



Review Article

Ethosome as a colloidal carrier for nasal drug delivery for brain targeting: a review

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ABSTRACT

As a non-invasive method that offers quick absorption, avoids hepatic first-pass metabolism, and promotes patient compliance, nasal medication delivery has garnered increasing interest. However, its efficacy is hampered by issues including mucociliary clearance and the restricted permeability of big or hydrophilic compounds. A possible remedy is offered by ethosomes, which are new phospholipid-based vesicular carriers enhanced with ethanol that improve drug solubility, stability, and penetration through the nasal mucosa. Their special deformable structure protects against enzymatic degradation and enables better trapping of a variety of medicinal substances, including small molecules, peptides, and proteins. Recent investigations have highlighted their potential to increase bioavailability, prolong drug release, and achieve targeted nasal delivery. Ethosomes, flexible lipid-based vesicular carriers enriched with ethanol, represent a novel strategy for enhancing drug absorption through the nasal mucosa. Their high deformability allows them to penetrate efficiently through both transcellular and paracellular pathways, while ethanol acts as a permeation enhancer by fluidizing epithelial membranes and opening tight junctions. Ethosomes also protect labile drugs such as peptides and proteins from enzymatic degradation and support sustained release, making them particularly valuable for brain targeting via the nasal route. This unique combination of flexibility, enhanced permeability, and protective capability positions ethosomes as an innovative and promising platform for improving nasal drug delivery and overcoming the limitations of conventional formulations.

1. INTRODUCTION

1.1 Background

According to the WHO, various brain disorders constitute an important source of morbidity. The main reason behind this remains untreated, mainly due to a major challenge of the cerebrospinal fluid brain barrier, blood-brain barrier, and various barriers, which are major obstacles for CNS therapies. Thus, there is a need to explore various novel drug delivery platforms that are qualified for overcoming these barriers to the effective delivery of drugs (Gawarkar-

Patil et al., 2024). Nasal drug delivery has emerged as a preferred method for administering drugs directly to the central nervous system. And this route is proposed for those drugs that are highly polar and can be delivered directly to the CNS. The nasal cavity is the only site in the human body where the nervous system has direct and continuous contact (Vyas et al., 2005). The drug is transported to the CSF through the olfactory pathway, which is the area where the subarachnoid space extends into the nasal cavity. Bypassing systemic circulation, nasal medication administration provides a direct route to the brain via

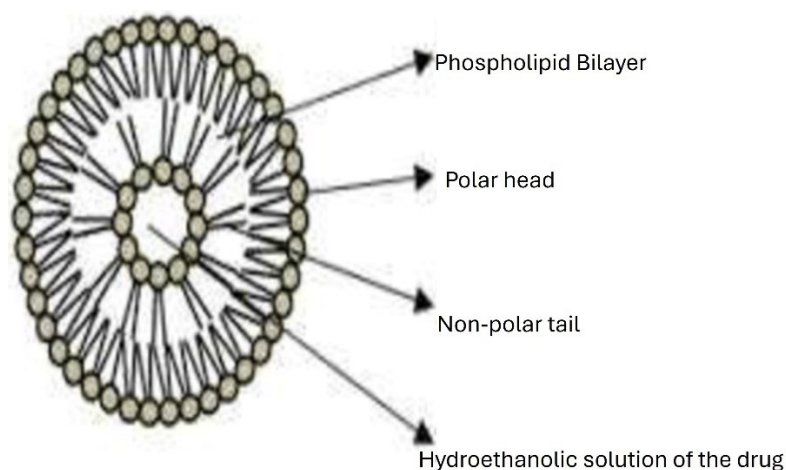


Figure 1: Structure of ethosomes

the olfactory and trigeminal nerves. When delivering large, hydrophilic molecules, such as peptides, proteins, and nanoparticles, that cannot pass across the blood-brain barrier via conventional means, this technique is particularly helpful. Because it guarantees quick drug absorption, it helps with acute illnesses like headaches, seizures, and strokes. By restricting drug exposure to other body areas, it also lessens systemic adverse effects. The avoidance of first-pass metabolism, which increases medication efficacy and bioavailability, is another significant benefit (Tiwari and Amiji, 2006).

1.2 Ethosome

Ethosomes are vesicular carriers composed of phospholipids, ethanol, and water, developed to enhance the delivery of drugs through the skin (transdermal) or through the mucosal layer. Ethosomes have a greater priority due to their ability to enhance the bioavailability of drugs, particularly for those that are poorly permeable across biological barriers. Various innovative carriers can be made into gel patches using ethosomes by adapting multiple novel methods.

1.3 Composition of ethosome

Ethosome's composition typically includes phospholipids (such as phosphatidylcholine), which form the bilayer structure that encapsulates the drug; a relatively high concentration of ethanol (20-45%), which imparts flexibility to the vesicles, disrupts the lipid packing of biological membranes, and acts as a powerful permeation enhancer; and water, which provides the continuous phase necessary for vesicle formation and stability (Figure 1). In some

formulations, additional excipients, such as cholesterol, are included to modulate membrane fluidity and improve stability. Meanwhile, stabilizers or surfactants may be added to optimize entrapment efficiency and shelf life further (Nerella and Vasudha, 2024). This unique combination of phospholipids and ethanol distinguishes ethosomes from conventional liposomes, making them highly deformable and capable of encapsulating both hydrophilic and lipophilic drugs. They are particularly effective for transdermal and transmucosal delivery, including nasal administration.

The phospholipids form the bilayer structure of the ethosome. These phospholipids provide the structural integrity of the vesicle (e.g., phosphatidylcholine). Ethanol serves as a crucial component that enhances skin permeability by disrupting the lipid bilayer of the stratum corneum and fluidizing the ethosomal lipid bilayer. Ethanol reduces the rigidity of the phospholipid bilayer, making the ethosome more flexible. It stabilizes the phospholipid bilayer. The water acts as a hydration medium for the vesicle. There are provisions for optional additives, such as cholesterol (to stabilize the vesicles), surfactant (to improve drug loading or stability), and other bioactive compounds (Raghuvanshi et al., 2022).

1.4 Special characteristics of ethosome

Ethosomes possess several distinctive characteristics that make them advantageous for drug delivery. They exhibit high deformability, offering greater flexibility than other carriers, such as conventional liposomes, in part due to the presence of ethanol, which can disrupt lipid packing. Their size

is typically nanometric, ranging from 50 nm to a few micrometers, allowing for enhanced penetration and bioavailability. Additionally, ethosomes exhibit high drug encapsulation efficiency, making them suitable for delivering both hydrophilic and lipophilic drugs (El-Shenawy et al., 2021).

2. ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The nasal cavity has various roles and comprises two large, irregular cavities. The nasal cavity plays a major role in humidifying and warming the inspired air. As the air passes through the nasal cavity, it helps to remove various minute airborne particles and debris accumulated before reaching the lower airways. The nasal cavity is surrounded by columnar epithelium. It also acts as a drainage for the secretions from adjacent paranasal sinuses and collects odor-bearing particles, transmitting them to the olfactory area, which is the superior portion of the nasal cavity (Gawarkar-Patil et al., 2024). The nose is mainly categorized into external and internal structures. The external nose is a pyramidal structure located at the center of the face and is composed of several components, including the nasal bones, upper and lower cartilages, and the nasal septum.

The nasal bone forms the bony part of the nose and is small and rectangular in shape, situated in the upper middle area of the face. It plays a crucial role in determining the structure and appearance of the nose, contributing to the bony framework of the face, and is surrounded by various bones superiorly, laterally, medially, and posteriorly. Its main functions include providing support, protection, and serving an aesthetic role (Kozlovskaya et al., 2014).

The cartilaginous part of the nose is divided into upper and lower cartilages, which are responsible for providing structure, flexibility, and forming the nasal framework. The upper cartilage includes the lateral nasal cartilage, located on both sides of the nose and connected to the nasal bones, providing structural support and aiding in airflow regulation, and the septal cartilage, a quadrangular flat structure situated in the midline that forms the anterior portion of the nasal septum, dividing the nasal cavity into left and right sides. The lower cartilage comprises the major alar cartilage (greater alar cartilage), which is U-shaped and forms the tip and sides of the nose, providing support to the nasal tip, and the minor alar cartilage, a small cartilage located posterior to the major alar cartilage that offers additional support to the nostrils and lateral nasal walls (Kozlovskaya et al., 2014).

The nasal septum is a vertical structure that divides the nasal cavity into two halves, maintaining nasal symmetry and supporting the overall nasal structure (Jones, 2001). It is composed of two main parts: a cartilaginous part and a bony part (Lane, 2004). The cartilaginous part, primarily formed by the septal cartilage, provides flexibility and shape to the anterior portion of the septum, while the bony part offers firm structural support to the posterior region. The surrounding structures of the nasal septum include the roof, which is formed by the cribriform plate of the ethmoid bone, and the floor, formed by the hard palate. The primary functions of the nasal septum are to regulate airflow between the nasal cavities and support the mucosal lining, which aids in filtering, humidifying, and conditioning inhaled air (Lane, 2004).

3. DRUG ABSORPTION THROUGH THE NOSE

The delivery of a drug and its absorption through the nose is called nasal drug delivery, due to the rapid onset of action and avoidance of first-pass metabolism; this route has gained significant attention. Due to its rich vascularization and large surface area, it is considered an ideal site for both systemic and localized drug delivery (Mygind and Dahl, 1998). Due to the presence of the olfactory region, the nasal route is considered effective in delivering drugs to the CNS by bypassing the blood-brain barrier. The olfactory region is considered highly specialised due to its direct anatomical and neuronal connections to the brain via the olfactory nerve.

Primarily, the drug disposition and intake of drug molecules occur in three zones of the nasal cavity, specifically the olfactory region, the respiratory region, and the vestibule. The olfactory region plays a major role in targeting drug molecules to the CNS and CSF through the epithelium; however, there is a limitation that access to the olfactory zone is difficult because it is located in the upper nasal cavity, below the superior turbinate and cribriform plate. The olfactory mucosa is highly vascularized, thereby increasing the surface area for absorption and facilitating the uptake of drug molecules. The presence of various enzymes in the olfactory region, mainly cytochrome P450 and UDP-glucuronyltransferase, helps metabolize the drug molecules, affecting their absorption and efficacy. The distribution of drugs to the brain is facilitated by various transporters, such as efflux transporters like P-glycoprotein (Mygind and Dahl, 1998).

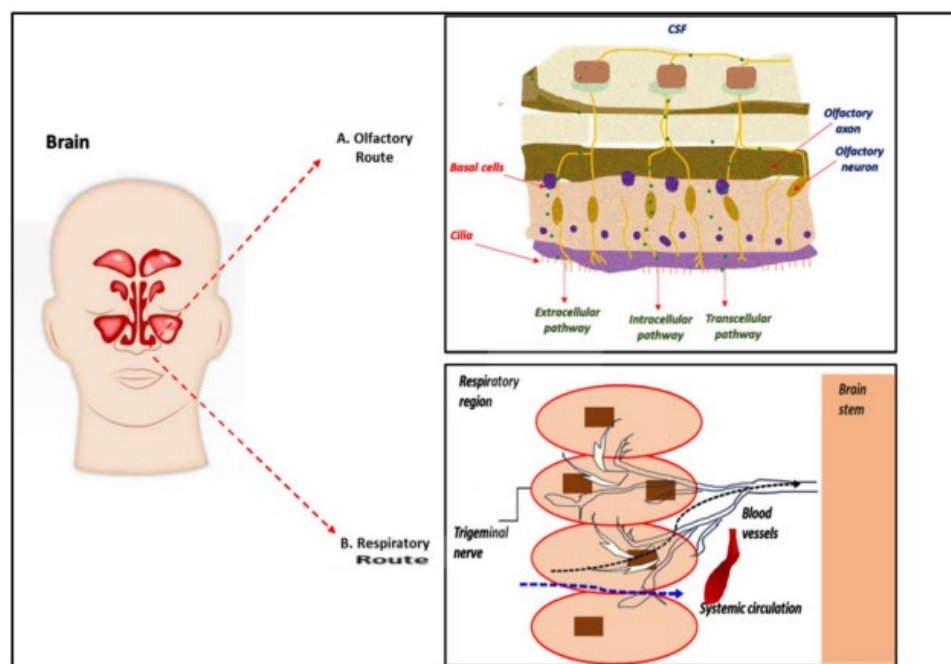


Figure 2: The mechanism of drug absorption through the nose.

Apart from the olfactory pathway, the trigeminal pathway also plays an important role in delivering the drug to the brain. The trigeminal nerve (cranial nerve) is one of the most important cranial nerves that provide sensory innervation to the face, head, and specific structures, in addition to performing a few motor functions. Mainly, the trigeminal nerve comprises three main branches (Gizurarson, 1993).

- Ophthalmic (V1): Supplies sensory information from the forehead, upper face, and scalp.
- Maxillary (V2): Serves the midface, nasal passages, sinuses, and upper jaw.
- Mandibular (V3): Transmits sensory signals from the lower jaw and controls some muscles involved in chewing.

The trigeminal pathway is a unique route for targeted drug delivery, primarily used for delivering brain therapies that cross the blood-brain barrier. Various mechanisms, including the mechanism of drug absorption through the nasal passages, are illustrated in Figure 2.

Several obstacles may limit the effectiveness of nasal drug delivery. While some medications, particularly peptides and proteins, can be broken down by enzymatic degradation in the nasal cavity, mucociliary clearance swiftly eliminates foreign compounds, thereby reducing the duration of drug residence. Poorly soluble drugs may not dissolve effectively in nasal secretions, and large molecules,

such as proteins and nanoparticles, have trouble being absorbed. High medication concentrations or frequent nasal delivery might also irritate and harm the nasal mucosa (Misra and Kher, 2012). Inconsistent dosing may also result from factors that affect drug absorption, such as allergies, infections, or nasal congestion. Additionally, the drug dosage is limited by the small volume that may be supplied (usually 25-200 μ L each nostril). To overcome these obstacles, formulation techniques that employ enzyme inhibitors and mucoadhesive agents, in addition to various permeation enhancers, are utilized (Ghori et al., 2015).

4. MECHANISM OF DRUG ABSORPTION BY ETHOSOMES

Numerous obstacles may restrict the mechanism of drug penetration by ethosome in nasal medication administration. Several crucial processes are involved in their drug penetration mechanism (Aute et al., 2012).

Drug absorption through the nasal mucosa is a complex process that integrates several mechanisms to enable both systemic delivery and direct brain targeting. The transcellular route is the primary pathway for small, lipophilic drugs, allowing passive diffusion across epithelial cell membranes due to favorable partitioning into lipid bilayers. In contrast, the paracellular route allows the movement of hydrophilic and low-molecular-weight molecules

through tight junctions between epithelial cells, although this pathway is generally limited due to the restricted pore size and dynamic regulation of junctional proteins. For drugs that resemble endogenous substrates, carrier-mediated transport systems, such as peptide, amino acid, and glucose transporters, facilitate absorption, making this pathway particularly important for certain therapeutic peptides and analogs (Illum, 2000). Larger biomolecules, nanoparticles, and vesicular carriers can be internalized by endocytosis or vesicular transport, which offers protection against enzymatic degradation within the nasal cavity. Beyond these classical absorption routes, the nasal pathway is distinguished by its ability to provide direct nose-to-brain delivery through neuronal transport via the olfactory epithelium and trigeminal nerve endings, enabling certain drugs to bypass the blood–brain barrier and achieve targeted delivery to the central nervous system. Factors such as drug lipophilicity, molecular weight, ionization, formulation pH, mucoadhesive properties, and the use of permeation enhancers significantly influence absorption efficiency. Physiological aspects, including mucociliary clearance, enzymatic activity, and blood flow, also play critical roles. Thus, the nasal mucosa serves as a versatile and highly promising route for drug administration, particularly for achieving rapid systemic absorption and targeting the central nervous system (Illum, 2000).

4.1 Sustained and Controlled Release

The vesicular shape of ethosomes permits the slow release of a drug, extending its effects and reducing the need for frequent dosages.

4.2 Interaction of ethosomes with the nasal mucosa

Ethosomes enhance drug delivery through the nasal mucosa by increasing membrane permeability due to their high ethanol content, which alters the lipid structure of the nasal epithelium. Their mucoadhesive characteristics contribute to extended drug retention, thereby increasing absorption. Due to their flexible and adaptable properties, ethosomes can readily integrate with the lipids of the nasal membrane, facilitating the direct transport of the drug. They also improve the solubility of both hydrophilic and lipophilic medications, which enhances bioavailability (Garg et al., 2017). Moreover, the vesicular nature of ethosomes protects drugs from enzymatic breakdown in the nasal cavity, resulting in improved therapeutic effectiveness. These attributes

position ethosomes as a promising system for efficient nasal drug delivery, especially for targeting the central nervous system.

5. BENEFITS OF ETHOSOME OVER OTHER CARRIERS

Compared to other vesicular models, the ethosome has various potential benefits due to its high ethanol content, which increases permeability, allowing drugs to penetrate biological membranes, such as the skin and nasal mucosa, more deeply. Ethosomes, in contrast to traditional carriers, offer improved mucoadhesion, longer retention, and efficient delivery of both hydrophilic and lipophilic medications. They are ideal for peptide and protein delivery due to their vesicular structure, which shields medications from enzymatic degradation. Ethosomes also ensure greater bioavailability by circumventing obstacles such as the blood–brain barrier and stratum corneum. They are a promising method for transdermal, nasal, and central nervous system drug delivery due to their non-invasiveness and controlled drug release, which further enhances their efficacy (Rattanapak et al., 2012).

5.1 Application of ethosome-based nasal formulation.

- Brain targeting for neurological disorders.
- Pain management.
- Hormonal therapy.
- Antimicrobial and antiviral therapy
- Vaccination and immunotherapy
- Treatment of respiratory disorder (Rattanapak et al., 2012).

6. USE OF ETHOSOMES IN CNS DISORDERS

The central nervous system comprises the spinal cord, and various disorders may affect it, leading to cognitive, motor, and behavioral impairment. Alzheimer's is a neurodegenerative disorder that leads to memory loss and cognitive decline. Parkinson's disease is a condition that is marked by motor dysfunction and tremors, and also causes progressive cell damage. Various traumatic injuries like traumatic brain injury (TBI) and spinal cord injury, strokes, which are caused by reduced blood flow to the brain, and epilepsy are condition that occurs due to recurrent seizures. When the immune system affects the CNS structure, autoimmune disorders such as MS and neuromyelitis optica occur (Pires et al., 2023).

Drug delivery for neurodegenerative diseases poses significant challenges due to the complex structure and protective mechanisms of the central nervous system, particularly the blood-brain barrier (BBB), which restricts the entry of most therapeutic agents. Effective treatment of conditions such as Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and Huntington's disease requires delivery systems that can not only cross the BBB but also target specific brain regions or cell types while minimizing systemic toxicity. Several innovative strategies have been developed to overcome these barriers. Nanoparticle-based carriers, such as liposomes, polymeric nanoparticles, and dendrimers, can be engineered to enhance BBB penetration and targeted delivery (Pires et al., 2023). Intranasal administration offers a non-invasive route to bypass the BBB via olfactory and trigeminal pathways.

Ethosomes are very effective in epilepsy treatment. The epilepsy management often involves chronic drug therapy, which means consistent plasma levels are significant. Through the ethosome, certain drugs like carbamazepine, phenytoin, or valproic acid can be delivered more effectively. They produce their effects by disrupting the skin lipid bilayer, which facilitates deeper penetration. The lipid compatibility facilitates drug transport through biological membranes. The ethosome vesicles have higher flexibility, which helps them squeeze through skin pores and reach systemic circulation (Bilapatte et al., 2025). The antimigraine medications such as sumatriptan, dihydroergotamine, or NSAIDS can be effectively delivered through ethosomes, which helps a faster onset of action on migraine. Ethosome helps in achieving a faster onset of action in acute migraine attacks (Hamzah et al., 2024; Verma et al., 2010).

7. STABILITY OF ETHOSOMAL NANOCARRIERS

Based on the vesicular structure and distribution, the stability of the ethosome can be determined. The ethosomal system may contain various drug entities in their initial suspension form or after incorporation into a particular dosage form, such as gel patches or creams. Research has shown promising results regarding the stability of ethosomes (Celia et al., 2009). A higher concentration of phospholipid may impact the stability of liposomes; the presence of cholesterol enhances membrane rigidity and stability. Various environmental factors may affect the stability of ethosomes. They are generally stable at low temperatures; however, room

temperature or higher temperatures may cause degradation or structural changes (13). The drugs with photosensitive characteristics should be protected from light to prevent oxidation or degradation. The various stabilization techniques include lyophilization, the use of antioxidants, and surface modification. Specific parameters are used to check out the stability, such as vesicle size, zeta potential, drug encapsulation efficiency, and physical appearance (Goindi et al., 2014; Pakhale Nilesh et al., 2019).

8. IRRITATION AND TOXICITY CONCERNS WITH NASAL MUCOSA

There are two important factors to be considered while discussing the irritation of ethosomes. Firstly, the ethanol content irritates the nasal mucosa because it disrupts tight epithelial junctions. This can be limited by combining it with mucoadhesive/stabilizing agents like chitosan to reduce irritation. The second factor is the phospholipid interaction. A higher concentration of phospholipid may trigger an inflammatory response in sensitive individuals. Various studies have shown that they may not cause long-term tissue damage with optimized formulations (Desai et al., 2023). The minimization of toxicity effects is shown in Table 1.

Table 1: Strategy to minimize toxicity effects

Strategy	Benefit
Reduce ethanol content	Less nasal irritation
Addition of mucoadhesive agents	Protects the nasal mucosa
Use of antioxidants	Reduce oxidative stress
Conduct cytotoxicity studies	Early safety screening

9. RECENT ADVANCES AND FUTURE PERSPECTIVES

Due to their unique ability to enhance medication penetration through the nasal mucosa, ethosomes hold great promise for use as carriers in future nasal drug administration. Due to their increased flexibility and fluidity, ethosomes — lipid-based vesicular carriers with a high ethanol content — permit better penetration into the tight junctions of nasal epithelial cells. This makes them ideal for administering medications that require rapid onset or have low oral bioavailability, such as proteins, peptides, and those targeting the central nervous system (Shelke et al., 2016). Furthermore, ethosome-based nasal administration improves patient compliance by avoiding first-pass metabolism and providing a non-invasive method. Ethosomes can overcome the main drawbacks of traditional nasal

drug delivery methods, including enzymatic degradation and mucociliary clearance, in addition to their improved penetration capabilities. Ethanol present in ethosomes not only increases vesicle deformability but also enhances penetration, thereby increasing medication absorption via the nasal mucosa and possibly enabling direct transport from the nose to the brain through the trigeminal and olfactory pathways. This creates novel therapy options for conditions affecting the central nervous system (CNS), such as depression, epilepsy, Parkinson's disease, and Alzheimer's disease. Furthermore, ethosomal carriers are adaptable for delivering a variety of therapeutic agents since they can encapsulate both hydrophilic and lipophilic medications (Nainwal et al., 2019).

Future innovations could include the use of bioadhesive polymers to extend residence time, smart ethosomal systems that can react to enzymes or nasal pH, improvements in stability for clinical translation, and large-scale manufacturing. All things considered, ethosomes represent a significant advancement in nasal medication delivery, which could potentially revolutionize non-invasive drug delivery for systemic and brain-targeted treatments (Nainwal et al., 2019).

10. CONCLUSION

Ethosomes hold considerable promise as novel nasal drug delivery vehicles due to their high entrapment efficiency, ultra-deformable structure, and ability to enhance drug penetration through the nasal mucosa. They can be used to deliver a variety of therapeutic agents, including proteins, peptides, and medications with low bioavailability, due to their biocompatibility and ability to encapsulate both hydrophilic and lipophilic medicines. Ethosomes can enhance systemic absorption and therapeutic efficacy by overcoming first-pass metabolism and enzymatic breakdown. Ethosomes may prove to be a viable approach for efficient, non-invasive, and patient-friendly nasal medication delivery systems with additional study, improvement, and clinical validation.

The nasal route, when combined with ethosomal carriers, presents a highly promising strategy for targeting the brain and treating central nervous system (CNS) disorders. By bypassing the blood-brain barrier through the olfactory and trigeminal pathways, ethosomes can deliver therapeutic agents directly to the brain with enhanced permeability, stability, and bioavailability. This not only improves drug efficacy but also minimizes systemic side effects, making ethosomes an important advancement in the management of neurological and

psychiatric conditions. With continued research and clinical validation, ethosome-based nasal delivery could significantly transform CNS drug therapy.

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

All data related to this manuscript have been disclosed within the article, and no additional datasets were generated or analyzed during the preparation of this review.

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