


Chapter 13

Exploring the Role of Phytomedicines in Neurodegenerative Disorders

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ABSTRACT

In today's world, neurological disorders, which encompass a variety of neurodegenerative, neuropsychiatric, and neurodevelopmental issues, are the leading causes of disability and mortality. One of the main causes of genesis of several brain disorders and the neuronal damage is oxidative stress, which is generated by an excess of reactive oxygen species (ROS). The aim of this study is to present an unbiased assessment of the evidence in favor of using phytomedicines to treat brain disorders. There is a captivating case for multidisciplinary teamwork among neuroscientists, pharmacologists, clinicians, and practitioners of traditional medicine, especially growing interest in plant medicine to improve the potential of phytomedicines in neurology. Phytomedicines offer a potential new frontier in the treatment of brain disorders with their multifaceted therapeutic approach based on natural sources.

DOI: 10.4018/979-8-3373-4627-4.ch013

INTRODUCTION

Neurodegenerative diseases (NDs) is one of the largest healthcare issues globally which impact millions and put a huge economic and social burden on the healthcare system. Such diseases, such as multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and Alzheimer's disease (AD), are all defined by progressive neuronal degeneration and the resulting cognitive and motor impairments, (Kakoti et al., 2022). Prevalence of these diseases is growing at an alarming pace as the world population is aging rapidly. As per the World Health Organization (WHO), more than 55 million individuals suffered from dementia in 2022, and by the year 2050, that number is projected to double (Misrani A et al., 2021). Between 60 and 70 percent of the cases of dementia are due to Alzheimer's disease alone. Equally, about 10 million people across the globe live with Parkinson's disease, whose rate of incidence has more than doubled over the last 25 years. Such dramatic figures highlight the need for the development of sound preventative and therapeutic interventions, (Kumar et al., 2025).

Phytochemicals, also referred to as phytonutrients, are a structurally diverse group of secondary metabolites that plants synthesize using complex biochemical pathways. These compounds possess significant bioactive properties, including antioxidant, anti-inflammatory, antibacterial, anticancer, and neuroprotective actions, but they are not essential for human survival like vital micronutrients. Extensive structural and functional diversity is exhibited by their diversity, encompassing polyphenols, flavonoids, carotenoids, alkaloids, terpenoids, glucosinolates, and saponins, (Hossain et al., 2025).

One of the most ubiquitous and studied groups is polyphenols, consisting of lignans, flavonoids, phenolic acids, and stilbenes. The C6-C3-C6 flavonoid structural motif containing flavanols (quercetin, kaempferol), flavones, isoflavones, and anthocyanins is particularly significant since it impacts antioxidant activity and interfaces with cellular signalling pathways, (Chagas et al., 2022). Anthocyanins are rich in berries, purple cabbage, and maize, which have also been noted to exhibit cardioprotective and anti-inflammatory actions beyond their role in visual pigmentation, (Kumar et al., 2023).

Carotenoids like lutein, lycopene, and β -carotene are isoprenoid pigments with a function in regulation of oxidative stress and photoprotection. They have preventive action against cardiovascular and chronic eye diseases and are vitamin A precursors. Compounds like artemisinin, menthol, and saponins are examples of terpenes and terpenoids that are structurally biosynthesized from five-carbon units of isoprene and have antimalarial, antibacterial, and lipid-lowering activity (Thakur M et al., 2020).

Alkaloids are nitrogen-containing compounds mostly found in medicinal plants with well-established pharmacological properties in both conventional and alternative medicine. Examples of these include morphine, caffeine, and berberine, (Aggarwal et al., 2025). Glucosinolates, which are found in plants of the Brassicaceae family, break down into physiologically active isothiocyanates, which are strong chemo preventive agents that activate detoxifying enzymes and modify epigenetics, (Connolly et al., 2021). In this review paper, we are going to discuss about pathophysiology, etiologic and role of herbs in the neurodegenerative disorder.

PATHOPHYSIOLOGY OF NEURODEGENERATIVE DISORDERS

The central nervous system promptly responds to injury and infection as a component of a robust immune system. In pathological circumstances, macrophages and other peripheral immune cells have the ability to penetrate the blood–brain barrier (BBB). The discovery and clarification of a robust network for interaction between the immune system and the central nervous system is one of the most significant recent advancements in medicine. The somatodendritic and axonal compartments are two functionally and physically separate regions in neurones, which make them highly polarised cells. Axons and dendrites are typically formed by a single long neurone. Neural circuits are highly specialised and very dependent on spatiotemporally controlled cargo movement for correct operation because to the high degree of morphological and functional polarisation. Transport of cargo along axons is facilitated by a process called axonal transport (AT), which relies on microtubules (MT). Motor proteins, adaptors, cargos, and MTs make up the AT machinery. MTs, intermediate filaments, and actin filaments make up the cytoskeleton, which is where AT takes place. Motor proteins, such as kinesin and dynein, transport cargo along longitudinally aligned MTs that run down the axon. The adaptors help bind and localise the payloads to the motor proteins by acting as linkers. Maintaining the structural and biochemical heterogeneity that characterises axonal subdomains is mediated by AT, which also controls the delivery of organelles bound by membranes from the cell body to synaptic compartments, removes and degrades old materials, and mediates the turnover of non-synaptic membranes and metabolic and cytoskeletal elements. Therefore, AT can be considered a key cellular activity that underlies the establishment and upkeep of neural architecture and connection across neurones' lifetimes. The somato-dendritic and axonal compartments are two functionally and physically separate regions in neurones, which make them highly polarised cells. Axons and dendrites are typically formed by a single long neurone. Neural circuits are highly specialised and very dependent on spatiotemporally controlled cargo movement for correct operation because to the high degree of morphological and functional polarisation. Transport of cargo along axons is facilitated by a process called axonal transport (AT), which relies on microtubules (MT). Motor proteins, adaptors, cargos, and MTs make up the AT machinery. MTs, intermediate filaments, and actin filaments make up the cytoskeleton, which is where AT takes place. Motor proteins, such as kinesin and dynein, transport cargo along longitudinally aligned MTs that run down the axon. The adaptors help bind and localise the payloads to the motor proteins by acting as linkers. Maintaining the structural and biochemical heterogeneity that characterises axonal subdomains is mediated by AT, which also controls the delivery of organelles bound by membranes from the cell body to synaptic compartments, removes and degrades old materials, and mediates the turnover of non-synaptic membranes and metabolic and cytoskeletal elements. Therefore, AT can be considered a key cellular activity that underlies the establishment and upkeep of neural architecture and connection across neurones' lifetimes. Reactive oxygen species can be beneficial in preventing the development of infections; however, they can also exacerbate neurological ailments. An overabundance of reactive oxygen species can result from mitochondrial failure, which can damage neurones and release cytosolic components that activate astrocytes and microglia in the vicinity. Reactive oxygen species, reactive nitrogen species, and other pro-inflammatory cytokines will be released by these microglia and astrocytes in the vicinity. The inflammatory response is facilitated, and neuronal injury is exacerbated by the secretion of these cytokines.

Consequently, chronic glial cell activation establishes a vicious cycle that exacerbates and prolongs long-term neurodegenerative processes (Rekatsina M et al., 2020).

ETIOLOGY AND PATHOGENESIS OF ALZHEIMER'S DISEASE

Neurons in AD patients become disabled. The neuron's capacity to generate the energy (via metabolism) necessary for effective coordination between them is inhibited in the early stages of AD. Additionally, they become unable of self-healing, which eventually results in the death of neuron cells. It is still unclear exactly what disrupts the neuron's normal function, but three pathological characteristics are being proposed as possible targets in light of recent advancements in medical research (Figure 1)

Figure 1. Alzheimer's progression



B-AMYLOID PLAQUES

A protein known as β -amyloid ($A\beta$) forms thick, sticky deposits of plaques that are tucked into the gaps between neurons. Other protein fragments, neurogenesis, and immune cells—specifically, microglia—encircle these plaques as well. These cells then break down the injured neurons and induce neuro-inflammation. $A\beta$ is a 39–43 amino acid peptide that aggregates spontaneously. It is a fragment of a bigger protein known as the amyloid precursor protein (APP). APP is crucial for the production of neurones, which are present both within and outside of cells. The sequential proteolytic cleavage of APP by β - and γ -secretases results in the production of $A\beta$, (Lacham-Hartman et al., 2025). The membrane-anchored aspartic protease β -secretase (β -site of APP cleaving enzyme; BACE) generates a soluble N-terminal fragment and a C-terminal fragment that is affixed to the membrane during the initial cleavage. Subsequently, γ -secretase cuts the C-terminal region to generate $A\beta$ peptides, which subsequently adhere to form plaques that are incapable of being degraded (Zhang et al., 2025). In accordance with the “ β -amyloid cascade,”

the accumulation of A β plaques initiates a chain reaction that is detrimental to neurones leading to neuroinflammation, which in turn leads to neurodegeneration.

NEUROFIBRILLARY TANGLES

Neurofibrillary tangles (NFTs) are a significant neuropathological characteristic of Alzheimer's disease (AD). The absence of cytoskeletal microtubules and tubulin-associated proteins has been identified in neurones that carry NFTs. Neurofibrillary lesions are most likely formed by signal transduction pathways involving protein phosphorylation and de-phosphorylation, even if the precise molecular mechanisms connecting cytoskeletal element loss to NFT development are still unknown. One example is the aberrant phosphorylation (hyperphosphorylation) of the microtubule-associated protein tau (Mapt), the main component of NFTs, in the brains of Alzheimer's disease (AD) patients when compared to non-demented persons. The process of amyotrophic lateral neuropathy (AD) involves epitope-specific hyperphosphorylation, which is thought to be the foundation for tau's mislocalization from axonal to somatodendritic neurones. According to Alonso et al. (2008), this change is believed to play a role in tau polymerisation and aggregation in addition to deregulating microtubule dynamics.

LOSS OF CHOLINERGIC NEURONS

When we learn, the cholinergic system is involved. Memory is another area where ACh has been linked in published studies. Additional research has shown that endogenous acetylcholine has a significant role in modulating learning and memory processes including acquisition, encoding, consolidation, reconsolidation, extinction, and retrieval. The memory loss seen in Alzheimer's disease (AD) patients is partly caused by the particular degeneration of these neurones, which highlights the role of the cholinergic neurones from the nucleus basalis of Meynert on memory. Another factor that can control ACh release in the forebrain is stress, which can alter biological and emotional outcomes through its effects on the hypothalamic-pituitary-adrenal (HPA) system. The activation of the HPA axis in response to a stressor agent is reduced in rats treated with the nicotinic receptor antagonist mecamylamine, according to research that assessed the role of the cholinergic system in mediating the stress response. In a similar vein, nicotine can activate nicotinic receptors to simulate ACh's actions on the HPA axis.

The cholinergic system also plays a crucial role in controlling when we sleep. Research has shown that stimulating certain areas of the brainstem with cholinergic neurones can enhance rapid eye movement (REM) sleep in a dose-dependent manner. The sensory cortex also employs ACh for a variety of modulatory tasks. By easing communication between the thalamus and the brain, ACh aids in auditory synaptic transmission. The visual cortex also relies on ACh for organisation and neuronal responsiveness. There is mounting evidence that ACh has a role in adult neurogenesis, (Bhattacharjee et al., 2020).

PHYTOMEDICINES IN ALZHEIMER'S DISEASE (AD)

For centuries, Traditional Chinese medicine (TCM) and Traditional Indian medicine (Ayurveda) have employed methods that involve the use of medicinal and other alternatives to drugs, (Sharma et al., 2019). Unusual treatment processes that have been passed down through the centuries and refined by extended use and experiences are still being implemented, based on a vast amount of data regarding the beneficial properties of a variety of plants, chemical substances, and innovative treatments. (Figure 2) It has also been shown that certain common household spices, such as ginger, cinnamon, rosemary, sage, garlic, and curcuma, can help prevent AD, (Gregory et al., 2021).

Figure 2. Exploring phytomedicines for parkinson disease



AYURVEDIC APPROACHES FOR THE TREATMENT OF AD

By observing the neuroprotective qualities of several extracts, the most recent scientific study has validated the effectiveness of Ayurvedic medicines in preventing AD. Asiatic pennywort (*Centella asiatica* (L.)) is one such herb, which can lower blood pressure, purify blood, and improve memory. In Ayurveda, its hydrophilic extracts are often employed to treat insomnia and stimulate the regeneration and healing of nerve cells, (Singh et al., 2021). Asiatic acid and asiaticoside are the two metabolites of Asiatic pennywort, are strong antioxidants, (Kushwah et al., 2023). Asiatic pennywort can effectively inhibit A β in mouse brains, as per as in vitro study. By preventing free radical formation, protecting against DNA damage, and inhibiting lipid peroxidation, it was also an antioxidant. Jatamansi root preparations in alcohol have been demonstrated by Lyle et al. to enhance learning and maintenance abilities and mitigate chronic fatigue syndrome effects in rats. Another herb, guggul (*Commiphora*), contains phenols, ferulic acid, and nonphenolic aromatic acids, among other very potent antioxidants that can be employed to treat AD. Neuroprotective

effects of guggul and Jatamansi and brain oxidative stress reduction are similar to those of Asiatic pennywort. Cat's claw (*Uncaria tomentosa*), a tropical vine, is recommended for the prevention and treatment of AD and pre-AD due to its immunomodulating and anti-inflammatory properties. Its ability to prevent aggregation and degradation of previously existing tau protein tangles and A β fibrils was indicated by the in vitro tests, (Snow et al., 2019). Curcuma longa, a most popular herb in this group, reduces A β levels and inflammation within cells, (Sivaraman et al., 2019). It regulates the cellular signal pathway and prevents formation of A β aggregates, (Sahiner et al., 2023). Three curcuminoids—curcumin, desmethoxycurcumin, and bisdemethoxycurcumin—fended normal human endothelial cells of the umbilical vein (HUVEC) and rat pheochromocytoma PC12 off A β attack. Many bioactive compounds under various headings are found in its extracts. There were twenty different phytochemicals identified in Brahmi ethanol extracts in total (Pramanik R et al., 2024). Ashwagandha (*Withania somnifera*) or winter cherry or Indian ginseng is one of the most prominent herbs with proven effectiveness for AD, (Menghani et al., 2021). Its alkaloids regulate ACh levels and reduce A β aggregation, which improves cognitive function. In vivo and in vitro experiments have indicated that ginseng possesses anti-inflammatory properties that involve reducing COX-2 enzyme levels, the key mediator in the inflammation process, and inhibiting inflammatory mediators like TNF- α , NF- κ B, IL-1 β , and IL6, (Ahn et al., 2017). Ethanol extracts from the roots as well as aerial parts of *Clitoria ternatea* plant (CT), commonly known as Shankpushpi, were evaluated by Taranalli and Cheeramkuzhy. When rats with amnesia produced by electroshock received a lower dose (300 mg/kg) of the extract, they demonstrated that memory function improved and the level of ACh in the brain increased. Both the root extract dosages (300 and 500 mg/kg) showed similar, but modestly greater, effects. Rosemary, or *Rosmarinus officinalis*, has been found to be beneficial in AD-related disorders because it possesses cyclooxygenase-2 (COX-2) inhibitors such as apigenin and eugenol, which are likely to exert anti-inflammatory actions. The root extract of *Oroxylum indicum* has many principal constituents in which baicalein exert a range of effects on significant pathway associated with AD including reduced tau protein hyperphosphorylation, inhibition of A β generation, reduction of oxidative stress, and regulation of AChE activity, (Baranowska-Wójcik et al., 2025).

TRADITIONAL CHINESE MEDICINES APPROACH FOR THE TREATMENT OF AD

Many active compounds used in TCM may make treating AD patients easier, (Zhang et al., 2015). Clinical testing has shown their value in the early prevention of the illness as well as in helping afflicted individuals' brain activity and cognitive abilities, (Zhang et al., 2019). For example, it has been demonstrated that extracts from *Coptis chinensis* Franch (Huang Lian), (Chen et al., 2020), *Polygonum multiflorum* Thunb. (He Shou Wu), (Ning et al., 2021), and *Polygala tenuifolia* Willd. (Yuan Zhi) reduce cognitive deficiencies and help heal pathological damage in AD, (Park et al., 2019). The traditional oriental herbal compound Soshiho-tang (SST), or Xiaochaihu-tangin in Chinese and Sho-saiko-to in Japanese, was found by Sohn et al., 2021 to inhibit AChE activation and A β aggregation in vivo in a mouse model of AD. As per Jin et al. (2019), Baicalin (BAI), a natural flavonoid isolated from *Scutellaria baicalensis* Georgi (Huang Qin), may suppress neuro-inflammatory reactions induced by microglia in AD mice brain via inhibiting TLR4/NF- κ B signal pathway and inflammasome NLRP3 activation. Sesame oil (SO),

which is rich in *Sesamum indicum* L. (Zhi Ma), was shown by Mohamed EA et al., 2021 to significantly improve learning capacity and reduce memory loss in rats administered AICl₃ (100 mg/kg) alone or combined with SO. Furthermore, it was shown that injection of AICl₃ caused histopathological changes, reduction in cerebral oxidative stress, and elevation in interleukin-1 beta (IL-1 β) and tumour necrosis factor-alpha (TNF α). Cuya Tet al., 2018 report that 1-(3,4 dihydroxy-5-methoxyphenyl)-7-(4-hydroxy-3-ethoxyphenyl) heptane-3,5-diyl diacetate and (E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hept-4-en-3-on, which are compounds present in ginger root extract, could potentially inhibit AChE in humans. By stimulating the glucagon-like peptide-1 receptor (GLP-1R), geniposide, an iridoid compound present in gardenia fruit (*Gardenia jasminoides* Ellis), protects against the neurotoxicity induced by A β , (Liu et al., 2015).

PHYTOMEDICINES IN PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is the second most common neurologic disorder in the world which is a neurologic disorder that primarily affects motor function, (Khan et al., 2019). It is characterized by stiffness, tremors, and difficulty with balancing and coordinating. The disease is caused by the loss of brain cells that produce dopamine, which disrupts nerve cell-to-nerve transmission, (Rear, 2015). Use of Traditional Chinese Medicine (TCM) as an adjunct or alternative therapy has been researched. Although Western medicine has primarily utilized drugs such as levodopa, TCM depends on the overall body functioning to cure PD symptoms by restoring harmony in the functioning of the body and equilibrium of Qi (energy).

ANTIOXIDANT PROPERTIES OF PHYTOMEDICINES USED IN TCM IN THE TREATMENT OF PD

TCM has been used as the alternative medicine because it possesses neuroprotective effects. It has been proved that neuroprotective compounds obtained from TCM, including β -asaron, chrysin, cannabidiol, and toonasinoids, are highly efficient in curing Parkinson's disease. These TCM have also exhibited anti-inflammatory, anti-oxidative, anti-tumour, analgesic, and antiseptic effects along with neuroprotective advantages. From a recent study, it was found that reduction in reactive oxygen species enhanced dopaminergic neuron regeneration and reduced α -synuclein toxicity, two of the prime indicators of Parkinson's disease, (Muhammad et al., 2022). The treatment methods currently used for neurological disorders are inefficient because they primarily benefit a small number of patients and merely reduce the symptoms to some extent without halting the disease process. Levodopa, selegiline, and carbidopa are among the medications approved by the US Food and Drug Administration to treat Parkinson's disease (PD). These medications successfully lessen PD symptoms and slow the illness's progression. However, because to safety concerns, they are not advised for prolonged use. For example, even though Levodopa administration caused the frequent onset of motor issues, it improved the relief of motor symptoms in the majority of PD patients. Numerous studies have demonstrated that TCM treatment is linked to mRNA-level post-transcriptional changes, (Bhushan et al., 2024). In the context of Parkinson's disease, these changes may be advantageous or extremely dangerous.

THERAPEUTICAL HERBS IN THE TREATMENT OF PD

Alpinia

The plant *Alpiniae oxyphyllae Fructus* (AOF) named as YizhiRen in Chinese, is the completely developed and dehydrated seed of the *Alpinia oxyphylla* Miq. plant. According to Zhang et al. (2018), it is commonly used in medicine to treat symptoms such as diarrhoea, vomiting, abdominal pain, and excessive salivation, and to improve the function of the kidneys, stomach, and spleen. Research on zebrafish models of Parkinson's disease has shown that an ethanol extract of AOF might mitigate the impairment of psychomotor performance and potentially halt the degeneration of dopaminergic neurones caused by 6-hydroxydopamine (6-OHDA). This is achieved by reducing inflammation (by downregulating the expression of interleukin-1 beta and tumour necrosis factor-alpha) and oxidative stress (by preventing the synthesis of nitrous oxide). *Alpiniae oxyphyllae* possess anti-inflammatory and antioxidant activities which are necessary in the prevention of the neuroinflammation and oxidative stress associated with the progression of Parkinson's disease. Additionally, extracts of *Alpiniae oxyphyllae* have been proved that it has the property of inhibiting alpha-synuclein aggregation, which is a protein misfolding and aggregation, targeting pathophysiology of Parkinson's disease. In addition, *Alpiniae oxyphyllae* extracts have been observed to modify neurotransmitter systems like serotonin, glutamate, and dopamine, which become dysregulated in Parkinson's disease. Through enhanced dopaminergic transmission and modulation of glutamatergic and serotonergic transmission, *Alpiniae oxyphyllae* can potentially treat the motor symptoms and alleviate depression and anxiety, significant non-motor symptoms of PD, (Zhang et al., 2019).

Astragalus

The dried root of *Astragalus membranaceus* (Fisch.) is referred to as *Astragali Radix*, or Huangqi in Chinese. In TCM, it is widely acknowledged and utilized as a therapeutic agent. At least three bioactive substances with neuroprotective properties have currently been identified in *Astragali Radix*: astragaloside IV, astraisoflavan, and astragalus polysaccharides. It is clear that oxidative stress, especially the existence of free radicals, plays a major role in the development of Parkinson's disease (PD), even though the precise mechanism of neuron loss in these individuals is still unknown. According to recent research (Yin et al., 2021), astragalus polysaccharides may be an effective method for reducing oxidative stress in dopaminergic neurones. *Astragali Radix* exhibits potential as a treatment for Parkinson's disease (Cui et al., 2023). It has the potential to function as an antioxidant, reduce inflammation, and defend neurones that produce dopamine. Its immunomodulatory properties and capacity to modulate neurotransmitter systems may alleviate Parkinson's disease symptoms.

Baicalein and Baicalin

Natural chemical baicalein affects levels of microRNAs (miRNAs) (18), which are potential new regulators of cell metabolism, proliferation, and death. Significantly, a multitude of microRNAs play a role in the identification, development, and management of PD. One example is the crucial function that hsa-miR-30b-5p plays in neurodegenerative illnesses, including Parkinson's

disease. MiR-30b-5p is highly expressed in PD patients who have received treatment. But how miR-30b-5p contributes to mitochondrial autophagy in PD is still unclear. At the molecular level, SIRT1 activation triggers mitochondrial autophagy. Control of mitochondrial autophagy in neural stem cells is regulated by the Bhlhe40/SIRT1 axis. The induction of mitochondrial autophagy is facilitated by SIRT1 through the AMPK/mTOR pathway. Very less is known about baicalein's potential to protect against PD by modulating miR-30b-5p and mitochondrial autophagy via the SIRT1/AMPK/mTOR axis. apoptosis was halted and oxidative stress was reduced by inhibiting the p38 mitogen-activated protein kinase signalling pathway, (Ma et al., 2021).

Camellia

Camellia sinensis L. Kuntze plant leaf is in the Theaceae family, are used to make green and black tea. Camellia, which is often called “green tea” in Chinese, is a plant that has minerals, polyphenols, and it contains small amounts of vitamins, amino acids, and carbohydrate. In the past, Infusions of camellia were frequently used as sleep aids or purifying agents to alleviate anxiety, migraines, and stomach problems, (Malar et al., 2020). Neuroprotective, anti-inflammatory, and antioxidant characteristics are some of the other pharmacological effects. Green tea polyphenols have long been recognized for their neuroprotective properties against Parkinson's disease pathogenesis. By inhibiting the Jun N-terminal kinase/Myosin light chain kinase pathway, green tea can prevent the breakdown of nerve cells in the hippocampal region, (Xu et al., 2021). Camellia sinensis extract was shown to have antioxidant properties and to correct immunohistochemical alterations caused by 6-OHDA lesions in male Wistar rats. According to a study by Bitu Pinto, Natalia et al., Camellia sinensis has neuroprotective potential, and its catechins are a powerful component of its anti-inflammatory and antioxidant qualities.

Licorice

Glycyrrhiza glabra is a very useful medicinal plant that comes from the Fabaceae family (sometimes called Leguminosae). It is also used a lot for food for both people and animals. A randomised double-blind clinical study that looked at liquorice as an extra treatment for Parkinson's disease patients found that it helped their symptoms a lot and didn't have any bad affects that could be seen. Glabridin is a naturally occurring flavonoid that is found in *Glycyrrhiza glabra*. Glabridin can protect neurones from PD-like symptoms caused by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) by blocking the ERK signalling pathway and lowering inflammation, (Zhao et al., 2017).

Morusalba

Morus alba L. is a plant that is highly beneficial and is frequently used in traditional medicine and Ayurveda. *Morus alba* is low in fat, but it is rich in essential nutrients, such as carbohydrates, protein, vitamins, and minerals. Mulberry fruit extract has been discovered by researchers to protect neurones from damage by enhancing the performance of dopaminergic neurones. This could potentially help individuals with chronic illnesses recover and prevent the onset of Parkinson's disease. A study conducted by Rebai Olfa et al. (2017) demonstrated that an extract from *Morus alba* leaves significantly reduced oxidative stress and mitigated the adverse effects of glyphosate

on the brain. The leaf extract also appears to have the capacity to reduce H₂O₂ levels, maintain stable iron and Ca²⁺ levels, and enhance SOD activity. As a result, the in vivo results suggest that mulberry leaf extract may serve as a herbal treatment for glyphosate-induced toxicity. The neuroprotective properties of *Morus alba* leaf extract may be attributed to the synergistic or antagonistic interactions among the numerous active phenolic compounds (Table 1).

Table 1. Therapeutic herbs for Parkinson's disease

| Herb (common / scientific) | Part / extract used | Major active compound(s) | Proposed mechanisms relevant to PD | Reference |
|---|--|---|---|---|
| <i>Alpinia / Alpiniae oxyphyllae</i> (YizhiRen) | Ethanol extract of seed (AOF) | (complex mixture; anti-inflammatory & antioxidant constituents) | ↓Neuroinflammation (↓ IL-1 β , ↓ TNF- α), ↓ oxidative stress (↓ NO), inhibition of α -synuclein aggregation, modulation of dopaminergic, glutamatergic and serotonergic transmission | Zhang Q et al., 2018; Zhang Z et al., 2019 |
| <i>Astragalus / Astragalus membranaceus</i> (Huangqi) | Dried root (Astragali Radix); extracts / isolated constituents | Astragaloside IV, astraisoflavan, astragalus polysaccharides | Antioxidant (scavenges ROS), anti-inflammatory, immunomodulation; protection of dopaminergic neurons; neurotransmitter regulation | Yin R et al., 2021; Cui D et al., 2023 |
| Baicalein & baicalin (from <i>Scutellaria baicalensis</i>) | Root extracts; purified baicalein / baicalin | Baicalein, baicalin (flavones) | Anti-inflammatory (↓ NLRP3, ↓ caspase-1), anti-apoptotic, mitochondrial protection (via CREB / GSK-3 β), inhibition of p38 MAPK; reduces microglial activation and proinflammatory cytokines | Rui W et al., 2020; Zhang X et al., 2017; Ma J et al., 2021 |
| <i>Camellia / Camellia sinensis</i> (green/black tea) | Leaf infusion / polyphenol extracts (catechins) | Epigallocatechin gallate (EGCG) and other catechins | Antioxidant, anti-inflammatory, inhibition of JNK/MLCK pathway, neuroprotection against toxin-induced degeneration | Malar DS et al., 2020; Xu Y et al., 2021; Jurado-Coronel et al., 2016 |
| <i>Licorice / Glycyrrhiza glabra</i> | Root extract; glabridin (flavonoid) | Glabridin and other flavonoids | Anti-inflammatory (↓ ERK signalling), neuroprotection against MPTP toxicity | Zhao Y et al., 2017 |
| <i>Mulberry / Morus alba</i> | Leaf or fruit extract (phenolic-rich) | Various phenolic compounds (flavonoids, phenolic acids) | Antioxidant (↑ SOD), reduces H ₂ O ₂ , stabilizes Fe ²⁺ /Ca ²⁺ , mitigates oxidative stress | Rebai Olfa et al., 2017 |

DELIVERY SYSTEMS AND BIOAVAILABILITY CHALLENGES

Neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, and stroke remain among the leading causes of disability and mortality worldwide. Current pharmacotherapies are often symptomatic, limited by side effects, or ineffective in halting disease progression. In this context, phytomedicines—bioactive compounds derived from plants—have emerged as promising alternatives due to their multitargeted mechanisms, antioxidant properties, and relatively favorable safety profiles, (Howes et al., 2011). However, their clinical application is hindered by poor bioavailability, instability, and limited penetration across the blood–brain barrier (BBB). Recent advances in enzymology and drug delivery systems are offering solutions to these challenges.

ENZYMOLGY IN NEUROLOGICAL DISORDERS

In the central nervous system (CNS), enzymes control important biochemical processes that affect neurotransmitter metabolism, oxidative stress, and neuroinflammation. A lot of neurological diseases have been caused by problems with how enzymes work. Acetylcholinesterase (AChE), for instance, is increased in Alzheimer's disease, which speeds up the breakdown of acetylcholine and makes it harder to think coherently. Alkaloids found in plants, like galantamine and huperzine A, naturally block AChE, which makes cholinergic signalling better, (Ma et.al., 2007). In the same way, monoamine oxidase (MAO) enzymes change how dopamine, serotonin, and norepinephrine are used, and too much of them can lead to Parkinson's disease. Flavonoids, such as quercetin and resveratrol, have weak MAO-inhibitory actions that make monoaminergic transmission robust, (de la Torre R et al., 2006).

Enzymes that neutralise free radicals are regulated by phytochemicals. To mitigate oxidative stress, a critical factor in neuronal mortality, polyphenols boost the activity of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase (SOD), and catalase, (Uttara et al., 2009). In addition, terpenoids and phenolics decrease neuroinflammation by inhibiting pro-inflammatory enzymes such cyclooxygenase (COX), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS), (Venkatesan et.al., 2017) (Table 2). The significance of enzymology in natural neurotherapeutics is shown by these interactions between enzymes and phytochemistry.

Table 2. Enzymology in neurological disorders

| Neurological Condition | Enzyme(s) Involved | Role / Pathophysiology | Clinical/Therapeutic Insights | Reference |
|--------------------------------|---------------------------------------|--|---|---|
| Parkinson's & Depression | Monoamine oxidase (MAO-A/MAO-B) | Degrades dopamine, serotonin, norepinephrine | MAO-B inhibitors (selegiline, rasagiline) are neuroprotective | Youdim & Bakhle, Br J Pharmacol, 2006 |
| Gaucher's Disease & PD risk | Glucocerebrosidase (GBA) | Deficient lysosomal degradation of glucocerebrosidase | Mutations increase risk of Parkinson's | Sidransky et al., N Engl J Med, 2009 |
| Alzheimer's & PD | Asparagine endopeptidase (AEP) | Cleaves tau, APP, α -synuclein under acidic stress | AEP inhibition proposed as therapy | Zhang et al., Nature, 2014 |
| ALS (familial) | Superoxide dismutase 1 (SOD1) | Mutations \rightarrow oxidative stress, motor neuron death | Basis for SOD1-targeted gene therapy | Rosen et al., Nature, 1993 |
| Tay-Sachs / Sandhoff | Hexosaminidases A & B | Deficiency causes GM2 ganglioside accumulation | Enzyme deficiency defines GM2 gangliosidosis | Gravel et al., The Metabolic Basis of Inherited Disease, 2001 |
| Niemann-Pick Disease | Acid sphingomyelinase | Deficiency \rightarrow sphingomyelin accumulation | Causes neurodegeneration, hepatosplenomegaly | Schuchman & Desnick, J Inher Metab Dis, 2017 |
| Homocystinuria | Cystathionine β -synthase (CBS) | Converts homocysteine \rightarrow cystathionine | Deficiency \rightarrow homocysteine buildup; B6 responsive | Mudd et al., N Engl J Med, 1985 |
| Mitochondrial Encephalopathies | Pyruvate dehydrogenase (PDH) | Converts pyruvate \rightarrow acetyl-CoA | Deficiency causes lactic acidosis, neurodeficits | Patel & Korotchkina, J Biol Chem, 2006 |

continued on following page

Table 2. Continued

| Neurological Condition | Enzyme(s) Involved | Role / Pathophysiology | Clinical/Therapeutic Insights | Reference |
|---------------------------|---|--|--|--|
| Maple Syrup Urine Disease | Branched-chain α -ketoacid dehydrogenase (BCKDH) | Deficient catabolism of BCAAs | Causes neurotoxicity; dietary control is therapy | Chuang et al., J Inherit Metab Dis, 2006 |
| Epilepsy, AD, ALS | Glutamine synthetase (GS) | Converts glutamate + ammonia \rightarrow glutamine | Dysfunction \rightarrow excitotoxicity, seizures | Eid et al., Neurochem Int, 2013 |

BIOAVAILABILITY AND DELIVERY CHALLENGES

Despite promising neuroprotective effects, most phytochemicals face pharmacokinetic limitations. Their clinical translation is impeded by:

1. Blood–Brain Barrier (BBB): Lipophilic and high-molecular-weight compounds poorly cross the BBB, restricting CNS access, (Pardridge et al., 2005).
2. First-pass metabolism: Many phytochemicals undergo rapid hepatic and intestinal metabolism by cytochrome P450 enzymes and esterases, leading to low systemic concentrations (Manach C et.al., 2004).
3. Poor solubility and stability: Hydrophobic compounds such as curcumin and resveratrol degrade quickly in biological fluids, (Anand et al., 2007).
4. Efflux transporters: P-glycoprotein and other efflux pumps actively expel phytochemicals from endothelial cells of the BBB, (Löscher et al., 2005).

These limitations necessitate advanced delivery systems to optimize therapeutic efficacy.

Potentially crucial neurology treatments based on phytomedicine are being developed through the convergence of phytochemistry, enzymology, and nanotechnology. Research in the future should centre on biomimetic nanoparticles that can pass the blood-brain barrier (BBB) via receptor-mediated pathways, personalised medicine methods, and formulations that target many targets at once. By influencing key enzymatic pathways, phytomedicines offer a wealth of neurotherapeutic agents. Nevertheless, their limited clinical value is due to low absorption and BBB limitations.

CHALLENGES AND FUTURE DIRECTION

Numerous obstacles prevent phytomedicines from being used therapeutically in neurology. Due to their low solubility, poor gastrointestinal absorption, and quick metabolism, many phytochemicals, including curcumin, quercetin, and resveratrol, have low systemic concentrations, (Anand et al., 2007). This makes poor bioavailability the most important problem. Additionally, most phytochemicals cannot pass through the blood–brain barrier (BBB) into the central nervous

system, and efflux transporters such P-glycoprotein actively remove a lot of chemicals, which prevents buildup in the brain (Pardridge, 2005).

Enzymatic interactions are complicated, which presents another difficulty. Acetylcholinesterase, monoamine oxidase, cyclooxygenase, and inducible nitric oxide synthase are only a few of the enzymatic pathways involved in neurological diseases. Phytochemicals may affect these processes in a way that isn't specific, which makes us worry about effects that aren't meant to happen, (Venkatesan et al., 2017). Genetic polymorphisms that cause changes in enzyme activity between people make therapeutic consistency even more difficult, (Ingelman-Sundberg et al., 2001). Also, phytochemical composition changes because herbal extracts are not standardised, which makes them less accurate and predictable in clinical applications, (Ekor, 2014).

Regulatory Challenges

Complex compound mixes are frequently found in phytomedicines, making it challenging to identify the specific ingredients causing therapeutic effects as well as to evaluate possible interactions and adverse consequences. The standardisation and quality control required for regulatory approval may be hampered by this diversity.

Regulations for herbal remedies differ per nation, ranging from stricter restrictions for pharmaceutical drugs to categories for traditional treatments. For academics and businesses looking to develop and market phytomedicines for neurodegenerative illnesses, this lack of harmonisation adds uncertainty and complication. Due to variables including plant species, place of origin, and harvesting conditions, phytomedicines may exhibit variety in their chemical content. It is difficult to guarantee constant product efficacy and quality because of this unpredictability. Regulatory agencies have reservations because there is frequently a lack of long-term safety evidence on phytomedicines, especially when they are used together with other drugs.

REFERENCES

- Aggarwal, A., Rajalekshmi, R., Aggarwal, A., & Agrawal, D. K. (2025). Plants, pills, and the brain: Exploring phytochemicals and neurological medicines. **International Journal of Plant, Animal and Environmental Sciences**, *15**, 90–114.
- Ahn, S., Singh, P., Castro-Aceituno, V., Yesmin Simu, S., Kim, Y. J., Mathiyalagan, R., & Yang, D. C. (2017). Gold nanoparticles synthesized using **Panax ginseng** leaves suppress inflammatory-mediators production via blockade of NF- κ B activation in macrophages. **Artificial Cells, Nanomedicine, and Biotechnology**, *45*(2)*, 270–276. DOI: 10.3109/21691401.2016.1146727
- Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: Problems and promises. **Molecular Pharmaceutics**, *4*(6)*, 807–818. DOI: 10.1021/mp700113r
- Baranowska-Wójcik, E., Gajowniczek-Ałasa, D., Pawlikowska-Pawłęga, B., & Szwajgier, D. (2025). The potential role of phytochemicals in Alzheimer's disease. **Nutrients**, *17*(4)*, Article 653. DOI: 10.3390/nu17040653
- Bhattacharjee, A., Ramakrishna, A., & Obulesu, M. (Eds.). (2020). *Phytomedicine and Alzheimer's disease*. CRC Press., DOI: 10.1201/9780429318429
- Bhushan, B., Singh, N. K., & Singh, R. (2024). Traditional Chinese medicine: Its growing potential in treating neurological disorders. **Pharmacological Research - Modern Chinese Medicine**, *11**. *Pharmacological Research. Modern Chinese Medicine*, 100422, 100422. Advance online publication. DOI: 10.1016/j.prmcm.2024.100422
- Chagas, M. D., Behrens, M. D., Moragas-Tellis, C. J., Penedo, G. X., Silva, A. R., & Gonçalves-de-Albuquerque, C. F. (2022). Flavonols and flavones as potential anti-inflammatory, antioxidant, and antibacterial compounds. **Oxidative Medicine and Cellular Longevity**, *2022**. *Oxidative Medicine and Cellular Longevity*, 9966750(1), 9966750. Advance online publication. DOI: 10.1155/2022/9966750 PMID: 36111166
- Chen, Y., Chen, Y., Liang, Y., Chen, H., Ji, X., & Huang, M. (2020). Berberine mitigates cognitive decline in an Alzheimer's disease mouse model by targeting both tau hyperphosphorylation and autophagic clearance. **Biomedicine & Pharmacotherapy**, *121**. *Biomedicine and Pharmacotherapy*, 109670, 109670. Advance online publication. DOI: 10.1016/j.biopha.2019.109670 PMID: 31810131
- Connolly, E. L., Sim, M., Travica, N., Marx, W., Beasy, G., Lynch, G. S., Bondonno, C. P., Lewis, J. R., Hodgson, J. M., & Blekkenhorst, L. C. (2021). Glucosinolates from cruciferous vegetables and their potential role in chronic disease: Investigating the preclinical and clinical evidence. **Frontiers in Pharmacology**, *12**. *Frontiers in Pharmacology*, 767975, 767975. Advance online publication. DOI: 10.3389/fphar.2021.767975 PMID: 34764875
- Cui, D., Chen, Y., Ye, B., Guo, W., Wang, D., & He, J. (2023). Natural products for the treatment of neurodegenerative diseases. **Phytomedicine**, *121**. *Phytomedicine*, 155101, 155101. Advance online publication. DOI: 10.1016/j.phymed.2023.155101 PMID: 37778246

- Cuya, T., Baptista, L., & Celmar Costa França, T. (2018). A molecular dynamics study of components of the ginger (*Zingiber officinale*) extract inside human acetylcholinesterase: Implications for Alzheimer disease. *Journal of Biomolecular Structure and Dynamics*, *36*(14), 3843–3855. DOI: 10.1080/07391102.2017.1401004
- de la Torre, R., Alvira, D., Pagès, N., & others. (2006). Flavonoids and the brain: Modulation of monoamine oxidase (MAO) activity. *Current Topics in Medicinal Chemistry*, *6*(17), 1841–1851. DOI: 10.2174/156802606778249801
- Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, *4*. *Frontiers in Pharmacology*, 177. Advance online publication. DOI: 10.3389/fphar.2013.00177 PMID: 24454289
- Gregory, J., Vengalasetti, Y. V., Bredeesen, D. E., & Rao, R. V. (2021). Neuroprotective herbs for the management of Alzheimer’s disease. *Biomolecules*, *11*(4), Article 543. DOI: 10.3390/biom11040543
- Hossain, M. S., Wazed, M. A., Asha, S., Amin, M. R., & Shimul, I. M. (2025). Dietary phytochemicals in health and disease: Mechanisms, clinical evidence, and applications—A comprehensive review. *Food Science & Nutrition*, *13*(3), Article e70101. DOI: 10.1002/fsn3.70101
- Howes, M. J., & Perry, E. (2011). The role of phytochemicals in the treatment and prevention of dementia. *Drugs & Aging*, *28*(6), 439–468. DOI: 10.2165/11591310-000000000-00000
- Ingelman-Sundberg, M. (2001). Pharmacogenomics of cytochrome P450 and its applications in drug therapy. *The Pharmacogenomics Journal*, *1*(2), 47–64. DOI: 10.1038/sj.tpj.6500017
- Jin, X., Liu, M. Y., Zhang, D. F., Zhong, X., Du, K., Qian, P., Yao, W. F., Gao, H., & Wei, M. J. (2019). Baicalin mitigates cognitive impairment and protects neurons from microglia-mediated neuroinflammation via suppressing NLRP3 inflammasomes and TLR4/NF-κB signaling pathway. *CNS Neuroscience & Therapeutics*, *25*(5), 575–590. DOI: 10.1111/cns.13086
- Jurado-Coronel, J. C., Echeverria, V., Hidalgo, O. A., Gonzalez, J., Aliev, G., & Barreto, G. E. (2016). Implication of green tea as a possible therapeutic approach for Parkinson disease. *CNS & Neurological Disorders - Drug Targets*, *15*(3), 292–300. <https://doi.org/DOI: 10.2174/1871527315666160201115350>
- Kakoti, B. B., Bezbaruah, R., & Ahmed, N. (2022). Therapeutic drug repositioning with special emphasis on neurodegenerative diseases: Threats and issues. *Frontiers in Pharmacology*, *13*. *Frontiers in Pharmacology*, 1007315, 1007315. Advance online publication. DOI: 10.3389/fphar.2022.1007315 PMID: 36263141
- Khan, A. U., Akram, M., Daniyal, M., & Zainab, R. (2019). Awareness and current knowledge of Parkinson’s disease: A neurodegenerative disorder. *International Journal of Neuroscience*, *129*(1), 55–93. <https://doi.org/DOI: 10.1080/00207454.2018.1501452>
- Kumar, A., P, N., Kumar, M., Jose, A., Tomer, V., Oz, E., Proestos, C., Zeng, M., Elobeid, T., K, S., & Oz, F. (2023). Major phytochemicals: Recent advances in health benefits and extraction method. *Molecules*, *28*(2), Article 887. DOI: 10.3390/molecules28020887

- Kumar, R., Pal, O. P., Kamboj, N., & Jaiswal, A. (2025). Phytonutrients in neuroprotection and neurodegenerative disorders. **Current Research in Nutrition and Food Science Journal**, *13*(Special Issue Phytonutrients June 2025).
- Kushwah, S., Maurya, N. S., Kushwaha, S., Scotti, L., Chawade, A., & Mani, A. (2023). Herbal therapeutics for Alzheimer's disease: Ancient Indian medicine system from the modern viewpoint. **Current Neuropharmacology**, *21*(4), 764–776. <https://doi.org/DOI: 10.2174/1570159X21666230315162353>
- Lacham-Hartman, S., Oren, O., Rabinovitch, M., & Papo, N. (2025). Neuroprotective functions of the APPI domain of amyloid precursor protein (APP): Reducing KLK6-mediated APP cleavage and A β 42 formation and aggregation. **International Journal of Biological Macromolecules**, *278*. *International Journal of Biological Macromolecules*, 146066, 146066. Advance online publication. DOI: 10.1016/j.ijbiomac.2025.146066 PMID: 40680950
- Li, S., Han, Q., Qiao, C., Song, J., Cheng, C. L., & Xu, H. (2008). Chemical markers for the quality control of herbal medicines: An overview. **Chinese Medicine**, *33*. *Chinese Medicine*, 7(1), 7. Advance online publication. DOI: 10.1186/1749-8546-3-7 PMID: 18588699
- Liu, J., Yin, F., Guo, L., Zhang, J., & Zidichouski, J. (2015). Molecular mechanisms of geniposide and genipin against Alzheimer's disease. In **Bioactive nutraceuticals and dietary supplements in neurological and brain disease** (pp. 221–227). Academic Press. <https://doi.org/DOI: 10.1016/B978-0-12-411462-3.00023-7>
- Löscher, W., & Potschka, H. (2005). Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. **NeuroRx**, *2*(1), 86–98. DOI: 10.1602/neuroRx.2.1.86
- Ma, J., Wang, R., Chen, T., Jiang, S., & Xu, A. (2021). Protective effects of baicalin in a **Caenorhabditis elegans** model of Parkinson's disease. **Toxicology Research**, *10*(3), 409–417. DOI: 10.1093/toxres/tfab021
- Ma, X., Tan, C., Zhu, D., Gang, D. R., & Xiao, P. (2007). Huperzine A from **Huperzia** species—An ethnopharmacological review. **Journal of Ethnopharmacology**, *113*(1), 15–34. DOI: 10.1016/j.jep.2007.05.030
- Malar, D. S., Prasanth, M. I., Brimson, J. M., Sharika, R., Sivamaruthi, B. S., Chaiyasut, C., & Tencomnao, T. (2020). Neuroprotective properties of green tea (**Camellia sinensis**) in Parkinson's disease: A review. **Molecules**, *25*(17), Article 3926. DOI: 10.3390/molecules25173926
- Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Bioavailability of polyphenols and flavonoids in humans. **The American Journal of Clinical Nutrition**, *79*(5), 727–747. DOI: 10.1093/ajcn/79.5.727
- Menghani, Y. R., Bhattad, D. M., Chandak, K. K., Taksande, J. R., & Umekar, M. J. (2021). Review: Pharmacological and herbal remedies in the management of neurodegenerative disorder (Alzheimer's). **International Journal of Pharmacognosy and Life Science**, *2*(1), 18–27. DOI: 10.33545/27072827.2021.v2.i1a.21

- Misrani, A., Tabassum, S., & Yang, L. (2021). Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. *Frontiers in Aging Neuroscience*, *13*. *Frontiers in Aging Neuroscience*, 617588, 617588. Advance online publication. DOI: 10.3389/fnagi.2021.617588 PMID: 33679375
- Mohamed, E. A., Ahmed, H. I., Zaky, H. S., & Badr, A. M. (2021). Sesame oil mitigates memory impairment, oxidative stress, and neurodegeneration in a rat model of Alzheimer's disease: A pivotal role of NF- κ B/p38MAPK/BDNF/PPAR- γ pathways. *Journal of Ethnopharmacology*, *267*. *Journal of Ethnopharmacology*, 113468, 113468. Advance online publication. DOI: 10.1016/j.jep.2020.113468 PMID: 33049345
- Muhammad, F., Liu, Y., Zhou, Y., Yang, H., & Li, H. (2022). Antioxidative role of traditional Chinese medicine in Parkinson's disease. *Journal of Ethnopharmacology*, *285*. *Journal of Ethnopharmacology*, 114821, 114821. Advance online publication. DOI: 10.1016/j.jep.2021.114821 PMID: 34838943
- Ning, F., Chen, L., Chen, L., Liu, X., Zhu, Y., Hu, J., Xie, G., Xia, J., Shi, K., Lan, Z., & Wang, P. (2021). Combination of *Polygoni multiflori* radix praeparata and *Acori tatarinowii* rhizoma alleviates learning and memory impairment in scopolamine-treated mice by regulating synaptic-related proteins. *Frontiers in Pharmacology*, *12*. *Frontiers in Pharmacology*, 679573, 679573. Advance online publication. DOI: 10.3389/fphar.2021.679573 PMID: 34393775
- Pardridge, W. M. (2005). The blood-brain barrier: Bottleneck in brain drug development. *NeuroRx*, *2*(1), 3–14. DOI: 10.1602/neurorx.2.1.3
- Park, H., Kang, S., Nam, E., Suh, Y. H., & Chang, K. A. (2019). The protective effects of PSM-04 against beta amyloid-induced neurotoxicity in primary cortical neurons and an animal model of Alzheimer's disease. *Frontiers in Pharmacology*, *10*. *Frontiers in Pharmacology*, 2, 2. Advance online publication. DOI: 10.3389/fphar.2019.00002 PMID: 30733674
- Pramanik, R., Dey, A., Chakrabarty, A. K., Banerjee, D., Narwaria, A., Sharma, S., Rai, R. K., Katiyar, C. K., & Dubey, S. K. (2024). Diabetes mellitus and Alzheimer's disease: Understanding disease mechanisms, their correlation, and promising dual activity of selected herbs. *Journal of Ethnopharmacology*, *333*. *Journal of Ethnopharmacology*, 118402, 118402. Advance online publication. DOI: 10.1016/j.jep.2024.118402 PMID: 38821139
- Rebai, O., Belkhir, M., Boujelben, A., Fattouch, S., & Amri, M. (2017). *Morus alba* leaf extract mediates neuroprotection against glyphosate-induced toxicity and biochemical alterations in the brain. *Environmental Science and Pollution Research*, *24*(10), 9605–9613. <https://doi.org/10.1007/s11356-017-8606-8>
- Rekatsina, M., Paladini, A., Piroli, A., Zis, P., Pergolizzi, J. V., & Varrassi, G. (2020). Pathophysiology and therapeutic perspectives of oxidative stress and neurodegenerative diseases: A narrative review. *Advances in Therapy*, *37*(1), 113–139. DOI: 10.1007/s12325-019-01148-5
- Rewar, S. (2015). A systematic review on Parkinson's disease (PD). *Indian Journal of Research in Pharmacy and Biotechnology*, *3*(2), 176–182.

- Rui, W., Li, S., Xiao, H., Xiao, M., & Shi, J. (2020). Baicalein attenuates neuroinflammation by inhibiting NLRP3/caspase-1/GSDMD pathway in MPTP-induced mice model of Parkinson's disease. *International Journal of Neuropsychopharmacology*, *23*(11), 762–773. DOI: 10.1093/ijnp/pyaa060
- Sahiner, M., Yilmaz, A. S., Gungor, B., & Sahiner, N. (2023). A review on phyto-therapeutic approaches in Alzheimer's disease. *Journal of Functional Biomaterials*, *14*(1), Article 50. DOI: 10.3390/jfb14010050
- Sharma, R., Kuca, K., Nepovimova, E., Kabra, A., Rao, M. M., & Prajapati, P. K. (2019). Traditional Ayurvedic and herbal remedies for Alzheimer's disease: From bench to bedside. *Expert Review of Neurotherapeutics*, *19*(5), 359–374. DOI: 10.1080/14737175.2019.1596803
- Singh, A. K., Rai, S. N., Maurya, A., Mishra, G., Awasthi, R., Shakya, A., Chellappan, D. K., Dua, K., Vamanu, E., Chaudhary, S. K., & Singh, M. P. (2021). Therapeutic potential of phytoconstituents in management of Alzheimer's disease. *Evidence-Based Complementary and Alternative Medicine*, *2021*. *Evidence-Based Complementary and Alternative Medicine : eCAM*, 5578574, 1–19. Advance online publication. DOI: 10.1155/2021/5578574 PMID: 34211570
- Sivaraman, D., Anbu, N., Kabilan, N., Kumar, M. P., Shanmugapriya, P., & Christian, G. J. (2019). Review on current treatment strategy in Alzheimer's disease and role of herbs in treating neurological disorders. *International Journal of Translational Research in Indian Medicine*, *1*(1), 33–43.
- Snow, A. D., Castillo, G. M., Nguyen, B. P., Choi, P. Y., Cummings, J. A., Cam, J., Hu, Q., Lake, T., Pan, W., Kastin, A. J., & Kirschner, D. A. (2019). The Amazon rain forest plant *Uncaria tomentosa* (cat's claw) and its specific proanthocyanidin constituents are potent inhibitors and reducers of both brain plaques and tangles. *Scientific Reports*, *9*(1), Article 561. DOI: 10.1038/s41598-019-38645-0
- Sohn, E., Kim, Y. J., & Jeong, S. J. (2021). Korean traditional herbal formula Soshiho-tang attenuates memory impairment and neuronal damage in mice with amyloid-beta-induced Alzheimer's disease. *Integrative Medicine Research*, *10*(3), Article 100723. DOI: 10.1016/j.imr.2021.100723
- Thakur, M., Singh, K., & Khedkar, R. (2020). Phytochemicals: Extraction process, safety assessment, toxicological evaluations, and regulatory issues. In *Functional and preservative properties of phytochemicals* (pp. 341–361). Academic Press., DOI: 10.1016/B978-0-12-818593-3.00011-7
- Uttara, B., Singh, A. V., Zamboni, P., & Mahajan, R. T. (2009). Oxidative stress and neurodegenerative diseases: A review. *International Journal of Molecular Sciences*, *10*(3), 781–796. <https://doi.org/DOI: 10.3390/ijms10030781>
- Venkatesan, R., Ji, E., & Kim, S. Y. (2017). Phytochemicals that regulate neuroinflammation. *Current Pharmaceutical Design*, *23*(44), 6685–6700. <https://doi.org/DOI: 10.2174/1381612823666170215164852>

- Xu, Y., Liu, S., Zhu, L., Dai, L., Qian, W., Zhang, J., Li, X., & Pan, W. (2021). Green tea protects against hippocampal neuronal apoptosis in diabetic encephalopathy by inhibiting JNK/MLCK signaling. **Molecular Medicine Reports**, **24*(2)*, Article 575. DOI: 10.3892/mmr.2021.12214
- Yin, R., Xue, J., Tan, Y., Fang, C., Hu, C., Yang, Q., Mei, X., & Qi, D. (2021). The positive role and mechanism of herbal medicine in Parkinson's disease. **Oxidative Medicine and Cellular Longevity**, **2021**, *Oxidative Medicine and Cellular Longevity*, *9923331(1)*, 9923331. Advance online publication. DOI: 10.1155/2021/9923331 PMID: 34567415
- Zhang, J., Yang, C., Wei, D., Li, H., Leung, E. L., Deng, Q., Liu, Z., Fan, X. X., & Zhang, Z. (2019). Long-term efficacy of Chinese medicine Bushen Capsule on cognition and brain activity in patients with amnesic mild cognitive impairment. **Pharmacological Research**, **146**, *Pharmacological Research*, *104319*, 104319. Advance online publication. DOI: 10.1016/j.phrs.2019.104319 PMID: 31220560
- Zhang, Q., Zheng, Y., Hu, X., Hu, X., Lv, W., Lv, D., Chen, J., Wu, M., Song, Q., & Shentu, J. (2018). Ethnopharmacological uses, phytochemistry, biological activities, and therapeutic applications of **Alpinia oxyphylla** Miquel: A review. **Journal of Ethnopharmacology**, **224**, 149–168. DOI: 10.1016/j.jep.2018.05.002
- Zhang, X., Du, L., Zhang, W., Yang, Y., Zhou, Q., & Du, G. (2017). Therapeutic effects of baicalein on rotenone-induced Parkinson's disease through protecting mitochondrial function and biogenesis. **Scientific Reports**, **7*(1)*, Article 9968. <https://doi.org/DOI: 10.1038/s41598-017-09824-0>
- Zhang, Y., Lin, C., Zhang, L., Cui, Y., Gu, Y., Guo, J., Wu, D., Li, Q., & Song, W. (2015). Cognitive improvement during treatment for mild Alzheimer's disease with a Chinese herbal formula: A randomized controlled trial. **PLoS ONE**, **10*(6)*, Article e0130353. DOI: 10.1371/journal.pone.0130353
- Zhang, Y., Qian, C., Chen, Y., He, W., & Guo, Z. (2025). Phototherapy via modulation of β -amyloid in combating Alzheimer's disease. **Aggregate**, **6*(5)*, Article e70020. DOI: 10.1002/agt2.70020
- Zhang, Z., Chen, J., Li, C., & others. (2014). Intranasal huperzine A-loaded nanostructured lipid carriers for brain delivery to treat Alzheimer's disease. **International Journal of Pharmaceutics**, **474*(1–2)*, 113–122. DOI: 10.1016/j.ijpharm.2014.08.003
- Zhang, Z., Zhang, S., Lui, C. N., Zhu, P., Zhang, Z., Lin, K., Dai, Y., & Yung, K. K. (2019). Traditional Chinese medicine-based neurorestorative therapy for Alzheimer's and Parkinson's disease. **Journal of Neurorestoratology**, **7*(4)*, 207–222. DOI: 10.26599/JNR.2019.9040023
- Zhao, Y., & Lu, Z. N. (2017). Glabridin attenuates MPTP-induced Parkinson disease by inhibiting extracellular regulated protein kinases signaling pathway. **Zhonghua Yi Xue Za Zhi**, **97*(26)*, 2050–2054. <https://doi.org/DOI: 10.3760/cma.j.issn.0376-2491.2017.26.010>