



CODEN [USA]: IAJPBB

ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: <http://www.iajps.com>

Review Article

HERBAL INTERVENTION OF NEURODEGENERATIVE DISEASES

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abstract:

Neurodegenerative disorders (NDs) are anticipated to become a major concern for both medicine and public health due to ongoing global demographic shifts. These disorders are characterized mainly by the degeneration or loss of neurons, which plays a critical role in severe mental illnesses. This neuronal damage results in numerous neuropsychiatric complications and permanent disabilities for affected individuals. Administering therapeutic agents to the brain in conditions like Huntington's disease, Alzheimer's disease, Parkinson's disease, and multiple system atrophy remains a significant challenge. Several plant species have shown neuroprotective effects, particularly by reducing protein misfolding, improving protein quality control mechanisms, and regulating oxidative stress. For instance, Bacopa monnieri, Curcuma longa (turmeric), Camellia sinensis (green tea), Moringa oleifera, and Withania somnifera (ashwagandha) have all exhibited effectiveness against protein aggregation and neurotoxicity observed in experimental models of Alzheimer's, Parkinson's, Huntington's, and prion diseases.

Key words: Neurodegeneration, loss of neurons, Alzheimer's disease, Huntington's disease, phytochemicals, herbs.

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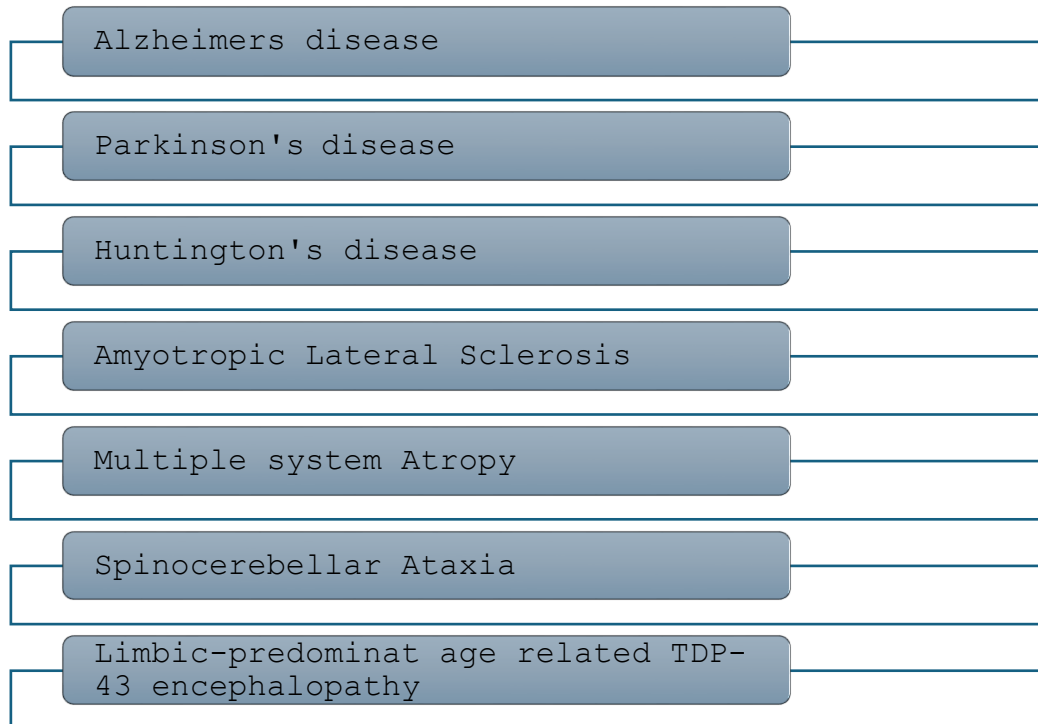
Please cite this article in press **E. Naga Deepthi et al., Herbal Intervention Of Neurodegenerative Diseases, Indo Am. J. P. Sci, 2025; 12(11).**

1.INTRODUCTION:

Neurodegenerative diseases (NDs) are defined by the targeted loss of neurons, which often leads to fatal outcomes [1,2]. These disorders include Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and various other progressive neuropsychiatric conditions [3, 4]. NDs generally occur in later stages of life and are commonly associated with a gradual decline in neurons and synaptic connections. The

specific symptoms of these diseases depend on the particular regions of the brain where neuronal degeneration takes place [5, 6]. Diagnosis of NDs primarily relies on clinical prevalence as well as corroborative magnetic resonance imaging (MRI) data [7]. The severity and progression of clinical symptoms are closely linked to the degree of neuronal loss [8, 9]. For example, the hippocampus—which plays a key role in declarative episodic memory—shows early neuronal degeneration in Alzheimer's disease [10].

➤ List of various neurodegenerative diseases:



Major types of neurodegenerative disorders (NDs)

2. ALZHEIMER'S DISEASE

The existence of a dementia syndrome serves as the basis for the clinical diagnosis of AD. According to standardized consensus criteria for dementia, the primary characteristic of the syndrome is the loss of intellectual capacity to the extent that it interferes with social or occupational functioning (American Psychiatric Association 1994) [11]. World Health Organization 1993 [12] The degree and severity of the cognitive impairments necessary to diagnose dementia vary amongst current clinical criteria.

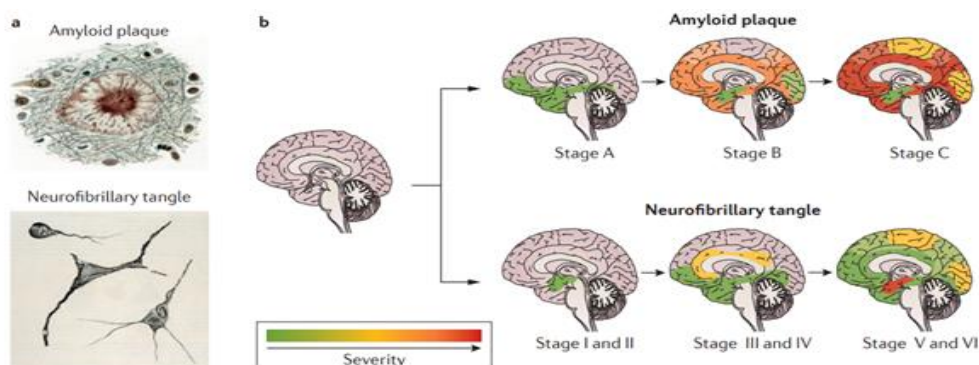


Fig. 1: This diagram illustrates the progression of Alzheimer's disease pathology—specifically the spread of amyloid plaques and neurofibrillary tangles in the brain over time.

Symptoms:

- Misplacing objects
- Forgetting conversation
- Problems remembering names
- Missing appointments ^[13].

Neuropathology:

The fourth part of the NIA/AA guidelines ^[14,15] updated the 1997 NIA/Reagan Institute neuropathological criteria for Alzheimer's disease (AD) ^[16]. Under this system, AD-related pathology is assessed across three parameters to generate an "ABC score."

- A (amyloid β , A β): Based on Thal phases, ranging from A0 (no A β /amyloid plaques) to A3 (advanced spread, phase 4–5).
- B (neurofibrillary tangles, NFT): Simplified Braak staging, from B0 (no NFT) to B3 (extensive cortical involvement, including primary motor and sensory areas).
- C (neurotic plaques, NP): CERAD-based scoring, from C0 (none) to C3 (frequent neurotic plaques).

Ginkgo biloba:

Source: It is obtained from the stem & leaves of ginkgo (or) maidenhair tree ^[17].

Family: Ginkgoaceae.

Chemical Constituents:

- Ginkgolides
- Ginkgotides
- Ginkgetin
- Bilobalide
- Ginkgolic acids ^[18].

3. PARKINSONISM DISEASE:

A prevalent neurodegenerative condition called Parkinson's disease (PD) results in significant impairment and a growing worldwide public health burden associated with motor and non-motor as well as mental issues. Developments in the genetic makeup of PD, starting with alpha-synuclein's discovery as the first autosomal dominant ^[19].

Symptoms:

- Rigidity
- Postural instability
- Rest tremor
- Increased resistance
- freezing, also known as motor blocks ^[20].

Neuropathology:

Parkinson's disease neuropathology is characterized primarily by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), especially the neuromelanin-containing A9 dopaminergic neurons. This loss leads to the depletion of dopamine in the striatum, causing the hallmark motor symptoms such as bradykinesia, rigidity, and tremor. A key pathological feature is the presence of Lewy bodies—intracellular inclusions composed mainly of aggregated alpha-synuclein protein. Early neuron loss in the SNpc is preceded by axon terminal loss in the striatum, indicating a substantial preclinical phase before motor symptoms appear. The degeneration extends to other brain regions including the locus coeruleus and autonomic nervous system, with a spreading pathology pattern described by Braak staging, starting from the medulla and olfactory bulb, progressing to the midbrain and cortex. The disease is considered a multisystem synucleinopathy caused by genetic and environmental factors ^[21].

St. John's Wort:

Source: St. John's wort (also known as hypericum or millepertuis). It is obtained from flowers of "Hypericum perforatum Linn" ^[22].

Family: Hypericaceae.

Chemical Constituents:

- Hypericin, pseudohypericin, and isohypericin;
- Flavonols (e.g., kaempferol, quercetin), flavones (e.g. Luteolin) and glycosides (e.g., hyperoside, isoquercitrin, Quercitrin, rutin)
- Hyperforin (2.0 to 4.5%) and adhyperforin (0.2 to 1.9%) ^[23].
- Proanthocyanidins
- Volatile oils (0.05–0.9%)

4. HUNTINGTON DISEASE:

The substantia nigra is a component of Huntington's disease. Layers 3, 5, and 6 of the cortex; the CA1 area of the parietal lobe's angular gyrus; the hippocampal region and cerebellar Purkinje cells ^[24]; and lateral tuberal nuclei of the centromedial ^[25] and hypothalamus thalamic

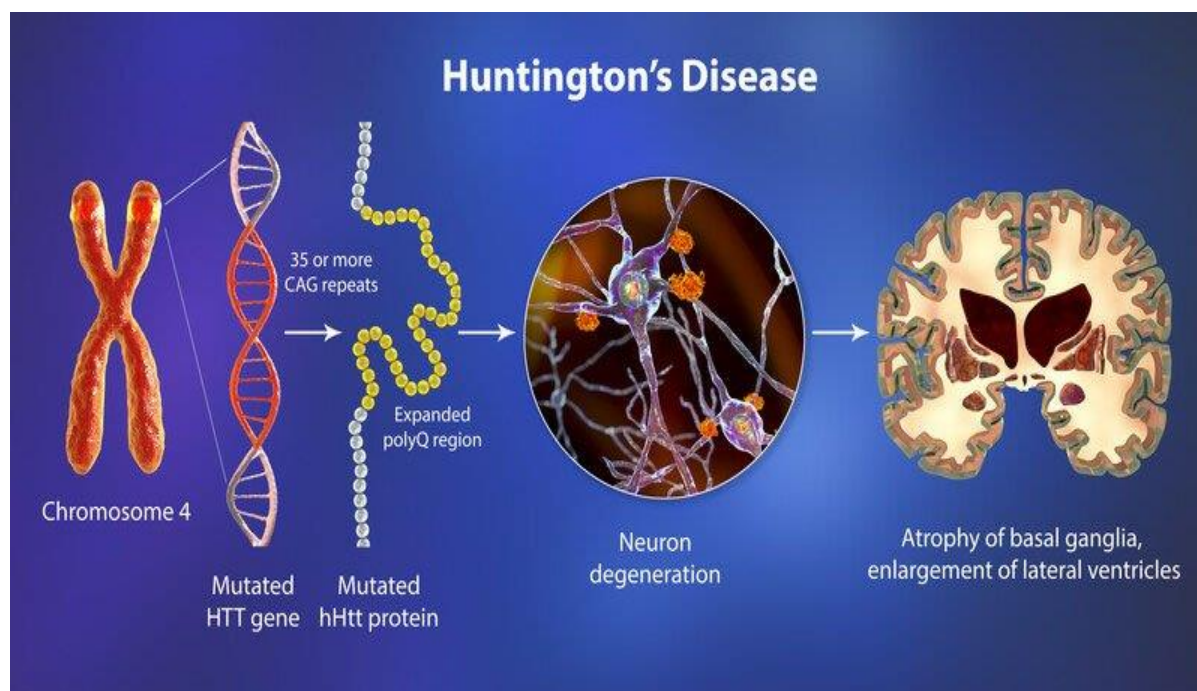


Fig.2 : Huntington's diseases:mutated gene, abnormal protien, neuron degeneration, brain atrophy, movement decline.

Clinical symptoms:

The triad of movement disorder, cognitive decline, and behavioral abnormalities—which typically begin at age 42—are the classic clinical features of HD. Huntington's chorea was its original name.

- The most incapacitating aspects of HD are frequently behavioral abnormalities.
- One of the components of the triad that defines the HD phenotype is cognitive impairment.
- The number of publications pertaining to HD has increased exponentially in recent years.

Neuropathology:

The neuropathology of Huntington disease (HD) is characterized primarily by progressive degeneration of the neostriatum, especially the caudate nucleus and putamen. This neuronal loss predominantly affects GABAergic medium spiny projection neurons, which make up about 95% of neurons in the neostriatum^[26]. The degeneration is bilateral and symmetrical, following a specific spatial and temporal pattern. In addition to the striatal loss, there is significant thinning and atrophy of the cerebral cortex, with selective neuronal loss in specific cortical layers. This cortical degeneration correlates with the psychiatric, cognitive, and neuropsychological symptoms seen in HD patients. The cerebellum and other brain regions can also show neurodegeneration in more advanced stages. This multi-regional brain involvement explains the complex spectrum of motor, psychiatric, and cognitive symptoms in Huntington

disease, highlighting it as a disease affecting both basal ganglia and cortical structures^[27].

Bacopa monnieri:

Source: The plant known as water hyssop (*Bacopa monnieri* L. Pennel).

Family: Plantaginaceae.

Chemical Constituents:

It includes active substances with a range of biological activities, including

- cucurbitacins
- alkaloids
- saponins.

5. AMYOTROPHIC LATERAL SCLEROSIS:

"Amyotrophic" describes weak, atrophying muscles. Numbness and fasciculation that indicate lower limb disease motor neurons. "Lateral sclerosis" describes the challenging Palpation of the spinal column's lateral columns. In autopsy specimens, the cord shows gliosis after development of the spinal cords.

Symptoms:

- Twitching and cramping of muscles, especially those in the hands and feet
- Loss of motor control in the hands and arms
- Trouble using arms and legs
- Tripping and falling
- Dropping things

Neuropathology:

Amyotrophic lateral sclerosis (ALS) neuropathology is characterized by progressive

degeneration of motor neurons in the spinal anterior horn and motor cortex, leading to muscle atrophy and weakness. A hallmark molecular feature in most ALS cases is the presence of TDP-43 immunoreactive neuronal cytoplasmic inclusions [28]. Motor neuron death in ALS resembles apoptosis, involving stages such as chromatolysis, somatodendritic attrition, and apoptosis, with elevated pro-apoptotic proteins observed. The disease spreads regionally, with motor neuron loss greatest at disease onset areas. ALS involves various pathogenic mechanisms like glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, defective axonal transport, and abnormal protein aggregation. Genetic mutations in genes such as SOD1, TDP-43, FUS, and C9orf72 contribute distinct molecular pathologies. Overall, ALS neuropathology features selective motor neuron degeneration, protein inclusions, and cellular dysfunctions driving progressive paralysis [29].

Chamomile

Source : It has two popular varieties:

1. Roman Chamomile (*Chamaemelum nobile*)
2. German Chamomile (*Chamomilla recutita*).

Family: Asteraceae/Compositae

Chemical Constituents:

- Essential oils with major components
- Flavonoids such as apigenin
- Coumarins including herniarin [30].

6. MULTIPLE SYSTEM ATROPHY:

Multiple system atrophy (MSA) is a rare, progressive neurodegenerative disorder affecting adults, characterized by the degeneration of brain and spinal cord nerve cells that control movement (the central nervous system) and automatic bodily functions (the autonomic nervous system).

Symptoms:

- Orthostatic hypotension (OH)
- Urinary bladder dysfunction
- Sexual dysfunction [59].

Neuropathology:

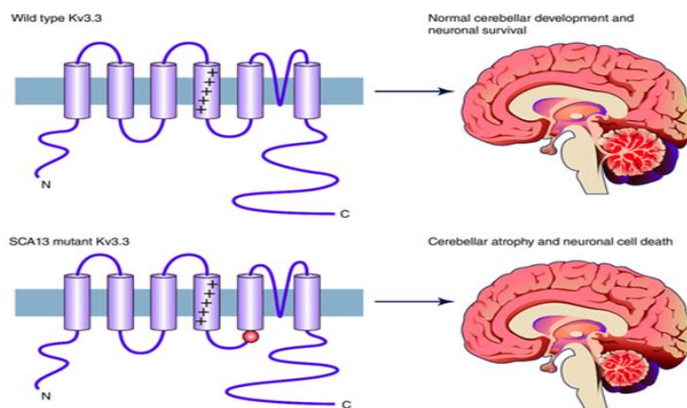


Fig. 3: Comparison between wild type Kv3.3 & SCA13 mutant Kv3.3, two forms of potassium channel protein.

Multiple system atrophy (MSA) is a progressive, fatal neurodegenerative disorder characterized neuropathologically by the presence of α -synuclein aggregates primarily within oligodendrocytes, known as glial cytoplasmic inclusions (GCIs), which is the diagnostic hallmark of the disease [31]. MSA is classified as an α -synucleinopathy due to this hallmark pathology. There are two main clinicopathological subtypes of MSA: MSA with predominant parkinsonism (MSA-P), associated with striatonigral degeneration; and MSA with predominant cerebellar ataxia (MSA-C), associated with olivopontocerebellar atrophy. The pathology involves widespread accumulation of α -synuclein in oligodendroglial cells, but α -synuclein aggregates are also found in neurons as neuronal cytoplasmic inclusions (NCIs) and other forms, though less frequently [32].

Curcumin:

Source: Turmeric (*Curcuma longa*).

Family: Zingiberaceae.

Chemical Constituents:

- Curcumin I (Diferuloylmethane)—the major component (~94%), with the chemical formula $C_{21}H_{20}O_6$. Its IUPAC name is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione
- Curcumin II (Demethoxycurcumin)—approximately 6%, with formula $C_{20}H_{18}O_5$.
- Curcumin III (Bis-demethoxycurcumin)—about 0.3%, with formula [33].

7. SPINOCEREBELLAR ATAXIA:

Spinocerebellar ataxia (SCA) refers to a group of genetic, progressive, degenerative diseases characterized by the deterioration of the cerebellum and sometimes other parts of the nervous system, including the spinal cord and brainstem.

SCAs are usually autosomal dominant, meaning only one copy of the faulty gene is needed to develop the disease [34].

Symptoms:

- Gait ataxia (unsteady, staggering walk)
- Poor coordination of hands, arms, and legs
- Frequent falls
- Clumsiness [35].

Neuropathology:

The neuropathology of spinocerebellar ataxia (SCA) is characterized by progressive neurodegeneration predominantly affecting the cerebellum, especially the Purkinje cells. This leads to cerebellar atrophy, astrogliosis, and loss of cerebellar cortical neurons. In some types, intranuclear ubiquitin-positive inclusions are observed. The disease mechanisms include expanded repeat mutations (such as CAG repeats encoding polyglutamine in several SCAs), leading to protein misfolding, transcriptional dysregulation, ion channel dysfunction, and impaired cellular processes such as autophagy and calcium homeostasis. Mutant proteins disrupt Purkinje cell morphology and firing, resulting in neurological deficits like ataxia. Different SCA subtypes show varying pathological features, but Purkinje cell loss with associated dendritic abnormalities remains a central hallmark across types.

Paeonia lactiflora

Source: It is obtained from the roots of *Paeonia obovata* and *Paeonia lactiflora*, which are perennials.

Family: Paeoniaceae.

Chemical Constituents:

Volatile oil constituents:

- Eucalyptol
- Caryophyllene.

8. LIMBIC-PREDOMINANT AGE-RELATED TDP-43 ENCEPHALOPATHY:

LATE (Limbic-predominant Age-related TDP-43 Encephalopathy) is diagnosed primarily by clinical presentation of amnesic dementia and confirmed postmortem by pathology showing accumulation of TDP-43 protein aggregates in limbic brain regions. Currently, no molecular biomarkers exist that are specific for TDP-43 pathology or LATE itself.

Symptoms:

- Repetitive speech and forgetfulness
- Getting lost or wandering

- Misplacing things
- Memory loss and difficulty remembering facts.

Neurodegenerative diseases:

The neuropathology of LATE (limbic-predominant age-related TDP-43 encephalopathy) in amyotrophic lateral sclerosis (ALS) features degeneration and loss of motor neurons primarily in the spinal anterior horn, motor cortex, and brainstem motor nuclei. A hallmark is the presence of TDP-43 proteinopathy, characterized by cytoplasmic inclusions of transactive response DNA-binding protein 43 (TDP-43) in neurons and glial cells. This pathology extends progressively from the motor regions to involve other areas such as the prefrontal cortex, basal ganglia, and hippocampus in later stages. Neurodegeneration involves apoptosis-like cell death and Wallerian degeneration of motor axons. Bunina bodies, eosinophilic cytoplasmic inclusions unique to ALS, are also observed. Gliosis replaces lost neurons, and disease severity correlates with the extent of TDP-43 pathology and neuronal loss [36].

Indian gooseberry

Source: It is obtained from the fruits of “*Embolia officinalis*.”

Family: Euphorbiaceae.

Chemical Constituents:

- Moisture: 81–82.8%
- Protein: 0.5–3.2%
- Fat: 0.1–0.46%
- Carbohydrate: 7.6–14.1%

9. Oxidative stress in NDs:

Oxidative stress, caused by an imbalance between reactive oxygen and nitrogen species (ROS and RNS) and antioxidants, damages cellular components like DNA, proteins, and lipids, contributing to neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's. While small amounts of ROS and RNS are essential for brain functions like cell signaling and memory, excessive levels lead to nerve cell death. The brain is especially vulnerable due to its high oxygen use, fatty acid content, and low antioxidants. Mitochondria and enzymes like NADPH oxidase produce ROS, which can generate highly reactive and harmful molecules through various reactions [37].

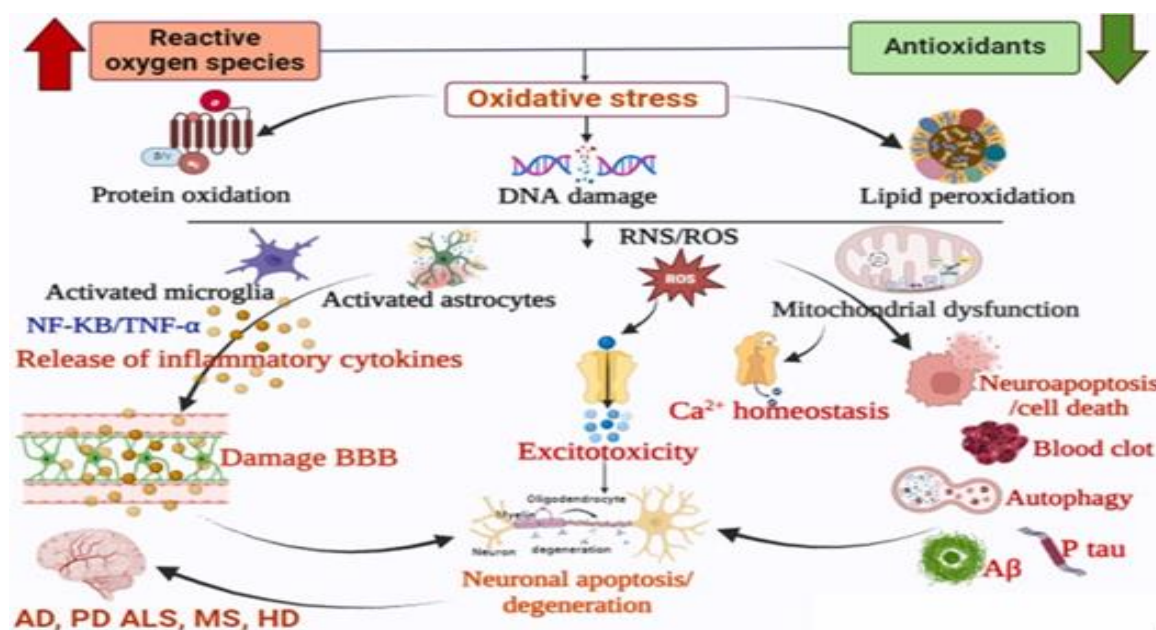


Fig. 4: Oxidative stress damages cellular macromolecules, activates glial inflammation, disrupts calcium and autophagy, and leads to neuronal death and neurodegeneration.

10. Major molecular mechanisms involved in NDs:

The complex process of neurodegeneration, which is frequently linked to aging, occurs when certain brain cells (nerve cells) stop functioning [38]. Clumps develop in various brain regions as a result of certain proteins in the brain not functioning properly in neurodegeneration [76]. Additional problems brought on by neurodegeneration include DNA damage, inflammation, and energy deficiencies. These cause cell death by progressively intensifying. Cells can die in a variety of ways, including by shutting down or disintegrating. The main molecular mechanisms pertaining to neurodegeneration have been thoroughly covered in the following section, which illustrates important mechanisms underlying NDs [39].

11. CONCLUSION:

Neurodegenerative disorders like Alzheimer's, Parkinson's, and Huntington's involve progressive neuronal loss and oxidative stress, leading to cognitive and motor decline. Herbal agents such as Bacopa, turmeric, green tea, ginseng, and Ginkgo show neuroprotective potential through antioxidant, anti-inflammatory, and anti-aggregative actions. Their bioactive compounds offer multi-targeted effects, and integrating phytochemicals with conventional therapies and advanced delivery systems may enhance treatment efficacy and slow disease progression.

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