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Original Research Article

The Potential of *Salvia officinalis* and *Habenaria intermedia* as Neuroprotective and Antidepressants: Investigating the therapeutic uses of traditional herbs

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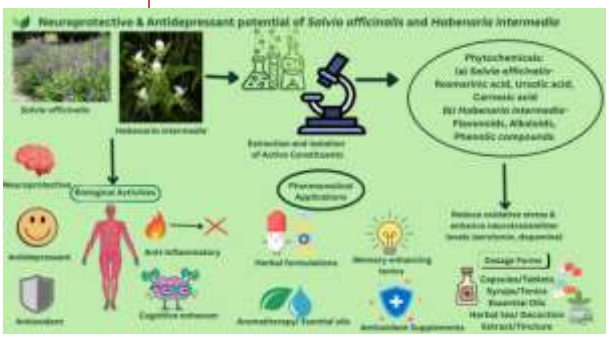
Abstract: The therapeutic potential of Salvia officinalis and Habenaria intermedia as neuroprotective and antidepressant agents represents an emerging frontier in the use of traditional herbs for mental health and neurological wellbeing. Conventional pharmaceutical treatments for depression and neurological disorders are often challenged by adverse effects, expense, and the possibility of relapse, creating a demand for safer and more accessible alternatives. This review places special emphasis on Salvia officinalis (Sage) renowned for its profound neuroprotective effects, including antioxidant, anti-inflammatory, and cognitive enhancing activities and Habenaria intermedia (Vriddhi), a celebrated Ayurvedic ingredient recognized for its rejuvenating and adaptogenic qualities as well as new evidence supporting its antidepressant efficacy. By drawing together insights from traditional medicine and recent research, this analysis highlights how these two herbs offer promising plant-based interventions for psychiatric and neurological disorders. The need for rigorous scientific studies is underscored; such work will further validate the role of these botanicals and support their integration into evidence-based therapies for brain health.

Keywords: Phytochemicals, Neurodegenerative diseases, Traditional medicine, Herbal neuro-protective etc.



INTRODUCTION

Depression is a serious public health issue and one of the main causes of mental health-related impairment in the world. It typically manifests during adolescence or early adulthood (ages 14–25), affecting approximately 4–5% of the global population annually1. Depression is associated with impaired personal relationships, academic and occupational decline, and an increased risk of comorbid conditions such as cardiovascular disease, obesity, and suicide2. As the second most prevalent cause of disability worldwide, depression is expected to overtake all other causes of disease burden by 2030, according to the World Health Organisation (WHO). With the prevalence of major depressive disorder increasing by 27.6% and anxiety disorders by 25.9% in 2020 alone, the COVID-19 pandemic made the mental health crisis even worse 3,4.

Neurobiologically, depression involves disruptions in monoamine neurotransmitters, particularly serotonin, dopamine, and norepinephrine5. In parallel, neurodegenerative diseases characterized by progressive neuronal loss—including Alzheimer's and Parkinson's diseases—are increasing due to aging, oxidative stress, chronic inflammation, and protein misfolding6. Conventional pharmacological treatments for depression and neurodegeneration are often limited by high costs, side effects, and variable efficacy, driving interest in alternative plant-based therapies7.

Medicinal herbs such as Panax ginseng, Withania somnifera, Bacopa monnieri, and Ginkgo biloba demonstrate neuroprotective and antidepressant effects via antioxidant, anti-inflammatory, and neurotransmitter-modulating mechanisms. Among these, Salvia officinalis (Sage, Lamiaceae) has gained attention for its cognitive-enhancing and neuroprotective properties8. Rich in flavonoids, terpenoids, and phenolic acids, S. officinalis has shown potential to improve memory and protect neurons from oxidative damage, suggesting its promise in treating neurodegenerative disorders such as Alzheimer's and Parkinson's disease. Similarly, Habenaria intermedia D. Don, an Ayurvedic herb, is traditionally used for its anti-stress and adaptogenic properties9.

When combined, these two herbs may provide a complementary and potentially safer approach to managing complex neurological and psychological conditions, integrating traditional knowledge with contemporary scientific research. Both S. officinalis and H. intermedia show promising neuroprotective and antidepressant effects, supporting their potential as therapeutic agents derived from traditional medicine. This study aims to systematically examine and summarize current evidence regarding the neuroprotective and antidepressant properties of Habenaria intermedia and Salvia officinalis, highlighting their potential as candidates for plant-based therapeutics10, 11.

RESULTS

Figure* (a) *Salvia officinalis

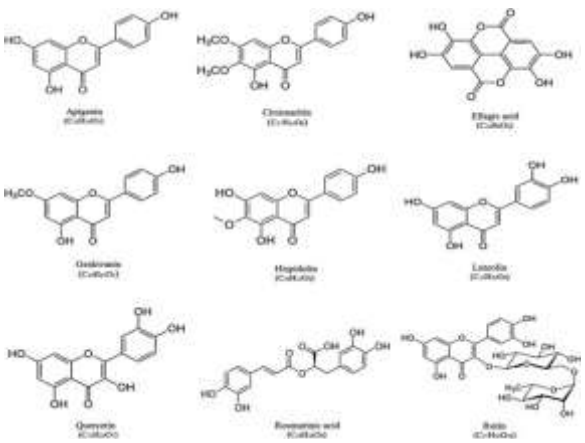
Figure* (b) *Habenaria intermedia

Table 1: Comparing the Morphologies of *Habenaria intermedia* and *Salvia officinalis* [12,13,14,15]

Feature	*Salvia officinalis*	*Habenaria intermedia*
Family	Lamiaceae	Orchidaceae
Growth Habit	Perennial, evergreen subshrub	Terrestrial herbaceous plant
Height	60–70 cm	30–60 cm
Stem	Erect, branched, square-shaped, woody at base	Slender, erect, unbranched, arises from underground tuber
Leaves	Opposite, oblong to lanceolate, grey-green, wrinkled, hairy	Alternate, lanceolate to ovate-lanceolate, sheathing base
Leaf Texture	Velvety, glandular trichomes (aromatic)	Smooth, non-glandular
Flowers	Bilabiate, violet/purple/blue, in terminal racemes/spikes	Small, greenish/yellowish, zygomorphic, in terminal spikes
Labellum (Lip)	Absent (typical Lamiaceae flower structure)	Present, deeply three-lobed, prominent
Fruit	Schizocarp splitting into four nutlets	Capsule (typical of orchids)
Root System	Fibrous, well-branched	Paired underground tubers (fleshy and ovoid)
Medicinal Part Used	Leaves (essential oils)	Tubers
Major chemical constituents	Rosmarinic acid, carnosic acid, carnosol, ursolic acid, α- and β-thujone,1,8-cineole, Camphor, Flavonoids (luteolin, apigenin)	Scopoletin, gallic acid, β-sitosterol, tannins, starch, alkaloids, flavonoids, phenolics
Traditional Use	Cognitive enhancement, memory, neuroprotection	Rejuvenation, adaptogen, antidepressant in Ayurveda

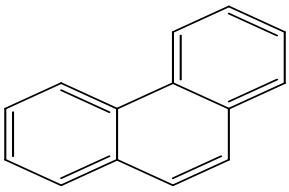
Ethnobotanical Significance: *Habenaria intermedia*, traditionally included in the Ayurvedic Ashtavarga, is considered a rasayana (rejuvenative) and vajikarana (aphrodisiac), used to enhance stamina, immunity, and reproductive health, particularly in Himalayan and tribal communities[16]. Its tubers are dried and used in decoctions, powders, and medicated ghee for fatigue, weakness, and sexual disorders. *Salvia officinalis* is widely used in Mediterranean, European, and Middle Eastern medicine for its antibacterial, anti-inflammatory, and carminative properties. Its leaves are consumed as teas, decoctions, or poultices to treat gastrointestinal, respiratory**,** and menstrual conditions, and also in ritual fumigation and purification[17].

Phytochemistry of *Salvia officinalis* and *Habenaria intermedia*: Essential oils comprise 90–98% of its volatile components, including α-thujone (12–43%), β-thujone, camphor (10–25%), and 1,8-cineole (4–15%). Other terpenoids include viridiflorol, β-caryophyllene, and borneol[18]. Phenolic compounds (rosmarinic acid, carnosic acid, carnosol) confer antioxidant and anti-inflammatory properties. Flavonoids (apigenin, luteolin) and diterpenoids contribute to neuroprotection, anticancer, and cytotoxic activities. *Habenaria intermedia* tuber extracts contain phenolic acids (e.g., sinapic acid), scopoletin, and gallic acid, which mediate anti-stress, immuno-modulatory, and neuroprotective effects. Alkaloids, flavonoids, and coumarins in the plant contribute to antioxidant, adaptogenic, and neuroprotective activities[19].

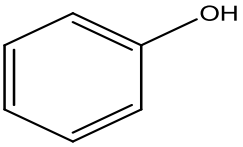


Recent studies highlight **sinapic acid** as a distinctive chemical marker useful in detecting adulteration or substitution of *H. intermedia* in herbal preparations[20]. Its tubers have also been reported to contain **scopoletin** and **gallic acid,** which are suggested to mediate its **anti-stress (adaptogenic)** and **immunomodulatory** effects through antioxidant mechanisms and possible modulation of the HPA axis. It has been demonstrated that genobiotic medicinal plants of the orchidaceae family

have more therapeutic significance due to their varied chemical composition. Phenanthrene, bi-benzene, flavone, sterol, terpenes, and alkaloids are present in these members[21]. Total phenols, thiamins, tannins, and calcium all are present in significant concentrations in *H. intermedia***.** Despite the fact that *Habenaria* species are utilized in traditional formulations, there are few scientific studies that support their therapeutic efficacy[22, 23].



Phenanthrene



Phenol

Rosmarinic acid, carnosic acid, and apigenin are major contributors to *Salvia officinalis's* neuroprotective profile, while sinapic acid, diverse flavonoids, alkaloids, and novel immunomodulatory compounds underlie neuroprotection in *Habenaria intermedia*. These phytochemicals work via antioxidant, anti-inflammatory, antiapoptotic, and neurotransmitter modulatory mechanisms[24].

Ethnopharmacology of *Habenaria intermedia* D. Don and *Salvia officinalis*: - *Habenaria intermedia* D. Don, an important member of the *Ashtavarga* group in Ayurvedic medicine, has been traditionally prescribed as a rasayana for promoting rejuvenation, enhancing vitality, and improving overall health[25]. Ethnomedical practices describe its tubers as potent aphrodisiacs and nervine tonics, widely used for managing conditions such as sexual debility, chronic fatigue, and general weakness. Indigenous communities frequently use oral decoctions and pastes to improve physical stamina and longevity, indicating its adaptogenic and restorative properties in traditional medicine. The Lamiaceae family's perennial plant, *Salvia officinalis* L., on the other hand, has a long history of use in Mediterranean and European ethnomedicine[26]. Due to its antimicrobial, anti-inflammatory, and carminative qualities, the leaves are primarily used as aqueous or alcoholic extracts, decoctions, and infusions to treat gastrointestinal issues, menstrual disorders, and respiratory conditions (such as coughing, sore throat, and cough)[27]. Sage's modern pharmaceutical significance in neuro-protection and memory enhancement is also consistent with its historical associations with spiritual purifying rituals and cognitive enhancement[28].

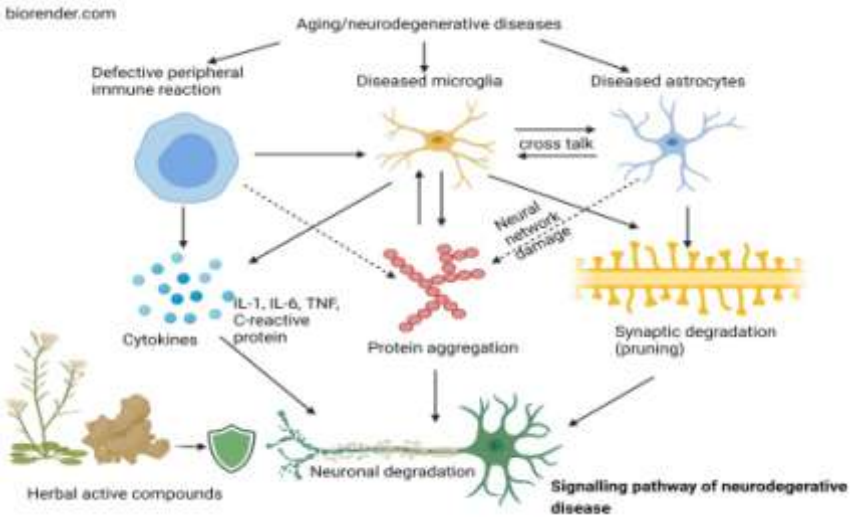
Role of Traditional Herbs in Neuropsychiatric Disorders: Traditional herbs such as *Salvia officinalis* and *Habenaria intermedia* offer multi targeted approaches for the management of neurodegeneration and depression, acting as free radical scavengers, anti-inflammatories, and modulators of neurotransmitter systems[29]. Their affordability and safety profiles make them attractive alternatives or adjuncts for those who may not tolerate conventional pharmaceuticals. However, further clinical research is required to confirm efficacy and establish safe dosing in humans, as most evidence to date remains preclinical or limited to small trials[30]. In summary, *Salvia officinalis* is supported by extensive preclinical data for its neuroprotective and antidepressant activity, while *Habenaria intermedia* is emerging as a novel traditional remedy with similar promise based on recent pharmacological screenings. Their therapeutic uses highlight the potential value of traditional herbs as sources for future neuropsychiatric treatments[31].

Traditional Applications for *Salvia officinalis and Habenaria intermedia*: Within their various medical systems, *Habenaria intermedia and Salvia officinalis* have unique yet culturally significant traditional uses[32]. One of the main members of the Ayurvedic Ashtavarga group, *H. intermedia*, has been used extensively as a rasayana for immunomodulation, vitality augmentation, and rejuvenation. Traditionally, its tubers have been used as nervine tonics and aphrodisiacs in the form of pastes, powders, or decoctions to treat general weakness, chronic weariness, and sexual debility. By contrast, *S. officinalis*, a crucial herb in European and Mediterranean ethnomedicine, is mostly used as a leaf infusion or decoction to treat respiratory conditions like cough and sore throat, as well as digestive issues because of its carminative qualities[33].

Mechanisms of Action in Neurodegenerative Disorders: The progressive loss and degradation of neurones in the central nervous system is a hallmark of neurodegenerative illnesses, which can result in movement deficits, cognitive decline, and other neurological dysfunctions. Understanding the various pathways that contribute to its aetiology is essential for creating successful treatment plans[37]. The key mechanisms involved include**:**

Table 2: Chemical Components, Pharmacological Actions, and Parts of *Salvia officinalis* and *Habenaria intermedia* [34,35,36]

Plant Name	Parts Used	Traditional Uses	Major Chemical Constituents	Pharmacological Activities
Habenaria intermedia	Tuberous roots	Rejuvenative, aphrodisiac, stamina enhancer	Polysaccharides, starch, simple sugars, phenolics, minor alkaloids	Antioxidant, immunomodulatory, adaptogenic, aphrodisiac, anti-fatigue
	Whole plant (limited)	General vitality, tonic	Glycosides, trace minerals	Energy booster, rejuvenative
Salvia officinalis	Leaves	Digestive aid, sore throat, antiseptic, antioxidant	Essential oils (thujone, cineole), phenolic acids (rosmarinic, caffeic), flavonoids	Antioxidant, anti-inflammatory, antimicrobial, neuroprotective, hypoglycemic
	Aerial parts	Anti-inflammatory, antimicrobial, memory enhancer	Terpenoids (camphor, borneol), tannins	Cognitive enhancer, metabolic regulator



Oxidative Stress: An imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms results in oxidative stress. Excess ROS damages proteins, lipids, and DNA, ultimately leading to neuronal injury and death. Oxidative stress plays a major role in the development of disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Salvia officinalis (sage), rich in phenolic compounds like rosmarinic acid and carnosic acid, exerts neuroprotective effects by scavenging free radicals and reducing oxidative damage38.

Inflammation: Chronic neuroinflammation accelerates the progression of neurodegenerative disorders. Activated microglial cells release pro-inflammatory cytokines and ROS, which damage neurons and impair function. Inflammatory pathways are strongly implicated in conditions including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Bioactive flavonoids and diterpenes in sage help attenuate these effects by inhibiting the production of inflammatory mediators and enzymes such as COX-239.

Protein Mis folding and Aggregation: A hallmark of many neurodegenerative diseases is the abnormal folding and aggregation of proteins. In Alzheimer's disease, amyloid-beta peptides accumulate into plaques, while in Parkinson's disease, alpha-

synuclein aggregates form Lewy bodies. These toxic protein deposits disrupt normal cellular functions and contribute to progressive neuronal death40.

Mitochondrial Dysfunction: The synthesis of energy and the survival of neurones depend heavily on mitochondria. Disrupted calcium homeostasis, increased ROS formation, and decreased ATP synthesis are all signs of mitochondrial dysfunction in neurodegenerative diseases. In Huntington's and Parkinson's disorders, this dysfunction is most noticeable41.

Impaired Protein Clearance: Efficient clearance of misfolded proteins and cellular debris is essential for maintaining neuronal health. Disruptions in protein degradation pathways including autophagy and the ubiquitin–proteasome system lead to the accumulation of toxic aggregates, contributing to the pathology of Alzheimer's and Parkinson's diseases42.

Reduced Neurogenesis and Synaptic Plasticity: Neurogenesis and synaptic plasticity are vital for memory formation and cognitive function. Emerging evidence suggests that sage extracts may enhance these processes by modulating signaling pathways such as brain-derived neurotrophic factor (BDNF), thereby supporting neuronal repair and resilience. Thus, The neuroprotective effects of Salvia officinalis and Habenaria intermedia are attributed to distinct bioactive compounds with antioxidant, anti-inflammatory, and neurotransmitter-modulating properties.43

A. Salvia officinalis: The key Neuroprotective Compounds are as follows:-

- Rosmarinic acid: A potent polyphenol with strong antioxidant and anti-inflammatory activity, protecting neurons from oxidative stress and modulating neuroinflammatory pathways.
- Carnosic acid: A diterpenoid with neuroprotective and cognitive-enhancing effects, known to activate antioxidant defense and reduce amyloid-beta toxicity.
- Apigenin: A flavonoid with anxiolytic properties, modulating GABA receptors and promoting neuronal health.
- Essential terpenoids (e.g., α-thujone, camphor): Exhibit anti-inflammatory and cholinergic effects, contributing to improved memory and neural protection.
- Other polyphenolic and flavonoid compounds: These further support neuroprotection by scavenging free radicals and enhancing synaptic plasticity44, 45.

B. Habenaria intermedia: The key Neuroprotective Compounds are as follows:-

- Phenolic acids (e.g., sinapic acid): Isolated from tuber extracts; demonstrate antioxidant properties by reducing oxidative stress and protecting neuronal integrity.
- Flavonoids: Present in significant quantities; play roles in free radical scavenging, anti-inflammatory activity, and modulation of neurotransmitter systems.
- Alkaloids, Coumarins, and Tannins: These classes in ethyl acetate fractions contribute to neuroprotection, anticonvulsant actions, and adaptogenic effects.

- Unique bioactive markers (e.g., HBR-4, HBR-5): Isolated compounds showing immunomodulatory and anti-inflammatory effects, including inhibition of the NLRP3 inflammasome, which is important for neuronal survival in inflammatory conditions 46, 47.

Safety and Tolerability: Both Salvia officinalis and Habenaria intermedia are generally considered safe when used in moderate or recommended amounts. Salvia officinalis contains thujone, a compound that may exhibit neurotoxic effects at high doses, making dosage control and duration of use important. Similarly, Habenaria intermedia is safe within traditional limits, though scientific data on its toxicity remain limited, warranting caution with excessive or prolonged use. For both plants, the use of standardized extracts with verified purity and controlled active compound content is recommended to ensure safety and therapeutic efficacy48.

Prospects for the Future: Future research on the neuroprotective and antidepressant potential of Salvia officinalis and Habenaria intermedia should address several key gaps in current knowledge. While preclinical studies support their efficacy and highlight promising bioactive compounds, comprehensive clinical trials are needed to confirm their safety, optimal dosing, and long-term tolerability in humans. Detailed investigation into molecular mechanisms such as the specific actions of rosmarinic acid, carnosic acid, sinapic acid, and various flavonoids will help elucidate how these herbs exert their neuroprotective and mood-regulating effects49, 50. Comparative and combination studies with standard pharmaceuticals may reveal synergistic benefits and expand therapeutic options for neurodegenerative and mood disorders. Innovations in phytochemical analysis and formulation could further transform these traditional remedies into effective, standardized neuroprotective agents. Ultimately, integrating ethnobotanical knowledge with modern clinical and molecular research will support the translation of these herbs from traditional use to scientifically validated and accessible treatments for central nervous system disorders51.

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