

Review Article

Recent Updates in the Treatment of Neurodegenerative Disorders Using Natural Compounds

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Received 20 January 2014; Revised 23 March 2014; Accepted 24 March 2014; Published 23 April 2014

Academic Editor: Ibrahim Khalil

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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 attentions of researchers have 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 insufficient 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, aggregation of β -amyloid ($A\beta$) 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 inflammation 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 inflammation. 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 intolerance while decreasing the levels of reduced glutathione, sulfation, 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 regulation of small molecules (solutes) 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 neurodegenerative 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 inflammatory 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 responsible 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 acetylcholine 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

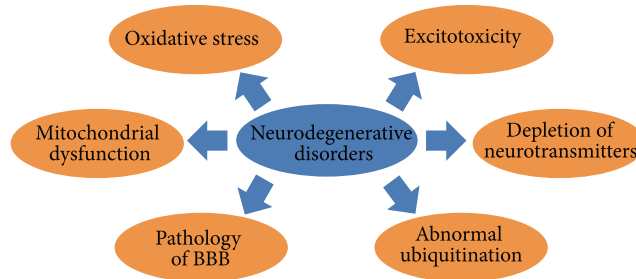


FIGURE 1: Various biological mechanisms contributing to neurodegenerative disorders.

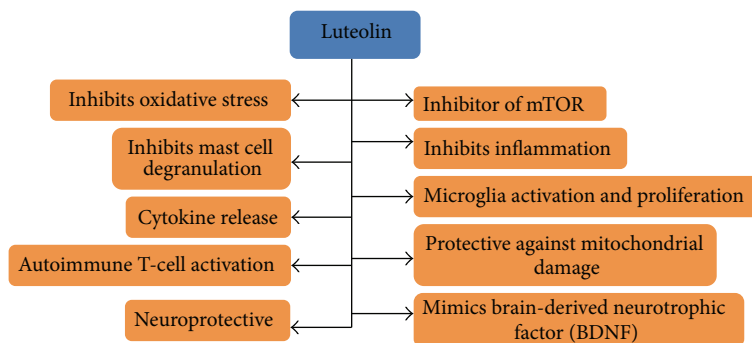


FIGURE 2: Luteolin (flavonoid) responsible for multiple biological functions.

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 amyloid 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 $A\beta$ and by protecting neuronal cell death [15]. On the other hand, *Embllica 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

TABLE 1: Role of various plants and their active constituents in brain disorders.

Plant	Active Compounds	Disorder	References
<i>Adhatoda vasica</i>	Vasicine, vasicol, vasicinol, arachidic, cerotic, linoleic and oleic acids	AD, PD	[6]
<i>Ginkgo biloba</i>	Amentoflavone	PD	[7]
<i>Mandukparni</i>	Asiaticoside	Schizophrenia	[8]
<i>Panax ginseng</i>	Ginsenoside	PD	[7]
<i>Rauwolfia serpentina</i>	Reserpine	Schizophrenia	[8]
<i>Withania somnifera</i>	Withaferin A, sitoindoside IX, physagulin D, withanoside IV, viscosalactone B	Schizophrenia	[8]

TABLE 2: Plants with antioxidant properties which could be applied in the therapy used in neurodegenerative diseases.

Plants	Active Compounds	References
<i>Abrus precatorius</i>	Glycyrrhizin, precol, abrol, gallic acid, abrine	[9]
<i>Acorus calamus</i>	α -asarone, β -asarone, eugenol	[6]
<i>Adhatoda vasica</i>	Vasicine, vasicol, vasicinol, arachidic, cerotic, linoleic, oleic acids	[6]
<i>Anogeissus leiocarpus</i>	Castalagin, flavogallonic acid	[9]
<i>Emblica officinalis</i>	Emblicanins A, B, punigluconin, pedunculagin, punicafolin, ellagic acid, gallic acid	[10]
<i>Entandrophragma angolense</i>	7 α -obacunyl acetate, cycloartane	[9]
<i>Khaya senegalensis</i>	Khayseneganin, luteolin, catechin	[9]
<i>Medicago sativa</i>	Soysaponin I, azukisaponin V	[6]
<i>Mentha spicata</i>	Spearmint oil, α , β -pinene, carvone, linalool, limonene	[6]
<i>Myrtus communis</i>	α -pinene, 1, 8-cineole, limonene	[6]
<i>Pavetta crassipes</i>	Quercetin	[9]
<i>Piper nigrum</i>	Piperine	[11]
<i>Salvia triloba</i>	Rosmarinic acid, ferulic acid, luteolin, quercetin	[11]
<i>Sonchus eruca</i>	Alkaloids, flavonoids, tannins, saponins	[12]
<i>Terminalia arjuna</i>	Arjunic acid, arjunolic acid, gallic acid, ellagic acid, proanthocyanidins	[10]
<i>Terminalia chebula</i>	Arjungenin, chebulosides, gallic acid, ellagic acid, luteolin, tannic acid, luteic acid, chebulic acid	[10]
<i>Tribulus terrestris</i>	Neohecogenin, β -D-galactopyranside	[6]
<i>Withania coagulans</i>	Coagulin, withanolide, withaferin A	[6]
<i>Withania somnifera</i>	Withaferin A, sitoindoside IX, physagulin D, withanoside IV, viscosalactone B	[6]

ways to treat the disorder. Considering this way of treatment, the neuroprotective phytochemicals were evaluated using *in silico* studies [7]. Phytochemicals such as baicalin, stigmaterol, emodin, curcumin, wogonin, and eriodictyol were found to be having binding energies of approximately -7 kcal/mol which was similar to talcapone (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 (*Rauwolfia 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 *Rauwolfia 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

TABLE 3: List of plants having antioxidative and anticholinesterase activity.

Plant	Active compounds	Properties	References
<i>Acorus calamus</i>	α -asarone, β -asarone, eugenol	Antioxidative, anticholinesterase	[13]
<i>Adhatoda vasica</i>	Vasicine, vasicol, vasicinol, arachidic, cerotic, linoleic, oleic acids	Anticholinesterase	[10]
<i>Bacopa monnieri</i>	Bacoside, brahmin, herpestine, d-mannitol, luteolin, apigenin	Anticholinesterase	[14]
<i>Brassica species</i>	Brassicasterol, sinapic acid, sinapine	Anti-inflammatory, neuroprotective, anticholinesterase	[15–17]
<i>Buddleja salviifolia</i>	Phenols, flavonoids, proanthocyanidins	Antioxidative, anticholinesterase	[18]
<i>Chamaecrista mimosoides</i>	Phenols, flavonoids, proanthocyanidins	Antioxidative, anticholinesterase	[18]
<i>Corydalis species</i>		AChE inhibition	[19]
<i>Corydalis ternate</i>	Protopine	Anticholinesterase, anti-amnesic	[20]
<i>Cymbopogon schoenanthus</i>	Piperitone, 2-carene	Antioxidative, anticholinesterase, antimicrobial	[21]
<i>Ferula assafoetida</i>	Cadinene, eremophilene	Anti-COX-1	[10]
<i>Ginkgo biloba</i>	Ginkgetin, ginkgolides-A, B	Anticholinesterase	[14]
<i>Myricaria elegans</i>	Crude extract	Anticholinesterase, antilipoxygenase	[22]
<i>Nardostachys jatamansi</i>	Angelicin, β -eudesmol, calarene, calarenol, elemol, nardol, oroselol	Antioxidative, anticholinesterase	[13]
<i>Origanum ehrenbergii</i>	Carvacrol, thymol	Antioxidative, anti-inflammatory	[23]
<i>Origanum syriacum</i>	Carvacrol, thymol	Antioxidative, anti-inflammatory, anticholinesterase	[23]
<i>Peganum harmala</i>	Norharmaline, harmine, harmalol	Anticholinesterase	[10]
<i>Piper nigrum</i>	Piperine	Antioxidative, anticholinesterase	[11]
<i>Ptychopetalum olacoides</i>	Lupeol, α , β -pinene	Anticholinesterase	[24]
<i>Salvia lavandulaefolia</i>	Essential oil, terpenes	Anticholinesterase	[25]
<i>Salvia miltiorrhiza</i>	Diterpenoid	Anticholinesterase	[26]
<i>Salvia miltiorrhiza</i>	Terpenes, tanshinones	Anticholinesterase	[26, 27]
<i>Salvia officinalis</i>	Polyphenols	Antioxidative, anticholinesterase	[28, 29]
<i>Salvia plebeian</i>	Essential oil	Antioxidative	[30]
<i>Salvia tiliifolia</i>	Phenols, flavonoids, proanthocyanidins	Antioxidative, inhibition of cholinesterase	[18]
<i>Salvia triloba</i>	Rosmarinic acid, ferulic acid, luteolin, quercetin	Antioxidative, anticholinesterase	[11]
<i>Schotia brachypetala (root)</i>	Phenols, flavonoids, proanthocyanidins	Antioxidative, anticholinesterase	[18]
<i>Schotia brachypetala (bark)</i>	Phenols, flavonoids, proanthocyanidins	Antioxidative, anticholinesterase	[18]
<i>Syzygium aromaticum</i>	Eugenol, trans- β -caryophyllene, α -humulene	Anti-COX-1	[10]
<i>Tabernaemontana divaricata</i>	Voafinidine, lupeol, α -amyrin, β -sitosterol	Anticholinesterase	[31]
<i>Terminalia chebula</i>	Penta-O-galloyl- β -D-glucose	Anticholinesterase	[32]
<i>Zingiber officinale</i>	Gingerol, shogaol, zingerone	Anti-COX-1	[10]

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.

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