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REVIEW

Nasal Delivery of Phytochemicals Using Nanocarriers: Therapeutic Opportunities and Translational Challenges

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Abstract: The integration of phytochemicals with nanotechnology represents a promising approach to enhance nasal drug delivery, improving therapeutic efficacy and targeted brain delivery. This review explores recent advances in phytochemical–nanotechnology formulations and their applications in managing neurodegenerative diseases, respiratory disorders, and cancers. Phytochemicals such as curcumin, resveratrol, and quercetin exhibit potent pharmacological properties but suffer from poor solubility and limited bioavailability. Nanotechnology-based systems-including nanoparticles, liposomes, and nanoemulsions-overcome these drawbacks by improving stability, absorption, and controlled release. However, challenges such as nasal mucosa irritation, formulation complexity, regulatory barriers, and scalability still impede clinical translation. Notably, encapsulation of curcumin in polymeric nanoparticles has been shown to enhance its solubility and bioavailability, producing improved therapeutic outcomes in preclinical Alzheimer's models. Overall, this review underscores the synergistic potential of phytochemicals and nanotechnology in developing innovative nasal delivery platforms capable of providing targeted, effective, and patient-friendly treatment options for a range of medical conditions.

Keywords: phytochemicals, nanotechnology, nasal drug delivery, therapeutic efficacy, neurodegenerative diseases, bioavailability

Introduction

Neurology disorders and central nervous system (CNS) disorders have emerged as a significant worldwide health problem and among the number of the most common causes of mortality and morbidity globally. World Health Organization (WHO, 2024) indicated that one out of three people, or about 3 billion, is living with a neurological condition today, with Alzheimer disease, Parkinson disease, stroke, and migraine being the major causes of morbidity and mortality worldwide.[1] The WHO (2025) also documents that the neurological disorders contribute to more than 11 million deaths each year and are on the increase because of the aging population and the lack of good treatments.[2] Along with these alarming statistics, the delivery of drugs to the brain is still a burning issue, since the blood-brain barrier (BBB) limits the penetration of most drug delivery systems, especially big or hydrophilic ones.[3–5] Nasal drugs delivery has attracted considerable interest as a non-invasive and effective CNS delivery method because it has direct access to the brain via the olfactory and trigeminal routes as well as avoiding the hepatic first-pass metabolism.[6,7] Its benefits are that it has rapid absorption of drugs, enhances patient compliance and may have localized or systemic effects. There are however various constraints of conventional nasal formulations which include: mucociliary clearance, enzyme degradation, low permeability through nasal epithelium and others which inhibit drug bioavailability and therapeutic effects.[7] Natural bioactive plant-derived phytochemicals have become potential therapeutic agents in CNS-related disorders because of their antioxidant, anti-inflammatory, neuro-protective, and anti-apoptotic effects.[8–10] It has shown

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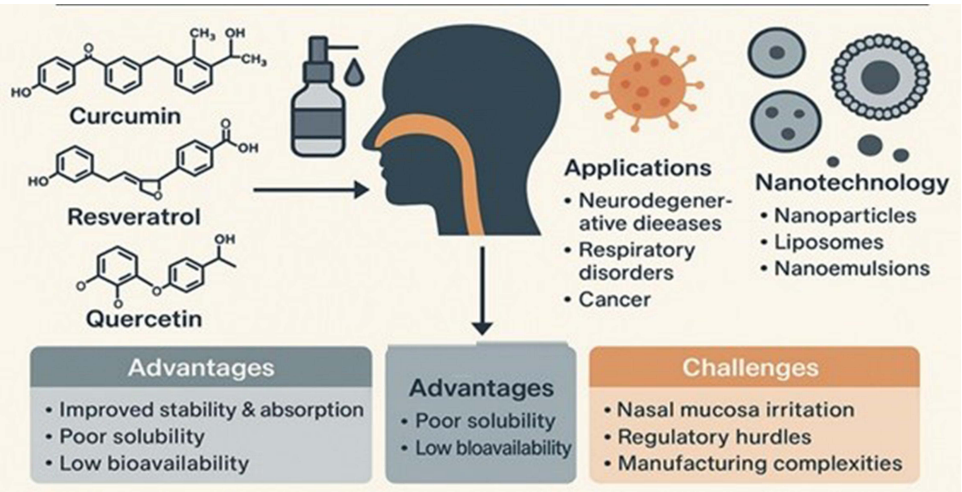
Graphical Abstract



promising preclinical results with compounds including curcumin, resveratrol, quercetin and berberine possessing the potential to reduce oxidative stress, b-amyloid aggregation, and neuronal apoptosis in the case of neurodegenerative diseases.[11,12] However, they have failed to be translated into clinical use because of low aqueous solubility, high metabolism, and low levels of membrane permeability, which makes them poorly bioavailable to the brain when delivered orally.[13–15]

Nanosystems such as nanocarriers-based nasal delivery system have demonstrated a lot of potential in addressing these types of barriers by enhancing the solubility, stability, and permeability of phytochemicals and offering a controlled and prolonged release.[16] The mucosal adhesion has been improved by the development of different nanocarriers, such as polymeric nanoparticles, lipid-based nanoparticles, liposomes, nanoemulsions, and dendrimers, to ensure the protection of encapsulated compounds against enzymes and the direct delivery of drugs to the brain.[17–19] Despite the developments, there exist a number of challenges to translating. These are the possible toxicity of the nanomaterials, physiological inconsistency of the nose in different patients, scalability of nanocarrier manufacturing, and regulatory barriers with regard to safety/standardization.[20,21] This is important to overcome such obstacles in order to bring nanotechnology-improved phytochemical nasal preparations out of lab success into clinical reality. In this review, the authors examine the therapeutic potential and translational issues of nasal administration of phytochemicals via nanocarriers. It underlines the latest innovations, preclinical results, and regulatory issues, giving an idea about how these new technologies might transform drug delivery into the CNS and improve patient outcomes.

Methodology

Objectives

The primary objective of this narrative review is to explore and synthesize current scientific knowledge on the integration of phytochemicals and nanotechnology in nasal drug delivery systems. Specifically, the review aims to carry out the following:

1. Describe the pharmacological potential of phytochemicals such as curcumin, resveratrol, quercetin, and berberine in nasal drug delivery.
2. Examine the innovations in nanotechnology-based carriers that enhance phytochemical delivery via the nasal route.
3. Identify therapeutic applications in central nervous system (CNS) disorders, respiratory diseases, and cancer.
4. Discuss the associated challenges, including mucosal irritation, regulatory concerns, and formulation stability.

Eligibility Criteria

Included studies met the following criteria: Peer-reviewed articles published in English. Original research, reviews, or systematic evaluations focused on phytochemicals and/or nanotechnology in nasal drug delivery. Publications describing pharmacokinetics, drug delivery mechanisms, therapeutic outcomes, or safety assessments of phytochemical-nanotechnology formulations. Studies published between January 2014 and April 2025.

Exclusion Criteria

The exclusion criteria were as follows:

Articles focusing solely on oral, intravenous, or transdermal drug delivery.

Studies lacking relevance to nasal formulations or without specific discussion of phytochemicals or nanocarriers. Non-English-language papers and conference abstracts without the full text.

Information Sources and Search Strategy

A comprehensive literature search was performed using the following electronic databases: PubMed, Scopus, Web of Science, Embase, and Google Scholar. Keywords and Boolean operators used included the following:

"Phytochemicals" AND "Nasal drug delivery";

"Nanotechnology" AND "Nasal administration";

"Curcumin OR Resveratrol OR Quercetin OR Berberine" AND "Nasal nanoparticles";

"Phytochemical nanoformulations" AND "Bioavailability";

"CNS disorders" OR "Respiratory diseases" OR "Cancer" AND "Nasal therapy".

Phytochemicals in Nasal Drug Delivery

Plants produce phytochemicals which function as therapeutic compounds that show antioxidant and anti-inflammatory and neuroprotective and antimicrobial actions.[8] Researchers have intensely studied four phytochemical compounds, which include curcumin, resveratrol, quercetin, and berberine, to address different health disorders spanning neurodegenerative conditions, respiratory issues, and cancers.[10] Because of their inadequate pharmacokinetic characteristics which cause low water solubility and bad permeability alongside swift metabolic clearance, these therapeutic compounds face numerous usage restrictions in clinical practice.[22] When given through traditional delivery routes, their absorption rates present significant challenges. Nasal drug delivery provides multiple benefits for phytochemicals because it specifically targets the central nervous system (CNS).[16] The nasal mucosa possesses high vascularization which enables quick absorption together with the olfactory and trigeminal nerve pathways that physically connect with the brain without needing to pass through the blood–brain barrier.[17] Among the treatment options for CNS disorders, nasal delivery stands out because it provides effective brain access and thus benefits patients with Alzheimer's and Parkinson's disease.[18] The nasal cavity encounters two main obstacles regarding phytochemical delivery due to mucociliary clearance and enzymatic breakdown processes.[20] Nanotechnology-based delivery systems show great potential as solutions to overcome the current delivery system's limitations.[12] The utilization of nanocarriers consisting of nanoparticles, liposomes, and nanoemulsions exists as a delivery method to protect phytochemicals from enzymatic degradation while simultaneously improving their permeability and solubility.[13] The delivery systems based on nanotechnology enhance both availability rates and controlled gradual release mechanisms so they optimize the medical effectiveness of phytochemicals.[14] The combination of nasal formulations enhanced through nanotechnology creates promising options for medical treatment of CNS disorders and respiratory diseases and other medical conditions.[21] Nasal drug delivery systems use important phytochemical substances as active delivery elements.[8] The scientific community actively studies phytochemicals as bioactive natural plant compounds because these compounds demonstrate various therapeutic properties.[9] These compounds benefit from nasal drug delivery because such an approach enables effective administration that benefits patients suffering from central nervous system disorders and respiratory diseases.[16] The nasal drug delivery system imparts several beneficial attributes since it operates without invasive techniques and eliminates both gastrointestinal transit and hepatic first-pass reduction, while accepting fast body absorption both into the bloodstream and directly reaching the

brain tissue through olfactory and trigeminal neural pathways.[17] Most phytochemicals with therapeutic value encounter various challenges including their inability to dissolve well in water and their restricted permeability while being unstable in biological systems and having limited availability in the body.[10] Phytochemical administration via the nose has been improved through nanotechnology platforms such as nanoparticles, nanoemulsions, liposomes, and nanostructured lipid carriers which address therapeutic challenges to elevate drug profiles.

Phytochemicals are bioactive compounds naturally synthesized by plants, offering diverse therapeutic effects including antioxidant, anti-inflammatory, neuroprotective, antimicrobial, and anticancer activities.[8] Among the most extensively studied phytochemicals are curcumin, resveratrol, quercetin, and berberine, which have demonstrated promising outcomes in managing a wide spectrum of health conditions such as neurodegenerative diseases (eg, Alzheimer's and Parkinson's disease), respiratory disorders, and cancer.[10] However, despite their therapeutic potential, most phytochemicals exhibit poor pharmacokinetic profiles, characterized by low aqueous solubility, limited membrane permeability, rapid metabolic degradation, and insufficient bioavailability, following conventional oral or parenteral administration.[22] The nasal route of drug delivery has emerged as a novel and effective alternative for bypassing the limitations associated with traditional delivery systems. The nasal mucosa is richly vascularized and enables rapid systemic absorption, while the olfactory and trigeminal neural pathways provide a direct anatomical connection to the brain, bypassing the blood–brain barrier (BBB), which is a formidable obstacle for CNS drug delivery.[16,17] These attributes make intranasal delivery highly suitable for targeting central nervous system (CNS) disorders, offering a non-invasive, fast-acting, and patient-friendly mode of administration with potential for brain-targeted therapeutic action. In CNS conditions such as Alzheimer's and Parkinson's diseases, the mechanisms of action of phytochemicals delivered intranasally are multifaceted:

Curcumin exerts anti-amyloidogenic effects by inhibiting β-amyloid aggregation, reduces neuroinflammation via NF-κB pathway inhibition, and attenuates oxidative stress through upregulation of Nrf2/HO-1 signaling. Resveratrol activates SIRT1 signaling and modulates mitochondrial biogenesis, thereby promoting neuronal survival and reducing neurodegeneration. Quercetin scavenges free radicals and inhibits pro-inflammatory cytokines such as TNF-α and IL-6, while promoting autophagy and synaptic integrity. Berberine enhances neuroplasticity via AMPK activation, modulates cholinergic neurotransmission, and inhibits tau hyperphosphorylation.

Nonetheless, nasal phytochemical delivery faces challenges such as mucociliary clearance, which rapidly removes formulations from the nasal cavity, and enzymatic degradation by nasal esterases and proteases.[20] To address these barriers, nanotechnology-based delivery systems have gained significant attention. Nanocarriers-including nanoparticles, nanoemulsions, liposomes, and nanostructured lipid carriers-serve as protective vehicles that enhance phytochemical stability, solubility, and permeability.[12,13] These systems facilitate sustained release, targeted delivery, and enhanced residence time on the nasal mucosa, significantly improving drug bioavailability and therapeutic efficacy.[14] The integration of phytochemical compounds with nanotechnology-enhanced nasal delivery systems offers a transformative strategy for the treatment of CNS and respiratory diseases. By overcoming pharmacokinetic limitations and leveraging direct nose-to-brain pathways, this approach optimizes drug delivery, minimizes systemic toxicity, and broadens the therapeutic utility of plant-based interventions.[21]

Diseases Potentially Treated Using Nasal Drug Delivery Technology

Nasal drug delivery (particularly the intranasal route targeting the brain via the olfactory and trigeminal pathways) is promising for a range of neurological, psychiatric, infectious, and inflammatory disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, glioblastoma, stroke, depression, anxiety disorders, and schizophrenia.[23] Other systemic and local diseases include migraine and cluster headaches, chronic pain, nasal polyps and allergic rhinitis, diabetes mellitus (eg, insulin nasal spray), COVID-19 (prophylactic vaccines or antiviral delivery), obesity (eg, intranasal leptin analogs), and hormonal deficiencies (eg, GnRH nasal formulations).[24] A comparison of nasal drug delivery versus conventional approaches, and their merits and limitations is shown in Table 1.

Table 1 Comparison of Nasal Drug Delivery vs Conventional Approaches

Feature	Nasal Delivery	Oral Delivery	Transdermal
Onset of Action	Rapid (bypasses BBB and first-pass metabolism)	Slow (first-pass metabolism)	Slow
Blood–Brain Barrier Penetration	Direct CNS access via olfactory/trigeminal nerves	Poor penetration	Very limited
Bioavailability	Moderate to High	Often low for CNS drugs	Variable
Patient Compliance	High (non-invasive)	High	Low (invasive)
Drug Degradation	Low (avoids GI enzymes)	High (GI degradation)	Low
Ease of Administration	Easy (self-administration possible)	Easy	Easy
Limitations	Dose limitations, mucociliary clearance, enzymatic degradation	Poor CNS targeting, first-pass metabolism	Limited to lipophilic drugs

Notes: Table 1 compares nasal, oral, and transdermal drug delivery systems, highlighting differences in onset of action, bioavailability, blood-brain barrier penetration, patient compliance, and associated limitations. It emphasizes the unique advantages of nasal delivery for rapid and direct central nervous system access.

Recent Approaches for Nasal Delivery of Phytochemicals: Advances and Challenges

The nasal route has proven to be an attractive non-invasive route of administering phytochemicals and therapeutic agents to the central nervous system (CNS). Due to the special anatomical linkage between the nasal mucosa, olfactory bulb, and brain, nasal drug delivery circumvents the blood-brain barrier (BBB), and provides a direct and quick route to the tissues of the brain cells. The pharmacological potential of natural compounds has been greatly improved by recent nanotechnology-based methods-namely, nanoemulsions, solid lipid nanoparticles (SLNs), polymeric nanoparticles and liposomes-in the treatment of neurodegradative and systemic diseases.[25,26]

Advances in Nose-to-Brain Delivery

In case of Alzheimer disease, lipid-based nanoparticles and nanoemulsions were extensively used to deliver antioxidant phytochemicals in forms of nanosized lipid-based nanoparticles and nanoemulsions into the nasal cavity. These systems are associated with an increase in solubility and brain bioavailability as well as the decrease of hepatic metabolism. Xu et al[27] revealed that curcumin-loaded solid lipid nanoparticles were better in brain uptake and cognitive protection than the oral formulations. Nevertheless, physicochemical instability and nasal irritation are still critical shortcomings.

On the same note, levodopa and other dopaminergic phytocompounds have been delivered using chitosan-based polymeric nanoparticles in Parkinson disease. Mucoadhesive and permeation-enhancing properties of chitosan extend the jurisdiction of chitosan in the nasal tract and advance drug bioavailability. The results of Lababidi et al[28] indicated that the intranasal administration of levodopa nanocarriers made of PLGA led to better dopaminergic activity and sustained release, which means that such a method can be used to substitute traditional oral treatment. However, enzymatic degradation and mucociliary clearance still leads to a decreased efficiency of formulations.

Nanostructured lipid carriers (NLCs) that entrap bioactive phytochemicals (CBD and terpenoids) to epilepsy have been found to have a better management effect on seizures by engaging the olfactory pathway quickly but circumventing the initial metabolism.[29] PEGylated liposomes, which carry anti-inflammatory biomolecules or plant-based immunomodulators (eg, curcumin, quercetin), have been shown to have non-invasive immune modulation but not to have good absorption of large molecules in the case of multiple sclerosis.[25]

Nanotechnology in Neuro-Oncology and Cerebrovascular Disorders

The latest data shows the advantage of nasal nanoformulations in glioblastoma and stroke/ischemia models. The brain-targeted delivery of temozolomide and flavonoid antioxidants based on gold nanoparticles and polymeric micelles has enabled reduction of systemic toxicity and tumor penetration.[30] Equally, neuroprotection after ischemic injury was

immediately realized by means of intranasal resveratrol- or edaravone-loaded nanoemulsions.[30] However, the issues of scalability and the necessity to conduct administration promptly are technical challenges.

Pain-Related Disorders and Psychiatric Disorders

Nanoformulations in the form of intranasal have demonstrated exceptional potential in the treatment of psychiatric illnesses in which phytochemicals have been observed to exhibit neuroprotective and anxiolytic properties. Nanoparticles of soluble lipids that encapsulate polyphenols or even herbal antidepressants like hyperforin have a faster onset and brain concentration than the orally administered counterparts.[31] Antipsychotic and flavonoid-based adjuvant nanoparticles on polymeric nanoparticles increase the adherence rate and reduce the systemic side effects in schizophrenia.[25] In the case of migraine and chronic pain, nanoemulsions and mucoadhesive nanoparticles allow fast analgesia and controlled release, albeit inconsistent nasal absorption in patients.

Nasal Nanoformulations Beyond the CNS

Nosotropic: Nasal nanotechnology has been extrapolated to a number of systemic conditions in addition to those of the nervous system. In diabetes mellitus, insulin-loaded chitosan nanoparticles and herbal insulin mimetics, including berberine, have offered needle-free, patient-friendly substitutes, which have attained controlled glycemic reactions.[32,33] Nano-based intranasal vaccines created with phytochemical adjuvants and chitosan have elicited a strong mucosal immune response in respiratory infections and COVID-19 to decrease viral propagation and transmission of infection.[25] Besides, intranasal administration of leptin analogs and plant-based appetite modulators have demonstrated the potential in the treatment of obesity throughout the enhancement of hypothalamic receptors, with GnRH-loaded liposomes also being considered in the treatment of hormone deficiencies, with pulsatile hormone release and the absence of side effects associated with injections.[26] In spite of these developments, there are a number of issues that limit clinical translation of nasal phytochemical nanoformulations. The low dose volume that can be administered in the nasal cavity, enzymatic breakdown of phytoconstituents, and interchangeability of mucosal absorption requires the development of more mucoadhesive, stimuli-responsive systems. The further development of nanocarriers is focused on hybrid nanocarriers, bioinspired delivery vehicles (exosomes, nanogels), and individually tailored nasal devices combining smart-release technologies. These together with computational modeling, and in-vitro nasal epithelium systems can move phytochemical nasal therapeutics towards optimization and regulative approval faster. Nasal nanotechnology is a radical advancement in terms of delivery of phytochemicals to the brain and the rest of the body. These nanoformulations enhance the therapeutic properties of natural products in neurodegenerative, psychiatric, metabolic, and infectious disease by bypassing the conventional pharmacokinetic barriers. It will be important that further interdisciplinary cooperation of formulation scientists, pharmacologists, and clinicians be required in order to translate these encouraging experimental results into safe, standardized, and effective clinical products. This is shown in Table 2.

Table 2 Challenges and Advantages of Nasal Nano-Formulations for Disease Therapy

Disease/Application	Delivered Nano-Formulation Example	Advantages of Nasal Nano-Formulation	Challenges/Limitations
Alzheimer's disease	Lipid-based nanoparticles (eg, solid lipid nanoparticles, nanoemulsions delivering donepezil or curcumin)	Direct brain targeting via olfactory pathway; bypasses blood–brain barrier (BBB); rapid onset of action	Nasal mucosal irritation; limited drug dose volume; formulation stability issues[25,26]
Parkinson's disease	Polymeric nanoparticles (eg, chitosan-levodopa or ropinirole nanocarriers)	Enhanced bioavailability and sustained drug release; improved patient compliance	Mucociliary clearance reduces residence time; potential for enzymatic degradation[28]
Epilepsy	Nanostructured lipid carriers (for carbamazepine, valproate)	Rapid seizure control; avoids first-pass metabolism	Drug leakage; challenges in achieving consistent dosing[29,30]

(*Continued*)

Table 2 (Continued).

Disease/Application	Delivered Nano-Formulation Example	Advantages of Nasal Nano-Formulation	Challenges/Limitations
Multiple sclerosis	PEGylated liposomes for interferon-β	Non-invasive immune modulation; avoids injection-related side effects	Protein instability; limited absorption for large biomolecules[25,26]
Glioblastoma	Gold nanoparticles, polymeric micelles delivering temozolomide	Targeted brain tumor delivery; reduced systemic toxicity	Nasal barrier permeability limits large molecules; reproducibility in humans[30]
Stroke/Ischemia	Nanoemulsions delivering neuroprotectants (eg, edaravone, resveratrol)	Fast CNS access post-stroke; improved drug solubility	Time-sensitive administration; formulation scalability[30,31]
Depression & Anxiety Disorders	Solid lipid nanoparticles with antidepressants (eg, fluoxetine, venlafaxine)	Faster onset; improved brain concentration compared to oral route	Short retention time; nasal enzymatic degradation[32,33]
Schizophrenia	Polymeric or lipid nanocarriers for antipsychotics (eg, risperidone, olanzapine)	Reduced systemic side effects; improved adherence	Drug precipitation; irritation potential[25,26]
Migraine/Cluster Headache	Nanoemulsion or nanogel formulations of triptans (sumatriptan, zolmitriptan)	Rapid pain relief; avoids gastrointestinal degradation	Limited drug load; patient variability in nasal absorption[30]
Chronic Pain	Mucoadhesive nanoparticles of opioids or peptide analgesics	Sustained release; reduced systemic adverse effects	Risk of local tolerance or inflammation[25,31]
Allergic Rhinitis/Nasal Polyps	Nano-suspensions of corticosteroids or antihistamines	Localized action; minimized systemic exposure	Formulation stability; dosing uniformity[25,31]
Diabetes Mellitus	Insulin-loaded chitosan nanoparticles	Needle-free insulin delivery; improved patient compliance	Variable absorption; mucosal irritation on chronic use[32]
COVID-19 and Respiratory Infections	Nano-based vaccines or antiviral nanoparticles (eg, chitosan-RBD nanovaccine)	Induces strong mucosal immunity; non-invasive mass vaccination	Regulatory and safety concerns; cold-chain storage requirements[25,28]
Obesity	Leptin analogs in nanoemulsion formulations	Central appetite regulation; improved BBB penetration	Leptin resistance; limited long-term data[25,26]
Hormonal Deficiencies	GnRH-loaded liposomes or polymeric nanoparticles	Pulsatile hormone release; avoids injection	Hormone instability; mucosal enzyme degradation[25,26]

Notes: Table 2 has summarized the therapeutic potential and formulation challenges of nasal nano-formulations in a variety of neurological, metabolic, and endocrine disorders. These superior delivery systems have major benefits of directing the brain, increasing bioavailability, and fast action, which surpass the defects of traditional routes. Nevertheless, the problems such as nasal mucosal irritation, formulation stability, enzymatic break down, and restricted dosing volumes remain to impede clinical translation and long-term use.

Why Phytochemicals are Essential for CNS-Related Diseases

Phytochemicals have been advocated as promising neuroprotective benefits because of their multitarget effects, antioxidant and anti-inflammatory impact, blood-brain barrier (BBB) permeability, neurogenesis promotion, and interactions with conventional therapeutic measures.[34] Examples of central nervous system (CNS) disorders that are caused by complex interplay of oxidative stress, neuroinflammation, amyloid aggregation, mitochondrial dysfunction, and neurotransmitter imbalance include Alzheimer's, Parkinson's, stroke, and multiple sclerosis. In contrast to the single-target synthetic drugs, the phytochemicals have pleiotropic activity-modulating several pathological pathways at the same time. An example is that curcumin prevents the aggregation of Ab, alleviates oxidative stress, and increases cholinergic signaling, whereas resveratrol and quercetin moderate mitochondrial biogenesis and inhibit neuroinflammatory responses.[35,36] In addition, phytochemicals stimulate neurogenesis and synaptic plasticity by increasing brain-derived neurotrophic factor (BDNF) and other brain signaling molecules necessary to keep neurons alive. Their comparatively low systemic toxicity and potential to interact with other existing drugs increase the therapeutic effects and safety. Nevertheless, it cannot be used clinically because of its low solubility and low BBB permeability; therefore, novel delivery systems, including nanocarriers and intranasal systems, are

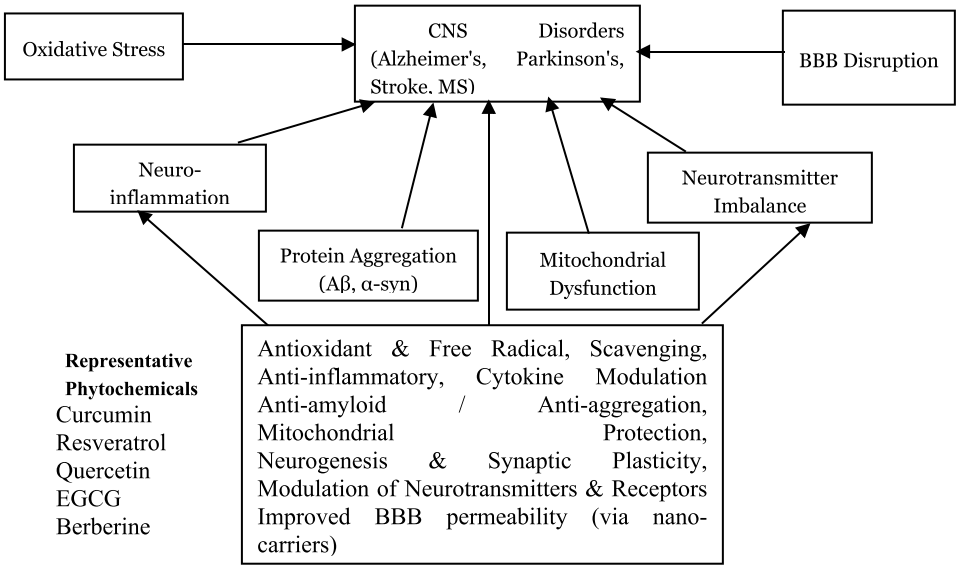


Figure 1 Why phytochemicals are needed for CNS-related ailments.

required.[37] Accordingly, there is new evidence to support the assertion that phytochemicals have not only neuroprotective properties but also high translational potential in preventing and treating CNS-related diseases. Figure 1 illustrates the multifactorial mechanisms underlying CNS disorders, highlighting oxidative stress, neuro-inflammation, mitochondrial dysfunction, neurotransmitter imbalance, and blood-brain barrier (BBB) disruption as key pathological factors. Phytochemicals such as curcumin, resveratrol, quercetin, EGCG, and berberine exert therapeutic benefits through antioxidant, anti-inflammatory, anti-amyloid, and neuroprotective actions. These compounds also promote neurogenesis, modulate neurotransmission, and enhance BBB permeability, particularly when delivered via nanocarriers.

Key Phytochemicals in Nasal Drug Delivery

These following sections demonstrate important phytochemicals used in nasal drug delivery together with their nanoformulations, along with target therapeutic areas, as shown in Table 3.

Table 3 Phytochemicals in Nasal Drug Delivery for Neurological and Respiratory Disorders

Phytochemical	Source Plant	Key Properties	Target Conditions	Nasal Delivery System	Mechanism of Action
Curcumin	Curcuma longa (Turmeric)	Anti-inflammatory, Antioxidant, Neuroprotective	Alzheimer's, Parkinson's, Depression	Solid lipid nanoparticles, Polymeric nanoparticles	Reduces oxidative stress, inhibits amyloid plaque formation[8,28–30]
Resveratrol	Grapes, Berries, Peanuts	Antioxidant, Anti-inflammatory, Neuroprotective	Alzheimer's, Parkinson's, Oxidative stress	Nanoemulsions, Liposomes, Polymeric micelles	Enhances mitochondrial function, reduces neuroinflammation[34–38]
Quercetin	Onions, Apples, Citrus fruits	Anti-inflammatory, Antiviral, Antioxidant	Allergic rhinitis, Asthma, Sinusitis	Nanoemulsions, Solid lipid nanoparticles	Stabilizes mast cells, inhibits inflammatory cytokines[39,40]
Berberine	Berberis spp., Hydrastis canadensis	Antimicrobial, Anti-inflammatory, Neuroprotective	Sinus infections, Neuroinflammation, Depression	Nanostructured lipid carriers (NLCs), Chitosan nanoparticles	Inhibits microbial growth, modulates neuroinflammation[41–43]
EGCG	Camellia sinensis (Green tea)	Antioxidant, Anti-inflammatory, Anti-carcinogenic	Alzheimer's, Cancer, Oxidative brain damage	Liposomal encapsulation, Polymeric nanoparticles	Scavenges free radicals, protects neurons from toxicity[44,45]

(*Continued*)

Table 3 (Continued).

Phytochemical	Source Plant	Key Properties	Target Conditions	Nasal Delivery System	Mechanism of Action
Ginsenosides	Panax ginseng	Neuroprotective, Anti-inflammatory, Immunomodulatory	Alzheimer's, Ischemic brain injury	Chitosan-coated nanoparticles, Mucoadhesive systems	Modulates neurotransmitter activity, reduces inflammation[46,47]
Thymoquinone	Nigella sativa (Black seed)	Anti-inflammatory, Antioxidant, Antimicrobial	Epilepsy, Asthma, Neuroinflammation	Polymeric nanoparticles, Lipid-core nanocapsules	Suppresses cytokines, modulates oxidative stress[48]
Bacopa Monnieri (Bacosides)	Bacopa monnieri	Neuroprotective, Memory-enhancing, Antioxidant	Cognitive decline, Dementia	Nanoparticles for olfactory mucosa delivery	Enhances synaptic plasticity, protects neurons[49–51]
Withaferin A	Withania somnifera	Anti-inflammatory, Anticancer, Immunomodulatory	Glioblastoma	Polymeric nanoparticles, NLCs	Inhibits NF-κB pathway, induces apoptosis in cancer cells[48–53]
Apigenin	Parsley, Chamomile	Anxiolytic, Anti-inflammatory, Antioxidant	Anxiety, Depression	Nanosuspensions	Enhances GABAergic signaling, reduces neuronal oxidative stress[48–53]
Kaempferol	Broccoli, Kale, Tea	Neuroprotective, Anti-inflammatory, Antioxidant	Alzheimer's disease	Polymeric and lipid-based nanoparticles	Reduces oxidative stress, inhibits neuroinflammatory mediators[48–53]

Notes: Table 3 shows different phytochemicals involved in nasal drug delivery, the source plant, key properties, target conditions, delivery system, and mechanism of action.

Curcumin

The hydrophobic polyphenolic compound from *Curcuma longa* (turmeric) root named curcumin shows active neuroprotective and antioxidant properties along with potent anti-inflammatory effects.[7] Numerous scientific documents demonstrate the ability of phytochemicals to manage CNS conditions including Alzheimer's disease, Parkinson's disease, and depression.[8] Clinical application of curcumin encounters difficulties because the compound shows inadequate water dissolution and quick breakdown by the body and limited absorption through the mouth.[7]

Both curcumin-loaded solid lipid nanoparticles and polymeric nanoparticles can be utilized as possible solutions to intranasal delivery system limitations.[9] Research has demonstrated that curcumin-loaded chitosan nanoparticles manage to adhere tightly to mucosal tissues while staying in the body longer and exhibiting better brain penetration when tested on animals.[10] The developed formulations show encouraging effects by enhancing brain function together with reducing amyloid plaque formation and lowering oxidative damage in experimental neurodegenerative conditions.[22]

Curcumin-loaded nasal nanoparticles showed strong anti-amyloid and anti-inflammatory activity in neuronal cell lines (eg, SH-SY5Y), reducing Aβ aggregation, ROS levels, and NF-κB activation. Intranasal curcumin (eg, with chitosan nanoparticles) in AD mouse models significantly improved cognitive performance, BDNF expression, and reduced tau hyperphosphorylation.[11,12] Table 2 shows major phytochemicals involved in nasal drug delivery, their source plants, and major therapeutic features.

Resveratrol

A natural polyphenol substance known as resveratrol occurs within grapes and red wine as well as berries and peanuts. Medical science considers resveratrol to have widely accepted benefits because it protects cells from oxidation and reduces inflammation and supports cardiovascular health.[13] When studied in brain research environments, researchers found that resveratrol boosts mitochondria activity and suppresses inflammatory responses and protects brain cells against the toxic effects of β-amyloid in patients with Alzheimer's disease.[8]

Resveratrol achieves high CNS bioavailability through nasal formulations based on nanoemulsions, liposomes, and polymeric micelles.[14] Research involving rodents with oxidative stress-induced neuronal damage demonstrated that nanoemulsion-formulated resveratrol improved both nose-to-brain delivery of the substance and antioxidant enzyme performance.[14] These

formulation methods both protect the brain tissue and serve as long-term solutions for continuous disease management in neurodegenerative conditions.[7] They also have demonstrated antioxidant and neuroprotective effects in cortical neurons and astrocyte cultures, and they enhanced SIRT1 activation and mitochondrial biogenesis. Intranasal resveratrol delivered via nanocarriers reduced neuroinflammation and improved memory and motor function in MPTP-induced Parkinsonian mice.[15,16]

Quercetin

Quercetin is abundantly found in onions, apples, capers, and citrus fruits. This bioactive compound exhibits strong anti-inflammatory, antiviral, and antioxidant properties, making it beneficial in the treatment of allergic rhinitis, sinusitis, and asthma.[17] However, its therapeutic application faces two major challenges: poor solubility and rapid degradation in chemical solutions.[9] To overcome these limitations, researchers have developed nasal formulations incorporating quercetin into nanoemulsions and solid lipid nanoparticles. These advanced systems enhance nasal mucosa retention, improve solubility, and effectively alleviate nasal congestion, reduce sneezing, and limit inflammatory cell infiltration in animal models of allergic rhinitis.[10,18]

Berberine

The isoquinoline alkaloid berberine is present in two medicinal plants and their derivatives, *Berberis vulgaris* and *Hydrastis canadensis*. Its antimicrobial, anti-inflammatory, and neuroprotective effects make berberine a suitable therapeutic agent for treating respiratory infections and CNS disorders.[19] However, the absorption of berberine is limited due to its low solubility in water and short half-life in the body. Nasal delivery of berberine using nanostructured lipid carriers (NLCs) and chitosan nanoparticles enhances mucosal uptake and enables direct brain transport.[20] Animal studies have confirmed that these delivery systems optimize berberine therapy by expanding its therapeutic potential and improving its ability to treat sinus infections, depression, and neuroinflammation.[19] Berberine exerts anticholinesterase activity and enhances AMPK activation in microglial cultures. Intranasal administration of berberine-loaded NLCs improved cognitive function, reduced oxidative burden, and attenuated pro-inflammatory cytokines in Alzheimer's disease (AD) rats.[21]

Epigallocatechin Gallate (EGCG)

Green tea (*Camellia sinensis*) produces EGCG as its major catechin, which exhibits remarkable antioxidant, anti-inflammatory, and anti-carcinogenic activities. These properties highlight its potential in the management of age-related brain disorders and certain cancers.[23] However, EGCG suffers from unstable chemical properties and poor bioavailability, as it is rapidly degraded in biological fluids. Encapsulation within liposomes or polymeric nanoparticles enhances CNS bioavailability, reduces oxidative brain damage, and improves stability.[23] Researchers have shown that EGCG-loaded nanoparticles decrease amyloid-beta toxicity and improve learning abilities in Alzheimer's models.[23] EGCG also inhibits amyloid fibril formation, protects hippocampal neurons from Aβ-induced toxicity, and reduces oxidative stress. Intranasal EGCG nanoparticles demonstrated effective brain accumulation, reduced cognitive deficits, and prevented synaptic loss in Alzheimer's disease models.[24]

Ginsenosides

As the main active components of Panax ginseng, ginsenoside saponins exhibit adaptogenic, neuroprotective, and immunomodulatory properties. Compounds such as Rg1, Rb1, and Rd have shown benefits in improving cognitive performance, reducing inflammation, and modulating immune function.[54] However, ginsenosides have poor bioavailability due to limited absorption and extensive metabolic breakdown in the liver. Intranasal delivery using chitosan-coated nanoparticles and mucoadhesive nanocarriers enables their passage through the nasal epithelium and enhances CNS uptake.[54] Animal studies have shown that intranasal ginsenosides improve spatial learning and memory in models of Alzheimer's disease and ischemia-induced brain damage. Ginsenosides promote neurogenesis, reduce oxidative damage, and enhance synaptic signaling in PC12 and SH-SY5Y cells. Intranasal delivery of ginsenoside-Rg1 improved spatial learning, increased cholinergic activity, and reduced microglial activation in AD models.[54]

Thymoquinone

Thymoquinone, an essential oil component of *Nigella sativa* (black seed), exhibits multiple pharmacological activities, including anti-inflammatory, antioxidant, and antimicrobial effects. It shows strong potential as a therapeutic agent for epilepsy, neuroinflammatory disorders, asthma, and allergic rhinitis.[35] Its clinical application is limited by poor solubility and short half-life. To overcome these barriers, researchers have developed lipid-core nanocapsules and biodegradable polymeric nanoparticles for nasal delivery. These formulations enhance bioavailability and therapeutic efficacy. Preclinical studies demonstrated that intranasal thymoquinone suppressed pro-inflammatory cytokines and reduced airway hyperresponsiveness in asthma models.[35]

Bacopa Monnieri Extracts (Bacosides)

Bacopa monnieri, widely used in Ayurvedic medicine, contains bacosides—triterpenoid saponins—with neuroprotective and memory-enhancing properties. These compounds support synaptic plasticity, promote neuroregeneration, and reduce oxidative damage.[55,56] Due to poor oral absorption and susceptibility to enzymatic degradation, nasal delivery has been investigated as a promising alternative. Intranasal administration of bacoside-loaded particles improves tissue penetration through the olfactory mucosa, resulting in better memory outcomes and reduced neuronal degeneration in animal studies.[56] This delivery route offers promise for the treatment of age-related cognitive decline and dementia.[57]

Additional Phytochemicals

Beyond commonly studied phytochemicals, other plant-derived compounds are under preclinical and clinical investigation for nasal delivery. Nanocarrier-based systems significantly enhance their therapeutic efficacy in neurological and oncological conditions.[58]

Withaferin A (*Withania somnifera*): Exhibits anti-inflammatory, immunomodulatory, and anticancer properties. It inhibits NF-κB signaling and induces apoptosis in cancer cells. Intranasal delivery using NLCs and polymeric nanoparticles improves blood–brain barrier penetration and demonstrates promise in treating glioblastoma.[58]

Apigenin (parsley, chamomile, celery): Possesses anti-inflammatory, antioxidant, and anxiolytic effects. Nasal delivery of apigenin-loaded nanosuspensions improved brain targeting and produced antidepressant and anxiolytic effects in animal models, indicating potential as a natural psychotropic agent with fewer side effects.[59]

Kaempferol (broccoli, tea, kale): Provides neuroprotective and antioxidant benefits and reduces inflammation. Intranasal lipid-based and polymeric nanoformulations improve its CNS bioavailability, supporting ongoing preclinical studies for Alzheimer's disease and other neurodegenerative disorders.[35]

Nanotechnology in Nasal Drug Delivery

Nanotechnology has revolutionized drug delivery by enabling the design of nanoscale carriers that improve the solubility, stability, and permeability of therapeutic agents.[59] In nasal delivery, nanocarriers such as nanoparticles, liposomes, nanoemulsions, dendrimers, and nanostructured lipid carriers (NLCs) are used to enhance the bioavailability of phytochemicals with poor absorption profiles.[60] These carriers protect drugs from enzymatic degradation in the nasal mucosa and facilitate absorption across the nasal epithelium.[61] A major advantage is their ability to provide controlled and sustained release, prolonging therapeutic effects and reducing dosing frequency.[62] Moreover, nanoparticles can be engineered to bypass the blood–brain barrier, improving CNS drug targeting. This makes nanotechnology a powerful strategy for treating CNS disorders and enhancing the efficacy of phytochemical-based nasal formulations.[63]

Physicochemical Factors Governing Nasal-to-Brain Transport

Successful nose-to-brain delivery depends significantly on the physicochemical attributes of nanocarriers.[64]

i. Particle Size: The optimal range is 100–200 nm for olfactory and trigeminal uptake; smaller particles (<100 nm) may be cleared rapidly, while larger particles (>300 nm) show poor epithelial penetration.[65]

ii. Surface Charge (Zeta Potential): Mildly positive charges (+10 to +30 mV) improve mucoadhesion by interacting with negatively charged mucins, enhancing nasal residence and absorption.[66]
iii. Lipophilicity: Lipophilic surfaces promote transcellular transport but may require balance to avoid excessive mucosal retention or cytotoxicity.
iv. Molecular Weight (MW): Molecules <1 kDa are more likely to permeate; larger payloads (eg, proteins) benefit from permeation enhancers or carrier-mediated strategies.[67]
v. Surface Modification: PEGylation, ligand conjugation, and chitosan-coating enhance targeting, stability, and retention.[68] In a murine study, chitosan-coated PLGA nanoparticles (~180 nm, +22 mV) loaded with curcumin demonstrated a 3.5-fold higher brain-targeting index and prolonged retention in the olfactory bulb compared to uncoated systems.[64]

These design factors collectively influence the pharmacokinetics and biodistribution of nasal nanomedicines and should guide future phytochemical-based delivery strategies.

Enhanced Drug Solubility and Stability

One of the primary challenges in drug formulation is the poor solubility and stability of many therapeutic compounds, including phytochemicals and large biomolecules such as peptides and proteins. Nanotechnology improves the solubility of hydrophobic drugs by encapsulating them within hydrophilic nanocarriers, such as liposomes or polymeric nanoparticles.[69] Additionally, these nanocarriers protect the encapsulated drug from degradation due to enzymatic activity or environmental factors, such as pH changes in the nasal cavity. By improving drug solubility and stability, nanotechnology enhances the overall bioavailability and therapeutic effect of the drug.[70]

Improved Drug Absorption and Permeability

Nanocarriers can significantly enhance drug absorption and permeability across the nasal mucosa. The nasal epithelium presents a barrier that limits the absorption of many drugs, especially large or poorly soluble molecules. Nanoparticles are small enough (ranging from 1 to 100 nm in size) to interact closely with the nasal mucosa, facilitating drug transport across the epithelial barrier.[71] Some nanocarriers can also be engineered with mucoadhesive properties, allowing them to adhere to the nasal mucosa, which prolongs the drug's residence time in the nasal cavity and increases the likelihood of absorption.[72] This is especially beneficial for targeting the brain, as nanocarriers can transport drugs through the olfactory and trigeminal nerve pathways, bypassing the blood–brain barrier.[73]

Targeted Drug Delivery

Nanotechnology allows for the precise targeting of drugs to specific sites in the body, which is particularly important in nasal drug delivery when aiming to treat localized conditions such as sinusitis, allergic rhinitis, or CNS disorders like Alzheimer's disease and Parkinson's disease.[73] By modifying the surface of nanocarriers with ligands or antibodies that bind to specific receptors on target cells, drugs can be delivered directly to the site of action, minimizing systemic side effects and improving therapeutic outcomes.[74] In the context of CNS disorders, nanocarriers enhance drug delivery across the blood–brain barrier via the nasal route, offering a non-invasive alternative to direct brain administration.[75]

Controlled and Sustained Drug Release

One of the major advantages of nanotechnology-based drug delivery systems is the ability to control the release of the drug over a prolonged period.[76] Nanoparticles, liposomes, and other nanocarriers can be designed to release their encapsulated drug payload slowly and continuously, ensuring sustained therapeutic effects. This controlled release mechanism helps maintain steady drug levels in the systemic circulation or at the target site, reducing the need for frequent dosing and improving patient compliance.[77] For example, in the treatment of chronic CNS disorders, sustained drug release from nanoparticles administered nasally can ensure consistent therapeutic concentrations in the brain over extended periods.[78]

Reduction of Systemic Side Effects

Because nanocarriers can deliver drugs more efficiently to the target site, they often require lower doses of the therapeutic agent to achieve the desired therapeutic effect. This targeted delivery and lower dosage reduce the risk of systemic side effects, which are a common issue with conventional drug formulations, especially in systemic therapies.[79] For instance, in nasal drug delivery for treating allergic rhinitis or sinusitis, nanocarriers can concentrate the drug at the site of inflammation in the nasal cavity, minimizing systemic exposure and reducing the risk of adverse effects elsewhere in the body.[80]

Versatility in Drug Formulation

Nanotechnology allows for the formulation of a wide range of drugs, from small molecules to large biomolecules like peptides, proteins, and even nucleic acids.[81] This versatility makes nanotechnology particularly valuable for nasal drug delivery, where the challenges of delivering diverse drug types are magnified due to the limited permeability and rapid clearance of the nasal mucosa. Nanocarriers can be engineered to carry hydrophobic or hydrophilic drugs, encapsulate delicate biomolecules to protect them from degradation, or co-deliver multiple drugs simultaneously. This flexibility is critical in developing novel therapies for complex diseases, such as neurodegenerative disorders or cancers, where multi-drug strategies may be required.[82]

Bypassing the Blood–Brain Barrier

One of the most significant advantages of nanotechnology in nasal drug delivery is the ability to bypass the blood–brain barrier (BBB), a major obstacle in the treatment of CNS disorders.[83] The nasal route offers direct access to the brain via the olfactory and trigeminal nerve pathways, but efficient delivery to the brain remains challenging.[84] Nanocarriers can enhance the transport of drugs across the nasal epithelium and into the brain by improving drug absorption and protecting the therapeutic agent from degradation.[85] This offers a non-invasive and effective way to deliver drugs directly to the brain, making it highly advantageous for treating neurological conditions like Alzheimer's, Parkinson's, and brain cancers.[86] These different aspects are presented in Table 2.

Recent Advances in Drug Delivery System to the CNS

Central nervous system (CNS)-targeted delivery has made significant advances in the last few years, which are significantly more than traditional formulations. As an example, intranasal delivery of therapeutic agents has become a very promising method of circumventing the Blood-Brain Barrier (BBB) by using the olfactory and trigeminal routes.[87] Thermosensitive in situ gel, cells and stem-cell-derived nanocarriers, and mitochondria-targeted neuroprotective cargo delivered intranasally are some of the current innovations in traumatic brain injury and neurodegeneration models.[88,89] In the meantime, nanoparticles based on lipids (LNPs, nanostructured lipid carriers (NLCs), and solid-lipid nanoparticles (SLNs) developed with the express purpose of nose-to-brain delivery have been gaining ground; they use mucoadhesive coatings, ligand-targeting, and stimuli-responsive release (Table 4).[90] More intricate computational modelling (as with physiologically-based pharmacokinetic modelling) is also underway to achieve improved prediction of brain uptake and scaling between animals and humans.[55] Together, these solutions will enhance the therapeutic payload delivery (small molecules, peptides, nucleic acids, and even cells) to the CNS with better precision, a lower systemic exposure, and increased patient compliance.

Limitations of Non-Nanoformulated Drug Delivery and Benefits of Nanoformulations in Pulmonary Targeting

Many drugs exhibit poor water solubility. The low dissolution rates of these drugs without nanoformulation keep them from being absorbed well at the site administered. Because solubility is crucial, lung mucosal surfaces are at a disadvantage if the drug is not a nanoformulation. Tiny particles are required to pass through the nose and into the lungs to have significant influence on alveoli.[91,92] Unlike mesofluids, nanoformulations can better enter the lung tissue because their ultra-small particles range from 100 to 500 nanometers. Furthermore, because non-encapsulated drugs are easily cleared from the lungs by the mucus and local macrophages, they do not stay in the lungs for long.[93] Because it is removed fast, the drug may not work as well and only last for a shorter period. There are also concerns about systemic toxicity. Since such drugs may spread all over the body, there is a bigger chance that they could negatively affect tissues

Table 4 Emerging Strategies for Enhancing Intranasal Nanocarrier Delivery to the Central Nervous System (CNS)

Strategy	Description	Key Benefit
Intranasal gels + nanoparticles	Thermoresponsive gel carriers that transition on contact with nasal mucosa, combined with nanocarriers for CNS agents.	Extended nasal residence, higher CNS delivery efficiency.[87]
Lipid-based nanosystems for nose-to-brain	Use of liposomes, SLNs, NLCs optimized for olfactory/trigeminal uptake.	Better solubility, targeting, and brain bioavailability.[88,89]
Mitochondria-targeted intranasal delivery	Targeting mitochondrial dysfunction in CNS disorders via intranasal route.	Opens new mechanistic territory for CNS therapeutics.[90]
Predictive modelling and translation	Use of PBPK and device/administration modelling for intranasal pathways.	Improved translation from preclinical to clinical settings.[55]

Notes: Table 4 summarizes emerging strategies enhancing intranasal delivery of therapeutics to the CNS, including hybrid gels, lipid-based nanosystems, and mitochondria-targeted approaches. These innovations improve drug solubility, residence time, and brain targeting, while predictive modeling supports better clinical translation of nasal-to-brain delivery systems.

other than the target. Nanoformulations address this problem by delivering the medicine selectively, reducing how much the body absorbs.

A further drawback is that there is no method to control the release of the drugs. With conventional delivery, there is usually a burst release, meaning the drug's levels can rise and fall sharply. Making nanoformulations stimuli-controlled or for ongoing release means better control of drug amounts for a longer period.[15] It is more efficient to send drugs into cells using nanoformulations. It is common for diseases to affect targets inside the cell, and through endocytosis, nanocarriers open up this type of drug delivery to drugs that cannot pass through on their own. In addition, degradation of ordinary drugs can be triggered by changes in the activity of certain enzymes, variations in pH, or presence of oxygen.[94] By encapsulating the drug in nanocarriers, the drug is protected against factors that can weaken it. Also, nanoformulations are made to carry ligands that stick to and target specific receptors inside the unhealthy tissue. Conventional formulations do not have active targeting, so they do not work as effectively at reaching diseased areas, since they use only passive diffusion. Nanoformulations have many benefits when delivering drugs to the lungs. Thanks to their nanoscale, nanoparticles are able to travel further in the body, remain stable, have a steady release, and aim for the right tissues or cells, all of which help make treatment easier and safer. Relevant nanocarriers and their key applications are shown in Table 5.

Table 5 Relevant Nanocarriers, Key Applications, and Enhancement in Nasal Drug Delivery

Aspect	Explanation	Relevant Nanocarriers	Key Applications
Enhanced Solubility and Stability	Nanocarriers encapsulate hydrophobic drugs, improving solubility and protecting against degradation.	Liposomes, Polymeric Nanoparticles	Phytochemical and protein stabilization[62,63]
Improved Absorption and Permeability	Small particle size and mucoadhesive properties enhance mucosal interaction and permeability.	Nanoemulsions, Chitosan Nanoparticles	CNS drugs, peptide delivery[64–67,69]
Targeted Drug Delivery	Ligand- or antibody-modified nanocarriers target specific cells or tissues, improving precision.	Ligand-Modified Nanoparticles, Dendrimers	Alzheimer's, Parkinson's, sinusitis[67–69]
Controlled and Sustained Release	Engineered carriers provide prolonged and controlled drug release, reducing dosing frequency.	Solid Lipid Nanoparticles, Nanostructured Lipid Carriers (NLCs)	Chronic CNS disorder management[70–72]
Reduced Systemic Side Effects	Localized delivery enables lower doses, minimizing systemic exposure and adverse effects.	Mucoadhesive Nanoparticles, Targeted Liposomes	Allergic rhinitis, sinusitis[73,74]
Formulation Versatility	Supports delivery of a wide range of drug types, including peptides, proteins, and nucleic acids.	Liposomes, Dendrimers, Nanocapsules	Complex diseases requiring multi-drug regimens[95,96]
Bypassing Blood–Brain Barrier	Facilitates direct nose-to-brain delivery via olfactory/trigeminal pathways, overcoming the BBB.	Polymeric Nanoparticles, NLCs, Nanoemulsions	Neurological disorders, brain cancer[75,76,97,98]

Notes: Table 5: Relevant nanocarriers, their key applications, and advantages in nasal drug delivery. Nanocarrier systems improve solubility, absorption, targeting, and controlled release, while facilitating nose-to-brain transport and reducing systemic side effects in neurological and respiratory therapies.

Therapeutic Applications of Phytochemicals and Nanotechnology in Nasal Drug Delivery

Phytochemicals, bioactive compounds derived from plants, are known for their therapeutic properties, including antioxidant, anti-inflammatory, neuroprotective, and antimicrobial activities.[99] However, their clinical application has been limited due to poor solubility, low bioavailability, and rapid metabolism. Nanotechnology has emerged as a transformative solution in nasal drug delivery by enhancing the solubility, stability, and permeability of phytochemicals.[100] This combination has opened new avenues for the treatment of various diseases, particularly those affecting the central nervous system (CNS), respiratory system, and cancer.[100] Therapeutic applications of phytochemicals in different disease conditions and the relevant nano-carrier systems are shown on Table 6.

Neurodegenerative Diseases

Neurodegenerative disorders such as Alzheimer's and Parkinson's disease are major challenges in modern medicine, largely due to the difficulty in delivering drugs across the blood–brain barrier (BBB). The nasal route offers a unique pathway for direct access to the brain via the olfactory and trigeminal nerve pathways, bypassing the BBB.[101] Phytochemicals like curcumin, resveratrol, and quercetin have shown neuroprotective properties, but their effectiveness is hindered by low bioavailability. Nanotechnology-based nasal delivery systems, such as nanoparticles and liposomes, have been developed to encapsulate these phytochemicals, enhancing their absorption and targeting the brain more effectively.[99] For instance, curcumin-loaded nanoparticles administered through the nasal route have shown potential in slowing the progression of Alzheimer's disease by reducing neuroinflammation and oxidative stress.[113] Further supporting this, Lan et al demonstrated that curcumin-primed olfactory mucosa-derived stem cells mitigate neuronal PANoptosis in cerebral ischemia by modulating microglial polarization, highlighting a novel cell-based therapeutic strategy for brain injuries via nasal delivery pathways.[114] Similarly, resveratrol nanoparticles have demonstrated neuroprotective effects in Parkinson's disease models.[102]

Respiratory Diseases

Phytochemicals have also been investigated for their potential in treating respiratory diseases such as asthma, allergic rhinitis, and chronic obstructive pulmonary disease (COPD).[103] Quercetin, a flavonoid with anti-inflammatory and anti-allergic properties, has been explored for nasal delivery to treat allergic rhinitis. However, its poor solubility limits its therapeutic effectiveness. Nanoemulsions and solid lipid nanoparticles

Table 6 Therapeutic Applications of Phytochemicals via Nanotechnology in Nasal Delivery

Therapeutic Area	Target Conditions	Key Phytochemicals	Nanocarrier Systems	Mechanism of Action/Benefit
Neurodegenerative Diseases	Alzheimer's, Parkinson's	Curcumin, Resveratrol, Quercetin	Nanoparticles, Liposomes	Bypasses BBB, reduces neuroinflammation and oxidative stress[99,101,102]
Respiratory Diseases	Asthma, COPD, Allergic Rhinitis	Quercetin, Berberine	Nanoemulsions, Solid Lipid Nanoparticles (SLNs)	Improves solubility and mucosal retention for sustained anti-inflammatory effects[103–105]
CNS Disorders (Mood/Cognition)	Depression, Anxiety, Epilepsy, Memory Loss	Curcumin, Resveratrol, Bacopa monnieri	Polymeric Nanoparticles, Nanoemulsions	Enhances brain targeting, improves mood, cognition[72,73]
Cancer	Glioblastoma, Lung Cancer	Curcumin, Thymoquinone, Resveratrol	Nanoparticles, Lipid-based Nanocarriers	Targets brain/lung tumors non-invasively, reduces systemic toxicity[106,107]
Sinusitis and Allergic Rhinitis	Nasal Inflammation, Sinus Infections	Curcumin, Berberine	Nasal Gels, Chitosan Nanoparticles	Prolonged mucosal retention, enhanced antimicrobial and anti-inflammatory action[108–110]
Viral and Bacterial Infections	COVID-19, Respiratory Tract Infections	Quercetin, Berberine	Mucoadhesive Nanoparticles, Nanoemulsions	Localized drug delivery for upper airway infections, reduced systemic exposure[7,111,112]

Notes: Table 6 presents the therapeutic applications of phytochemicals in nasal delivery in terms of nanocarrier, target condition, and mechanism of action and benefits.

have been developed to deliver quercetin through the nasal route, improving its bioavailability and providing longer-lasting relief from allergic symptoms.[102] Similarly, berberine, an alkaloid known for its anti-inflammatory and antimicrobial properties, has been used in nanocarrier systems to treat sinusitis and respiratory infections when delivered nasally.[104] Notably, Tang et al optimized spermidine-modified PLGA nanoparticles for pulmonary fibrosis, underscoring the utility of surface-engineered nanocarriers in enhancing drug delivery to respiratory tissues.[105]

CNS Disorders

Beyond neurodegenerative diseases, nasal delivery of phytochemicals using nanotechnology has been explored for treating a range of CNS disorders, including depression, anxiety, and epilepsy. For instance, resveratrol and curcumin nanoparticles have been studied for their anxiolytic and antidepressant effects, showing enhanced brain targeting and therapeutic outcomes when administered nasally.[73] Bacopa monnieri extracts (bacosides), known for their cognitive-enhancing properties, have also been delivered via nanocarriers to improve memory and cognition in Alzheimer's disease models.[72]

Cancer

The potential of phytochemicals in cancer therapy is well-documented, with compounds like curcumin, resveratrol, and thymoquinone showing anticancer properties. Nasal delivery offers a non-invasive route for targeting tumors in the brain and respiratory tract, bypassing the limitations of systemic chemotherapy. Nanoparticle-based nasal formulations of curcumin have shown promising results in preclinical studies for treating glioblastoma, a highly aggressive brain tumor.[106] Similarly, thymoquinone-loaded nanoparticles have demonstrated anticancer activity against lung cancer when delivered nasally, providing a targeted and less invasive treatment option.[107]

Sinusitis and Allergic Rhinitis

Sinusitis and allergic rhinitis are common inflammatory conditions affecting the nasal mucosa. Phytochemicals with anti-inflammatory properties, such as curcumin and berberine, have been explored for their therapeutic effects in treating these conditions.[108] Nanotechnology has enabled the formulation of these phytochemicals into nasal sprays or gels, improving their retention time in the nasal cavity and enhancing their therapeutic efficacy.[109] Berberine nanoparticles, for example, have shown significant potential in treating sinus infections due to their antimicrobial and anti-inflammatory effects when administered nasally.[110]

Viral and Bacterial Infections

Nasal drug delivery of phytochemicals combined with nanotechnology is also being explored for the treatment of viral and bacterial infections. Phytochemicals such as quercetin and berberine have demonstrated antimicrobial activity, and their nasal delivery via nanocarriers offers a localized approach to treating infections in the nasal cavity and respiratory tract.[111] This has gained attention, particularly in the context of respiratory infections like COVID-19, where nanotechnology-based nasal delivery systems are being investigated as a potential therapeutic or preventive strategy.[112]

The combination of phytochemicals and nanotechnology in nasal drug delivery has opened up new possibilities for treating a wide range of diseases, from neurodegenerative and CNS disorders to respiratory diseases, cancer, and infections. By enhancing the bioavailability and therapeutic efficacy of phytochemicals, nanotechnology-based nasal formulations hold great promise for improving patient outcomes in a variety of clinical contexts.[7]

Innovations in Phytochemical-Nanotechnology Formulations

Recent advances in nanotechnology have paved the way for innovative formulations that enhance the delivery and therapeutic efficacy of phytochemicals, particularly when administered through the nasal route. Phytochemicals, despite their well-known health benefits, often suffer from limitations such as poor solubility, low bioavailability, and rapid metabolism. Nanotechnology addresses these issues by creating nanoscale delivery systems that protect, stabilize, and

Table 7 Summary of Innovations in Phytochemical-Nanotechnology Nasal Delivery Systems

Innovation Type	Phytochemicals Used	Key Features	Delivery System
Nanoemulsions and Mucoadhesive Systems	Curcumin, Quercetin	Encapsulation efficiency >99%, +25 mV zeta potential, sustained release >6 hrs	Cationic nanoemulsion with chitosan[10,25,116]
Lipid Nanocarriers and Solid Systems	Curcumin, Quercetin	NLCs with ~130 nm size, −18 mV charge, 4× brain bioavailability vs free drug	Solid lipid nanoparticles/NLCs[117–119]
Polymeric and Hybrid Nanocarriers	Quercetin, Resveratrol	Encapsulation efficiency ~85%, CNS targeting index 3.2, thiolated chitosan enhanced uptake	Polymeric nanocapsules/ transferosomes[7,111,112,115,116,120–124]
Therapeutic Potency and Pharmacokinetics	Curcumin, Resveratrol	3.5× increase in AUCbrain/AUCplasma, anti-inflammatory and antioxidant activities	Nanoemulsion gel/NLCs[125–127]

Notes: Table 7 summarizes recent nanotechnology-based innovations for nasal delivery of phytochemicals such as curcumin, quercetin, and resveratrol. It highlights the delivery systems, key physicochemical features, and therapeutic advantages, supported by relevant references.

improve the permeability of these compounds.[115] Several cutting-edge innovations have emerged, revolutionizing the delivery of phytochemicals via nasal formulations. Some of these innovations are shown on Table 7.

Nanoparticles

Nanoparticles, including polymeric nanoparticles, lipid-based nanoparticles, and metallic nanoparticles, are widely used to encapsulate phytochemicals like curcumin, resveratrol, and quercetin. These nanoparticles enhance the solubility of hydrophobic phytochemicals and facilitate their absorption across the nasal mucosa.[120] For example, curcumin-loaded nanoparticles have been designed for nasal delivery to treat neurodegenerative disorders like Alzheimer's disease, providing controlled and targeted drug release directly to the brain.[121] Innovations in surface modifications of nanoparticles, such as adding ligands or antibodies, allow for targeted delivery, enhancing their specificity for disease sites such as brain cells or inflamed tissues.[122]

Liposomes

Liposomes are spherical vesicles that can encapsulate both hydrophilic and hydrophobic drugs, making them versatile carriers for a range of phytochemicals. In nasal drug delivery, liposomal formulations of phytochemicals like resveratrol and thymoquinone have been developed to enhance their stability and bioavailability.[116] Liposomes have the added advantage of being biocompatible, and their lipid bilayer structure mimics cell membranes, which improves drug absorption through the nasal mucosa. Recent innovations include the development of long-circulating and pegylated liposomes, which extend the residence time of phytochemicals in the nasal cavity, promoting sustained drug release.[123]

Nanoemulsions

Nanoemulsions are another significant innovation in nasal delivery systems. These are fine oil-in-water or water-in-oil emulsions with droplet sizes in the nanometer range. Nanoemulsions improve the solubility and stability of poorly soluble phytochemicals such as curcumin and quercetin.[128] They also enhance mucosal permeability and promote faster and more efficient absorption through the nasal mucosa. Nanoemulsions can be formulated with mucoadhesive agents, allowing them to remain in the nasal cavity for longer periods, improving the overall therapeutic effect of the phytochemical.[129]

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) represent newer innovations that combine the advantages of lipid-based carriers and nanoparticles. SLNs and NLCs have been successfully used to deliver phytochemicals like quercetin and berberine through the nasal route.[129] These carriers provide excellent stability, controlled release, and enhanced bioavailability of phytochemicals. Moreover, their biocompatibility makes them suitable for long-term use in chronic conditions like neurodegenerative diseases and respiratory disorders.[124]

Nanoemulsions and Mucoadhesive Systems

Nanoemulsions remain one of the most studied systems for intranasal delivery due to their ability to enhance solubility and absorption of phytochemicals. Several formulations have demonstrated promising encapsulation efficiencies exceeding 95% for curcumin and quercetin, with average particle sizes ranging from 110 to 150 nm.[116,122] Surface charge plays a pivotal role, with positively charged systems (+20 to +30 mV) showing prolonged nasal retention via mucoadhesion.[10,116]

In a recent primary study, curcumin and quercetin co-loaded into a cationic nanoemulsion exhibited >99% encapsulation efficiency, drug loading of 6–8%, and significantly enhanced in vitro antiviral activity. The optimized formulation showed uniform size (110 nm), polydispersity index < 0.3, and positive zeta potential (+25 mV), all favorable for mucosal uptake.[25,122] Furthermore, the addition of chitosan improved gelling behavior and muco-adhesion, sustaining drug release for over 6 h in simulated nasal fluid.

Muco-adhesive nanoemulsion systems co-loaded with curcumin and quercetin have been reported to exhibit high encapsulation efficiency, nanoscale particle sizes (~120 nm), and improved brain bioavailability in vivo, while maintaining nasal mucosal safety in preclinical models.[116,122]

Lipid Nanocarriers and Solid Systems

Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) have proven effective in sustaining release and protecting labile phytochemicals during transit. A 2022 study demonstrated that a quercetin-curcumin-loaded NLC system achieved encapsulation efficiencies of 91–93%, with brain bioavailability of curcumin improved 4-fold compared to the free drug after intranasal administration.[117,118] The NLCs measured approximately 130 nm in diameter and displayed a slightly negative surface charge (~−18 mV), which enhanced epithelial compatibility and diffusion. In terms of dosing, these systems typically deliver 50–150 µg of phytochemicals per actuation, a range that has demonstrated pharmacokinetic consistency in rodent models.[119] Optimization parameters such as lipid ratio, surfactant blend, and inclusion of bioadhesive agents (eg, carbopol or poloxamers) are central to achieving sustained mucosal residence and reduced mucociliary clearance.

Polymeric and Hybrid Nanocarriers

Polymeric nanoparticles, especially those incorporating chitosan, PLGA, or Eudragit®, offer controlled release and robust stability under nasal pH conditions. Advancing this field involves the integration of nanomedicine with traditional phytochemical strategies, offering scalable approaches for natural product delivery.[124] A recent investigation on quercetin-loaded polymeric nanocapsules reported a particle size of 140 nm, encapsulation efficiency of 85%, and brain-targeting index of 3.2, showing superior localization in CNS tissue after intranasal delivery.[123] In this case, thiolated chitosan coating not only enhanced muco-adhesion but also opened tight junctions transiently, increasing paracellular transport.

Moreover, resveratrol transferosomes prepared using lecithin and edge activators demonstrated enhanced permeability, with >80% release over 12 h, highlighting their value in sustained nose-to-brain targeting.[111]

Therapeutic Potency and Pharmacokinetics

Formulations delivering curcumin and quercetin have shown significant CNS impact in vivo. A rat study employing a nanoemulsion gel system showed a 3.5-fold increase in AUCbrain/AUCplasma, with histological sections confirming no mucosal damage.[26] Another study on resveratrol NLCs documented brain-targeting efficiency of 2.7 and relative nasal bioavailability of 41% compared to the oral route, suggesting strong translational promise.[125]

Importantly, such formulations not only enhance absorption but also maintain or improve pharmacodynamic activity. Studies confirmed anti-inflammatory, neuroprotective, and antioxidant effects, quantified by reductions in TNF-α and IL-6 levels, and increases in catalase and superoxide dismutase (SOD) activity following treatment.[126,127]

Challenges in Phytochemical and Nanotechnology-Based Nasal Drug Delivery

While the integration of phytochemicals and nanotechnology in nasal drug delivery systems offers significant therapeutic advantages, several challenges must be addressed to optimize their efficacy and ensure clinical applicability.

Bioavailability and Stability

A major limitation in nasal phytochemical delivery lies in maintaining adequate bioavailability and chemical stability. Many phytochemicals are susceptible to oxidative degradation and enzymatic breakdown during nasal transit. Moreover, their poor aqueous solubility leads to subtherapeutic absorption. Nanotechnology-based encapsulation addresses these issues to some extent; however, the complexity of formulating stable, reproducible nanocarriers capable of ensuring consistent release and absorption remains a significant formulation challenge.[128,129]

Nasal Mucosa Irritation and Immunogenicity

Some nanocarriers and phytochemical payloads may induce localized irritation or immunogenic reactions. For instance, positively charged systems may disrupt epithelial tight junctions if not carefully engineered. Repeated administration raises concerns about potential inflammation, epithelial thinning, or allergic sensitization.[130] Though muco-adhesive polymers like chitosan and poloxamers are often well tolerated, long-term safety profiles must be established. Additionally, immunomodulatory effects of certain phytochemicals, while therapeutic, may pose risks if not appropriately balanced, especially under chronic exposure.

Controlled Release and Dosing Complexity

Balancing rapid onset with sustained release is particularly difficult in nasal delivery. Immediate action is often required for CNS targeting, yet prolonged therapeutic levels are critical for chronic conditions. Designing dual-release or multi-phase delivery systems is a formulation challenge, especially when dealing with multiple phytochemicals with varied solubility and permeability characteristics.[118] Furthermore, intranasal dosing must consider variable nasal physiology, such as mucus turnover and enzymatic activity, which can affect both drug release and absorption.

Regulatory Hurdles

Agencies such as the FDA and EMA emphasize the need for detailed Chemistry, Manufacturing, and Controls (CMC) documentation, including nanoparticle size, polydispersity, excipient safety, and batch reproducibility. Under the ICH Q8–Q10 guidelines, developers must demonstrate robust quality systems, risk assessments, and product understanding throughout formulation and scale-up.[119] Further challenges arise due to the dual classification of many phytochemical–nanocarrier systems as both drug and biologic, complicating regulatory pathways. Although a few nanoformulations have progressed to clinical trials, the lack of harmonized regulatory standards for intranasal nano-based therapeutics remains a key translational bottleneck.[125,126]

Manufacturing and Scale-Up Constraints

The production of nanocarriers at an industrial scale remains a barrier to commercialization. Techniques such as high-pressure homogenization, solvent evaporation, and spray-drying require tight control of process parameters to ensure batch-to-batch consistency. Incorporating phytochemicals with variable purity profiles adds another layer of complexity. Moreover, stability concerns-especially regarding aggregation, oxidation, or loss of drug payload—limit the shelf life and scalability of many formulations.[127,131] Despite the exciting potential of phytochemical and nanotechnology-based nasal drug delivery systems, addressing these challenges is crucial for their successful translation into clinical practice. Continued research and development efforts are essential to optimize formulations, ensure safety and efficacy, and navigate regulatory pathways.[132,133] Table 8 presents different innovations and challenges associated with phytochemical-nanotechnology nasal drug delivery.

Table 8 Challenges in Phytochemical-Nanotechnology Nasal Drug Delivery

Challenge Area	Key Issues	Implications
Bioavailability and Stability	Low solubility, enzymatic degradation, oxidative instability; difficult nanocarrier formulation	Subtherapeutic absorption and poor pharmacokinetics; limited clinical utility[123,129]
Nasal Mucosa Irritation and Immunogenicity	Local irritation, epithelial disruption, immunogenicity, long-term safety concerns	Potential adverse effects and patient non-compliance in chronic use[130]
Controlled Release and Dosing Complexity	Balancing rapid and sustained release; varied drug solubility and nasal physiology impact dosing	Reduced therapeutic effectiveness and patient-specific variability in outcomes[118]
Regulatory Hurdles	Complex regulatory classification; stringent CMC requirements; lack of harmonized standards	Delayed approval, increased development cost and uncertain clinical translation[119]
Manufacturing and Scale-Up Constraints	Process complexity, variability in phytochemical purity, stability and batch reproducibility issues	Commercialization barriers due to inconsistent product quality and short shelf life[127,131,132]

Notes: Table 8 outlines the major challenges in nasal delivery of phytochemicals, including issues of bioavailability, mucosal irritation, dosing complexity, regulatory hurdles, and manufacturing constraints. These barriers impact therapeutic effectiveness, patient compliance, and the successful clinical translation of nanocarrier-based systems.

Conclusions and Future Directions

Conclusion

Nano-delivery of phytochemicals in nasal cavity offers a promising non-invasive method of central nervous system (CNS) disease treatment by facilitating a fast action response, efficient targeting into the brain, and elevated bioavailability. Nanoformulations, including nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes and polymeric nanoparticles, have been shown to demonstrate high potentials in addressing the limitations associated with the conventional therapies due to high encapsulation efficiency, protracted drug delivery and biocompatibility. Nevertheless, issues of formulation stability, mucociliary clearance, dosage accuracy, mass-produced manufacturing and standardization of regulation remain. The future studies are aimed at exploring to maximize the nanocarrier design, clinical trials, and translational models to achieve safety and therapeutic efficacy.

Future Directions

At this point, an alarming lack of information regarding clinical research on the use of nasal delivery during CNS disorders assessment of phytochemical-based nanocarriers is disturbing. Further studies are necessary to have a meaningful clinical translation; however, the standardized evaluation of long-term safety, immunogenicity, pharmacokinetics, and chronic exposure profiles should be adopted in future studies in both preclinical and human models. The precise and responsive delivery systems of patient specific, customizable delivery systems (responsive mucoadhesive platforms, multifunctional nanocarriers, and stimuli-sensitive formulations) will enhance the efficacy and precision of therapy. In addition, there is urgent need to harmonize regulations and to build clear classification of phytochemical-loaded nasal nanomedicines to direct product approval and commercialization. Increasing inter-disciplinary partnership between academia, pharmaceutical industries, clinicians and regulatory agencies will play a critical role in narrowing the gap between preclinical promise and clinical validation, scalability and accessibility by patients. Finally, a concerted effort on the direction of translational studies, standard procedures, and ethical clinical trials will hasten the implementation of such innovative therapies in neuropharmacology.

Data Sharing Statement

Data sharing is not applicable as no datasets were generated in this article.

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Author Contributions

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Disclosure

The authors declare no competing interests in this work.

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