Phytopharmaceuticals for brain disorders: An Indian perspective

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Abstract
The increasing prevalence of central nervous system (CNS) disorders in India, including neurodegenerative diseases like Alzheimer's and Parkinson's, alongside mental health issues such as depression and anxiety, presents a significant health challenge. Traditional Indian medicinal plants, including *Bacopa monnieri, Withania somnifera, Centella asiatica,* and *Curcuma longa,* demonstrate promising neuroprotective and cognitive-enhancing effects supported by both preclinical and clinical evidence. However, their therapeutic application is hindered by challenges such as poor solubility, limited blood-brain barrier permeability, rapid metabolism, and stability concerns. To address these issues, innovative formulation strategies, including nanoformulations and prodrugs, are being investigated to improve bioavailability and efficacy. By combining traditional knowledge with modern pharmaceutical approaches, Indian phytopharmaceuticals have the potential to offer effective, safe, and affordable treatments for CNS disorders, enhancing the quality of life for those affected.

Keywords: Phytopharmaceuticals, Central nervous system (CNS) Disorders, Neurodegenerative diseases

1. Introduction
CNS disorders, including neurodegenerative diseases, psychiatric conditions, and neurological disorders, are on the rise in India, significantly contributing to the national health burden. The prevalence of these disorders is alarming due to increasing life expectancy, lifestyle changes, and other contributing factors:

- **Neurodegenerative disorders**: India is witnessing a surge in cases of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. For instance, Alzheimer's disease affects about 4 million people in India, with the number expected to rise as the population ages. Parkinson's disease prevalence is also increasing, with estimates suggesting around 300,000 to 400,000 individuals currently affected (1,2).
- **Psychiatric conditions:** Mental health disorders such as depression, anxiety, bipolar disorder, and schizophrenia are becoming more common. According to the National Mental Health Survey (2015-16), nearly 150 million Indians require mental health interventions, with depression affecting over 45 million people (3).

- **Neurological disorders:** Epilepsy is one of the most common neurological conditions in India, affecting about 10 million people. Stroke, another major neurological disorder, has also become more prevalent due to risk factors such as hypertension and diabetes (4,5).

2. Traditional Indian medicinal plants with CNS activity

Bacopa monnieri (Brahmi) is a renowned brain tonic used to enhance memory, reduce anxiety, and protect neurons from oxidative stress, making it a candidate for treating neurodegenerative diseases (6).*Withania somnifera* (Ashwagandha) is an adaptogen that reduces stress, anxiety, and depression, while also improving cognitive function and offering neuroprotection (7). *Centella asiatica* (Gotu Kola) is used to enhance memory, reduce anxiety, and protect against neuroinflammation (8). *Nardostachys jatamansi* (Jatamansi) has sedative properties and is effective in treating insomnia, epilepsy, and depression (9). *Convolvulus pluricaulis* (Shankhpushpi) is a cognitive enhancer that helps reduce anxiety and oxidative damage in the brain (10). *Mucuna pruriens* (Velvet Bean), rich in L-DOPA, is used to manage Parkinson's disease and depression (11). *Curcuma longa* (Turmeric) is valued for its anti-inflammatory and antioxidant effects, improving cognitive function and memory while preventing neurodegeneration (12). *Acorus calamus* (Vacha) is known for its calming and anti-epileptic properties, promoting mental clarity and reducing stress. These plants hold immense potential for developing phytopharmaceuticals targeting CNS disorders (13).

3. Preclinical and clinical evidence for Indian phytopharmaceuticals in CNS disorders

3.1. *Bacopa monnieri* (Brahmi)

- **Preclinical evidence:** Animal studies have shown that *Bacopamonnieri* possesses strong neuroprotective and cognitive-enhancing properties. It improves spatial memory, reduces oxidative stress, and modulates neurotransmitters like acetylcholine. Studies on rodents demonstrated that Bacopa reduces cognitive deficits induced by Alzheimer's disease models, supporting its role in neuroprotection.
- **Clinical evidence:** Several randomized controlled trials (RCTs) have demonstrated Bacopa's efficacy in improving memory and cognitive function in healthy adults and elderly populations. A clinical study on elderly individuals with age-associated memory impairment showed significant improvements in memory retention and learning. Another trial found Bacopa to reduce anxiety and improve cognitive processing speed in healthy subjects (14).

3.2. *Withania somnifera* (Ashwagandha)

- **Preclinical evidence:** Ashwagandha has demonstrated anti-anxiety, anti-depressant, and neuroprotective effects in preclinical models. Animal studies have shown that it can reduce stress by regulating cortisol levels and enhancing resilience to chronic stress. It also supports neurogenesis and has potential benefits in treating neurodegenerative diseases such as Alzheimer's and Parkinson's.
- **Clinical evidence:** Ashwagandha has shown promising results in clinical trials for reducing stress and anxiety. In one study, patients with anxiety disorders experienced a significant reduction in anxiety and serum cortisol levels after treatment with Ashwagandha extract. In trials involving cognitive function, it was shown to improve memory, attention, and information processing in individuals with mild cognitive impairment (15).

3.3. *Centella asiatica* (Gotu Kola)

- **Preclinical evidence**: Gotu Kola has been extensively studied for its neuroprotective, cognitive-enhancing, and anxiolytic effects. Animal studies indicate that it enhances learning and memory in Alzheimer's models by reducing beta-amyloid toxicity and oxidative stress in the brain. Its antioxidant properties help protect against neuronal damage.
- **Clinical evidence:** In clinical studies, Gotu Kola has shown improvements in cognitive function and anxiety reduction. A study involving elderly patients with cognitive decline demonstrated enhanced memory and learning. Another clinical trial found Gotu Kola to be effective in reducing anxiety in patients with generalized anxiety disorder (GAD) (16).

3.4. *Nardostachys jatamansi* (Jatamansi)

- **Preclinical evidence:** Animal studies have indicated that Jatamansi has sedative, anti-depressant, and anti-convulsant properties. It modulates serotonin and GABA levels in the brain, offering potential benefits for epilepsy, insomnia, and anxiety. Preclinical models of depression have shown that Jatamansi alleviates symptoms by modulating neurotransmitter levels.
- **Clinical evidence:** Although clinical studies are limited, Jatamansi has been traditionally used for its calming effects. Preliminary human studies suggest that it may improve sleep quality and reduce symptoms of anxiety. Further clinical trials are needed to establish its efficacy in CNS disorders (17).

3.5. *Convolvulus pluricaulis* (Shankhpushpi)

- **Preclinical evidence:** Shankhpushpi has shown promising results in animal studies as a cognitive enhancer and neuroprotective agent. It has been found to improve memory and learning in animal models of cognitive impairment and Alzheimer's disease by modulating cholinergic activity and reducing oxidative stress.
- **Clinical evidence**: While clinical evidence is still emerging, some studies have demonstrated the potential of Shankhpushpi in enhancing memory and cognitive performance in both healthy adults and patients with cognitive decline. Clinical trials have also shown its anxiolytic effects, helping reduce symptoms of stress and anxiety (18).

3.6. *Mucuna pruriens* (Velvet Bean)

- **Preclinical evidence**: *Mucunapruriens* is well-known for its high content of L-DOPA, which is a precursor to dopamine. Preclinical studies have demonstrated its neuroprotective effects in Parkinson's disease models, where it protects dopaminergic neurons and improves motor function. It has also shown anti-depressant effects in preclinical models.
- **Clinical evidence:** Clinical trials have confirmed the efficacy of Mucuna in managing Parkinson's disease. A study comparing *Mucunapruriens* with standard L-DOPA treatment found it to be more effective in improving motor function and with fewer side effects. Additionally, its neuroprotective effects suggest a potential for long-term benefits in Parkinson's patients (19).

3.7. *Curcuma longa* (Turmeric)

- **Preclinical evidence:** Curcumin, the active component of turmeric, has been shown to have strong anti-inflammatory, antioxidant, and neuroprotective properties in preclinical models of neurodegenerative diseases like Alzheimer's and Parkinson's. It reduces beta-amyloid plaques, oxidative stress, and neuroinflammation, key contributors to cognitive decline.
- **Clinical evidence:** Clinical studies have found curcumin to improve memory and attention in elderly patients with mild cognitive impairment. One RCT demonstrated that curcumin supplementation improved cognitive function in healthy older adults. Furthermore, studies have shown its efficacy in reducing depressive symptoms and improving mood, likely due to its impact on serotonin and dopamine levels (20).

3.8. *Acorus calamus* (Vacha)

- **Preclinical evidence:** Vacha has demonstrated neuroprotective, anti-epileptic, and cognitive-enhancing properties in animal models. Preclinical studies suggest that it may reduce seizure activity and improve memory by modulating neurotransmitter levels, particularly acetylcholine and GABA.
- **Clinical evidence:** Clinical evidence for Vacha is limited, but its traditional use in Ayurveda for treating epilepsy, anxiety, and cognitive decline is well-documented. Further research is needed to validate its therapeutic potential in human clinical trials (21).

Table 1. Medicinal plants and their bioactive compounds in the management of CNS disorders: parts used, bioactive constituents, and mechanisms of action

Plant	Part Used	Bioactive Constituents	CNS Disorder Type	Mechanism of Action
Bacopa monnieri	Leaves	Bacosides, Alkaloids	Alzheimer's, Memory Disorders	Antioxidant, modulates acetylcholine levels, reduces oxidative stress (22)
Withania somnifera	Roots	Withanolides, Sitoindosides	Anxiety, Depression, Alzheimer's	Modulates cortisol levels, neurogenesis support, reduces neuroinflammation (23)
Centella asiatica	Whole Plant	Asiaticoside, Madecassoside	Cognitive Decline, Anxiety	Antioxidant, reduces beta-amyloid toxicity, neuroprotective properties (24)
Nardostachys jatamansi	Rhizomes	Sesquiterpenes, Valeranone	Insomnia, Epilepsy, Depression	Sedative, anti-convulsant, modulates serotonin and GABA (25)
Convolvulus pluricaulis	Whole Plant	Convolvamine, Scopoletin	Anxiety, Cognitive Disorders	Enhances cholinergic activity, reduces oxidative stress (26)
Mucuna pruriens	Seeds	L-DOPA	Parkinson's, Depression	Increases dopamine levels, neuroprotection for dopaminergic neurons (27)
Curcuma longa	Rhizomes	Curcumin	Alzheimer's, Cognitive Impairment	Anti-inflammatory, reduces beta-amyloid plaques, antioxidant effects (28)
Acorus calamus	Rhizomes	α-Asarone, β-Asarone	Epilepsy, Anxiety	Modulates acetylcholine and GABA levels, anti-epileptic properties (29)

4. Formulation challenges and bioavailability

Phytopharmaceuticals offer significant therapeutic potential for CNS disorders but face several formulation challenges that impact their bioavailability. Key issues include poor solubility, which limits absorption; difficulty crossing the blood-brain barrier (BBB); rapid metabolism leading to short half-lives; and stability concerns due to degradation from light, heat, and oxygen. To overcome these obstacles, various formulation strategies are employed. Nanoformulations, such as nanoparticles, nanoemulsions, and solid lipid nanoparticles, enhance solubility and permeability, improving absorption and BBB transport. Surface modification of nanocarriers can facilitate targeted delivery to the brain, while intranasal delivery methods provide direct access to CNS pathways. Prodrugs and co-administration with bioenhancers, like piperine, can help extend the half-life of phytochemicals.

Additionally, encapsulation in biodegradable polymers aids in stabilizing these compounds and providing sustained release. Despite these challenges, ongoing research aims to enhance the efficacy and bioavailability of Indian phytopharmaceuticals for CNS applications, making them promising candidates for future therapeutic development (30,31).

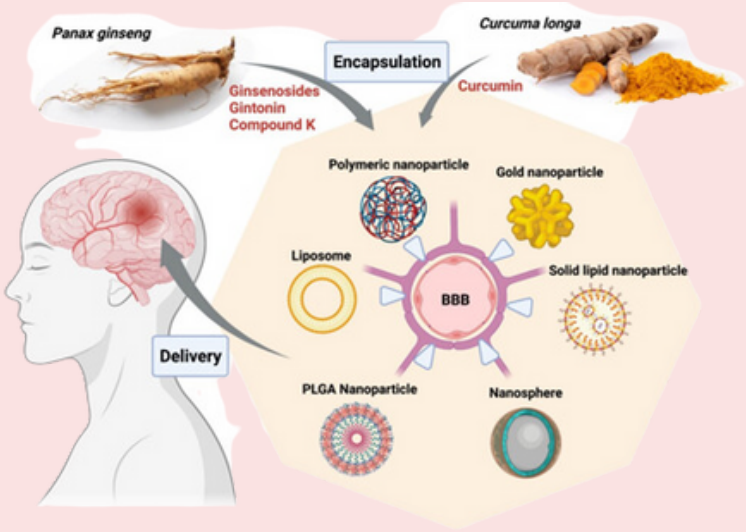

Figure 1. Nanoparticles of phytoconstituents for various CNS disorders

5. Conclusion

Indian phytopharmaceuticals hold significant promise for treating Central Nervous System (CNS) disorders, supported by both traditional practices and scientific research. Key medicinal plants like *Bacopamonnieri, Withaniasomnifera, and Curcuma longa* have shown neuroprotective and cognitive-enhancing effects in studies. However, challenges such as poor solubility, limited blood-brain barrier permeability, rapid metabolism, and stability issues hinder their therapeutic application. Innovative formulation strategies, including nanoencapsulation and the use of prodrugs and bioenhancers, are being explored to improve bioavailability and efficacy. The combination of traditional knowledge with modern pharmaceutical techniques has the potential to develop effective, safer, and more affordable treatments for CNS disorders, ultimately enhancing the quality of life for many affected individuals.

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