropic Factor
SOD 1	Superoxide Dismutase 1
TDP-43	TAR DNA-Binding Protein 43
NAC	Non-Abeta Component
PCD	Programmed Cell Death
CMA	Chaperone Mediated Autophagy
GSK-3β	Glycogen Synthase Kinase-3β
INOS	Inducible Nitric Oxide Synthase
EGCG	Epigallocatechin-3-Gallate
6-OHDA	6-Hydroxydopamine
VTA	Ventral tegmental area
MPP+	1-Methyl-4-Phenyl Pyridinium
3-NPA	3-Nitropropionic Acid

1. Introduction

Neurons are the building blocks of the nervous system which includes the brain and spinal cord. Neurons normally don't reproduce or replace themselves, so when they become damaged or die they cannot be replaced by the body.

Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons. Etymologically, the word is composed of the prefix "neuro-, " which designates nerve cells (i.e., neurons), and "degeneration, " which refers to, in the case of tissues or organs, a process of losing structure or function. Thus, in the strict sense of the word, neurodegeneration corresponds to any pathological condition primarily affecting neurons. In practice, neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomic systems; they arise for unknown reasons and progress in a relentless manner. Conversely, neoplasm, oedema, haemorrhage, and trauma of the nervous system, which are not primary neuronal diseases, are not considered to be neurodegenerative disorders. Diseases of the nervous system that implicate not neurons but rather their attributes, such as the myelin sheath as seen in multiple sclerosis, are not neurodegenerative disorders either, nor are pathologies in which neurons die as the result of a known cause such as hypoxia, poison, metabolic defects, or infections.

Many neurodegenerative diseases–including amyotrophiclateralsclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) – occur as a result of neurodegenerative processes. These debilitating and incurable conditions are characterized by loss of neuronal cell function and are often associated with atrophy of the affected nervous system structures. An important subset of neurodegenerative disease concerns dementi as associated with aging. Alzheimer's disease (AD) is the most common clinically recognized dementia in aging populations, and 43% of people 85 or older are thought to suffer from Alzheimer's in the United States. Parkinson's disease (PD), another common nervous system disorder associated with the elderly, affects 1- 3% of the population over 60. United Nations population projections estimate a world population of 400 million people 80 years of age or older by the year 2050. Given the financial, societal and personal impact of the burden of these diseases, determining causes, prevention and treatment has become a major focus of basic and clinical research.

Study of the aetiology of neurodegenerative diseases shows association with genetic factors to be variable within populations for one disease state. Even in the case of Huntington's disease (HD), which is linked to a specific gene, how mutant Huntington's protein effects downstream symptoms of the disorder, including dementia, is not fully understood. The molecular basis of the effects of genetic variation, lifestyle and environmental factors including trauma and infection involves multiple signaling pathways. Neuropathological hallmarks of dementia include β-amyloid plaques and neurofibrillary tangles in AD, and Lewy body inclusions in PD. However, while protein aggregation clearly plays a role in neurodegenerative disease, there is evidence these are signatures of neuronal damage and additional causative elements remain to be discerned. The role of inflammation is an active area of investigation, as is the role of nitric oxide signaling. The effects of these and other key events on transcriptional regulation and initiation of apoptosis and neuro toxicity continues to be intensively explored.

2. Neurodegenerative Diseases

a) Alzheimer's Disease

Alzheimer's disease is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus (1).

Alzheimer's disease has been hypothesized to be a misfolded protein disease (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain (2). Plaques are made up of small peptides, 39–43aminoacids in length, called beta-amyloid (also written as A-beta or Aβ). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a trans membrane protein that penetrates through the neuron's membrane (3). APP is critical to neuron growth, survival and post-injury repair. In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis. One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques (4, 5).

b) Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disorder (6) and manifests as brady kinesia, rigidity, resting tremor and posture instability. The crude prevalence rate of PD has been reported to range from 15 per 100, 000 to 12, 500 per 100, 000, and the incidence of PD from 15 per 100, 000 to 328 per 100, 000, with the disease being less common in Asian countries (7, 8). Parkinson's disease is a degenerative disorder of the central nervous system. It results from the death of dopamine-generating cells in the substantia nigra, a region of the mid brain; the cause of cell-death is unknown. The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells (9, 10). The alpha-synuclein-ubiquitin complex cannot be directed to the proteasome. This protein accumulation forms protein aceouscytoplasmic inclusions called Lewy bodies (11, 12). The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles–the endoplasmic reticulum and the Golgi apparatus (13). Certain proteins like Rab1may reverse this defect caused by alpha-synuclein in animal models. Membrane damage by alpha- synucle in could be another Parkinson's disease mechanism.

The main known risk factor is age. Susceptibility genes including α-synuclein, leucine-rich repeat kinase 2 (LRRK-2), and glucocerebrosidase (GBA) have shown that genetic predisposition is another important causal factor (14).

c) Huntington's disease

HD causes astrogliosis (15) and loss of medium spiny neurons (16, 17). Areas of the brain are affected according to their structure and the types of neurons they contain, reducing in size as they cumulatively lose cells. The areas affected are mainly in the striatum, but also the frontal and temporal cortices (18). The striatum's subthalamic nuclei send control signals to the globus pallidus, which initiates and modulates motion. The weaker signals from subthalamic nucleithus cause reduced initiation and modulation of movement, resulting in the characteristic movements of the disorder, notably chorea (19).

Mutant Huntingtin is an aggregate-prone protein. During the cells' natural clearance process, these proteins are retrograde transport to the cell body for destruction by lysosomes. It is a possibility that these mutant protein aggregates damage the retrograde transport of important cargoes such as BDNF (Brain- derived neurotrophic factor) by damaging molecular motors as well as microtubules (20).

d) Amyotrophic lateralsclerosis

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a disease in which motor neurons are selectively targeted for degeneration. In1993, missense mutations in the gene encoding the antioxidant enzyme Cu/Zn superoxide dismutase 1 (SOD1) were discovered in subsets of patients with familial ALS. This discovery led researchers to focus on unlocking the mechanisms for SOD1- mediated diseases. However, the pathogenic mechanism underlying SOD1 mutant toxicity has yet to be resolved. Recent independent research by Nagai et al. (21) and Di Giorgio et al. (22) provide in vitro evidence that the primary cellular sites where SOD1 mutations act are located on astrocytes. Astrocytes then cause the toxic effects on the motor neurons (23).

Conventional as well as traditional medicines are used for treating various neurodegenerative disorders. These days much attention is drawn towards the established traditional systems of herbal remedies for many brain disorders, generating positive hopes for the patients.

3. Mechanisms of Neurodegenerative diseases

a) Genetics

Many neurodegenerative diseases are caused by genetic mutations, most of which are located in completely unrelated genes. In many of the different diseases, the mutated gene has a common feature: a repeat of the CAG nucleotide triplet. CAG encodes for the amino acid glutamine. A repeat of CAG results in a polyglutamine (polyQ) tract. Diseases showing this are known as polyglutamine diseases (24). Nine inherited neurodegenerative diseases are caused by the expansion of the CAG trinucleotide and poly Q tract. Two examples are Huntington's disease and the spinocerebellar ataxias. The genetics behind each disease are different and often unknown (24).

b) Protein misfolding

Several neurodegenerative diseases are classified as proteopathies as they are associated with the aggregation of misfolded proteins.

- **Alpha-synuclein**: can aggregate to form insoluble fibrils in pathological conditions characterized by Lewy bodies, such as Parkinson's disease, dementia with Lewy bodies, and multiple systematrophy. Alpha-synuclein is the primary structural component of Lewy body fibrils. In

addition, an alpha-synuclein fragment, known as the non-Abeta component (NAC), is found in amyloid plaques in Alzheimer's disease.
- **Tau**: hyperphosphorylated tau protein is the main component of neurofibrillary tangles in Alzheimer's disease.
- **Beta amyloid**: the major component of senile plaques in Alzheimer's disease.

c) Intracellular mechanisms

Protein degradation pathways
Parkinson's disease and Huntington's disease are both late-onset and associated with the accumulation of intracellular toxic proteins. Diseases caused by the aggregation of proteins are known as proteinopathies, and they are primarily caused by aggregates in the following structures:

- Cytosol, e.g. Parkinson's &Huntington's
- Nucleus, e.g. Spinocerebellar ataxia type 1(SCA1)
- Extra-cellularly excreted proteins, amyloid-β in Alzheimer's disease

There are two main avenues eukaryotic cells use to remove troublesome proteins or organelles:

Ubiquitin–proteasome: protein ubiquitin along with enzymes is key for the degradation of many proteins that cause proteinopathies including polyQ expansions and alpha-synucleins. This is the primary route cellsuse to degrade proteins (25).

Autophagy–lysosome pathways: a form of programmed cell death (PCD), this becomes the favourable route when a protein is aggregate- prone meaning it is a poor pro tea some substrate. This can be split into two forms of autophagy: Macroautophagy and Chaperone-mediated autophagy (CMA) (25).

Macroautophagy is involved with nutrient recycling of macromolecules under conditions of starvation, certain apoptotic pathways, and if absent, leads to the formation of ubiquinated inclusions. Experiments in mice with neuronally confined macroautophagy-gene knockouts develop intraneuronal aggregates leading to neurodegeneration.

Chaperone-mediated autophagy defects may also lead to neurodegeneration. Research has shown that mutant proteins bind to the CMA-pathway receptorson lysosomal membrane and in doing so block their own degradation as well as the degradation of other substrates (25).

Membrane damage
Damage to the membranes of organelles by monomericoroligomeric proteins could also contribute to these diseases. Alpha-synuclein can damage membranes by inducing membrane curvature (26) and cause extensive tubulation and vesiculation when incubated with artificial phospholipid vesicles. Extensive induction of membrane curvature is deleterious to the cell and would eventually lead to cell death.

d) Mitochondrial dysfunction
The most common form of cell death in neurodegeneration is through the intrinsic mitochondrial apoptotic pathway. This pathway controls the activation of caspase-9 by regulating the release of cytochrome c from the mitochondrial intermembrane space (IMS). Reactive oxygen species (ROS) are normal byproducts of mitochondrial respiratory chain activity. ROS concentration is mediated by mitochondrial antioxidants such as manganese superoxide dismutase (SOD2) and glutathione peroxidase. Over production of ROS (oxidative stress) is a central feature of all neurodegenerative disorders. In addition to the generation of ROS, mitochondria are also involved with life-sustaining functions (27). There is strong evidence that mitochondrial dysfunction and oxidative stress play a casual role in neurodegenerative disease pathogenesis, including in four of the more well-known diseases Alzheimer's, Parkinson's, Huntington's, and Amyotrophic lateral sclerosis. Neurons are particularly vulnerable to oxidative damage due to their strong metabolic activity associated with high transcription levels, high oxygen consumption, and weak antioxidant defense.

e) DNA Damage
The brain metabolizes as much as a fifth of consumed oxygen, and reactive oxygen species produced by oxidative metabolism are a major source of DNA damage in the brain. Damage to a cell's DNA is particularly harmful because DNA is the blueprint for protein production and unlike other molecules it cannot simply be replaced by re-synthesis. The vulnerability of post-mitotic neurons to DNA damage (such as oxidative lesions or certain types of DNA strand breaks), coupled with a gradual decline in the activities of repair mechanisms, could lead to accumulation of DNA damage with age and contribute to brain aging and neurodegeneration. DNA single-strand breaks are common and are associated with the neurodegenerative disease ataxia-oculomotor apraxia. Increased oxidative DNA damage in the brain is associated with Alzheimer's disease and Parkinson's disease (28).

Axonal Transport
Axonal swelling and spheroids have been observed in many different neurodegenerative diseases. This suggests that defective axons are not only present in diseased neurons, but also that they may cause certain pathological insult due to accumulation of organelles. Axonal transport can be disrupted by a variety of mechanisms including damage to: microtubules, cargoes, and mitochondria.

Programmed cell Death
Programmed cell death (PCD) is death of a cell in any form, mediated by an intracellular program (29). This process can be activated in neurodegenerative diseases including Parkinson's disease, amyotrophiclateralsclerosis, Alzheimer's disease and Huntington's disease. There are, however, situations in which these mediated pathways are artificially stimulated due to injury or disease.

Apoptosis (type I)
Apoptosis is a form of programmed cell death in multicellular organisms. It is one of the main types of programmed cell death (PCD) and involves a series of biochemical events leading to a characteristic cell

morphology and death. Two types apoptotic pathways that is Extrinsic and Intrinsic apoptotic pathways, that results from the activation of caspases.

Autophagic (type II)
Autophagy is essentially a form of intracellular phagocytosis in which a cell actively consumes damaged organelles or misfolded proteins by encapsulating the minto an autophagosome, which fuses withaly so some to destroy the contents of the autophagosome. Many neurodegenerative diseases show unusual protein aggregates. This could potentially be a result of underlying autophagic defect common to multiple neurodegenerative diseases. It is important to note that this is a hypothesis.

Cytoplasmic (type III)
The final and least understood PCD mechanism is through non-apoptotic processes. These fall under Type III, orcytoplasmic cell death. Many other forms of PCD are observed but not fully understood or accepted by the scientific community (30).

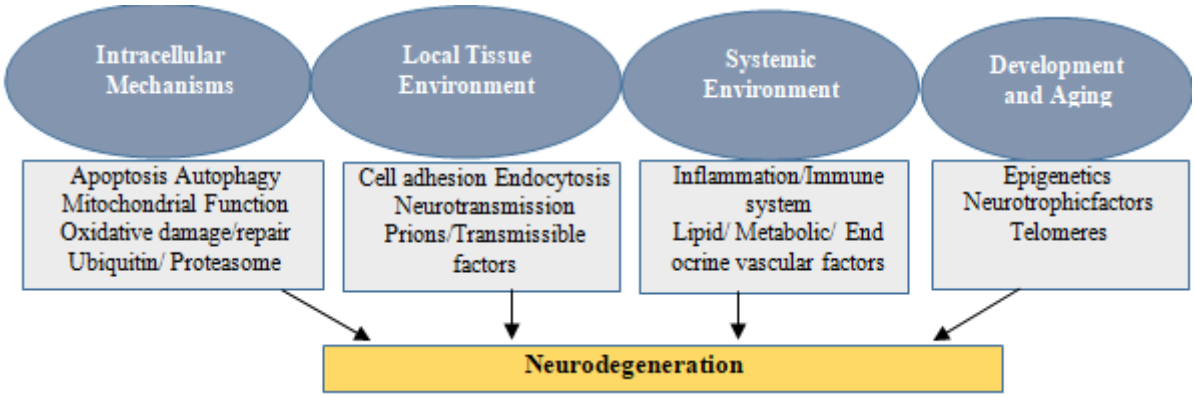

Figure 1: Mechanisms of Neurodegeneration

4. Conventional Treatment

Parkinson's disease
Deep brain stimulation of the subthalamic nucleus has been shown to ameliorate symptoms in patients with advanced disease. Depression, dementia, and psychosis are common psychiatric problems associated with Parkinson's disease. Psychosis is usually drug induced and can be managed initially by reducing antiparkinsonian medications (31, 32).

Table 1: Conventional treatment of Parkinson's disease

Medications	Adverse effects	Indications and comments
Anticholinergics Benzotropine (Cogentin) Trihexyphenidyl (Artane)	Dry mouth, dry eyes, constipation Hypotension, cognitive impairment, urinary retension.	Used for symptomatic control of parkinson's disease associated with more adverse effects than other drugs.
Carbidopa/levodopa Immediate and sustained release carbidopa/levodopa (sinemet)	Nausea, somnolence, dyskinesia, hypotension, hallucinations.	Levodopa is the most effective medication and remains the primary treatment; no added benefit for motor complications with sustained-release versus immediate release preparations.
COMT Inhibitors Entacapone (Comtan)	Diarrhoea; exacerbates levodopa adverse effects; bright orange urine.	Useful for managing motor fluctuations in patients taking levodopa;
Tolcapone (Tasmar)	Diarrhoea; exacerbates levodopa adverse effects; rare liver failure (liver function monitoring needed)	levodopa dose may need to be reduced if dyskinesia appears.
Dopamine agonists	Nausea, headache, dizziness Somnolence;	
Bromocriptine (Parlodel) Pergolide (Permax)	hallucinations; nausea; oedema; fibrosis of cardiac valves, lung, and retroperitoneum; retroperitoneal and pulmonary fibrosis.	Useful for early and advanced disease.
Pramipexole (Mirapex) Ropinirole (Requip)	Nausea, sleep attacks, oedema, hallucinations, hypotension.	Useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking levodopa. 2) Useful for early disease and in patients with Parkinson's disease and motor fluctuations.
MAO-B Inhibitors Selegiline (Eldepryl)	Nausea, insomnia, drug interactions with other MAO inhibitors/tyramine.	Useful for symptomatic control of parkinson's disease and as adjunct therapy for patients with parkinson's disease and motor fluctuations.
Rasagaline (Azilect)	Weight loss, hypotension, dry mouth, drug interactions with other MAO inhibitors/ tyramine.	
NMDA receptor inhibitor Amantidine (Symmetrel)	Nausea, hypotension, hallucinations, confusion, oedema.	Useful for treating akinesia, rigidity, tremor, dyskinesia.

Huntington's disease
No treatments can alter the course of Huntington's disease. But medications can lessen some symptoms of movement and psychiatric disorders. And multiple interventions can help a person adapt to changes in his or her abilities for a certain amount of time. Medication management is likely to

evolve over the course of the disease, depending on the overall treatment goals. Also, drugs to treat some symptoms may result in side effects that worsen other symptoms (33, 34, 35).

Table 2: Conventional treatment of Huntington's disease Medication for movement and psychiatric disorders:

Medications	Adverse effects	Indications and comments
Monoamine depletors Xenazine	Risk of worsening or triggering depression or other psychiatric conditions, nausea, drowsiness, restlessness	Specifically approved by the Food and Drug Administration to suppress the involuntary jerking and writhing of Huntington's disease.
Antipsychotic drugs Haloperidol(Haldol) Chlorpromazine	Suppressing movements, worsens involuntary contractions and muscle rigidity.	Beneficial in treating chorea.
Antidepressants Citalopram (Celexa) Escitalopram (Lexapro) Fluoxetine (Prozac, Sarafem) Sertraline (Zoloft)	Nausea, diarrhoea, drowsiness, low blood pressure.	These drugs may also have some effect on treating obsessive-compulsive disorder.
Antipsychotic drugs Quetiapine (Seroquel) Risperidone (Risperdal) Olanzapine (Zyprexa)	Stiffness and shakiness, sleepiness and slowness, weight gain.	May suppress violent outbursts, agitation, and other symptoms of mood disorders or psychosis.
Mood stabilising drugs Valproate (Depacon) Carbamazepine (Carbatrol) Lamotrigine (Lamictal)	Hand tremor, increased thirst, Diarrhoea, vomiting, weight gain.	Help to prevent the highs and lows associated with bipolar disorder.
Other drugs Risperidone (Risperdal) Quetiapine (Seroquel)	Worsens symptoms	They may have fewer side effects but still should be used with caution.

Alzheimer's disease

Current Alzheimer's medications can help for a time with memory symptoms and other cognitive changes. Two types of drugs are currently used to treat cognitive symptoms: (36)

Table 3: Conventional treatment of Alzheimer's disease

Medications	Adverse effects	Indications and comments
Cholinesterase inhibitors Donepezil (Aricept) Galantamine (Razadyne) Rivastigmine (Exelon)	Diarrhoea, nausea, loss of appetite, sleep disturbances.	It improve neuropsychiatric symptoms, such as agitation or depression, as well.
Antidepressants Zolpidem (Ambien) Eszopiclone (Lunesta)	Increase confusion, risk of falls.	This is used with great caution.
Anti-anxiety drugs Clonazepam (Klonopin) Lorazepam (Ativan)	Increase the risk of falls, confusion, dizziness.	This is used with great caution.

Amyotrophic lateralsclerosis

Two medications are currently approved by the Food and Drug Administration for the treatment of ALS (37).

Table 4: Conventional treatment of Amyotrophic lateral sclerosis

Medications	Adverse effects	Indications and comments
Rilutek	Dizziness, gastrointestinal conditions and liver changes.	It appears to slow the disease's progression.
Radicava	Bruising, gait disturbances, hives, swelling and shortness of breath.	It reduced the decline in daily functioning associated with ALS.

5. Natural Products and their Bioactive Components

Researchers identified some naturally occurring chemical compounds in plants, i.e., phytochemical through various research programs, and these are used for the management of neurodegenerative diseases. Phytochemicals are generally accepted to be safe with minimal side effects. Identification and characterization of new medicinal plants to cure neurodegenerative diseases and brain injuries resulting from stroke is the major and increasing scientific interest in recent years. There are more than 120 traditional medicines that are being used for the therapy of Central Nervous System (CNS) disorders in Asian countries. In the Indian System of medicine the following medicinal plants have shown promising activity in neuropsycho pharmacology: Allium sativum, Bacopamonnierae, Centellaasiatica, Celastruspaniculatus, Nicotianatobaccum, Withaniasomnifera, Ricinuscommunis, Salviaofficinalis, Ginkgobilob, Huperizaserrata, Angelicasinensis, Uncariatomentosa, Hypericumperforatum, Physostigmavenosum, Acoruscalmus, Curcuma longa, Terminalia chebula, Crocus sativus, Enhydrafluctuans, Valerianawallichii, Glycyrrhizaglabra, Reservatrol, Green tea, Sulforaphane, Nardostachysjatamansi, Gastrodiaelata, Mucunapruriens, Celastrol, Sesamol, Marijuana, Beriberine, etc (38).

Neuroprotective effects of phytoconstituents

Nootropic herb refers to the medicinal role of various plants/parts for their neuroprotective properties by the active phytochemicals including alkaloids, steroids, terpenoids, saponins, phenolics, flavonoids, etc. Phytocompounds from medicinal plants play a major part in maintaining the brain's chemical balance by acting upon the function of receptors for the major inhibitory neurotransmitters. Medicinal plants viz. Valeriana officinalis, Nardostachysjatamansi, With aniasomnifera, Bacopamonniera, Ginkgo biloba and Panax ginseng have been used widely in a variety of traditional systems of therapy because of their adaptogenic, psychotropic and neuroprotective properties (39).

Some phytoconstituents that present in some neuroprotective plant species: (40)

Terpenoids: Gastrodiaelata, Ginkgo biloba, Biota orientalis.

Glycosides: Ginkgo biloba, Melissa officinalis, Plantago ovate.

Volatile oils: Origanumdictamnus, Menthapiperita, Rosmarinus officinalis.

Alkaloids: Bacopamonnieri, Withaniasomnifera, Areca catechu.

Saponins: Bacopamonnieri, Dipsacus asper, Panax ginseng.

Phenolics: Curcuminoids, Reservatrol, Cassia siamea, Magnolia officinalis.

Flavanoids: Girsiumsetidens, Aster scaber, Passiflora actinia, Acelnikoense, Alnusglutinosa, Alpiniaofficinavum Hance, Schisandrachinensis.

Table 5: Some plants reported to possess neuroprotective effects

Plant species	Phytoconstituents	Use
Camellia sinensis (Tea plant)	Green tea catechins, caffeine, theanine, theaflavins	Alzheimer's disease
Brassica oleracea (Broccoli, Cabbage)	Isothiocyanate sulforaphane	Alzheimer'sdisease
Gastrodiaelata (Tien Ma)	Terpenes, benzyl alcohol, vanillyl alcohol, vanillin, and vanillic acid	Parkinson's disease
Mucunapruriens (Velvet bean)	Genisten, Phytic acid, Glutathione, Nicotine, Lecithin, Gallic acid, Harmine	Parkinson's disease
Bacopamonnieri (Water hyssop)	Bacosides, alkaloid brahmine, nicotine, and herpestine	Huntingson's disease
Citrus fruits (Lemon, Orange)	Hespiridine	Huntingson's disease
Berberies vulgaris (Barberry)	Beriberine	Amyotropic lateral sclerosis
Medicinal Marijuana (Cannabis)	Cannabinoids	Amyotropic lateral sclerosis
Rosemarinus officianalis (Rose mary)	Carnosic acid, Rosemarinic acid	Alzheimer's disease Parkinson's disease

6. Natural Products and its Study Methods

a) Green Tea

Green tea is a type of tea that is made from Camellia sinensis leaves. The efficacyofEpigallocatechin-3-gallate (green tea) in the treatment of Alzheimer's disease is found by in vitro and in in vivo preclinical studies.

Figure 2: Green tea leaves

In vitro studies: an update: In vitro studies on the anti-neuroinflammatory effects of EGCG have been performed on different cells. Results from these studies showed that the anti-neuroinflammatory capacity of EGCG is mainly associated to the inhibition of microglia-induced cytotoxicity. Lin et al. demonstrated that EGCG was able to suppress the neurotoxicity induced by Aβ, through the activation of the glycogen synthase kinase-3β (GSK-3β) and the inhibition of c-Abl/FE65 nuclear translocation. Wei et al., investigated on the inhibitory effects of EGCG on microglial activation induced by Aβ and on neurotoxicity in Aβ-stimulated EOC 13.31(cell line of microglia). Results revealed that EGCG was able to suppress the expression of TNFα, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) and to restore the levels of intracellular antioxidants against free radical-induced pro-inflammatory effects in microglia, the nuclear erythroid-2 related factor 2 (Nrf2) and the heme oxygenase-1 (HO-1).

In another study, Bieschke et al. showed that EGCG converted the large mature Aβ fibrils into smaller forms with no toxicity for mammalian cell (41). All these data suggest that EGCG may be considered an important agent with neuroprotective properties against AD.

In vivo preclinical studies: an-update: The neuroprotective effects of EGCG have been also demonstrated by in vivo experiments on several animal models. The EGCG was able to decrease Aβ levels and plaques formation in atransgenic mouse model when was injected intraperitoneally (20 mg/kg). Similar results were obtained by the same group of researchers, when EGCG administered orally in drinking water (50mg/kg), reduced Aβ deposition in the same mutantmice (42). In another study based on the generation of transgenic mouse models of AD, Li et al., investigated on EGCG (orally 20 mg/kg/day, for 3 months) capacity to interfere with Aβ deposits in different brain areas. Data emerged by immunohistochemistry, showed that Aβ deposits were reduced by 60% in the frontal cortex and 52% in the hippocampus. The authors engineered nanolipidic EGCG particles to improve oral's bioavailability of EGCG. By using this system in mouse model of AD's disease, the ability of EGCG for the treatment of AD was enhanced more than two-fold respect to treatment with free EGCG (43).

These data strongly suggest that EGCG could be used as a therapeutic agent for the treatment and the prevention of AD.

b) Sulforaphane

Figure 3: Cruciferous vegetables

It is obtained from cruciferous vegetables such as broccoli, Brussels sprouts, and cabbages. Among phytochemicals, isothiocyanatesulforaphane, derived from the hydrolysis of the glucosinolateglucoraphanin mainly present in Brassica vegetables, has demonstrated neuroprotective effects in several in vitro and in vivo studies. In particular, evidence suggests that sulforaphane beneficial effects could be mainly ascribed to its peculiar ability to activate the Nrf2/ARE pathway. Therefore, sulforaphane appears to be a promising compound with neuroprotective properties that may play an important role in preventing neurodegeneration.

The neuroprotective effects of SF against oxidative stress, in terms of protein carbonyl formation and cytotoxicity elicited by hydrogen peroxide, could be ascribed to its ability to induce proteasome expression in murine neuroblastoma Neuro2A cells. In similar cellular models, Park et al. confirmed the ability of SF to enhance the proteasome activities and to protect the neuronal cells from Aβ1–42-mediated cytoxicity. More recent studies reported that SF induced the expression of heat shock protein 27, demonstrating that SF- stimulated proteasome activity may contribute to cytoprotection. These data suggest that induction of proteasome by SF may facilitate the clearance of the Aβ1–42 peptides and lead to the improvement of protein misfolding in AD.

Kim et al. (44) investigated the potential neuroprotective effects of SF in an Aβ1–40peptide-induced AD acute mouse model. In particular, they recorded the ability of SF to ameliorate the cognitive function impairment although it did not directly interact with Aβ. These findings reinforce the indirect neuroprotective effects of SF against Aβ toxicity.

One year later, oral administration of SFN to AD-like mouse model decreased cholinergic neuronal loss, thereby; ameliorating the cognitive impairment caused by the prior administration of aluminum and D-galactose, and the occurrence of these events was ascribed to the ability of SFN to activate the Nrf2 pathway. In a subsequent study, the same authors reported that administration of SFN in the experimental animals significantly decreased the level of Aβ-plaque in both the hippocampal and cerebral cortex of mice, suggesting that SFN could ameliorate damages caused by Aβ-fragment cytotoxicity in AD-mouse model. Moreover, a study conducted by Lee et al. using scopolamine-induced memory impairment in a mouse model, It was shown that SFN enhances the cholinergic system activity by up-regulating acetylcholine (Ach) and choline acetyltransferase levels in hippocampal and cerebral cortex regions, as well as decreasing acetyl cholinesterase (AchE) activities, which in a way, prevents the setup and escalation of neurodegeneration.

c) Gatrodiaelata

Figure 4: Gatrodiaelata

Gastrodiaelata is a saprophytic perennial herb in the Orchidaceae family. Recent studies suggest that gastrodin is also protective against PD pathological changes. In a PD rat model established by injecting 6-hydroxydopamine (6-OHDA) to the right midbrain ventral tegmental area (VTA), gastrodin could improve rotation behavior of PD rats and increase the expression of TH-positive neurons in VTA, showing a protective effect on TH-positive neurons. Gastrodin could also reduce a poptosis in vivo and in vitro. In a 6-OHDA-induced rat model. In 1-methyl-4-phenylpyridinium (MPP+)-stimulated SH-SY5Y cells, pretreatment of gastrodin was able to inhibit apoptosis. There is the treatment of gastrodin could prevent MPTP-induced oxidative stress as measured by MDAin midbrain.

Glial cell activation also plays an important role in the pathology of PD. Microglial cells mediate immune responses by secreting many factors such as cytokines, chemokines, prostaglandins, ROS, RNS, and growth factors, some of which could enhance oxidative stress and trigger apoptotic cascades in neurons.

Lietal. (2012) reported that gastrodin was able to reduce the number of activated microglial cells and down-regulate nigral IL-1β and TNF-α expression in a rotenone-induced PD rat model, indicating gastrodin could alleviate microgial cells activation in PD substantia nigra. GE was effective in inhibiting both, the increased production of reactive oxygen species (ROS) and increase in Bax/Bcl- 2ratio, cleavedcaspase-3 and PARP proteolysis. GE might prove to be a valuable therapeutic agent for the treatment of various neurodegenerative diseases including progressive Parkinson's disease (PD) (45).

d) Mucunapruriens

Its English common names include velvet bean, Bengal

velvet bean, Florida velvet bean, etc.

Figure 5: Mucunapruriens

Mucunapruriens is a medicinal plant that is well known to naturally contain L-dopa (4–7%), which might be attributed to its neuroprotective effects against PD. However, the presence of other phytochemicals in M. pruriens, including polyphenols (tannins, flavonoids, gallic acid, phenolic acids), saponins, terpenoids, alkaloids, and fatty acids, have been reported with various pharmacological activities. Recent studies also suggest that phytochemicalsapart from L-dopa may also contribute to the overall neuroprotective activities of M. pruriens. Therefore, in this study, we prepared a M. pruriens seed extract (MPE) containing reduced L-dopa levels (<0.1%), which was subsequently evaluated for its neuroprotective effects using a panel of in vitro and in vivo assays. The seeds of M. pruriens were extracted/solvent-solvent partitioned in varying solvents to yield extracts, which were evaluated for L-dopa content by liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI– MS/MS). The L-dopa levels in the initial methanol M. pruriens seeds extract was 28.0%, which was significantly reduced to 0.03% in the ethylacetate M. pruriens extract (MPE). As even this low level (0.03%) of L-dopa could impart biological effects, we evaluated a pure L-dopa solution (<0.1%) in several of the in vitro assays (46).

Unresolved inflammation and excessive oxidant production by microglia are lethal to both neuronal and non-neuronal cells in the CNS and have been associated with PD. All of the Mucuna extracts including the crude methanol, hexanes, ethyl acetate (MPE), butanol, and water extracts (at 25 µg/mL) were evaluated for their protective effects against H2O2-induced toxicity in BV-2 cells. Only the MPE significantly increased the viability of BV-2 cells exposed to H2O2. Therefore, we evaluated the effects of MPE on oxidative stress induced by H2O2 in viability greater than 90.3% at 24 h. The cell viability of H2O2- treated BV-2 cells decreased by 39.2%, as compared with the control group. Although MPE, at concentrations of 12.5, 25, and 50 µg/mL, showed a trend to ameliorate the H2O2-induced cytotoxicity in BV-2 cells, only MPE at a concentration of 25 µg/mL significantly increased the cell viability of H2O2- treated BV-2 cells, by 18.6%. The protective effects of MPE against the production of ROS by H2O2 in BV-2 cells were then evaluated

e) Bacopamonnieri

Figure 6: Bacopamonnieri

B. monnieri is an herb used in Ayurveda, where it is also known as "Brahmi". 3-nitropropionic acid, a complex II inhibitor of the electron transport chain, causes Huntington disease-like symptoms after administration into animals. However, primary mechanisms are not clearly understood.

Inhibition of 3-NPA-Induced Oxidative Stress in Mitochondria of BrainRegions Invitro

Mitochondria isolated from different brain regions viz., cortex (Ct), cerebellum (Cb), hippocampus (Hc), pre-incubated with Bacopamonnieri extract (BME) (0.5 and 1 lg/ml) for 30 min. Further, untreated and BME pretreated mitochondria were exposed to 3-NPA (2 mM) for 1 h. The extent of oxidative damage was evaluated in terms of malondialdehyde (MDA) formation, ROS generation, and hydroperoxide levels. BME caused significant diminution of basal MDA levels (39–49%) at both concentrations in striatum mitochondria, while 3-NPA (2 mM) markedly elevated the MDA levels (113%). BME pretreatment completely inhibited the 3-Nitro propionic acid (NPA)-induced LPO (lipid peroxidation). Likewise, 3-NPA exposure resulted in robust ROS. Generation (120%) and HP levels (126%) instriatal mitochondria which were also abolished by BME pretreatment. Likewise, 3-NPA also caused marked enhancement in the levels of ROS and HP in mitochondria of other brain regions which were also abolished by BME pretreatment

Prophylactic Efficacy of BME Against 3-NPA-Induced Oxidative Stress Invivo

The dosage of BME was selected based on a preliminary dose determinative study. Prepubertal male mice were orally administered with BME (5 mg/kg bw) for a period of 10 days (prophylaxis group). Both untreated and mice given BME prophylaxis were administered 3-NPA (75 mg/kg bw, i.p.) on days 9 and 10 and killed 24 h after the last dose. Mice given physiological saline served as the untreated controls. Biochemical analysis was carried out incytosolic preparations obtained from brain regions viz., Ct, Cb, and Hc. BME treatment alone resulted in a significant decrease in the basal levels of oxidative markers in cytosol (MDA-23%; ROS-24%; HP-38%). Among mice administered 3-NPA, the cytosol exhibits robust elevation in MDA (70%), ROS (65%), and HP (57%) levels suggesting induction of oxidative stress in vivo. Interestingly, BME prophylaxis significantly diminished 3-NPA-mediated oxidative damage

(47).

f) Hespiridine

Figure 7: Citrus fruits

Hesperidin (Hsd) is a flavanone glycoside found in citrus fruits. Its aglycone form is called hesperetin. Its name is derived from the word "hesperidium", for fruit produced by citrus trees.

Previous studies showed that Hsd has neuroprotective effects both invitro and invivo.eg, neuroprotective effects on amyloid β, 3-propionic acid-induced and H2O2-induced Neurotoxicity (48). The neuroprotective effects of Hsd is mainly mediated by its antioxidant and antiinflammatory activities. The Hsd promotes neuronal crest survival without affecting the cell differenciation and proliferation. The Hsd, through the activation of the P13 and MAP kinase pathways, protects neuron from death. At the same time, Hsd increases the neuronal population by neuronal progenitorsviaastrocytes. This effect suggested for a new therapeutic strategy in the treatment of neurodegenerative diseases.

The mitochondrial toxin 3-nitropropionic acid (3-NP) effectively induces specific behavioral changes, primarily manifested as prepulse inhibition (PPI) deficit of selective striatal lesions in rats and primates mimicking those in HD. The implications of nitricoxide in a variety of neurodegenerative diseases attract attention to study the possible role of flavonoids in interaction with nitric oxide pathways involved in HD.

Systemic administration of 3-NP to rats for 5 days (20 mg/kg) caused reduction of locomotor activity by days 2 and 5, 55% deficit of PPI response, elevation of cortical, striatal and hippocampal malondialdehyde (MDA) levels by 63%, 41% and 56%, reduction of respective catalase activity by 50%. Electron microscopic ultrastructural examination showed marked mitochondrial swelling, perivascularoedema and shrunken nerve cells. Pretreatment with hesperid in (100 mg/kg) ahead of 3-NP prevented any changes of locomotor activity or PPI response, slightly increased cortical, striatal and hippocampal MDA levels by 10%and reduce drespective catalase activity by 22%, 20% and 5%. This study suggests a potential neuroprotective role of hesperid in against 3-NP-induced Huntington's disease-like manifestations (49).

g) Beriberine

Beriberine obtained from Berries vulgaris. In rat cerebral cortex, berberine inhibits synaptosomal glutamate release. By down regulating several pro inflammatory pathways. It presumably reduces the neuroinflammatory component of ALS. Berberine activates AMPK apparently by inhibiting mitochondria, resulting into increased glycolysis.

Figure 8: Berries vulgaris

In a study on rat astrocyte primary cultures, berberine and the alkaloid extract of B. aetnensis roots were able to restore the oxidative status modified by glutamate and the levels of TG2 (Tissue transglutaminase) to control values. Consequently, berberine or the alkaloid extract of B. aetnensis roots are able to ameliorate the excessive production of glutamate, protein misfolding and aggregation, mitochondrial fragmentation, and neurodegeneration. Berberineisa PPAR gamma inhibitor.

In the central nervous system regions of the sporadic and familial FTLD (Fronto temporal lobar degeneration) and ALS patients, TDP-43 (TAR DNA- binding protein 43) has been identified as the major component of Ubiquitanone

Inclusions which is abnormally hyperphosphorylated, ubiquitinated, and cleaved into C-terminal fragments to form detergent-insoluble aggregates. So far, the effective drugs for FTLD and ALS neurodegenerative diseases are yet to be developed. Autophagy has been demonstrated as the major metabolism route of the pathological TDP-43 inclusions, hence activation of autophagy is a potential therapeutic strategy for TDP-43 pathogenesis in FTLD and ALS. Berberine, a traditional herbal medicine, is an inhibitor of mTOR (mammalian target of rapamycin) signal and an activator for autophagy. Berberine has been implicated in several kinds of diseases, including the neuronal-related pathogenesis, such as Parkinson's, Huntington's and Alzheimer's diseases. However, the therapeutic effect of berberine on FTLD or ALS pathology has never been investigated.

Berberine is able to reverse the processing of insolubleTDP-43 aggregates formation through deregulation of mTOR/p70S6K signal and activation of inhibitor, 3-MA (Methyl adenine), reverses the effect of berberine on reducing the accumulation of insoluble TDP-43 and aggregates formation (50).

h) Medicinal Marijuana

Cannabinoids are obtained from Medicinal Marijuana used for the treatment of amyotropic lateral sclerosis.

Figure 9: Cannabis leaf

Not only the cannabinoid medicine potentially useful in symptom control of ALS, but it also has the potential to be useful in direct treatment for the disease, which could lead to slowing progression and increasing survival. In 2004, Raman et al. published an animal study showing evidence that delta-9- tetrahydrocannabinol (THC) (the psychoactive cannabinoid) may be useful in preventing ALS progression by reducing oxidative damage (i.e. damage caused to cells and tissues by free radicals) and excitotoxicity (i.e. excessive stimulation of a neuron, leading to damage), both of which can result in damage and death of motor neuron cells.

Using transgenic mice (type: SOD1 [G93A], which act as models for humans with ALS) in a 2005 study, Weydt et al. found that the use of the cannabinoid cannabinol (CBN)could possibly delay the onset of ALS-like symptoms, but would not necessarily change length of survival. Using the same class of transgenic mice, Bilsland et al. found that utilization of a synthetic cannabinoid may be useful in stopping progression of ALS-like symptoms. Interestingly, they also found that inactivation of the FAAH enzyme (fatty acid amidehydrolase) (which normally acts to increase levels of the endocannabinoid an andamide) was able to stop disease signs from appearing. However, in neither case was there an increase in length of survival. It was also found that inactivation of CB1 receptors did not affect onset of symptoms, but did result in a longer life span. This last finding shows that whatever potential exists for cannabinoid medicine in potential treatment of ALS, efficacy is unlikely a result of CB1 receptor activation. This body of evidence also signals that both stimulating and specifically inhibiting endocannabinoid receptors may modulate various disease processes like ALS.

A recent systematic review and meta-analysis of double-blind randomized controlled trials that compared any cannabis preparation to placebo among subjects with chronic pain showed a total of eighteen completed trials.

The studies indicate that cannabis is moderately efficacious for treatment of chronic pain. In the setting of ALS, cannabis use should be dose-titrated to the point of comfort. If additional opiate medications are needed to get effective pain control, then the anti-emetic effect of cannabis may help with the nausea sometimes associated with use of opioids. Use of cannabis may lower the need for opiate medications and may be safely used concomitantly as the opioid receptor system is distinct from the cannabinoid system. In addition to pain, spasticity is also a major problem for patients with ALS. Cannabis has an inhibitory effect via augmentation of gamma-amino-butyric acid (GABA) pathways in the central nervous system. This produces motor neuron inhibition at spinal levels in mice. Several past studies have suggested that cannabinoid therapy provide at least a subjective reduction of spasticity, although virtually all of the studies have been done in patients with multiple sclerosis (MS). In addition to pain and spasticity, there are other pharmacological effects of cannabis that may be useful for ALS patients. Patients with ALS and bulbar symptoms also usually have difficulty controlling and swallowing the saliva that is normally present in the oral cavity. Patients with ALS previously have reported that cannabis is at least moderately effective at reducing symptoms of pain, spasticity, drooling, appetite loss, and depression (51).

Maximum cannabinoid blood levels are only reached up to 6 hours post ingestion, with a much longer half-life, as long as 20–30 hours (138). This would also apply to any orally ingested cannabinoid, including dronabinol (Marinol). Dronabinol is available as a Schedule III (CIII) controlled substance per the Drug Enforcement Agency (DEA) guidelines (138). The DEA still considers botanical cannabis as a Schedule I (CI) controlled substance, dangerous and without medical use (139). However, consider that natural cannabis contains, at best, 20% THC.

Rosmarinus officinalis

A member of the mint family Lamiaceae, native to the Mediterranean region. Rosemary contains a number of potentially biologically active compounds, including antioxidants such as carnosic acid and rosmarinic acid. Carnosic acid is easily converted to carnosol by oxidation (Kim et al., 2006). Recently, naturally occurring antioxidants were found to reduce the risk of neurodegenerative diseases (Heo and Lee, 2004). In addition, carnosol and carnosic acid promoted the synthesis of nerve growth factor in glial cells (52).

Figure 10: Rosemarinus officinalis

Viuda-Marto et al. (2010) claim that the essential oil obtained from Rosemary can be considered good source of natural compounds with significant antioxidant activity, which can be attributed to the high percentage of the main constituents or to synergy among the different oil constituents. In the study of Park et al. (2008), possible protective effects of carnosic acid on neurotoxicity induced by dieldrin, an organochlorine pesticide implicated in sporadic Parkinson's disease were examined and results suggest that carnosic acid may safeguard dopaminergic neuronal cells from environmental neurotoxins by enhancing brain derived neurotrophic factor and repressing apoptotic molecules. In the study of Park et al. (2010), the neuroprotective effects of R. officinalis extract on H2O2-induced apoptosis in human dopaminergic cells were investigated. Findings indicate that R. officinalis is able to protect the neuronal cells against H2O2-induced injury and suggest that R. officinalis might potentially serve as an agent for prevention of several human neurodegenerative diseases caused by oxidative stress and apoptosis (53).

The study by Kim et al. (2010) examined possible protective effects of carnosol on sodium nitroprusside-induced cytotoxicity in C6 glial cells and results suggest that carnosol possesses abilities to inhibit sodium nitroprusside- mediated glial cell death through modulation of apoptotic events and induction of heme oxygenase 1 expression. Posadas et al. (2009) attempted to answer the hypothesis whether rosemary extract can enhance antioxidant defenses and improve antioxidant status in aged rats and it was found that supplementing the diet of aged rats with rosemary extract produced a decrease in antioxidant enzyme activity, lipidperoxidationandreactiveoxygenspecieslevelsthatwassign ificant for catalase activity in heart and brain, nitric oxide synthase in heart, and lipid peroxidation and reactive oxygen species levels in different brain tissues. These observations suggest that the rosemary supplement improved the oxidative stress status in old rats. The beneficial effects of rosemary where also investigated by Shimojo et al. (2010) in Alzheimer's model mice; rosemary extract and, in particular, rosmarinic acid imparted a prominent effect on motor performance, body weight loss, morphology of motor neurons and clinical scoring as well as the survival of Alzheimer's model mice, strongly suggesting that this herb could be one of the preferential ones to control the symptoms of Alzheimer's disease and, possibly, other neurodegenerative diseases such as Parkinson's disease (54).

7. Advantages of Natural drugs

There are a number advantages associated with using herbal medicines as opposed to pharmaceutical products (55). Examples include the following:

- **Reduced risk of side effects**: Most herbal medicines are well tolerated by the patient, with fewer unintended consequences than pharmaceutical drugs. Herbs typically have fewer side effects than traditional medicine, and may be safer to use overtime.
- **Effectives with chronic conditions**: Herbal medicines tend to be more effective for long-standing health complaints that don't respond well to traditional medicine.
- **Lower cost**: Another advantage to herbal medicine is cost. Herbs cost much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.
- **Widespread availability**: Yet another advantage of herbal medicines are their availability. Herbs are available without a prescription. You can grow some simple herbs, at home. In some remote parts of the world, herbs may be the only treatment available to the majority of people. More affordable than conventional medicine.
- **Promote natural healing.**
- **Strength in immune system.**
- Stabilizes hormones and metabolism.

8. Conclusion

Plant-derived bioactive compounds, in addition of directly being developed as drugs, also serve as prototype drug molecules known as 'lead compounds', and as pharmacological probes to help better understand pharmacological and biochemical mechanisms. Obviously natural products will continue to be extremely important as sources of medicinal agents.

The WHO estimates that 80% of people in the developing countries of the world rely on the traditional medicine for their primary health care, and about 85% of traditional medicine involves the use of plant extracts. This means that about 3.5 to 4 billion people in the world rely on plants as sources of drugs. Due to the insufficiency in understanding the exact pathophysiology of neurodegenerative disorders, they still present a great challenge in finding an appropriate treatment to these devastating diseases. Clinical treatment of neurodegenerative conditions is palliative and relies, in most cases, on improving stimulation at the relevant receptors by either increasing levels of the endogenous neurotransmitter or by the use of substances which have a similar agonist response.

Moreover, the development of new drugs for neurodegenerative disorders, very specifically to make the motor each the brain is complicated. The isolation of specific phytoconstituents from ethanopharmacologically important plants may lead to identification of novel neuroprotective agents or neurotonic agents. The least number of drugs currently available for the treatment of neurodegenerative disordersandtheiradversedrugreactionsacceleratestheneedfore xploitationof alternative molecules from plant sources.

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