

## Emerging roles of key phytoconstituents in management of neurological disorders; Withaferin A, Bacoside A, Apigenin and Tetrahydrocurcumin

Shahina<sup>1</sup>, Simran Sharma<sup>1</sup>, Neha Kumari<sup>1</sup>, Tamanna Kumari<sup>1</sup>, Kritika Thakur<sup>1</sup>  
Diksha Thakur<sup>2</sup>

Student, Shiva Institute of Pharmacy, Chandpur, Bilaspur, H.P<sup>1</sup>

Assistant Professor, Shiva Institute of Pharmacy, Chandpur, Bilaspur, H.P<sup>2</sup>

Corresponding Author – Shahina

Date of Submission: 07-05-2026

Date of Acceptance: 18-05-2026

### Abstract

Neurological disorders such as Alzheimer's, depression, Parkinson's, dementia, neuroinflammation is the major health burden in now days due to their complicated pathophysiology and limitation of current fabricated therapies. Consequently, phytochemical of medicinal plant plays an important role in managing the brain chemical balance by inducing the function of receptor for major inhibitory neurotransmitter. This review focus on four main phytoconstituent that are; Withaferin A – It derived from *Withania somnifera* which act as anti-amyloid, antioxidant and anti-inflammatory agent by targeting on Alzheimer's and Parkinson's disease. Bacoside A-It derived from *Bacopa monnieri* which show their action in synaptogenesis and act as antioxidant, neuroprotector by targeting on cognitive dysfunction and age-related memory decline. Apigenin-It found in *Matricaria chamomilla* which show their effect on GABAergic modulation by targeting on convulsions and anxiety. Tetrahydrocurcumin-It is the major metabolite of curcumin which improve blood brain barrier penetration and show anti-oxidant, anti-inflammatory effects. These substances provide impactful action against neurodegeneration by modulating critical pathways such as neuroinflammation through Nuclear Factor kappa-light-chain-enhancer of activated B cells inhibition, oxidative stress by nuclear factor erythroid 2-related factor activation and preventing the platelet aggregation. This review highlights how phytoconstituents show multitargeted actions against the neurological disorders and explore underlying mechanisms involve in their action. Thus, phytoconstituent have a great potential in the prevention and treatment of neurological disease.

Keyword:-Neurological disorders, Withaferin A, Bacoside A, Apigenin, Tetrahydrocurcumin,

Neuroinflammation, Anti-oxidants and Neuroprotection.

### I. INTRODUCTION

Currently the neurological disorders play a significant challenge related to the healthcare systems worldwide. These conditions can vitally impact an individual's well-being, which leads to emotional, physical and cognitive impairment[1]. Management of neurological disorders regularly requires specialized health care, including treatment accessibility from medical experts, various diagnostic tools, and complex treatment options[2]. Unfortunately, most real-world scenarios lack sufficient resources to provide adequate care for patients with neurological disorders[3]. Furthermore, the complexity of these disorder makes treatment and diagnosis difficult, leading to diagnostic error and delayed care, which can intensify symptoms and overloading the burden on patients and health care [4]. Parkinson's disease is thought to be a composite neuropsychiatric conditions/illness. These signs and symptoms comes under the wide categories of affect like anxiety, depression, perception and thinking that is psychosis and motivation that is impulse control disorders[5].

Alzheimer's disease (AD) is a primary neurodegenerative dementia and one of the major causes of disability in older people. AD is clinically characterized by a progressive and global cognitive impairment that affects a person's ability to perform everyday activities and is related with brain changes that include the extracellular accumulation of beta-amyloid plaques outside neurons and intraneuronal deposition of tau tangles inside. Typical depressive symptoms in AD are insomnia, social withdrawal, reduced purpose-oriented behaviour, loss of interest in once-enjoyable activities and hobbies, guilt, hopelessness, and sadness. Anxiety and depression

often overlap, especially in patients with mild AD nevertheless. Anxiety and depression in AD have been largely studied. [6]

Several limitations and challenges are evident in the current treatment. The available pharmacological treatments for neurodegenerative disorders primarily offer symptomatic relief and do not address the underlying disease pathology. Many pharmacological interventions are associated with adverse effects, which can limit their long-term use and tolerability. The cost of long-term care for individuals with neurodegenerative disorders can be financially burdensome for both patients and healthcare systems. In conclusion, the current therapies for neurodegenerative disorders, while offering some relief, are far from ideal. They primarily address symptoms and come with limitations and challenges related to efficacy, tolerability, and accessibility [7].

*W. somnifera* is potentially useful for many neurological disorders such as epilepsy, Alzheimer's disease, Parkinson's disease, cerebral ischaemia. *W. somnifera* possesses several other pharmacological properties, such as anti-inflammatory, anti-diabetic, cardioprotective, anti-hepatitis, anti-osteoporotic, and anti-neoplastic activities. In traditional medicine, *W. somnifera* has been used as an anti-microbial and aphrodisiac, thyroid dysfunction, and insomnia [8,9].

Bacoside A has been used as a therapeutic agent for various disorders especially neurodegenerative disease. This herb was used by Ancient Vedic scholars due to its pharmacological effect, especially as a nerve tonic and nootropic booster [10]. It is traditionally used as a neural tonic and memory enhancer. *B. monnieri* is also known to help attenuating dementia or decline in mental ability [11].

Apigenin improved serotonin, dopamine and epinephrine levels, which were altered in depressive animals. Apigenin play important roles in neuronal survival, synaptic plasticity, cognitive function and mood behaviour. Reviews have shown the pharmacological activities of apigenin, especially against some neurological diseases[12]. Tetrahydro curcumin (THC) inhibits ferroptosis and restores blood-brain barrier (BBB) function by activating the Keap1/Nrf2 signaling pathway, thereby alleviating neurological dysfunction induced by cerebral ischemia-reperfusion[13].

## II. Phytoconstituents and their Neurological Action

### 2.1 Withaferin A

Withaferin A (WFA) was recognized as the most active phytoconstituents of the plant *Withania somnifera* (WS) which have various medicinal properties in case of various disorders. *Withania somnifera* (L.) Dunal (WS) is a widely used medicinal practices across the world since ancient times. It belongs to the Solanaceae family, offers therapeutical effects for many human diseases including arthritis, epilepsy, depression, diabetes [plant which is also known as Ashwagandha with easily identifiable importance. The leaves of the *withania somnifera* being used as raw material for the isolation of Withanolides steroid compounds. This Ayurvedic herb, known for its many beneficial health care [14]. Withanolides are steroidal lactones which have ergostane skeleton with multiple biological and pharmacological actions. Withanolides particularly exist in the solanaceae family of plant genera ; including *Withania*, *Physalis*, *Datura* etc. Among all the Withanolides constituents isolated to till date withaferin A (WA) is most significant and has achieved the interest of many pharmaceutical scientists, research scientists and clinical pharmacists which focus on developing and discovering new drugs. WS has been utilized as foundational herb in various traditional ayurvedic formulations for improving strength, immunity and multiple health issues. This astonishing plant has many pharmacological activities such as anti-inflammatory, antistress, antioxidant, anticonvulsant, immunomodulatory, antiproliferative properties. WS inhabits the most powerful position among the plants of ayurvedic rasayana. From more than 3000 years in both indigenous medical transition and ayurveda[15]. It is also used in the treatment of neurodegenerative disorders as well as rheumatism, arthritis musculoskeletal[16]. Due to the growing research on Ashawgandha its potential as natural remedy has been highlighted for many health issues.[17]

Mechanism:

Antiamyloid:

One of the primary causes of neurodegeneration in the brain is A $\beta$  accumulation. Therefore, amyloid  $\beta$  is one of the therapeutic targets for potential treatments for neurological illnesses. In order to prevent and treat neurological disorders, substances that may facilitate the accumulation and aggregation of this peptide are sought after.

WA may shield the brain from amyloid-beta plaques' harmful effects. The study showed that WA reduced the release of amyloid  $\beta$  and that amyloid-beta negatively impacts neuronal architecture and functions[18]. WA possesses inhibitory activities

against developing a pathological marker of Alzheimer disease by reduction of amyloid plaque aggregation and tau protein accumulation[19].

Antioxidant:

WA was evaluated for antioxidant activity using major free-radical scavenging enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX), and NADPH dehydrogenase levels. It exhibits anti-oxidative activity by increasing the levels of various antioxidant enzymes, which reduce the free radicals or stress formed in the affected cells and provide a healthy mitochondrial function [20]. Study demonstrated that nuclear factor erythroid 2 related factor 2[Nrf2] is suitable for stripping oxidized protein and maintain homeostasis following oxidative stress[21].

Anti-inflammatory:

WFA has been historically used in traditional medicine for its anti-inflammatory and adaptogenic properties. WFA attenuated key cachexia-associated pathways, including NF- $\kappa$ B signaling, NLRP3 inflammasome activation, while promoting proteostasis and mitochondrial homeostasis. It exhibits the anti-inflammatory effect via suppressing nuclear transcription factor NF- $\kappa$ B and nuclear factor erythroid 2 related factor 2[Nrf2]. However, nuclear receptors participate in its anti-inflammatory mechanism still needs to be further explored. The transcription factor NF- $\kappa$ B is one of the main players involved in inflammatory responses during which NF- $\kappa$ B becomes rapidly activated. However, to maintain homeostasis, this NF- $\kappa$ B activation profile is only transient. Nevertheless, deregulation of NF- $\kappa$ B activity is often observed and can lead to chronic inflammatory diseases Hereby WA directly inhibits IKK catalytic activity.[19,22,23]

Target disorders:

Alzheimer's disease:

W. somnifera root extract has shown promising results in the treatment of Alzheimer's diseases by altering different pathological processes like accumulation of amyloid beta plaques in the brain, increased muscarinic receptor binding affinity, decreasing apoptotic cell death of neurons through the migration of nuclear factor erythroid 2-related factor 2 (Nrf2) to the nucleus etc[24].It is a transcription factor that regulates the activity of antioxidant enzymes and protects the cells against oxidative damage. The transcription factor increases the expression of the neuroprotective enzyme heme oxygenase-1 and increased insulin-degrading

enzyme (IDE) production, which causes the degradation of A $\beta$ . Withaferin-A could lead to increased cholinergic transmission in certain areas of the brain, like the basal ganglia and cerebral cortex, which can lead to improved cognitive function by enhancing the binding of acetylcholine to muscarinic M1 receptor. In Alzheimer's disease, the NF- $\kappa$ B pathway blocks the phagocytosis of A $\beta$  fibrils, which leads to the accumulation of A $\beta$  fibrils and neuroinflammation in the brain. Withaferin-A has been shown to inhibit the activation of NF- $\kappa$ B by stopping phosphorylation of NF- $\kappa$ B by inhibiting stimulation of I $\kappa$ B kinase. It also inhibited the activation of NF- $\kappa$ B by attacking the catalytic site of I $\kappa$ B kinase and preventing neuroinflammation.[25,26]

Parkinson's Disease:

Parkinson's Disease (PD), a multifactorial movement disorder, is neuropathologically characterized by age-dependent neurodegeneration of the dopaminergic neurons in Substantia nigra. In PD, the loss of dopamine-producing neurons is mainly responsible for PD-associated symptoms. The treatment of PD, using L-Dopa and other classes of drugs such as dopamine agonists, monoamine oxidase inhibitors, and anticholinergic agents, provides only symptomatic relief. Long-term use of these drugs produces side effects which contribute to disease progression. Withania somnifera offers nigrostriatal dopaminergic neuroprotection by modulating oxidative stress, apoptotic machinery and shown excellent potential in PD treatment. Withanolides A, one of the active compounds in Withania somnifera, facilitated the neurite outgrowth and reconstruction of synapses in PD models.[27,28]

2.2Bacoside A

Bacopa monnieri, also known as Brahmi or Waterhyssop, is a plant used in Ayurveda for its memory-enhancing properties and control of blood sugar levels. It contains active compounds such as alkaloids, saponins, and cucurbitacins, which have various biological activities. The plant has been studied for its potential in treating Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder (ADHD), depression, improving memory, thinking skills, insomnia, seizures, and anxiety[29]. Recently, this plant has been widely described for its pharmacologically active phytoconstituents, such as bacosaponin C, bacosides A and B etc. It is believed that some neurotransmitters associated with cognitive

processes, including acetylcholine, serotonin, and GABA (gamma-aminobutyric acid), are more highly active which improve cognitive functions[30]. Bacoside mechanism of action in brain diseases may be related to its ability to modulate neurotransmission, neurogenesis, neuronal plasticity, intracellular signaling, epigenetics, cerebral blood flow, energy metabolism, protein folding, endoplasmic reticulum stress, neuroendocrine system[31]. Specific brain regions that are affected by bacoside A experience an increase in protein and RNA production, oxidative stress protection, improved cerebral blood flow, and enhanced synaptic activity[32].

#### Mechanism:

##### Synaptogenesis:

Neurogenesis, the generation of new neurons, and synaptic plasticity, which allows synapses to strengthen and weaken with passage of time, are essential to learning, memory, and global brain function. In neurodegenerative disease states such as AD and PD, compromised neurogenesis and dysfunction of synapses play a profound role in both cognitive and motor impairment. Bacoside A encourage neurogenesis and synaptic plasticity through the modulating of neurotrophic factors, neurotransmitter concentrations, and connectivity between neurons, the principal regulators of neurogenesis are brain-derived neurotrophic factor (BDNF), which protects neurons, aids differentiation, and maintains synaptic plasticity. Bacosides activate dendritic sprouting and synaptogenesis with the consequent enhancement of memory and learning. Another significant factor is nerve growth factor (NGF), which has a key function in the support of cholinergic neurons. Bacoside evoke signaling cascades like the cAMP response element-binding protein (CREB) cascade important for memory formation. Through stimulation of neurogenesis and synaptic plasticity, medicinal plants restore cognitive capacity and retard neurodegenerative disease progression[33,34].

##### Antioxidant and neuroprotective effects:

Bacosides successfully establish a healthy antioxidant environment in various tissues especially in the brain. Free radical scavenging, suppression of lipid peroxidation and activation of antioxidant enzymes by bacosides help to attain a physiological state of minimized oxidative stress. It may enhance the antioxidant defence systems in the brain by activating specific enzymes and reducing

oxidative stress; it can also reduce the levels of harmful metal ions, such as iron and copper, which contribute to oxidative damage in the brain. The bioactive chemicals in *Bacopa monnieri* may either block the enzyme responsible for degrading the neurotransmitter acetylcholine (acetylcholinesterase) or stimulate the enzyme responsible for producing acetylcholine (choline acetyltransferase). Altering acetylcholine levels may improve cognitive performance[35,36,37].

##### Targeted disorder:

##### Cognitive dysfunction:

Cognitive decline is a common phenomenon observed in an aging population[38]. *Bacopa monnieri* (often called brahmi) is a botanical frequently used in Ayurvedic medicine. The main indications for using *Bacopa* in Ayurvedic medicine are memory improvement, insomnia, epilepsy, and as an anxiolytic. Many clinical studies have demonstrated improvements in verbal learning, delayed word recall, memory acquisition, and anxiety reduction with using *Bacopa*. It has been described as a calming cognitive enhancer. The triterpenoid saponins are believed to be responsible for most of the herb's pharmacological actions. The cognitive-enhancing properties of *Bacopa* are likely from the presence of a group of saponins collectively referred to as bacosides. Purified bacosides A and B, as well as *bacopa* alcoholic extract, may facilitate learning ability, memory, and cognitive performance. Some possible mechanisms which may lead to cognitive improvement include modulation of acetylcholine release, muscarinic cholinergic receptor binding, and choline acetylase activity. The saponins in *Bacopa* modulate hypothalamic-pituitary-adrenal axis output and protect the hippocampus [39]. The bioactive phytochemicals present in *Bacopa* include a group of steroidal saponins known as Bacosides (A and B), bacosides III, IV, V, and bacosaponins A, B, C, D, E, and F which are responsible for neuroprotection, enhance memory, and antioxidant properties. bacosides improve cognitive function through antioxidant support, modulation of neurotransmitters, increasing cerebral blood flow and improve synaptic activity [40].

##### 2.3 Apigenin

Apigenin is one of the abundant flavonoids in fruits and vegetables and has been suggested to possess neuroprotective effects against some neurological disorders. It is a potent antioxidant and has been shown to exhibit anti-inflammatory, antitumorogenic

and antimicrobial activities . Its ability to cross the blood–brain barrier is important as it contributes to its pharmacological activity against neurological disorders [41,42].

Mechanism:

GABAergic modulation:

Apigenin also has the potential to produce beneficial effects in epilepsy – one of the most common CNS diseases. It is generally considered that an imbalance between gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission and glutamatergic excitatory neurotransmission plays a fundamental role in the manifestation of acute seizures and in epilepsy. Apigenin may alter both GABAergic and glutamatergic systems, thereby affecting seizure susceptibility. It exerts complex modulatory action on GABA<sub>A</sub> receptors. It also inhibits 4-aminopyridine-induced glutamate release. Furthermore, the neuroprotective properties of apigenin may also contribute to its potential in alleviating epilepsy-related neurodegeneration. Repeated and prolonged seizures occurring in epilepsy may contribute to severe neuronal damage primarily affecting the hippocampus, entorhinal cortex, amygdala, and other brain areas. Importantly, a significant loss in subsets of hippocampal GABAergic neurons can be observed in patients suffering from epilepsy.

To date, apigenin has been found to have antiseizure and neuroprotective effects in the kainic acid-induced seizure. It protected against neuronal death in the CA3 region of the hippocampus by attenuating oxidative stress and reducing the release of cytochrome c. It was also demonstrated that post-ischemic administration of apigenin can reduce seizures [43,44].

Anticonvulsant and Anti-anxiety effect:

Apigenin is a flavonoid present in plants like chamomile. It shows some promising effect in preclinical studies for easing seizures and anxiety. Most of its effects come from its interaction with the GABA<sub>A</sub> receptor. Basically, apigenin binds to the same spot as benzodiazepines and ramps up GABA's inhibitory action, which calms down overactive neurons. In seizure apigenin delays them, shortens their duration, and helps protect the brain from damage. Apigenin also reduces anxiety-like behaviors. It shows similar effects as typical benzodiazepines but there is no risk of dependence. Apigenin has antioxidant and anti-inflammatory properties that help in neuroprotection and keep neurons stable. So basically apigenin is used for treating epilepsy and anxiety disorders.[45,46]

Target Disorders:

Anxiety:

Apigenin is well known for its relaxing and anti-anxiety properties . Recent research validated apigenin's ability to relax muscles in animal models according to research published by Nakazawa et al., the dopaminergic system is involved in the possible antidepressant effect of apigenin. At the same time, another study demonstrated the role of  $\alpha$ -adrenergic, dopaminergic, and 5-HT<sub>3</sub> serotonergic receptors in mediating the antidepressant action of apigenin. Monoamine oxidase (MAO) activity was likewise reduced by apigenin. The inhibition of MAO increases levels of monoamines such as serotonin in the brain, which is linked to the disappearance of depressive symptoms. The functioning of gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors has been shown in several cases to be inhibited by apigenin, and antagonizing these receptors may relieve depression[47].

Epilepsy:

The most pressing demand in both research and development of therapies for epilepsy is to prevent it from developing or progressing. In order to tackle this significant problem effectively, there is an urgent need for novel conceptual breakthroughs. Epigenetic changes (e.g. methylation of DNA; acetylation of histones; and many others) are now firmly established as having functional roles in the mechanisms of both developing and progressing epilepsy. The methylation theory of epileptogenesis holds that changes in DNA methylation are involved in subsequent progression of epilepsy; global (or whole genome) hypermethylation is especially associated with chronic epilepsy. Similarly, acetylation changes/histone acetylation have been identified in both the development of epilepsy and the resulting sequelae. There exist both clinical and experimental examples of how neither the development of epilepsy nor progression of epilepsy can be stopped by metabolic and biochemical approaches. In ways that allow for normal functioning of the brain (i.e. B.M.T. and B.E.M.), it is believed that metabolic and biochemical manipulations will prevent any number of novel and/or previously unrecognized epigenetic functions from being involved in the development of epilepsy and the continuing seizure state. This review will consider some of the epigenetic mechanisms involved in the development of epilepsy and how metabolic and biochemical interactions could potentially play a role in the process of epileptogenesis[48].

**Tetrahydrocurcumin:-**

Tetrahydrocurcumin (THC) is an important reduction product of curcumin (CUR), which is a well-known yellow pigment found in turmeric, possessing excellent antioxidant, anti-inflammatory, and antimicrobial properties. THC shows more solubility, stability, and bioavailability compared to CUR but with the same biological effects[49].

**Mechanism:**

**Improve blood brain barrier(BBB) penetration:**

Tetrahydrocurcumin (THC) suppresses ferroptosis and improves the integrity of the blood-brain barrier (BBB) via stimulation of the Keap1/Nrf2 signaling pathway, consequently reducing neurological impairment caused by cerebral ischemia-reperfusion injury. The neuroprotective effects of THC in cerebral damage, specifically focusing on its possible inhibition of ferroptosis and enhancement of BBB integrity[50].

**Antioxidant and anti-inflammatory:**

THC is a strong antioxidant molecule by inhibiting the production of reactive oxygen species (ROS) and preventing high glucose-induced oxidative stress and fibrosis via SIRT1 signaling pathway. THC is a powerful suppressor of the generation of a range of inflammatory cytokines, mainly via modulation of the expression levels of numerous pro-inflammatory mediators and signaling pathways such as TNF- $\alpha$ , IL-6, and MIP-2. THC, an important phytocannabinoid, can regulate the expression of

inflammatory factors through 3 different signaling pathways (TLR4, MAPKs and NF- $\kappa$ B) which makes THC act as an anti-inflammatory factor by regulating inflammation via JAK/STAT, Nrf2/HO-1 and JNK/ERK signaling pathways. THC has also demonstrated inhibitory effects on the NF- $\kappa$ B/VEGF/MMP-9 signalling axis in certain experimental paradigms[51,52,53].

**Target Disorders:-**

**Alzheimer’s disease:**

THC has demonstrated its ability as a neuroprotectant through its capability to regulate the Ras/ERK signaling pathway, thus relieving cell cycle arrest and preventing apoptosis of microglial cells in Alzheimer’s disease [54]. THC is capable of neutralizing the rise in reactive oxygen species that occurs due to A $\beta$ , as well as inhibiting the fall in mitochondrial membrane potential and caspase activation. THC provides neuroprotection for human neurons against toxicity caused by A $\beta$  [55].

**Depression:**

THC increases anti-inflammatory and neuroprotective function which could aid in safely augmenting SSRI's for depression[56]. The anti-depressive effects of THC are mediated by TGF- $\beta$ 1 activation, p-SMAD3/SMAD3 and SIRT1 expression upregulation, BDNF and GDNF upregulation, and iNOS and TNF- $\alpha$  downregulation[57]

**III. Comparative mechanism:-**

Source	Mechanism of action	Target condition
Withania somnifera	Prevent beta amyloid plaque formation and reduce neuronal Death. Protects dopaminergic neurons from degeneration. Improves cognitive function by reducing oxidative damage.	Alzheimer’s disease.  Parkinson’s disease.  General neuroprotective.

Bacoside A	<p>Enhance learning.</p> <p>Shows anti-epileptic effect by Stabilizing neuronal activity.</p> <p>Supports long-term memory and reduces age-related decline.</p>	<p>Memory disorder.</p> <p>Epilepsy.</p> <p>Cognitive decline.</p>
Apigenin	<p>Acts like a natural anxiolytic/ Antidepressant.</p> <p>Mild anticonvulsant due to GABAergic effect.</p> <p>Protects neurons from inflammation and oxidative damage.</p>	<p>Anxiety and depression.</p> <p>Epilepsy.</p> <p>Neurodegeneration</p>
Tetrahydrocurcumin	<p>Prevent beta-amyloid aggregation and oxidative stress.</p> <p>Protects neuron from oxidative mitochondrial damage.</p> <p>Reduce neuronal cell death and improve recovery.</p>	<p>Alzheimer's disease</p> <p>Parkinson's disease</p> <p>Stroke/Ischemia</p>

#### IV. Conclusion:

In this review Withaferin A, Bacoside A, Apigenin and Tetrahydrocurcumin shows the significant therapeutic action especially due to their anti-inflammatory, antioxidant and neuroprotective properties these phytoconstituents assist in improving oxidative stress, neuronal function and may helps in the management of neurological disorders.

These phytoconstituents have lot of future potential because of their natural sources, they are generally safer and effective. With more research these phytoconstituents could be used together with other drugs to work in a better and modified way to enhance effectiveness and can be developed as novel drugs. These can be use to synthesis nanoparticles which can lead to better drug delivery system, enhance bioavailability and targeted therapy with low toxicity. Additionally, they have promising future prospective in the field of healthcare against various chronic and life threatening disorders.

#### Reference:-

- [1] Fornari, A., Lanza, M., Guastafierro, E., Marcassoli, A., Sismondo, P., Curatoli, C., ... & Leonardi, M. (2025). Inequities in neurological care: Access to services, care gaps, and other barriers—A systematic review. *European Journal of Neurology*, 32(1), e16553.
- [2] Ferrara, P., Andreone, V., Bandini, F., Del Sette, M., Longoni, M., Marconi, R., ... & Neurology, Healthcare Task Force of the Italian Society of Neurology. (2025). The role of neurology in the development of community healthcare within the Italian national health service. The position of the Italian society of neurology (SIN). *Neurological Sciences*, 46(8), 3363-3375.
- [3] Samanta, D., & Landes, S. J. (2021). Implementation science to improve quality of neurological care. *Pediatric neurology*, 121, 67-74.

- [4] Ningrum, D. N. A., & Kung, W. M. (2023). Challenges and perspectives of neurological disorders. *Brain Sciences*, 13(4), 676.
- [5] Weintraub, D., Aarsland, D., Chaudhuri, K. R., Dobkin, R. D., Leentjens, A. F., Rodriguez-Violante, M., & Schrag, A. (2022). The neuropsychiatry of Parkinson's disease: advances and challenges. *The Lancet Neurology*, 21(1), 89-102.
- [6] Botto, R., Callai, N., Cermelli, A., Causarano, L., & Rainero, I. (2022). Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline. *Neurological Sciences*, 43(7), 4107-4124.
- [7] Kharat, S., Mali, S., Korade, G., & Gaykar, R. (2024). Navigating neurodegenerative disorders: A comprehensive review of current and emerging therapies for neurodegenerative disorders. *J NeurosciNeurolDisord*, 8, 033-04.
- [8] Lerose, V., Ponticelli, M., Benedetto, N., Carlucci, V., Lela, L., Tzvetkov, N. T., & Milella, L. (2024). *Withania somnifera* (L.) Dunal, a potential source of phytochemicals for treating neurodegenerative diseases: A systematic review. *Plants*, 13(6), 771.
- [9] Ram, N., Peak, S. L., Perez, A. R., & Jinwal, U. K. (2021). Implications of Withaferin A in neurological disorders. *Neural Regeneration Research*, 16(2), 304-305.
- [10] Fatima, U., Roy, S., Ahmad, S., Ali, S., Elkady, W. M., Khan, I., ... & Hassan, M. I. (2022). Pharmacological attributes of *Bacopa monnieri* extract: Current updates and clinical manifestation. *Frontiers in nutrition*, 9, 972379.
- [11] Sekhar, V. C., Viswanathan, G., & Baby, S. (2019). Insights into the molecular aspects of neuroprotective bacoside A and bacopaside I. *Current neuropharmacology*, 17(5), 438-446.
- [12] Olasehinde, T. A., & Olaokun, O. O. (2024). The beneficial role of apigenin against cognitive and neurobehavioural dysfunction: A systematic review of preclinical investigations. *Biomedicines*, 12(1), 178.
- [13] Zhang, S., Han, J., Fan, Z., Wang, H., Liu, L., Liu, L., ... & Deng, H. (2025). Tetrahydrocurcumin Ameliorates Cerebral Ischemia-Reperfusion Injury and Restores Blood-Brain Barrier Dysfunction by Inhibiting Ferroptosis. *CNS Neuroscience & Therapeutics*, 31(11), e70662.
- [14] Bungau, S., Vesa, C. M., Abid, A., Behl, T., Tit, D. M., Purza, A. L., ... & Endres, L. (2021). Withaferin A—A promising phytochemical compound with multiple results in dermatological diseases. *Molecules*, 26(9), 2407.
- [15] Sharma, V., Sehgal, R., & Gupta, R. (2024). *Withania somnifera*: A potential rejuvenator of medicinal system for healthcare. *Journal of Drug Delivery & Therapeutics*, 14(4).
- [16] Sultana, T., Okla, M. K., Ahmed, M., Akhtar, N., Al-Hashimi, A., Abdelgawad, H., & Haq, I. U. (2021). Withaferin A: from ancient remedy to potential drug candidate. *Molecules*, 26(24), 7696.
- [17] Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., ... & Cielecka-Piontek, J. (2023). *Ashwagandha* (*Withania somnifera*)—current research on the health-promoting activities: a narrative review. *Pharmaceutics*, 15(4), 1057.
- [18] Yang, L., Zou, Y., Fan, J., Yin, P., Qin, H., Li, Z., ... & Li, S. C. (2025). Withaferin A rescues brain network dysfunction and cognitive deficits in a mouse model of Alzheimer's disease. *Pharmaceutics*, 18(6), 816.
- [19] Das, R., Rauf, A., Akhter, S., Islam, M. N., Emran, T. B., Mitra, S., ... & Mubarak, M. S. (2021). Role of withaferin A and its derivatives in the management of Alzheimer's disease: Recent trends and future perspectives. *Molecules*, 26(12), 3696.
- [20] Bungau, S., Vesa, C. M., Abid, A., Behl, T., Tit, D. M., Purza, A. L., ... & Endres, L. (2021). Withaferin A—A promising phytochemical compound with multiple results in dermatological diseases. *Molecules*, 26(9), 2407.
- [21] Della Porta, M., Maier, J. A., & Cazzola, R. (2023). Effects of *Withania somnifera* on cortisol levels in stressed human subjects: a systematic review. *Nutrients*, 15(24), 5015.
- [22] Singh, M., Kukreja, R. C., Nagarajan, D., & Kakar, S. S. (2025). Therapeutic potential of Withaferin A in cancer-induced muscle and cardiac wasting. *Journal of Ovarian Research*, 18(1), 218.
- [23] Logie, E., & Vanden Berghe, W. (2020). Tackling chronic inflammation with withanolide phytochemicals—A withaferin a perspective. *Antioxidants*, 9(11), 1107.
- [24] Panda, P., & Mohapatra, R. (2024). *Withania somnifera*: a promising neuroprotective ally against Alzheimer's disease. *Aging Pathobiology and Therapeutics*, 6(4), 183-185.
- [25] Bashir, A., Nabi, M., Tabassum, N., Afzal, S., & Ayoub, M. (2023). An updated review on phytochemistry and molecular targets of *Withania somnifera* (L.) Dunal (*Ashwagandha*). *Frontiers in Pharmacology*, 14, 1049334.
- [26] Tancreda, G., Ravera, S., & Panfoli, I. (2025). Preclinical Evidence of *Withania somnifera* and *Cordyceps* spp.: neuroprotective properties for the

management of Alzheimer's disease. *International Journal of Molecular Sciences*, 26(11), 5403.

[27]. Singh, B., Pandey, S., Rumman, M., Kumar, S., Kushwaha, P. P., Verma, R., & Mahdi, A. A. (2021). Neuroprotective and neurorescue mode of action of Bacopa monnieri (L.) Wettst in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced Parkinson's disease: an in silico and in vivo study. *Frontiers in pharmacology*, 12, 616413.

[28]. Sukumaran, S. S., Pereira, F. G. B., & Peter, M. C. S. (2021). Therapeutic Potential of Withania somnifera Extract for Parkinson's Disease: Impact on Neuronal Synaptic Integrity and Hormonal Regulation. *Journal of Endocrinology and Reproduction*, 25(2), 111-120.

[29]. Gościński A, Stasiłowicz-Krzemień A, Szelaż M, Pawlak J, Skiera I, Kwiatkowska H, Nowak N, Bernady K, Trzaskoma P, Zimak-Krótkopad O, Cielecka-Piontek J. Bacopa monnieri: Preclinical and Clinical Evidence of Neuroactive Effects, Safety of Use and the Search for Improved Bioavailability. *Nutrients*. 2025 Jun 5;17(11):1939. doi: 10.3390/nu17111939. PMID: 40507208; PMCID: PMC12158153.

[30]. Karati, D., Mukherjee, S., & Roy, S. (2025). The antioxidant potential of bacoside and its derivatives in Alzheimer's disease: the molecular mechanistic paths and therapeutic prospects. *Toxicology Reports*, 14, 101945.

[31]. Valotto Neto, L. J., Reverete de Araujo, M., Moretti Junior, R. C., Mendes Machado, N., Joshi, R. K., dos Santos Buglio, D., ... & Barbalho, S. M. (2024). Investigating the neuroprotective and cognitive-enhancing effects of Bacopa monnieri: a systematic review focused on inflammation, oxidative stress, mitochondrial dysfunction, and apoptosis. *Antioxidants*, 13(4), 393

[32]. Nishanth, B. J., Vijayababu, P., & Kurian, N. K. (2023). Bacopa monnieri extract as a neuroprotective and cognitive enhancement agent. *International Journal of Drug Discovery and Pharmacology*, 44-56.

[33]. Dash, R., Mitra, S., Dash, N., Barua, L., Mazumder, K., & Moon, I. S. (2026). Bacopa monnieri Promotes Neuronal Development by Regulating the Neurotrophin Signaling Pathway. *International Journal of Molecular Sciences*, 27(7), 3048.

[34]. Mahalakshmi, V., Modi, C. M., Admuthe, N. B., Khan, Y., & Choudhari, S. S. (2025). NEUROPROTECTIVE EFFECTS OF MEDICINAL PLANTS IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE. *Cuestiones de Fisioterapia*, 54(4), 7368-7378.

[35]. Dobrek, L., & Głowacka, K. (2023). Depression and its phytopharmacotherapy—a narrative review. *International Journal of Molecular Sciences*, 24(5), 4772.

[36]. Nishanth, B. J., Vijayababu, P., & Kurian, N. K. (2023). Bacopa monnieri extract as a neuroprotective and cognitive enhancement agent. *International Journal of Drug Discovery and Pharmacology*, 44-56.

[37]. Palollathil, A., Najar, M. A., Amrutha, S., Pervaje, R., Modi, P. K., & Prasad, T. S. K. (2024). Bacopa monnieri confers neuroprotection by influencing signaling pathways associated with interleukin 4, 13 and extracellular matrix organization in Alzheimer's disease: A proteomics-based perspective. *Neurochemistry international*, 180, 105864.

[38]. Valotto Neto LJ, Reverete de Araujo M, Moretti Junior RC, Mendes Machado N, Joshi RK, dos Santos Buglio D, Barbalho Lamas C, Direito R, Fornari Laurindo L, Tanaka M, et al. Investigating the Neuroprotective and Cognitive-Enhancing Effects of Bacopa monnieri: A Systematic Review Focused on Inflammation, Oxidative Stress, Mitochondrial Dysfunction, and Apoptosis. *Antioxidants*. 2024; 13(4):393.

[39]. Walker, E. A., & Pellegrini, M. V. (2023). Bacopa monnieri.

[40]. Eraiah, M., Shekhar, H. C., Lincy, J., & Thomas, J. (2024). Effect of Bacopa monnieri extract on memory and cognitive skills in adult humans: a randomized, double-blind, placebo-controlled study. *J. Psychiatry Cogn. Behav*, 8, 168.

[41]. Olasehinde TA, Olaokun OO. The Beneficial Role of Apigenin against Cognitive and Neurobehavioural Dysfunction: A Systematic Review of Preclinical Investigations. *Biomedicines*. 2024 Jan 13;12(1):178. doi: 10.3390/biomedicines12010178. PMID: 38255283; PMCID: PMC10813036.rders.

[42]. Sanaye, P. M., Mojaveri, M. R., Ahmadian, R., Jahromi, M. S., & Bahramsoltani, R. (2022). Apigenin and its dermatological applications: A comprehensive review. *Phytochemistry*, 203, 113390.

[43]. Socała, K., Kowalczyk-Vasilev, E., Komar, M., Szalak, R., Wyska, E., & Wlaż, P. (2025). Effect of apigenin on seizure susceptibility, parvalbumin immunoreactivity, and GABA<sub>A</sub> receptor expression in the hippocampal neurons in mice. *European Journal of Pharmacology*, 996, 17.

[44]. Marafiga, J. R., Pasquetti, M. V., & Calcagnotto, M. E. (2021). GABAergic interneurons

in epilepsy: More than a simple change in inhibition. *Epilepsy & Behavior*, 121, 106935.

[45]. Sepahvand, A., Studzińska-Sroka, E., Ramak, P., & Karimian, V. (2021). *Usnea* sp.: Antimicrobial potential, bioactive compounds, ethnopharmacological uses and other pharmacological properties; a review article. *Journal of Ethnopharmacology*, 268, 113656.

[46]. Fang, Y., Song, G., Lin, J., Ye, X., & Huang, S. (2021). Predicting the occurrence of early seizures after cerebral venous thrombosis using a comprehensive nomogram. *Epilepsy Research*, 178, 106820.

[47]. Alghamdi, A., Almuqbil, M., Alrofaidi, M. A., Burzangi, A. S., Alshamrani, A. A., Alzahrani, A. R., ... & Asdaq, S. M. B. (2022). Potential antioxidant activity of apigenin in the obviating stress-mediated depressive symptoms of experimental mice. *Molecules*, 27(24), 9055.

[48]. Boison, D., & Rho, J. M. (2020). Epigenetics and epilepsy prevention: The therapeutic potential of adenosine and metabolic therapies. *Neuropharmacology*, 167, 107741.

[49]. Zhu, L., Xue, Y., Feng, J., Wang, Y., Lu, Y., & Chen, X. (2023). Tetrahydrocurcumin as a stable and highly active curcumin derivative: A review of synthesis, bioconversion, detection and application. *Food Bioscience*, 53, 102591.

[50]. Zhang, S., Han, J., Fan, Z., Wang, H., Liu, L., Liu, L., ... & Deng, H. (2025). Tetrahydrocurcumin Ameliorates Cerebral Ischemia–Reperfusion Injury and Restores Blood–Brain Barrier Dysfunction by Inhibiting Ferroptosis. *CNS Neuroscience & Therapeutics*, 31(11), e70662.

[51]. Zeng, A., Quan, Y., Tao, H., Dai, Y., Song, L., & Zhao, J. (2025). The Role of Tetrahydrocurcumin in Tumor and Neurodegenerative Diseases Through Anti-Inflammatory Effects. *International Journal of Molecular Sciences*, 26(8), 3561

[52]. Zhu, L., Xue, Y., Feng, J., Wang, Y., Lu, Y., & Chen, X. (2023). Tetrahydrocurcumin as a stable and highly active curcumin derivative: A review of synthesis, bioconversion, detection and application. *Food Bioscience*, 53, 102591.

[53]. González, Y., Mojica-Flores, R., Moreno-Labrador, D., Pecchio, M., Rao, K. J., Ahumado-Monterrosa, M., ... & Lakey-Beitia, J. (2023). Tetrahydrocurcumin derivatives enhanced the anti-inflammatory activity of curcumin: synthesis, biological evaluation, and structure–activity relationship analysis. *Molecules*, 28(23), 7787.

[54]. Xiao Y, Dai Y, Li L, Geng F, Xu Y, Wang J, Wang S, Zhao J. Tetrahydrocurcumin ameliorates Alzheimer's pathological phenotypes by inhibition

of microglial cell cycle arrest and apoptosis via Ras/ERK signaling. *Biomed Pharmacother*. 2021 Jul;139:111651. doi: 10.1016/j.biopha.2021.111651. Epub 2021 May 8. PMID: 34243602.

[55]. Zeng, A., Quan, Y., Tao, H., Dai, Y., Song, L., & Zhao, J. (2025). The Role of Tetrahydrocurcumin in Tumor and Neurodegenerative Diseases Through Anti-Inflammatory Effects. *International Journal of Molecular Sciences*, 26(8), 3561.

[56]. Guo, Y., Xie, J., Luo, H., Yuan, Y., Long, F., Meng, J., ... & Shao, H. (2026). Tetrahydrocurcumin for Major Depressive Disorder with Therapeutic Potential and Mechanistic Insights from Clinical and Preclinical Studies. *Molecular Neurobiology*, 63(1), 323.

[57.] Yang, Y., Yang, J., Ma, T., Yang, X., Yuan, Y., & Guo, Y. (2023). The role and mechanism of TGF- $\beta$ 1 in the antidepressant-like effects of tetrahydrocurcumin. *European Journal of Pharmacology*, 959, 176075.