Neuroscience Research and Clinical Practice

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Review

Intranasal Herbal Neurotherapeutics in Neurodegenerative Disorders: Preclinical Advances and Translational Implications

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Abstract

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease represent major global health challenges characterized by progressive neuronal loss, neuroinflammation, oxidative stress, and cognitive and motor dysfunction. Despite advances in modern neuroscience, existing therapies remain largely symptomatic, with limited disease-modifying efficacy, partly due to restricted blood-brain barrier (BBB) penetration and long-term safety concerns. Intranasal delivery has emerged as a promising complementary strategy for central nervous system targeting by exploiting olfactory and trigeminal neural pathways to bypass the BBB. This review critically evaluates intranasal delivery of Indian traditional herbal medicines for neurodegenerative disorders, integrating perspectives from Ayurveda, Siddha, and Unani systems with contemporary preclinical and translational research. Herbal interventions, including whole plant extracts (e.g., *Bacopa monnieri, Centella asiatica*) and isolated phytochemicals (e.g., withanolides from *Withania somnifera*, curcuminoids from *Curcuma longa*) incorporated into experimental intranasal and nanoformulations, demonstrate multimodal neuroprotective actions. These include modulation of neuroinflammatory pathways, attenuation of oxidative stress, stabilization of mitochondrial function, and enhancement of synaptic plasticity. Advances in intranasal nanotechnology, particularly nanoparticle-based and mucoadhesive delivery systems, have improved phytoconstituent bioavailability, nasal residence time, and brain targeting efficiency. However, clinical evidence remains limited, and challenges related to extract standardization, long-term safety, pharmacokinetics, and regulatory approval persist. Overall, intranasal herbal therapy represents a promising translational strategy that warrants rigorous clinical validation before routine clinical application.

Keywords

Neurodegenerative disorders,Intranasal delivery, Nose-to-brain transport, Herbal neurotherapeutics, Nanoparticle-based delivery, Traditional medicine

Article History

Received: 27 November 2025 Revised: 19 January 2026

Accepted: 27 February 2026 Available Online: 04 March 2026

1. Introduction

Neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease are among the leading causes of disability and mortality worldwide [1]. These disorders are characterized by progressive neuronal loss, cognitive impairment, motor dysfunction, and behavioral disturbances. According to the Global Burden of Disease Study, neurological disorders affect over one-third of the global population, with AD and related dementias accounting for more than 23 million disability-adjusted life years, and Parkinson's disease contributing over 3 million disability-adjusted life years globally [2]. Epidemiological projections from the World Health Organization and Global Burden of Disease models suggest that the prevalence of neurodegenerative disorders will continue to rise substantially due to population aging, although estimates vary depending on the modeling framework used [3].

Current pharmacological interventions for neurodegenerative disorders primarily provide symptomatic relief and do not significantly alter disease progression [4]. Cholinesterase inhibitors used in AD, dopaminergic therapies in Parkinson's disease [5], and immunomodulatory agents in multiple sclerosis are associated with limited long-term efficacy and notable adverse effects [6]. A major therapeutic challenge underlying these limitations is the blood-brain barrier (BBB), which restricts the entry of most therapeutic agents into the central nervous system, including many phytoconstituents with demonstrated neuroprotective potential. Consequently, numerous compounds that show promising antioxidant, anti-inflammatory, and neurotrophic effects *in vitro* fail to achieve adequate brain concentrations *in vivo*. These constraints highlight the urgent need for novel, safe, and integrative therapeutic strategies capable of overcoming BBB-related limitations while targeting multiple pathogenic mechanisms such as oxidative stress, neuroinflammation, mitochondrial dysfunction, and synaptic degeneration.

Indian traditional medical systems including Ayurveda, Siddha, and Unani offer a rich repository of herbal formulations historically used to preserve cognitive function and manage neurological disorders [7,8]. Herbs such as *Withania somnifera* [9], *Bacopa monnieri* [10], and *Curcuma longa* [11] contain diverse phytochemicals with antioxidant, anti-inflammatory, and neuroprotective properties. Importantly, these systems emphasize nasal administration (Nasya/Nasiyam) as a direct therapeutic route to influence brain function by targeting the central nervous system [12,13]. In this context, the present review critically examines the potential of intranasal delivery of Indian traditional herbal medicines for neurodegenerative disorders, integrating traditional knowledge with contemporary pharmacological, nanotechnological, and translational research perspectives.

2. Literature Search Strategy and Study Selection

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Keywords included combinations of "intranasal delivery," "nasal administration," "Indian traditional herbs," "Ayurveda," "Siddha," "neurodegeneration," "Alzheimer's disease," "Parkinson's disease," "nanoparticles," "mucoadhesive gels," and "neuroprotection." All retrieved citations were exported into reference management software (Zotero 6.0). Automated duplicate detection was first performed using Digital Object Identifier (DOI), PubMed Identifier (PMID), and title matching algorithms. Subsequently, manual verification was conducted to identify residual duplicates based on author names, journal, year, and minor title variations. Through this two-step process, the duplicate records were identified and removed prior to title and abstract screening.

Inclusion criteria: (1) preclinical or clinical studies involving intranasal delivery, (2) herbal or phytochemical-based interventions, (3) relevance to neurodegenerative disorders or central nervous system (CNS) targeting, (4) English-language publications.

Exclusion criteria: (1) non-nasal routes of administration, (2) non-neurological indications, (3) non-herbal synthetic compounds, (4) conference abstracts without full text.

The review period spanned 2000-2024. Classical Ayurvedic, Siddha, and Unani texts were included to provide historical context. During screening, variability in herbal extract standardization was documented but not used as an automatic exclusion criterion. Studies were categorized based on whether they reported (1) quantified marker compounds (e.g., bacoside content, withanolide percentage, curcuminoid concentration), (2) extract type (aqueous, ethanolic, hydroalcoholic), and (3) physicochemical characterization in nanoformulations (particle size, zeta potential, encapsulation efficiency). Extracts lacking detailed phytochemical profiling were included in qualitative synthesis but interpreted with caution regarding translational applicability and reproducibility. Study selection followed a PRISMA-style screening process as given in the Figure 1 below:

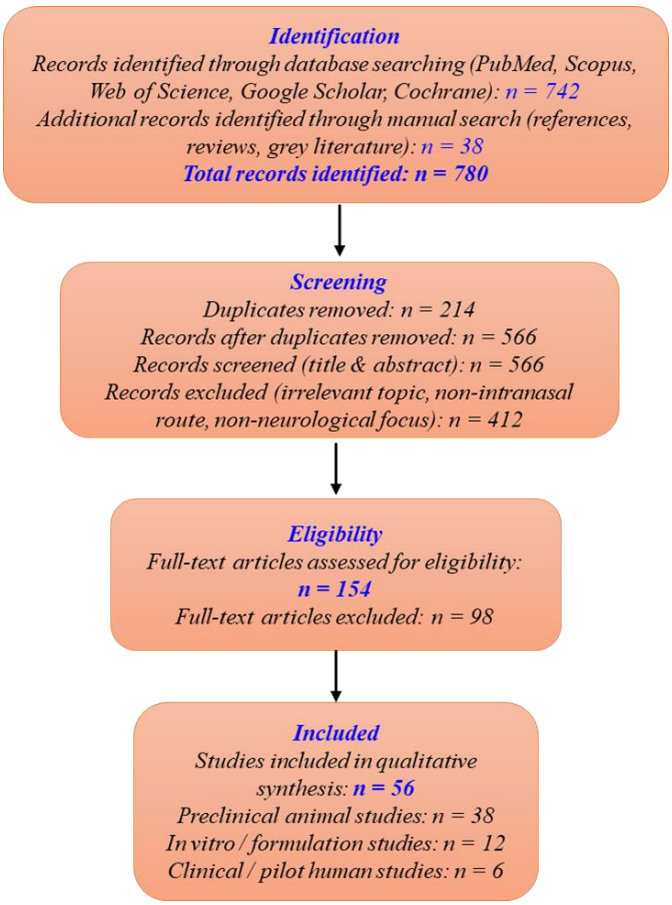

Figure 1. PRISMA flow diagram illustrating the literature search and study selection process for intranasal delivery of Indian traditional herbs and herbal nanoparticle systems in neurodegenerative disorders.

A total of 780 records were identified through database searching and manual sources. After removal of duplicates, 566 records were screened based on title and abstract, of which 412 were excluded for irrelevance. Full-text articles (n = 154) were then assessed for eligibility. To ensure methodological rigor, a study was considered methodologically sufficient if it reported at least the following analytical parameters: (1) a clear description of intranasal formulation composition; (2) dosing regimen and administration protocol; (3) defined neurodegenerative or CNS-related outcome measures (behavioral, biochemical, histological, or imaging-based); and (4) statistical analysis of results. Studies lacking formulation characterization, dosage specification, defined outcome measures, or statistical reporting were classified as methodologically insufficient. Following full-text evaluation, 98 studies were excluded for the following reasons: not employing intranasal delivery (n = 34); inclusion of non-herbal or synthetic drugs only (n = 21); lack of neurodegenerative disease-related outcomes (n = 19); insufficient methodological or formulation details (n = 14); and non-English language or inaccessible full-text articles (n = 10). Finally, 56 studies were included in the qualitative synthesis.

3. Traditional Indian Medical Perspectives on Neurodegeneration

In Indian traditional systems, neurodegeneration was understood as an imbalance in bodily elements, leading to depletion and dysfunction of neural and supportive tissues. In Ayurveda, such degeneration was often associated with depletion of marrow and nervous tissue (Majja dhatu kshaya) and aggravated Vata dosha (the energy principle governing movement and neural function) [14,15]. Majja dhatu nourishes the brain (mastishka), bones, and nervous network, and its depletion can manifest as vertigo, visual disturbances, cognitive decline, and loss of strength. Medicated nasal therapy (Nasya) was traditionally recommended to maintain or restore brain health, along with Medhya Rasayana cognitive tonics such as *Bacopa monnieri* (Brahmi), *Withania somnifera* (Ashwagandha), and *Convolvulus pluricaulis* (Shankhpushpi) to enhance memory, intellect, and neural resilience [16].

Similarly, Siddha medicine attributed neurological decline to derangements of Vatha, a principle analogous to neural functional balance [8]. Therapies such as medicated nasal instillations (Nasiyam), nasal powders (Podi Nasiyam), and aromatic inhalations (Sugantha Nasiyam) employed herbs including *Centella asiatica* (Vallarai), *Withania somnifera* (Amukkara), and *Tinospora cordifolia* (Seenthil) to pacify Vatha, restore strength, and safeguard cognitive functions [7]. Also, in Unani medicine, neurological and cognitive disorders were conceptualized as cerebral inflammation (Ufoonat-e-Dimagh) and paralysis or loss of function (Istirkha) [17]. Nasal administration of herbal oils such as almond oil (Roghan-e-Bādām) and Viola Odorata (Roghan-e-Banafsha) was used to enhance memory, clear cerebral channels, and

support cognitive clarity [18]. Folk medicine practices included fumigation with aromatic herbs such as *Acorus calamus* (Vacha), *Curcuma longa* (Turmeric), and *Nardostachys jatamansi* (Jatamansi) to calm the nervous system and stimulate mental alertness [19-21].

Overall, Indian traditional medicine, particularly Ayurveda and Siddha, emphasized the use of herbs to maintain cognitive health and prevent neurodegeneration [22]. Modern studies suggest that these herbs exert neuroprotective effects through antioxidant, anti-inflammatory, anti-apoptotic, and neurotransmitter-modulating mechanisms, providing a scientific basis for their traditional applications [23,24]. Table 1 summarized the key Indian traditional herbs, their active compounds, proposed neuroprotective mechanisms, and the evidence supporting their effects from preclinical and clinical studies.

Table 1. Indian traditional herbs: active compounds, neuroprotective mechanisms, and supporting evidence.

S.No	Herb	Active Bioactives	Neuroprotective Mechanisms	Evidence
1	*Bacopa monnieri*	Bacosides	Improved cognition, antioxidant, anti- inflammatory	Meta-analyses and Randomized Controlled Trial (RCTs) show improved memory, attention, and cognitive performance in adults; preclinical models show antioxidant and anti-apoptotic neuroprotection [25,26].
2	*Convolvulus pluricaulis* (Shankhpushpi)	Alkaloids, Glycosides	Preclinical learning/memory effects	Animal studies support memory enhancement; clinical evidence is minimal [27].
3	*Withania somnifera*	Withanolides	Nootropic, anti-inflammatory, preclinical neuroprotection	Animal studies demonstrate neuroprotective and neurite-promoting effects; limited human clinical data for cognitive improvement [28,29].
4	*Centella asiatica*	Asiaticoside, Madecassoside	Antioxidant, neurogenesis, mitochondrial protection	Preclinical neuroprotective effects in rodents; small human trials suggest improved cognitive function and mood [30,31].
5	*Ginkgo biloba* (EGb 761)	Flavonoids, Terpene lactones	Antioxidant, mitochondrial support, cerebral circulation	Meta-analyses in Mild Cognitive Impairment (MCI)/dementia show modest cognitive benefits; preclinical studies confirm mitochondrial protection and anti-oxidative effects [32,33].
6	*Curcuma longa* (Curcumin)	Curcuminoids	Antioxidant, anti-amyloid, anti-inflammatory (preclinical)	Strong preclinical evidence for neuroprotection, amyloid reduction; human trials show mixed results due to bioavailability limitations [34,35].
7	*Nardostachys jatamansi*	Nardostachone, Valerenic acid	Antioxidant, GABAergic modulation	Preclinical neuroprotection; clinical evidence very limited [36].
8	*Ocimum sanctum* (Tulsi)	Eugenol, Ursolic acid	Antioxidant, anti-inflammatory	Preclinical antioxidant and anti-stress effects; human cognitive studies limited [37,38].
9	*Tinospora cordifolia*	Tinosporaside	Antioxidant, immunomodulatory	Preclinical neuroprotective and anti-inflammatory evidence; human neurodegenerative data sparse [39].
10	*Acorus calamus*	β-Asarone	Antioxidant, cholinergic modulation	Preclinical neuroprotective studies; clinical evidence absent [40].

Collectively, these studies highlighted the potential of Indian traditional herbs as complementary or adjunctive strategies against neurodegenerative disorders. Their neuroprotective effects were mediated through multiple mechanisms, including antioxidant and anti-inflammatory actions, modulation of Nuclear factor kappa B (NF-κB), Nuclear factor erythroid 2-related factor 2 (Nrf2), brain-derived neurotrophic factor (BDNF), and Mitogen-activated protein kinase (MAPK) signaling pathways, enhancement of synaptic plasticity, and regulation of neurotransmitter systems [41-44]. Despite promising preclinical and limited clinical evidence, translation into routine clinical practice remained constrained by challenges in bioavailability, blood-brain barrier penetration, and optimal dosing strategies.

4. Intranasal Delivery of Herbal Neurotherapeutics: Mechanistic Rationale and Advanced Formulation Strategies

4.1 Mechanistic Advantages of Intranasal Herb Delivery

Intranasal administration of traditional Indian medicinal formulations has emerged as a promising strategy for targeting neurodegenerative disorders by enabling direct access to the CNS [13,45]. Unlike oral or systemic routes, intranasal delivery bypasses the BBB, allowing bioactive compounds to reach the brain via the olfactory and trigeminal neural pathways. These pathways provide a unique anatomical and physiological basis for rapid and efficient nose-to-brain transport, forming the mechanistic foundation for intranasal herbal neurotherapeutics [46].

The olfactory pathway delivers compounds to the olfactory bulb and forebrain through sensory neurons, while the trigeminal pathway extends transport to the brainstem, cerebellum, and deeper cortical structures, supporting both regional and global CNS distribution. This dual-route transport underpins the neurotherapeutic potential of intranasal herbal formulations.

4.2 Challenges of Oral Herbal Delivery and BBB Limitations

A key barrier in neurodegenerative therapeutics is the restrictive nature of the BBB, composed of tight endothelial junctions, pericytes, and astrocytic end-feet, which limits penetration of hydrophilic or high-molecular-weight compounds [47]. Many herbal bioactives including bacosides, withanolides, and curcuminoids show poor oral bioavailability and limited CNS exposure despite promising *in vitro* efficacy [13,48].

Intranasal delivery circumvents these limitations by exploiting olfactory and trigeminal neuronal connections, minimizing systemic exposure, first-pass metabolism, and dose-related toxicity [49,50]. For example, preclinical studies demonstrate that intranasal administration of *Bacopa monnieri, Withania somnifera*, and *Centella asiatica* improves memory, reduces oxidative stress, modulates neuroinflammation, and promotes synaptic plasticity [51,52]. Additional studies show reductions in amyloid-β accumulation and neurodegenerative pathology in experimental models of Alzheimer's and Parkinson's diseases [42,44]. Table 2 summarizes clinical and preclinical studies evaluating intranasal herbal therapies, including nanoparticle- and mucoadhesive-based systems, with outcomes, CNS bioavailability, and mechanistic insights.

Table 2. Preclinical evidence of intranasal herbal/phytochemical or natural compound delivery to the CNS.

Natural Agent/Formulation	Delivery System/Model	Target/Model	Key Findings
Withanolide A (*Withania somnifera* phytochemical)	Intranasal solution, mouse	Global cerebral ischemia model	Brain penetration after intranasal administration; reduced ischemic damage and neurodegeneration [9].
Curcumin & chrysin	Mesoporous silica nanoparticles (MSNP), *in vitro*/olfactory cells	Nose-to-brain delivery model	Nanoparticle formulation enhanced cellular uptake and olfactory cell interaction, suggesting feasibility of intranasal phytochemical transport [53].
Natural phytochemicals	Intranasal route (literature review)	Various CNS disorder scenarios	Intranasal delivery can bypass BBB and deliver flavonoids, terpenes, cannabinoids, and other natural compounds to CNS; nanocarriers often improve brain targeting [54].
Multiple herbal active components	Systematic review of intranasal herbal medicines	Multiple disease targets	Identified preclinical intranasal herbal studies showing CNS targeting potential, rapid absorption, and overcoming systemic barriers [13]

Collectively, these preclinical studies and systematic reviews demonstrate that intranasal delivery of herbal and natural compounds is a feasible and mechanistically promising strategy for CNS targeting, supporting neuroprotective potential across multiple phytochemical classes. While direct clinical evidence in neurodegenerative disorders remains limited, these findings establish a strong rationale for leveraging advanced formulation approaches such as nanoparticles and mucoadhesive gels to optimize nose-to-brain transport, enhance bioavailability, and enable controlled CNS delivery. The following section discusses these advanced formulation strategies for intranasal herbal neurotherapeutics.

4.3 Advanced Formulation Strategies for Intranasal Herbal Delivery

Recent advances in intranasal nanotechnology have enhanced the translational potential of herbal neurotherapeutics by improving stability, bioavailability, and brain targeting [55,56]. Nanoparticle-based systems (PLGA [poly(lactic-co-glycolic acid)], chitosan, solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions) protect thermolabile and poorly water-soluble phytoconstituents, facilitating transport across the nasal epithelium via both transcellular (endocytosis-mediated) and paracellular (tight junction modulation) pathways [55,57]. Surface functionalization with mucoadhesive polymers (chitosan, polyethylene glycol (PEG), poloxamers) enhances nasal residence time and targeting of the olfactory region [56].

Mucoadhesive intranasal gels provide complementary benefits by prolonging mucosal residence and enabling controlled diffusion. Polymers such as carbopol, chitosan, hydroxypropyl methylcellulose (HPMC), and xanthan gum interact with mucin to reduce mucociliary clearance [58,59]. *In situ* pH- and thermosensitive gels form localized matrices in the olfactory region, prolonging drug retention and enhancing CNS exposure for both herbal and synthetic actives [41]. Preclinical studies confirm enhanced hippocampal and cortical concentrations, with modulation of neuroinflammatory and oxidative stress pathways, upregulation of BDNF, and improved cognitive/behavioral outcomes [11,60]. Table 3 presents a comparative overview of nanoparticle and mucoadhesive gel systems, including mechanisms, formulation components, advantages, limitations, and representative preclinical outcomes.

This mechanistic understanding provides a foundation for integration with traditional Nasya/Nasiyam therapy, linking polymer-based mucoadhesion and controlled diffusion principles to traditional Ayurvedic and Siddha intranasal practices.

Table 3. Comparative summary of nanoparticle-based and mucoadhesive intranasal delivery systems for herbal neurotherapeutics [49,56,60,61].

Parameter	Nanoparticle Systems	Mucoadhesive Gels
Primary Mechanism	Protection of labile phytoconstituents, enhanced epithelial permeation, sustained release	Prolonged mucosal residence, controlled diffusion of actives
Transport Pathway	Transcellular & paracellular via olfactory and trigeminal nerves	Extended mucosal contact & gradual diffusion across nasal epithelium
Formulation Components	Polymeric nanoparticles: PLGA, chitosan, PEG-modified particles. Lipid-based: solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), Nanoemulsions	Carbopol, chitosan, HPMC, thermosensitive *in situ* gels
Key Advantages	Improves solubility and stability of hydrophobic compounds (e.g., *bacosides*, *withanolides*, *curcuminoids*), enhances brain targeting, reduces first-pass metabolism	Enhances residence time, reduces dosing frequency, allows controlled diffusion for sustained CNS exposure
Limitations	Complex synthesis, scale-up challenges, potential nasal irritation	Limited drug loading, viscosity variation, slower onset of delivery compared with nanoparticles
Representative Outcomes	Higher brain/plasma ratio, enhanced CNS bioavailability, reduced oxidative stress and neuroinflammation in preclinical models	Prolonged CNS exposure, steady-state release, improved behavioral and cognitive outcomes in animal models
Examples of Herbal Applications	*Bacopa monnieri*, *Withania somnifera*, *Curcuma longa* encapsulated in PLGA nanoparticles, SLNs, or NLCs	Mucoadhesive gels loaded with *Curcuma longa*, *Ginkgo biloba*, *Bacopa monnieri* for sustained nasal delivery

5. Integration of Mechanistic Principles with Traditional Nasya/Nasiyam

The mechanistic rationale of intranasal delivery aligns with traditional Ayurvedic and Siddha practices, where Nasya and Nasiyam administer medicated oils, powders, and aromatic preparations to enhance cognition and mental clarity [62,63]. Nanocarrier and gel strategies offer a contemporary pharmacological framework that conceptually aligns with traditional Nasya practices utilizing the nasal route for central nervous system targeting, while differing substantially in formulation design and characterization [13]. While preclinical studies strongly support the efficacy of intranasal herbal formulations, clinical evidence remains extremely limited. Most studies are short-term, focus on crude extracts or experimental formulations, and lack comprehensive pharmacokinetic and safety assessments. Well-designed phase II/III trials with standardized formulations, optimized dosing, and rigorous safety evaluation are urgently needed to translate these promising approaches into clinical practice.

5.1 Preclinical and Clinical Evidence, Safety, and Regulatory Considerations

Preclinical evidence evaluating intranasal herbal neurotherapeutics demonstrates therapeutic efficacy across diverse experimental models of neurodegeneration, with consistent behavioral, biochemical, and histopathological improvements [42,44,51]. In transgenic and toxin-induced rodent models of Alzheimer's disease, intranasal curcumin and *Bacopa monnieri*-based nanoformulations significantly reduced amyloid-β aggregation, suppressed microglial activation, decreased lipid peroxidation markers such as malondialdehyde, and enhanced endogenous antioxidant defenses including superoxide dismutase and catalase activity [11,42,60]. These biochemical improvements correlated with enhanced performance in memory paradigms such as the Morris water maze and novel object recognition tests [51,52].

In ischemic and Parkinsonian models, intranasal withanolide-enriched formulations demonstrated preservation of dopaminergic neuronal integrity in the substantia nigra, reduction in pro-inflammatory cytokines including Tumor necrosis factor alpha (TNF-α) and Interleukin-1 beta (IL-1β), attenuation of mitochondrial dysfunction, and improved motor coordination assessed by rotarod, pole test, and open-field analysis [9,44]. Similarly, *Centella asiatica*-based intranasal systems were associated with upregulation of BDNF, stabilization of mitochondrial membrane potential, and improved spatial learning outcomes [30,60].

Importantly, pharmacokinetic analyses of nanoparticle-based systems consistently reported enhanced brain bioavailability and significantly higher brain-to-plasma concentration ratios compared with oral administration, supporting effective nose-to-brain transport [53,55,57]. Although most studies were short-term and conducted in controlled laboratory settings, the convergence of behavioral improvements, attenuation of oxidative and inflammatory biomarkers, and histological evidence of neuroprotection provides encouraging translational support for intranasal herbal delivery as a mechanistically plausible and promising investigational strategy in neurodegenerative models.

Human clinical evidence for intranasal herbal therapy in neurodegenerative disorders is scarce, with most data remaining preclinical and only a few pilot or registered human trials. Safety concerns include β-asarone-associated toxicity from *Acorus calamus*, chemical instability of curcumin, and potential nasal mucosal irritation following repeated intranasal administration [64,65]. Pharmacokinetic and long-term safety data are limited, restricting rational dose optimization and clinical translation.

Despite these limitations, several studies provide preliminary evidence of feasibility and CNS engagement. For example, a patented intranasal herbal preparation administered daily for six months in children with autism spectrum disorder improved inhibitory control, mental flexibility, and planning, together with increased prefrontal and anterior cingulate cortex activity, demonstrating measurable effects on brain function [66]. Similarly, intranasal administration of traditional herbal nasal drops in healthy adults enhanced frontal lobe and anterior cingulate cortex electrical activity, indicating physiological CNS modulation [67].

Additional investigations of classical Nasya therapy underscore its therapeutic potential in neurological or neuro-related conditions. In migraine patients, a double-blind randomized trial of Nasya using Vrihatajivakadhya oil (6 drops per nostril for 14 days) significantly improved clinical outcomes without adverse events [68]. Small studies on facial paralysis (Ardita) reported symptomatic relief following Nasya administration, and single-group studies combining Anu Taila Nasya with oral herbal therapy (Shatyadi Vati) for allergic rhinitis demonstrated symptom improvement [68,69]. An ongoing open-label randomized trial is evaluating Anu Taila Nasya versus fluticasone nasal spray in adults with allergic rhinitis, illustrating the first formal clinical investigations of intranasal herbal therapy [70].

Regulatory considerations present an additional translational barrier. Intranasal herbal-nanoparticle formulations occupy a hybrid space between traditional medicines and advanced drug-delivery systems. In India, classical nasal therapies are regulated under the Ayush framework, whereas reformulation with nanocarriers or synthetic excipients may classify products as new drugs or drug-device combinations under the Central Drugs Standard Control Organization [71]. Internationally, the U.S. Food and Drug Administration regulates such products as botanical drugs requiring Investigational New Drug approval and Good Manufacturing Practice compliance, while the European Medicines Agency applies the Herbal Medicinal Products Directive with heightened scrutiny for nanotechnology-based systems [72,73]. The absence of harmonized guidelines for intranasal herbal-nanotechnology hybrids remains a critical challenge for clinical translation.

5.2 Challenges and Future Directions

Despite promising preclinical data, several challenges remain. Standardization of herbal extracts is necessary to ensure reproducibility and consistent bioactive content. Optimal intranasal dosing requires careful investigation to balance efficacy and safety [74]. Long-term safety, toxicity, and pharmacokinetic studies are limited and warrant further research. Nanoparticle and mucoadhesive formulations have been investigated to improve nasal absorption and increase mucosal residence time [75]. Although promising safety and early translational data exist, no intranasal therapy for neurodegenerative disorders has yet achieved marketing approval. Only a limited number of agents including intranasal insulin, rivastigmine, and APH-1105 have progressed to early human trials, with few completed results and no definitive phase III outcomes to date. This underscores the absence of adequately powered phase II/III trials for intranasal herbal or nanoformulated therapies, which remains a key barrier to clinical translation [76,77]. Regulatory and ethical considerations for clinical translation of intranasal herbal therapy also require careful attention. Harmonizing traditional practices with modern standards, as emphasized in global integration models, could guide policy development, standardization, and safe clinical implementation [78].

6. Conclusion

Intranasal delivery of Indian traditional herbs represents a promising and integrative therapeutic strategy for managing neurodegenerative disorders. Preclinical and translational studies have demonstrated significant neuroprotective, anti-inflammatory, and cognitive-enhancing effects, providing preliminary mechanistic support consistent with traditional nasal therapies such as Nasya and Nasiyam. The development of advanced nasal delivery systems, including nanoparticles and mucoadhesive gels, has further enhanced absorption, bioavailability, and brain targeting. Future research should prioritize formulation standardization, validation of synergistic herbal combinations, and well-designed comparative clinical studies against existing pharmacotherapies, along with addressing the regulatory and translational challenges essential for clinical adoption. Overall, integrating traditional herbal wisdom with modern neuroscience and advanced intranasal drug delivery platforms offers a scientifically grounded and patient-centered approach to neuroprotection and cognitive restoration.

Acknowledgement

I am grateful to Dr. A. Muthuvel, Assistant Professor in the Division of Biochemistry, Department of Integrative Health and Translational Research, for his unwavering support, as well as to the National Institute of Siddha for their invaluable cooperation and institutional assistance.

Funding

This research was not supported by any specific grants from public, commercial, or non-profit funding agencies.

Conflict of Interest

The author declares no conflict of interest.

Generative AI Statement

The author declares that no Gen AI was used in the creation of this manuscript.

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