Neurodegenerative diseases are characterized by protein aggregates and inflammation as well as oxidative stress in the central nervous system (CNS). Multiple biological processes are linked to neurodegenerative diseases such as depletion or insufficient synthesis of neurotransmitters, oxidative stress, abnormal ubiquitination. Furthermore, damaging of blood brain barrier (BBB) in the CNS also leads to various CNS-related diseases. Even though synthetic drugs are used for the management of Alzheimer’s disease, Parkinson’s disease, autism, and many other chronic illnesses, they are not without side effects. The attention of researchers has been inclined towards the phytochemicals, many of which have minimal side effects. Phytochemicals are promising therapeutic agents because many phytochemicals have anti-inflammatory, antioxidative as well as anticholinesterase activities. Various drugs of either synthetic or natural origin applied in the treatment of brain disorders need to cross the BBB before they can be used. This paper covers various researches related to phytochemicals used in the management of neurodegenerative disorders.

1. Introduction

Various neurodegenerative (progressive loss of structure and/or function of neurons) disorders share many common features at both cellular and subcellular levels. Intracellular and extracellular changes could be observed in Alzheimer’s, Parkinson’s, Huntington’s, and other neurodegenerative diseases. As far as cellular and subcellular biological events are concerned, the cytosol and endoplasmic reticulum are responsible for the synthesis of new structural and functional protein molecules. Mechanisms of translational as well as posttranslational modifications are highly complex and sophisticated in nature. Any polypeptide that fails to fold properly is directed to its degradation processes or known as autophagy and ubiquitin proteasome system [1, 2].

Neurodegenerative disorders are usually characterized by accumulation of abnormal protein aggregation that leads to inflammation as well as oxidative stress in the central nervous
system (CNS). Parkinson’s disease (PD) and Alzheimer’s
disease (AD) are the most common disorders of nervous
system caused by environmental and genetic influences [3–
5]. It has been observed that various types of biological
mechanisms are associated with neurodegenerative disorders
such as oxidative stress, aggregates of proteins in neurons,
depletion or in sufficient synthesis of neurotransmitters,
degradation of neurotransmitters in the synaptic cleft due
to the higher activity of enzymes, abnormal ubiquitination,
mitochondrial dysfunction, and excitotoxicity of neurons as
well as disarrangement or damage of the blood brain barrier
(BBB) (Figure 1).

AD is characterized by cognitive decline, neuronal loss,
neuronal inflammation, and neuronal death, which is also
known as apoptosis and/or necroptosis. Moreover, aggrega-
tion of β-amyloid (Aβ) is one of the main features of AD. The
formation of hyperphosphorylated Tau (microtubule-
associated protein) in the neurons is also linked with AD. PD
is a movement disorder which is characterized by abnormal
aggregation of α-synuclein protein in the neurons [33].
Similarly, abnormal long polyglutamine (PolyQ) may lead to
Huntington’s disease [34].

Another important brain disorder related to CNS inflam-
mation and characterized by learning and social disabilities
with no definite pathogenesis is known as autism spectrum
disorder (ASD). Multiple biochemical and molecular features
could be observed for the neurodegeneration in the brain of ASD [35, 36] including oxidative stress [37, 38], activated
astrocytes and microglia [39, 40], neuronal loss [35, 40],
elevated levels of 8-oxo-guanosine [41], and development of
proinflammatory cytokines [40, 42].

Children with ASD tend to behave differently under stress
or when exposed to certain foods, showing skin allergies
[43]. Neurotensin with release of corticotrophin-releasing
hormone under stressful conditions stimulates the microglia
and mast cells leading to neurotoxicity and focal brain inflam-
mation. In case of ASD, various pathological states could
be observed but not in all ASD children including allergic
symptoms, increased anti-brain protein autoantibodies, high
anxiety, increased oxidative stress, and increased food intol-
erance while decreasing the levels of reduced glutathione, sul-
fation, and methylation [43]. Luteolin (a flavonoid) showed
inhibitory effects on human mast cells that release tumor
necrosis factor (TNF) [44]. Luteolin such as epigallocatechin
gallate inhibits [45] mammalian target of rapamycin (mTOR)
which stimulates the mast cells and microglia proliferation
[46, 47] leading to the retardation of the release of TNF which
could initiate apoptosis, necroptosis, and/or inflammation in
the biological system. Various important biological actions
of luteolin are illustrated (Figure 2) which may be helpful in
children of ASD.

2. Blood Brain Barrier (BBB)

The blood brain barrier (BBB) is responsible for the reg-
ulation of small molecules (solute) between the CNS and
the blood circulation. Three different kinds of barriers could
be observed where the central nervous system and blood
interact; arachnoid barrier, blood-cerebrospinal fluid (CSF)
barrier and the BBB. The neurons in the CNS signal by
sending action potentials through which neurons interact in
the biological system. The BBB had tight junctions between
cells responsible for the reduction of flux mechanism through
the paracellular pathway and intercellular cleft (physical
barrier) and mediation of solute flux mechanisms (transport
barrier) as well as enzyme metabolizing molecules (metabolic
barrier). Moreover, the functions of barriers are equally
operated in physiological and pathological states of BBB
[48]. The tight junctions present between the astrocytes
(part of the BBB) are composed of claudin and occludin
proteins. Damage in these proteins or tight junctions can
lead to the loss of BBB integrity with functional barrier
loss [49, 50]. Various drugs, either synthetic or natural,
may have their own mode of action but drugs used in
the treatment of brain disorders have to cross the BBB to
gain entry into the CNS, since structural and/or functional
dysfunction in the BBB leads to inflammatory changes in
the tissue such as movement of immune mediators in the
brain, further contributing to the neurodegenerative process
[51].

3. Inhibition of Cholinesterase Activity

Stimulating acetylcholine release in the brain region is
one of the ways used in the treatment of neurodegenera-
tive disorder such as AD that can further contribute to
dementia and decline in higher cognitive function [52].
The pathological state of CNS particularly related to AD
is characterized by neurofibrillary tangles, derangement of
neurotransmitters in the neurons and synaptic cleft, and
β-amyloids plaques all of which are related inflamma-
tory mechanisms [53–55]. Both acetylcholinesterase (AChE)
and butyrylcholinesterase (BChE) are responsible for the
breakdown of acetylcholine in the synaptic region and low
levels of acetylcholine has been found to be related to
age-related disorders that leads to loss of cognitive ability
[18, 56].

Reactive oxygen species (ROS) developed as a result
of oxidative stress in the biological system can contribute
to damage of biological macromolecules and as a result
pathological state at cellular level can become more evident.
Such pathogenic state plays a crucial role in the aging process
[57]. Cholinesterase inhibitors are not commonly used in
allopathic and current treatments do not lead to sufficient
production of acetylcholine to help in the management of
AD [18]. The research in the field of phytochemicals has
developed into investigation of natural compounds respon-
sible for antioxidative (Table 2) and antiaging properties that
can also be useful for neurodegenerative disorders [18, 58].
It is important to stimulate the cholinergic receptors in
the CNS or enhance the prolonged production of acetyl-
choline in the synaptic cleft with the help of such active
constituents that could retard the activities of AChE and
BChE in the neuronal system. When the inhibition of enzyme
activities is 60% or more by the plants extracts, compounds
are generally considered as strong inhibitors (Table 3) [59].

4. Anti-Inflammatory and Antioxidative Activities

Various medicinal plants have anti-inflammatory activities by inhibiting cyclooxygenase-1 (COX-1) that surrounds amyloids plaque in microglia. The accumulation of COX-1 enzyme in microglia in AD patients may be responsible for the local increase in oxidative stress and prostaglandin synthesis [10]. Ferula assafoetida, Syzygium aromaticum, and Zingiber officinalis have previously been reported to have activity against COX-1 enzyme [10]. F. assafoetida has previously been used as memory enhancer, antibacterial, antispasmodic, and antihelminthic in traditional medicines. Z. officinalis showed not only anti-COX-1 activity but also free radical scavenging activity that may be contributed to the presence of important phytochemicals such as gingerols and shogaols [10].

Sinapic acid (Brassicaceae) shows anti-inflammatory activity and can act as a neuroprotective agent by decreasing the levels of Aβ and by protecting neuronal cell death [15]. On the other hand, Emblica officinalis may be used in the treatment of mental disorders and as anti-inflammatory agent [60]. Several natural polyphenols such as vitamins, flavonoids, phenolic acids, and other polyphenols including thymol, ellagic acid, and eugenol have antioxidant properties and may be used for neurodegenerative diseases as promising therapeutic agents (Tables 1 and 3).

5. Computational Approaches towards Neurodegenerative Disorders

With the advancements in computational fields, particularly in the field of bioinformatics, the understanding of biological system at molecular level has improved drastically. The action of enzymes with their substrates, the synthesis of proteins, degradation of various biological macromolecules, ubiquitination, and many other processes could be observed with various computational programs including in silico molecular docking strategies. The normal homeostasis including metabolic equilibrium associated with many complex biological mechanisms under the supervision of autonomic nervous system as well as prediction for pathological state and possible therapeutic suggestions.

Jeyam et al. [7] used the in silico techniques for the understanding of molecular behavior of some traditional medicines for the management of PD. The loss of dopamine is considered as prominent feature of PD. Currently, levodopa (L-Dopa) is given in the form of supplementation for the management of PD. Catecholamine-O-methyltransferase (COMT), an enzyme, is responsible for the metabolism and conversion of L-Dopa into 3-O-methyl dopa. Hence, the inhibition of COMT may be one of the important
ways to treat the disorder. Considering this way of treatment, the neuroprotective phytocompounds were evaluated using in silico studies [7]. Phytochemicals such as baicalin, stigmasterol, emodin, curcumin, wogonin, and eriodictyol were found to be having binding energies of approximately $-7$ kcal/mol which was similar to tacapone (synthetic drug to enhance the levodopa treatment) indicating that amentoflavone from Ginkgo biloba and ginsenoside from Panax ginseng are perceived as very good inhibitors for COMT as well as good adjuvants for L-dopa management. Kuhn and Kollman [61] studied and calculated the free energy activation of COMT considering the molecular dynamics of this enzyme. Moreover, Lee and Kim [62] investigated human COMT for designing anti-PD drug by using the ligand docking and comparative homology modeling.

Ayurveda medication has been evaluated for schizophrenia using in silico techniques [8]. Schizophrenia is associated with misbalancing of various chemicals of the brain involving the glutamate and dopamine. Studies on schizophrenia indicated that patients have abnormalities in brain structure such as decreased size of certain brain regions, enlargement of fluid-filled cavities, and less metabolic activities. Moreover, patients have delusions and hallucinations. From the Indian medication, three plants (Rauvolfia serpentina, Withania somnifera, and Mandukparni) were selected for the investigation of their role in the management of schizophrenia by using the tools of bioinformatics. The active molecules from these plants were docked with RGS-4 protein (regulator for G protein signaling-4) considered to be responsible for schizophrenia. The docking of RGS-4 protein with the combinations of reserpine, withanolide, and asiaticoside from Rauvolfia serpentina, Withania somnifera, and Mandukparni, respectively, showed that such combination therapy could be helpful in the management of schizophrenia [8].

### 6. Conclusion

In future, phytochemicals could be used as promising therapeutic agents for neurodegenerative disorders due to their anti-inflammatory and antioxidative as well as anti-cholinesterase activities. The neurodegenerative disorders...
such as AD, PD, Huntington’s, and others share common features at cellular and subcellular levels as well as sharing mostly common molecular signaling pathways that may lead to apoptosis, necroptosis, and inflammation. Overall phytochemicals provide promising alternatives to current therapies for neurodegenerative disorders.

**Conflict of Interests**
The authors declare that they have no conflict of interests.

### Table 3: List of plants having antioxidative and anticholinesterase activity.

<table>
<thead>
<tr>
<th>Plant</th>
<th>Active compounds</th>
<th>Properties</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acorus calamus</em></td>
<td>α-asarone, β-asarone, eugenol</td>
<td>Antioxidative, anticholinesterase</td>
<td>[13]</td>
</tr>
<tr>
<td><em>Adhatoda vasia</em></td>
<td>Vasicine, vasicol, arachidic, cerotic, linoleic, oleic acids</td>
<td>Anticholinesterase</td>
<td>[10]</td>
</tr>
<tr>
<td><em>Bacopa monnieri</em></td>
<td>Bacoside, brahmin, herpestine, d-mannitol, luteolin, apigenin</td>
<td>Anticholinesterase</td>
<td>[14]</td>
</tr>
<tr>
<td><em>Brassica species</em></td>
<td>Brassicasterol, sinapic acid, sinapine</td>
<td>Anti-inflammatory, neuroprotective, anticholinesterase</td>
<td>[15–17]</td>
</tr>
<tr>
<td><em>Buddleja salviifolia</em></td>
<td>Phenols, flavonoids, proanthocyanidins</td>
<td>Antioxidative, anticholinesterase</td>
<td>[18]</td>
</tr>
<tr>
<td><em>Chamaecrista mimosoides</em></td>
<td>Phenols, flavonoids, proanthocyanidins</td>
<td>Antioxidative, anticholinesterase</td>
<td>[18]</td>
</tr>
<tr>
<td><em>Corydalis species</em></td>
<td>Protopine</td>
<td>Anticholinesterase, anti-amnesic</td>
<td>[20]</td>
</tr>
<tr>
<td><em>Cymbopogon schoenanthus</em></td>
<td>Piperitone, 2-carene</td>
<td>Antioxidative, anticholinesterase, antimicrobial</td>
<td>[21]</td>
</tr>
<tr>
<td><em>Ferula assafoetida</em></td>
<td>Cadinene, eremophilene</td>
<td>Anti-COX-1</td>
<td>[10]</td>
</tr>
<tr>
<td><em>Ginkgo biloba</em></td>
<td>Ginkgetin, ginkgolides-A, B</td>
<td>Anticholinesterase</td>
<td>[14]</td>
</tr>
<tr>
<td><em>Myricaria elegans</em></td>
<td>Crude extract</td>
<td>Anticholinesterase, antilipoxygenase</td>
<td>[22]</td>
</tr>
<tr>
<td><em>Nardostachys jatamansi</em></td>
<td>Angelicin, β-eudesmol, calarene, calarenol, elemol, nardol, orosol</td>
<td>Antioxidative, anticholinesterase</td>
<td>[13]</td>
</tr>
<tr>
<td><em>Origanum ehrenbergii</em></td>
<td>Carvacrol, thymol</td>
<td>Antioxidative, anti-inflammatory</td>
<td>[23]</td>
</tr>
<tr>
<td><em>Origanum syriacum</em></td>
<td>Carvacrol, thymol</td>
<td>Antioxidative, anti-inflammatory, anticholinesterase</td>
<td>[23]</td>
</tr>
<tr>
<td><em>Peganum harmala</em></td>
<td>Norharmane, harmine, harmalol</td>
<td>Anticholinesterase</td>
<td>[10]</td>
</tr>
<tr>
<td><em>Piper nigrum</em></td>
<td>Piperine</td>
<td>Antioxidative, anticholinesterase</td>
<td>[11]</td>
</tr>
<tr>
<td><em>Psychoptelum olacoides</em></td>
<td>Lupeol, α, β-pinene</td>
<td>Anticholinesterase</td>
<td>[24]</td>
</tr>
<tr>
<td><em>Salvia lavandulaefolia</em></td>
<td>Essential oil, terpenes</td>
<td>Anticholinesterase</td>
<td>[25]</td>
</tr>
<tr>
<td><em>Salvia miltiorrhiza</em></td>
<td>Diterpenoid</td>
<td>Anticholinesterase</td>
<td>[26]</td>
</tr>
<tr>
<td><em>Salvia miltiorrhiza</em></td>
<td>Terpenes, tanshinones</td>
<td>Anticholinesterase</td>
<td>[26, 27]</td>
</tr>
<tr>
<td><em>Salvia officinalis</em></td>
<td>Polyphenols</td>
<td>Antioxidative, anticholinesterase</td>
<td>[28, 29]</td>
</tr>
<tr>
<td><em>Salvia plebeian</em></td>
<td>Essential oil</td>
<td>Antioxidative</td>
<td>[30]</td>
</tr>
<tr>
<td><em>Salvia tiliifolia</em></td>
<td>Phenols, flavonoids, proanthocyanidins</td>
<td>Antioxidative, inhibition of cholinesterase</td>
<td>[18]</td>
</tr>
<tr>
<td><em>Salvia triloba</em></td>
<td>Rosmarinic acid, ferulic acid, luteolin, quercetin</td>
<td>Antioxidative, anticholinesterase</td>
<td>[11]</td>
</tr>
<tr>
<td><em>Schottia brachypetala (root)</em></td>
<td>Phenols, flavonoids, proanthocyanidins</td>
<td>Antioxidative, anticholinesterase</td>
<td>[18]</td>
</tr>
<tr>
<td><em>Schottia brachypetala (bark)</em></td>
<td>Phenols, flavonoids, proanthocyanidins</td>
<td>Antioxidative, anticholinesterase</td>
<td>[18]</td>
</tr>
<tr>
<td><em>Syzygium aromaticum</em></td>
<td>Eugenol, trans-β-caryophyllene, α-humulene</td>
<td>Anti-COX-1</td>
<td>[10]</td>
</tr>
<tr>
<td><em>Tabernaemontana divaricata</em></td>
<td>Voafnidine, lupeol, α-amyrin, β-sitosterol</td>
<td>Anticholinesterase</td>
<td>[31]</td>
</tr>
<tr>
<td><em>Terminalia chebula</em></td>
<td>Penta-O-galloyl-β-D-glucose</td>
<td>Anticholinesterase</td>
<td>[32]</td>
</tr>
<tr>
<td><em>Zingiber officinale</em></td>
<td>Gingerol, shogaol, zingerone</td>
<td>Anti-COX-1</td>
<td>[10]</td>
</tr>
</tbody>
</table>

### References


