RESEARCH PAPER

Plant-Mediated Nanoparticles for Nose-to-Brain Delivery: A Novel Approach for CNS Drug Targeting

Sayali S. Patil[1], Pramod B. Patil[2], Sachin S. Mali[2], Pradip S. Pawde[3], Rahul S. Adnaik[4], Sachin A. Nitave[1*]

[1] Dr. J. J. Magdum Trust's Anil Alias Pintu Magdum Memorial Pharmacy College, Dharangutti, Kolhapur, India

[2] Bharati Vidyapeeth College of Pharmacy, Kolhapur – 416013, India. Email: sachinmali143@gmail.com; ORCID: 0000-0002-8104-5854

[3] S. R. Institute of Pharmacy, Udgir, Maharashtra, India – 413517

[4] Anandi Pharmacy College, Kolhapur, Maharashtra, India – 416200

[1*] Corresponding Author: Dr. Sachin A. Nitave (SAN), Principal, Dr. J. J. Magdum Trust's Anil Alias Pintu Magdum Memorial Pharmacy College, Dharangutti, Kolhapur, India. Email: sachinnitave@gmail.com

Received: 06th Feb, 2026 | **Revised:** 12th Mar, 2026 | **Accepted:** 07th May, 2026 | **Available Online:** 15th May, 2026

ABSTRACT

The effective delivery of therapeutic agents to the central nervous system (CNS) remains a major challenge due to the restrictive nature of the blood-brain barrier (BBB). Intranasal (nose-to-brain) delivery has emerged as a promising non-invasive strategy that enables direct drug transport to the brain via olfactory and trigeminal pathways, thereby bypassing the BBB. In parallel, plant-mediated (green synthesized) nanoparticles have gained considerable attention owing to their biocompatibility, eco-friendly synthesis, and intrinsic therapeutic potential. These nanoparticles, synthesized using phytoconstituents such as polyphenols, flavonoids, and alkaloids, exhibit enhanced drug loading, stability, and targeted delivery. This review comprehensively discusses the mechanisms of nose-to-brain transport, the role of plant-mediated nanoparticles in improving CNS drug delivery, and their applications in neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, and brain tumors. Furthermore, current challenges, recent advancements, and future research directions are highlighted to facilitate clinical translation.

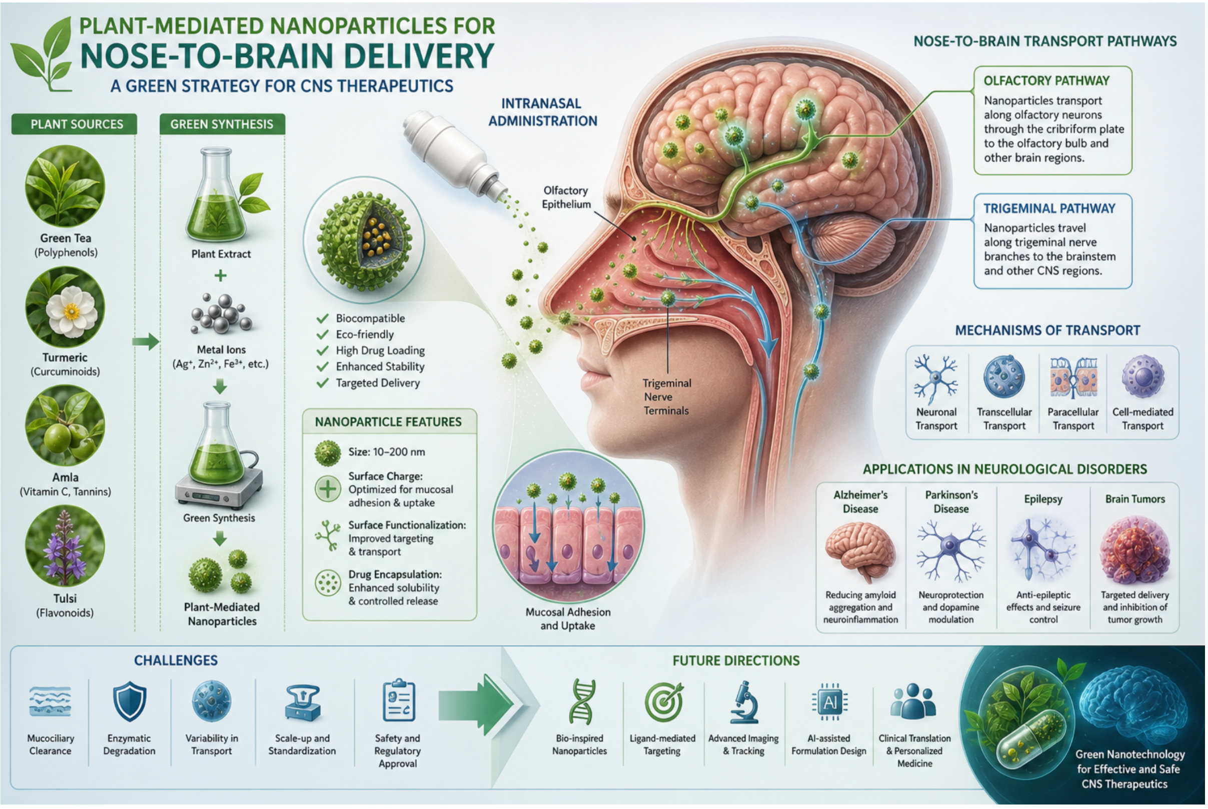
Keywords: Nose-to-brain delivery, green synthesis, nanoparticles, CNS targeting, phytoconstituents, neurotherapeutics

How to cite this article: Patil SS, Patil PB, Mali SS, Pawde PS, Adnaik RS, Nitave SA. Plant-Mediated Nanoparticles for Nose-to-Brain Delivery: A Novel Approach for CNS Drug Targeting. Int J Drug Deliv Technol. 2026;16(41s): 679-683. DOI: 10.25258/ijddt.16.41s.74

Source of support: Nil.

Conflict of interest: None

Graphical Abstract



1. Introduction

Neurological disorders affecting the central nervous system (CNS), including neurodegenerative diseases and intracranial tumors, represent a growing global health concern due to their progressive nature and limited therapeutic outcomes[1]. A primary challenge in treating these conditions lies in the presence of the blood-brain barrier (BBB), a highly specialized and selectively permeable interface that tightly regulates molecular exchange between systemic circulation and neural tissue. Structurally, the BBB comprises endothelial cells interconnected by tight junctions, supported by astrocytes and pericytes, which collectively restrict the penetration of nearly all macromolecules and the majority of small therapeutic agents[2].

As a consequence, conventional drug delivery approaches often fail to achieve therapeutically effective concentrations within the brain. Factors such as enzymatic degradation, poor lipid solubility, efflux transporter activity, and hepatic first-pass metabolism further compromise drug bioavailability and clinical efficacy[3]. These limitations necessitate the development of alternative delivery strategies capable of circumventing the BBB while ensuring targeted and efficient drug transport.

Among emerging approaches, intranasal administration has gained considerable attention as a non-invasive and direct route for delivering therapeutics to the brain. This strategy utilizes unique anatomical connections between the nasal cavity and the CNS, primarily through olfactory and trigeminal neural pathways, thereby bypassing systemic circulation and minimizing metabolic loss[4,5]. The rapid onset of action and reduced systemic exposure make this route particularly advantageous for CNS targeting.

Parallel to these developments, nanotechnology has introduced innovative solutions to longstanding drug delivery challenges. Nanoscale carriers enhance drug solubility, protect bioactive molecules from degradation, and facilitate controlled as well as site-specific delivery[6]. Within this domain, plant-mediated nanoparticles also referred to as green-synthesized nanoparticles have emerged as a promising alternative to conventional nanocarriers.

These systems employ bioactive plant constituents such as polyphenols, flavonoids, terpenoids, and alkaloids as natural reducing and stabilizing agents during nanoparticle synthesis. This approach not only eliminates the need for hazardous chemicals but also imparts additional therapeutic properties, including antioxidant and neuroprotective effects, thereby enhancing overall efficacy[7, 8].

The integration of intranasal delivery with plant-mediated nanotechnology offers a synergistic platform for CNS drug targeting. By combining direct nose-to-brain transport with biocompatible and functionalized nanoparticles, this strategy holds significant potential to improve therapeutic outcomes in neurological disorders.

2. Nose-to-Brain Drug Delivery Pathways

2.1 Olfactory Pathway

The olfactory route represents one of the most direct pathways for delivering drugs from the nasal cavity to the brain. The olfactory epithelium, located in the upper nasal region, contains specialized receptor neurons that establish a direct connection with the olfactory bulb. Therapeutic agents deposited in this region can be transported via intracellular mechanisms such as endocytosis or through extracellular diffusion pathways along neuronal channels[9,10]. This mode of delivery enables rapid drug transport while avoiding systemic metabolism.

2.2 Trigeminal Pathway

In addition to the olfactory system, the trigeminal nerve provides an alternative route for drug transport to the CNS. It innervates the respiratory epithelium and facilitates the movement of molecules toward the brainstem and spinal cord regions. This pathway is particularly important for targeting deeper brain structures and complements olfactory transport mechanisms[9, 11].

2.3 Systemic Absorption Pathway

A fraction of intranasally administered drugs may be absorbed into systemic circulation through the highly vascularized nasal mucosa. These molecules can subsequently cross the BBB to reach the brain; however, this indirect route is generally less efficient compared to neuronal pathways and may be associated with systemic side effects[5].

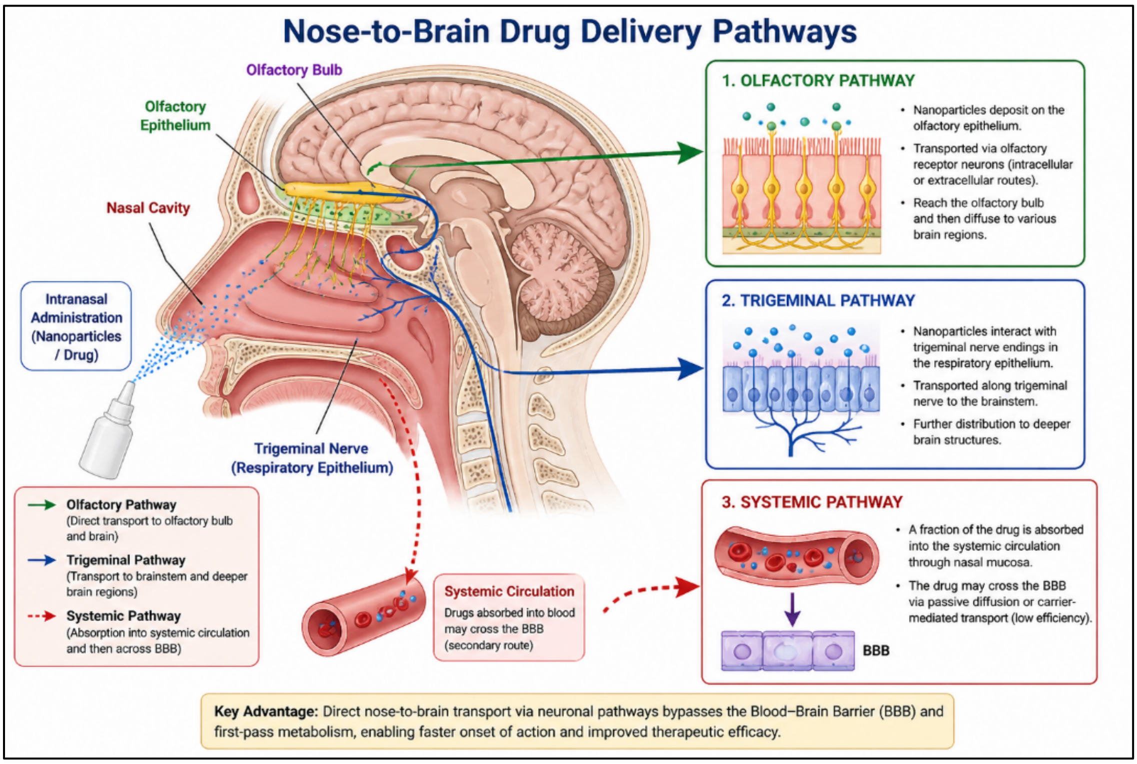


Fig 1: Schematic Representation of Nose-to-Brain Drug Delivery Pathways

Schematic illustration of intranasal drug delivery pathways showing transport from the nasal cavity to the brain via the olfactory and trigeminal nerves. The olfactory pathway enables direct access to the olfactory bulb, while the trigeminal pathway facilitates drug distribution to deeper brain regions. A minor fraction of the drug may also enter systemic circulation before crossing the blood-brain barrier.

3. Plant-Mediated Nanoparticles

3.1 Green Synthesis Mechanism

Green synthesis of nanoparticles is based on the utilization of plant-derived biomolecules to reduce metal ions into nanoscale particles. Phytoconstituents such as phenolics, flavonoids, and terpenoids play a dual role by acting as electron donors for reduction reactions and as stabilizing agents that prevent aggregation[7,12]. This biologically driven process offers a safer and more sustainable alternative to traditional chemical and physical synthesis methods.

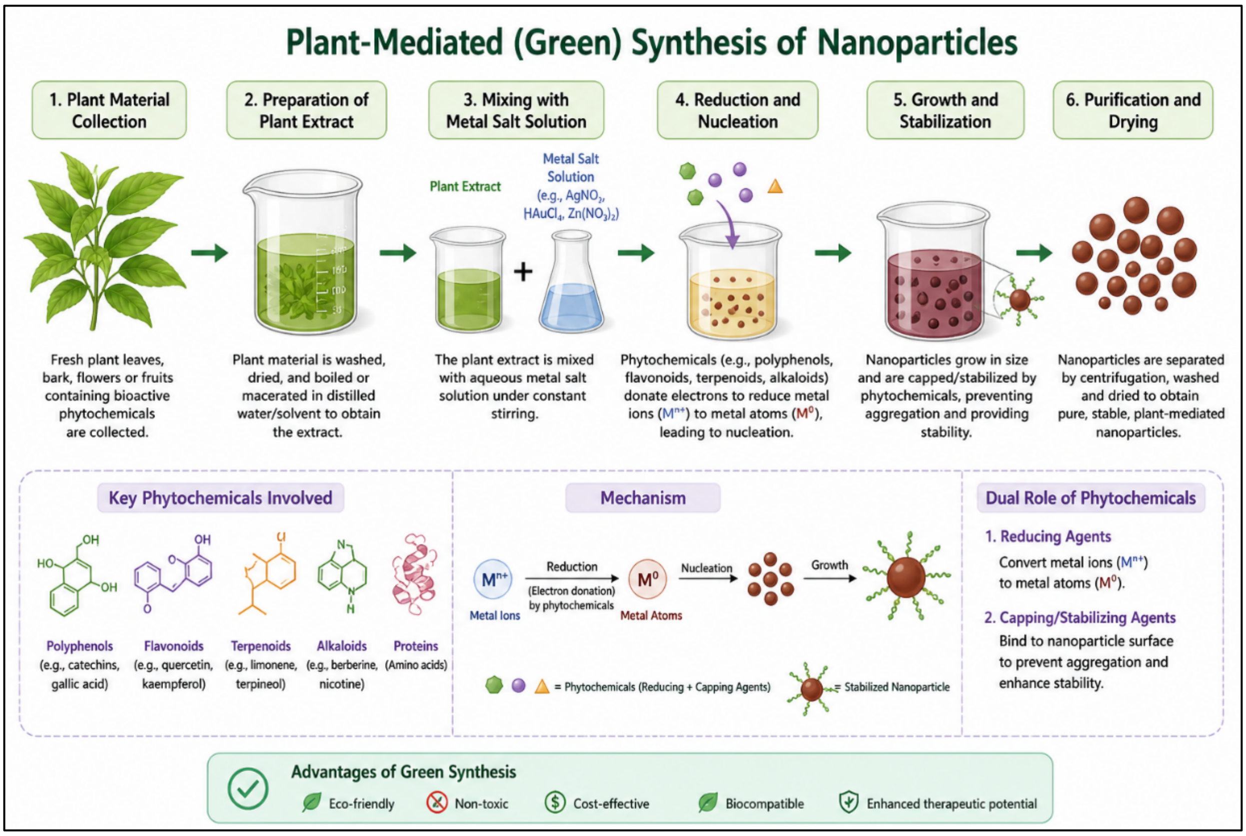


Fig 2: Green Synthesis of Plant-Mediated Nanoparticles

Mechanism of plant-mediated (green) synthesis of nanoparticles. Phytoconstituents such as polyphenols and flavonoids act as reducing agents to convert metal ions into nanoparticles, while simultaneously serving as capping agents to stabilize the formed nanostructures

3.2 Types of Nanoparticles

Various nanoparticle systems have been successfully synthesized using plant extracts, including:

- Silver nanoparticles, widely recognized for their antimicrobial and neuroprotective properties[13]
- Gold nanoparticles, commonly used in targeted drug delivery and diagnostic imaging[14]
- Zinc oxide nanoparticles, exhibiting anti-inflammatory and anticancer activities[16]
- Polymeric nanoparticles, designed for sustained and controlled drug release[17]

4. Mechanisms of Nanoparticle Transport

The enhanced efficiency of plant-mediated nanoparticles in nose-to-brain delivery can be attributed to multiple transport mechanisms:

- Cellular uptake via endocytosis followed by transcellular transport across epithelial barriers[18]
- Modulation of tight junctions enabling paracellular diffusion[19]
- Axonal transport along olfactory neurons facilitating direct brain entry[10]
- Mucoadhesive interactions that prolong residence time within the nasal cavity, improving absorption[20]

5. Applications in CNS Disorders

5.1 Alzheimer's Disease

Nanoparticles loaded with phytoconstituents such as curcumin and resveratrol inhibit amyloid-beta aggregation, reduce oxidative stress, and improve cognitive function[21,22].

5.2 Parkinson's Disease

Intranasal delivery of dopamine-loaded nanoparticles enhances brain targeting and improves motor function while reducing systemic side effects[23].

5.3 Epilepsy

Nanoparticle-based intranasal formulations improve the bioavailability of anticonvulsants and enable rapid seizure control[24].

5.4 Brain Tumors

Plant-mediated nanoparticles enable targeted delivery of chemotherapeutic agents, enhancing tumor accumulation and minimizing systemic toxicity[25].

6. Recent Advances

Recent years have witnessed substantial progress in the application of green nanotechnology for central nervous system (CNS) drug delivery, particularly through the integration of plant-derived biomaterials with nanoscale systems. These advancements highlight the versatility of plant-mediated nanoparticles in enhancing therapeutic efficacy and targeting precision.

For instance, silver nanoparticles synthesized using *Azadirachta indica* (neem) extracts have demonstrated notable neuroprotective potential, primarily attributed to their antioxidant and anti-inflammatory properties[13]. Similarly, polymeric nanoparticles encapsulating curcumin have shown improved permeability across the blood-brain barrier (BBB), thereby enhancing its bioavailability and therapeutic performance in neurodegenerative conditions[21].

Gold nanoparticles fabricated using green tea polyphenols have exhibited promising anti-Alzheimer's activity, including inhibition of amyloid-beta aggregation and reduction of oxidative stress[14]. In addition, zinc oxide nanoparticles derived from *Moringa oleifera* extracts have been reported to exert significant anti-inflammatory effects, further supporting their application in neuroinflammatory disorders[15].

Collectively, these findings underscore the potential of plant-mediated nanocarriers as multifunctional systems capable of both drug delivery and intrinsic therapeutic action.

Table 1: Summary of key recent studies highlighting plant-mediated nanoparticle systems and their applications in CNS drug delivery

Plant Source	Nanoparticle Type	Loaded/Active Compound	Therapeutic Application	Key Outcome
Azadirachta indica	Silver nanoparticles (AgNPs)	Phytoconstituents	Neuroprotection	Reduced oxidative stress and inflammation
Camellia sinensis (Green tea)	Gold nanoparticles (AuNPs)	Polyphenols	Alzheimer's disease	Inhibition of amyloid aggregation
Moringa oleifera	ZnO nanoparticles	Bioactive compounds	Neuroinflammation	Anti-inflammatory activity
—	Polymeric nanoparticles	Curcumin	Neurodegenerative disorders	Enhanced BBB permeability and bioavailability

7. Regulatory and Toxicological Considerations

Although plant-mediated nanoparticles present a promising alternative to conventional delivery systems, their successful clinical translation is contingent upon comprehensive safety evaluation and regulatory compliance. The physicochemical characteristics of nanoparticles, including particle size, surface charge, morphology, and dose, can significantly influence their biological interactions and potential toxicity[26].

One of the major challenges lies in the inherent variability of plant extracts used in green synthesis. Differences in phytochemical composition due to geographical, seasonal, and extraction conditions can affect nanoparticle reproducibility, stability, and therapeutic consistency[27-29].

Regulatory authorities such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require detailed characterization of nanomaterials, including pharmacokinetic profiling, biodistribution studies, immunogenicity assessment, and long-term toxicity evaluation prior to approval[28-30]. Therefore, establishing standardized protocols for synthesis and characterization is critical for advancing plant-based nanomedicines toward clinical use.

8. Challenges and Limitations

Despite encouraging preclinical outcomes, several limitations hinder the widespread application of plant-mediated nanoparticles in CNS drug delivery:

- Inconsistency in phytochemical composition of plant extracts, leading to variability in nanoparticle synthesis
- Challenges associated with scale-up production and batch-to-batch reproducibility
- Instability and aggregation of nanoparticles during storage and administration
- Limited availability of clinical data supporting efficacy and safety
- Complex and evolving regulatory frameworks for nano-enabled herbal formulations

Addressing these challenges is essential for ensuring reliability, safety, and translational success.

TABLE 2: Challenges and Future Strategies in Plant-Mediated Nanoparticle-Based CNS Delivery

Challenges	Impact	Proposed Strategies
Variability in plant extract composition	Affects reproducibility and consistency	Standardization of extraction protocols
Scale-up limitations	Difficulty in industrial production	Development of scalable green synthesis methods
Nanoparticle instability	Aggregation and reduced efficacy	Surface modification and stabilizers
Limited clinical data	Hinders regulatory approval	Conduct of well-designed clinical trials
Regulatory complexity	Delays product approval	Harmonization of global guidelines

9. Future Perspectives

Future research in this domain should focus on the development of advanced and clinically translatable nano-delivery systems. Emphasis should be placed on ligand-functionalized nanoparticles that enable receptor-mediated targeting to specific brain regions, thereby improving therapeutic precision.

Additionally, the design of mucoadhesive and stimuli-responsive nanoparticles could enhance nasal residence time and facilitate controlled drug release in response to physiological triggers. The incorporation of bioactive polyphenols such as curcumin and berberine into nano-carriers offers a promising strategy for achieving synergistic therapeutic effects.

Furthermore, large-scale production techniques, standardized characterization methods, and well-designed clinical trials are necessary to validate efficacy and safety. Harmonization of global regulatory guidelines will also play a crucial role in accelerating the clinical adoption of plant-mediated nanomedicine.

10. Conclusion

Plant-mediated nanoparticles represent an innovative and sustainable approach for nose-to-brain drug delivery, combining the advantages of green synthesis with the precision of nanotechnology. Their ability to circumvent the blood-brain barrier, enhance drug bioavailability, and provide targeted delivery makes them highly attractive for the treatment of CNS disorders.

However, challenges related to standardization, scalability, and regulatory approval remain significant barriers to clinical translation. Future advancements should focus on overcoming these limitations through interdisciplinary research, robust validation studies, and regulatory alignment. With continued progress, plant-based nanocarriers hold substantial promise as next-generation platforms for effective CNS therapeutics.

DECLARATIONS

Funding

The authors declare that no specific funding was received for this work from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval

This article does not contain any studies involving human participants or animals performed by any of the authors.

Informed Consent

Not applicable.

Author Contributions

All authors contributed equally to the conception, design, literature review, drafting, and revision of the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgements

The authors acknowledge the support provided by their respective institutions and colleagues in the completion of this work.

Consent for Publication

All authors have reviewed and approved the manuscript and consent to its publication.

Plagiarism Statement

The authors confirm that this manuscript is original, has not been published previously, and is not under consideration for publication elsewhere.

References

1. Illum L. Nasal drug delivery—possibilities, problems and solutions. *J Control Release*. 2019;307:1–16.
2. Djupesland PG. Nasal drug delivery devices: characteristics and performance. *Drug Deliv Transl Res*. 2020;10(2):227–237.
3. Ahmed S, Ikram S. Green synthesis of nanoparticles using plant extracts: an overview. *J Adv Res*. 2016;7(1):17–28.
4. Mittal AK, Chisti Y, Banerjee UC. Synthesis of metallic nanoparticles using plant extracts. *J Nanopart Res*. 2019;21:1–20.
5. Singh P, Kim YJ, Zhang D, Yang DC. Biological synthesis of nanoparticles: a review. *Trends Biotechnol*. 2021;39(2):154–167.
6. Feigin VL, Nichols E, Alam T, et al. Global burden of neurological disorders. *Lancet Neurol*. 2020;19(3):255–265.
7. Pardridge WM. The blood–brain barrier: bottleneck in brain drug development. *NeuroRx*. 2005;2(1):3–14.
8. Patel MM, Patel BM. Crossing the blood–brain barrier: recent advances in drug delivery to the brain. *CNS Drugs*. 2017;31(2):109–133.
9. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev*. 2019;143:47–66.
10. Saraiva C, Praça C, Ferreira R, et al. Nanoparticle-mediated brain drug delivery: overcoming blood–brain barrier to treat neurodegenerative diseases. *J Control Release*. 2016;235:34–47.
11. Iravani S. Green synthesis of metal nanoparticles using plants. *Green Chem*. 2019;21(1):18–39.
12. Hanson LR, Frey WH. Intranasal delivery bypasses the blood–brain barrier. *Nat Rev Drug Discov*. 2008;7(2):145–156.
13. Crowe TP, Greenlee MH, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. *Mol Pharm*. 2018;15(2):589–601.
14. Roy A, Bulut O, Some S, et al. Green synthesis of silver nanoparticles: biomolecule-nanoparticle interactions and applications. *Colloids Surf B Biointerfaces*. 2022;202:111–118.
15. Sharma D, Kanchi S, Bisetty K. Biogenic synthesis of silver nanoparticles and their applications in neuroprotection and biomedical systems. *Mater Sci Eng C*. 2021;119:111–126.
16. Khan I, Saeed K, Khan I. Green synthesized gold nanoparticles and their applications in Alzheimer's disease therapy. *Nanomedicine*. 2022;17(2):101–120.
17. Kaur H, Kaur G. Zinc oxide nanoparticles synthesized using plant extracts: anti-inflammatory and biomedical applications. *Mater Today Chem*. 2023;27:101–110.
18. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles-based drug delivery systems. *Colloids Surf B Biointerfaces*. 2020;75(1):1–18.
19. Koo H, Huh MS, Ryu JH, et al. Nanoparticle targeting strategies for drug delivery. *Chem Soc Rev*. 2021;50(2):1–24.
20. Khan AR, Liu M, Khan MW, et al. Progress in brain targeting drug delivery system by nasal route. *Int J Nanomedicine*. 2020;15:1–23.
21. Md S, Khan RA, Mustafa G, et al. Nose-to-brain delivery of nanoparticles for CNS disorders: mechanisms and applications. *Eur J Pharm Sci*. 2021;159:105–115.
22. Gänger S, Schindowski K. Tailoring formulations for intranasal delivery. *Expert Opin Drug Deliv*. 2018;15(2):1–16.

23. Maiti P, Dunbar GL. Use of curcumin-loaded nanoparticles for Alzheimer's disease. *J Alzheimers Dis*. 2021;80(1):1–15.
24. Rehman SU, Shah SA, Ali T, et al. Role of polyphenols in neuroprotection via nano-delivery systems. *Nutrients*. 2022;14(3):1–20.
25. Shinde RL, Devarajan PV. Nanoparticle-mediated dopamine delivery for Parkinson's disease. *ACS Chem Neurosci*. 2021;12(4):1–12.
26. Patel K, Padhye S, Nagarsenker M. Intranasal drug delivery for epilepsy management. *Epilepsy Res*. 2020;159:106–118.
27. Kumari P, Ghosh B, Biswas S. Nanocarriers for brain tumor targeting. *Nanomedicine*. 2021;16(10):1–15.
28. Fadeel B. Safety assessment of nanomaterials and nanotoxicology. *Nat Nanotechnol*. 2018;13(6):1–12.
29. Rastogi L, Arunachalam J. Variability and reproducibility issues in green nanoparticle synthesis. *Biotechnol Rep*. 2022;34:e007015.
30. European Medicines Agency. Reflection paper on nanotechnology-based medicinal products for human use. London: EMA; 2023.