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INTRANASAL POLYHERBAL NANOEMULSION- BASED DRUG DELIVERY FOR BRAIN TARGETING: A PROMISING STRATEGY FOR MIGRAINE THERAPY

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ABSTRACT: Migraine is a multifactorial neurovascular disorder involving activation of the trigeminovascular system, cortical spreading depression (CSD), neurogenic inflammation, and dysregulation of calcitonin gene related peptide (CGRP) signaling. Conventional oral and parenteral therapies are limited by brain penetration, first-pass metabolism, and systemic adverse effects. The review highlights a polyherbal nanoemulsion- based intranasal drug delivery system as a targeted and non-invasive strategy for migraine management. The intranasal route enables direct nose-to- brain transport through the olfactory and trigeminal neural pathways, facilitating rapid drug delivery to key brain regions while bypassing the blood brain barrier, minimizes systemic exposure, and enhances drug bioavailability. The proposed nanoemulsion incorporates three bioactive phytoconstituents: thymoquinone (*Nigella sativa*), withanolides (*Withania somnifera*), and menthol (*Mentha piperita*), which collectively target multiple interconnected migraine pathways. Thymoquinone exerts potent anti- inflammatory and antioxidant effects by downregulating nuclear factor-kappa B (NF- κ B), inhibiting pro-inflammatory cytokines (TNF- α , IL-6). Withanolides demonstrate neuroprotective and anti-stress activity by modulating the hypothalamic- pituitary-adrenal (HPA) axis, reducing cortisol levels, and preventing neuronal apoptosis through antioxidant enzyme upregulation. Menthol activates transient receptor potential melastatin-8 (TRPM8) channels, leading to analgesic effects via modulation of calcium influx and inhibition of trigeminal nociceptive signaling, thereby reducing CGRP release. Nanoemulsion systems enhance solubility, mucosal permeation, and nasal residence time, enabling efficient drug transport across the nasal epithelium. The nanoscale droplet size further supports neuronal uptake and intracellular delivery. Overall, the synergistic combination of these phytoconstituents offers a multi-targeted therapeutic approach addressing neuroinflammation, oxidative stress, and central sensitization. This strategy represents a promising platform for rapid, targeted, and effective migraine therapy with improved patient compliance and reduced systemic toxicity.

INTRODUCTION: Migraine is a persistent and disabling neurovascular disorder characterized by recurrent episodes of moderate to severe headache, frequently followed by nausea, vomiting, sensitivity to light, and sensitivity to sound.

It is one of the most prevalent neurological conditions worldwide, significantly affecting the quality of life and daily productivity of patients. According to the world health organization, migraine ranks among the leading causes of disability globally, particularly among young and middle-aged individuals ¹.

The pathophysiology of migraine is quite complicated, including triggers the trigeminovascular system, the secretion of neuropeptides such as calcitonin gene-related

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peptide (CGRP), and neuroinflammatory processes. These events lead to vasodilation of cerebral blood vessels and sensitization of central pain pathways. In addition, oxidative stress and mitochondrial dysfunction are also implicated in the progression and severity of migraine attacks².

Despite the availability of various pharmacological treatments, including triptans, nonsteroidal anti-inflammatory drugs, and preventive therapies, effective management of migraine remains challenging. This is mainly due to poor drug penetration into the brain, delayed onset of action, systemic adverse effects, and reduced patient compliance. The presence of the blood-brain barrier (BBB) further restricts the delivery of therapeutic agents to the central nervous system, thereby limiting clinical efficacy³.

To overcome these limitations, alternative drug delivery strategies have been extensively explored. Among them, intranasal drug delivery has emerged as a promising non-invasive approach for direct nose-to-brain transport, enabling rapid drug absorption and bypassing the BBB. This route provides a unique advantage for targeting neurological disorders such as migraine^{4,5}.

In recent years, nanoemulsion-based drug delivery systems have gained considerable attention due to their small droplet size, enhanced solubility, improved stability, and ability to facilitate drug transport across biological membranes^{6,7}. Furthermore, the incorporation of herbal bioactive compounds into nanoemulsion systems offers a polyherbal approach with synergistic therapeutic effects, reduced toxicity, and improved safety profiles⁸. Bioactives derived from medicinal plants such as *Nigella sativa*, *Withania somnifera*, and *Mentha piperita* have demonstrated significant anti-inflammatory, antioxidant, and neuroprotective properties relevant to migraine management. Therefore, this review aims to provide a comprehensive overview of migraine pathophysiology, limitations of conventional therapies, and the potential of polyherbal nanoemulsion-based intranasal drug delivery systems for effective brain targeting. Additionally, recent advances, formulation strategies, safety considerations, and future perspectives for clinical translation are discussed⁹.

Blood-Brain Barrier: The blood-brain barrier (BBB) is a highly selective and dynamic physiological barrier that regulates the transport of substances from the systemic circulation to the central nervous system. It is composed of endothelial cells, astrocytes, pericytes, and a basement membrane, which together maintain cerebral homeostasis while restricting the entry of most therapeutic agents¹⁰. Although the BBB protects the brain from harmful substances, it poses a major challenge for effective drug delivery in neurological disorders such as migraine¹¹. Overcoming this barrier is therefore critical for achieving efficient brain targeting and improved therapeutic outcomes.

Migraine is associated with central neuro-inflammation, altered neurotransmitter signalling, and activation of the trigeminovascular system, all of which require adequate drug concentrations within specific brain regions for effective therapy¹². However, the BBB restricts the passage of most hydrophilic and high-molecular-weight drugs, permitting mainly small and lipophilic molecules to cross *via* passive diffusion¹³. In addition, efflux transporters such as P-glycoprotein further reduce intracerebral drug accumulation, thereby limiting therapeutic efficacy¹¹.

Oral drug delivery remains the most common route for migraine treatment, but it is associated with a delayed onset of action, variable absorption, and poor bioavailability¹⁴. During acute migraine attacks, gastrointestinal disturbances such as nausea, vomiting, and gastric stasis further compromise oral absorption, leading to inadequate pain control and poor patient compliance¹⁵.

Frequent and long-term use of conventional anti-migraine drugs, including triptans and ergot derivatives, may result in adverse effects such as cardiovascular complications and medication-overuse headache^{14,16}. The need to administer higher doses to overcome BBB limitations further increases the risk of systemic toxicity. Although emerging therapies targeting the calcitonin gene-related peptide (CGRP) pathway have shown significant clinical efficacy, their high cost, injectable mode of administration, and limited availability continue to pose substantial challenges, especially in developing countries².

Overall, BBB-associated restrictions, systemic side effects, and inconsistent clinical outcomes highlight significant unmet needs in migraine therapy.

As a result, there is a crucial need for alternative methods that can circumvent the BBB and facilitate prompt targeting of the brain. Utilizing intranasal drug administration, particularly when paired with innovative carrier systems such as nanoemulsions, presents a viable approach to address these challenges and enhance treatment effectiveness in migraine management¹⁷.

Pathophysiology of Migraine: Migraine is a complex neurovascular disorder involving multiple interconnected mechanisms, including neuronal hyperexcitability, activation of the trigeminovascular system, and neuroinflammation. The exact pathogenesis is not fully understood; however, several well-established theories explain the initiation and progression of migraine attacks¹⁸.

A key mechanism involved in the development of migraine is the activation of the trigeminovascular pathway. This system comprises trigeminal nerve fibers that innervate cerebral blood vessels and the meninges. Upon activation, these nerve endings release vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP), substance P, and neurokinin A. Among these mechanisms, activation of the trigeminovascular system and CGRP signalling are currently considered central events in migraine pathophysiology.

CGRP contributes to pain transmission, neurogenic inflammation, and sensitization of nociceptive pathways, while vascular changes are now considered part of a broader neurovascular process rather than the sole cause of migraine^{19, 20}.

Neuroinflammation is another key contributor to migraine development. The release of inflammatory mediators from activated trigeminal neurons results in increased vascular permeability and sensitization of peripheral and central nociceptive pathways. This sensitization enhances pain perception and contributes to the recurrence and severity of migraine attacks²¹.

Cortical spreading depression (CSD) is also considered an important mechanism, particularly in migraine with aura. CSD is characterized by a

wave of neuronal depolarization subsequently leads to suppression of brain activity, which spreads across the cerebral cortex.

This phenomenon is associated with alterations in cerebral blood flow and activation of trigeminal afferents, further contributing to headache generation²².

Oxidative stress and mitochondrial dysfunction have also been implicated in migraine pathogenesis. Excessive reactive oxygen species (ROS) and impaired mitochondrial energy metabolism can lead to neuronal damage and heightened susceptibility to migraine triggers. Additionally, these factors may exacerbate neuroinflammatory responses and pain signaling pathways²³.

Furthermore, dysfunction of central neurotransmitter systems, including serotonin (5-HT), dopamine, and glutamate, plays a significant role in migraine. Alterations in serotonin levels are particularly associated with the initiation of migraine attacks, which form the basis for the use of triptans in migraine therapy.

Current understanding indicates that migraine involves dysfunction of distributed central neuronal networks responsible for sensory processing, pain modulation, and cortical excitability. Alterations in serotonergic, dopaminergic, and glutamatergic neurotransmission contribute to these complex neuronal mechanisms²⁴.

Overall, migraine is a multifactorial disorder involving complex interactions between vascular, neuronal, inflammatory, and biochemical pathways. Understanding these mechanisms is essential for the development of effective therapeutic strategies.

In this context, targeting neuroinflammation, oxidative stress, and neuronal signaling through advanced drug delivery systems such as polyherbal nanoemulsion-based intranasal formulations presents a promising approach for improved migraine management²⁵.

The pathophysiology of migraine is illustrated in **Fig. 1** (created using AI tools and modified by author).

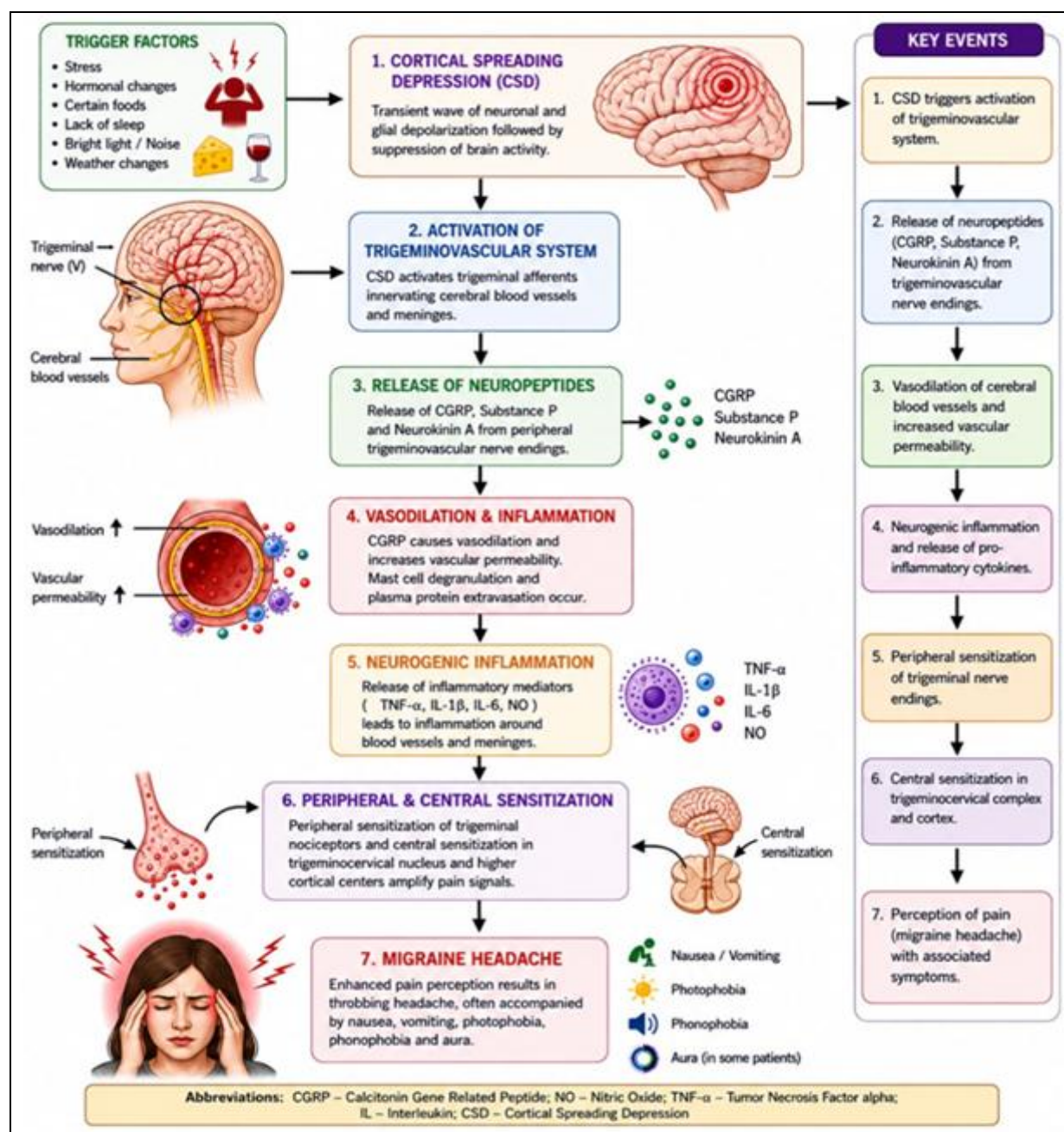


FIG. 1: PATHOPHYSIOLOGY OF MIGRAINE

Intranasal Route for Brain Targeting: The intranasal route is a promising non-invasive approach for delivering therapeutic agents to the central nervous system. This route utilizes the specialized anatomy of the nasal cavity and its neuronal connections with the brain through the olfactory and trigeminal pathways, potentially facilitating nose-to-brain transport²⁶.

Nasal Cavity Anatomy: Before exploring drug absorption and penetration *via* this route, it is essential to gain a comprehensive understanding of the anatomy and physiological functions of the nasal cavity, a highly complex structure. The nasal

cavity consists of three main regions: the vestibular region, which has a surface area of approximately 0.6 cm²; the olfactory region, with a surface area ranging from 2 to 12.5 cm²; and the respiratory region, which comprises the largest portion of the cavity and plays a major role in drug absorption.

The nasal cavity has various functions, including respiration and olfaction²⁷. It plays a role in maintaining the humidity and temperature of inhaled air, along with clearance external pathogens²⁸. The anatomical basis of intranasal drug delivery is illustrated in **Fig. 2**.

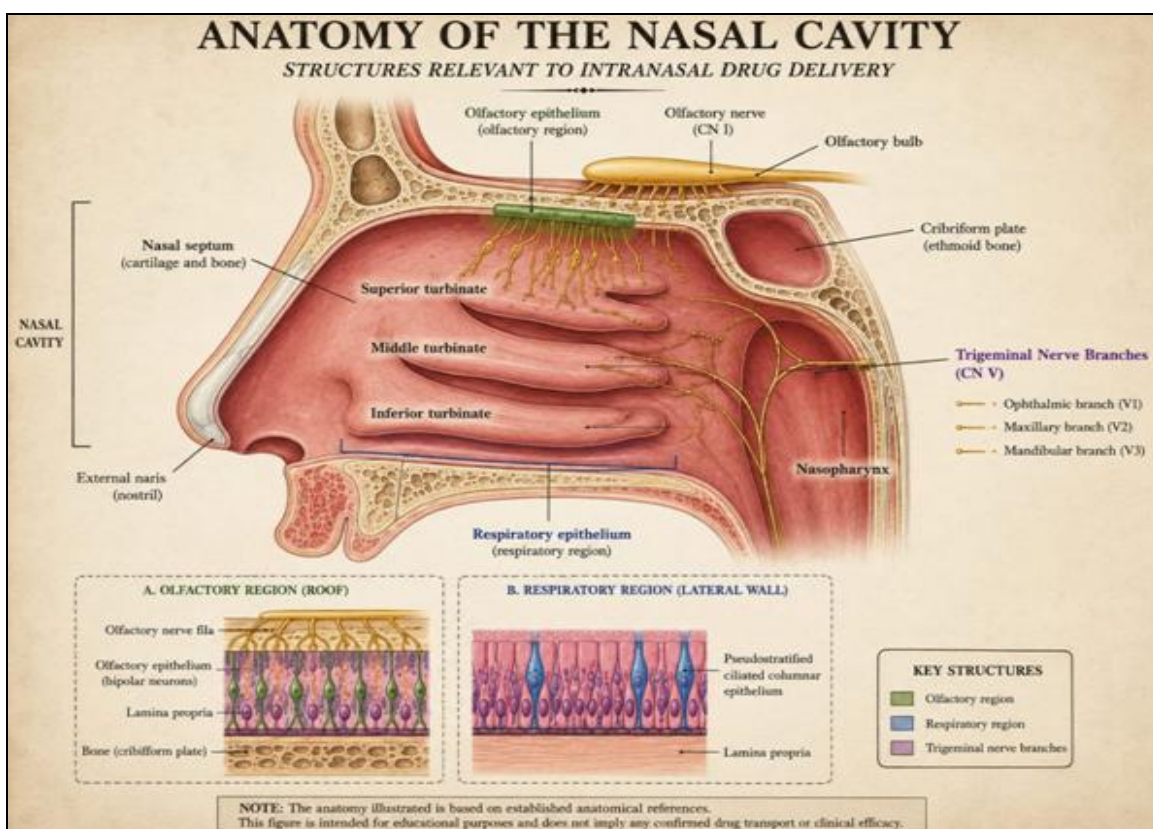


FIG. 2: ANATOMY OF THE NASAL CAVITY HIGHLIGHTING STRUCTURES RELEVANT TO INTRANASAL DRUG DELIVERY, INCLUDING THE OLFATORY REGION, RESPIRATORY REGION, AND TRIGEMINAL NERVE PATHWAYS. (CREATED USING AI TOOLS AND MODIFIED BY AUTHOR)

The nasal cavity is divided into three key regions:

Vestibular Region: The anterior part is lined with squamous epithelium, serving as a protective barrier. The vestibular region of the nasal cavity acts as a barrier against pathogens and does not participate in absorption in its anterior portion. It contains mucus and nasal hairs, which help trap and filter airborne particles before they enter the nasal passages. Moreover, it is less porous due to limited vascularization and a smaller surface area²⁹.

Respiratory Region: Among the three regions, this represents the largest part of the nasal cavity and is lined with ciliated pseudostratified epithelium and goblet cells. Its high vascularity enables rapid systemic absorption. The respiratory region accounts for the largest surface area and is composed of ciliated respiratory epithelium along with highly vascularized nasal turbinate composed of erectile and sinusoidal tissues³⁰.

Olfactory Region: Situated in the superior part of the nasal cavity, this region contains olfactory sensory neurons directly connected to the olfactory

bulb, making it a crucial site for direct nose-to-brain drug transport. The olfactory region consists of basal cells, olfactory receptor neurons, and supporting (sustentacular) cells. The olfactory receptor neurons, which are bipolar neurons, transmit signals through the epithelium to the olfactory bulb³¹.

Intranasal Pathways for Brain Targeting:

Olfactory Pathway: The olfactory region, situated in the superior part of the nasal cavity, the olfactory pathway is considered one of the principal routes that may contribute to nose-to-brain drug transport following intranasal administration.

This region houses olfactory receptor neurons, whose axons project directly into the olfactory bulb, establishing a unique neuronal connection between the nasal cavity and the central nervous system (CNS)³². Drugs or nanocarriers administered intranasally can traverse the olfactory epithelium through multiple mechanisms, including transcellular, paracellular, or endocytic transport, followed by axonal transport or perineural diffusion. Once transported, they reach the olfactory bulb and are subsequently distributed to

higher brain regions, including the cortex, hippocampus, amygdala, and hypothalamus³³.

A potential advantage of this pathway is that it may facilitate drug transport to the central nervous system while partially avoiding some limitations associated with the blood-brain barrier. However, the extent of brain delivery varies depending on the drug and formulation characteristics. The olfactory pathway is anatomically divided into the olfactory epithelium, olfactory tract, and olfactory bulb, and functionally classified into two main transport routes: intraneuronal (intracellular) and extraneuronal (extracellular)³⁴. In the intraneuronal pathway, drugs are internalized by olfactory neurons via endocytosis and then transported along axons to the olfactory bulb. In contrast, the extraneuronal pathway involves diffusion of drugs through perineural channels surrounding the olfactory neurons, allowing them to reach the olfactory bulb without entering the neurons³⁵.

Collectively, these transport mechanisms may contribute to nose-to-brain delivery and support the potential application of intranasal nanoformulations for central nervous system drug delivery. Nevertheless, successful brain targeting should be confirmed through appropriate pharmacokinetic and bio-distribution studies³⁶.

Trigeminal Pathway: The trigeminal nerve, a major cranial nerve, innervates both the respiratory and olfactory regions of the nasal cavity, offering an additional pathway for nose-to-brain drug transport. Following intranasal administration, drug molecules can be absorbed through the ophthalmic and maxillary branches of the trigeminal nerve, allowing delivery to the brainstem, cerebellum, and spinal cord. This pathway is particularly important for targeting caudal brain regions that may not be efficiently reached via the olfactory route³⁷.

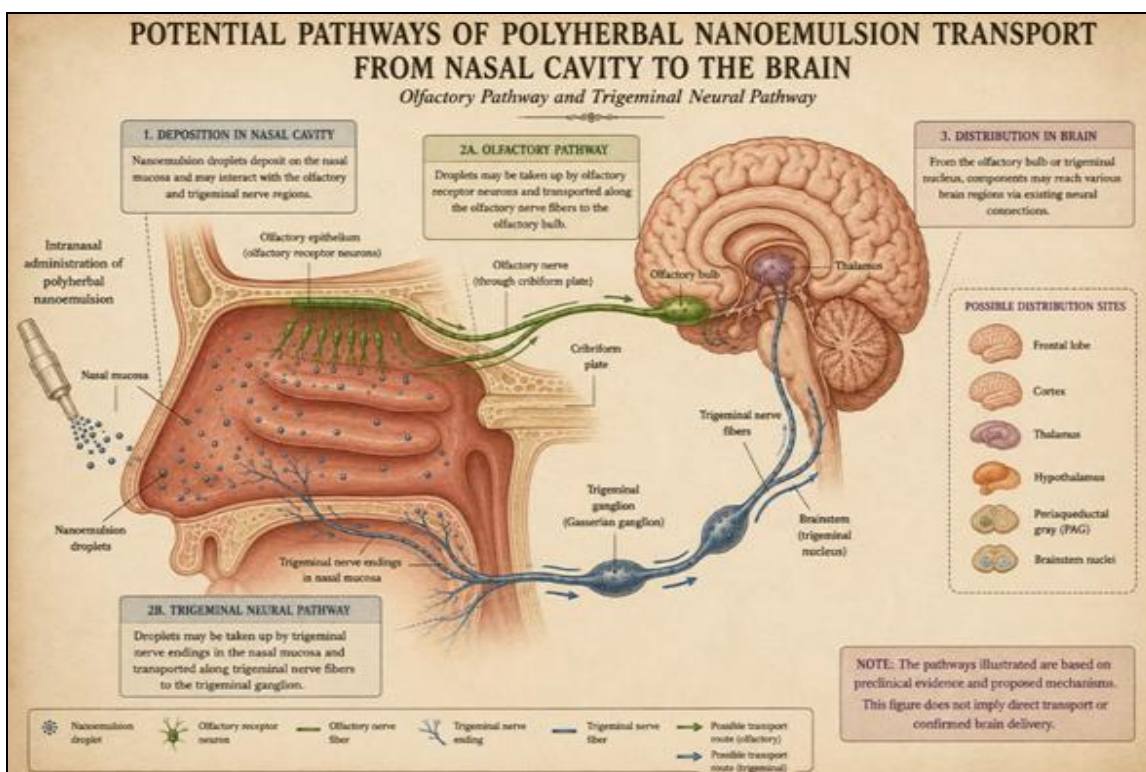


FIG. 3: PROPOSED OLFACTORY AND TRIGEMINAL NEURAL PATHWAYS INVOLVED IN THE POTENTIAL TRANSPORT OF INTRANASALLY ADMINISTERED POLYHERBAL NANOEMULSION FROM THE NASAL CAVITY TO THE BRAIN. THE ILLUSTRATION IS BASED ON PRECLINICAL EVIDENCE AND PROPOSED MECHANISMS. (CREATED USING AI TOOLS AND MODIFIED BY AUTHOR)

Anatomically, the trigeminal nerve has three major branches: ophthalmic, maxillary, and mandibular. Among these, the ophthalmic and maxillary divisions play the most significant role in nasal

drug transport because they innervate the nasal mucosa, respiratory epithelium, and meninges^{38, 39}. After absorption, drugs can travel along these branches and gain direct access to the CNS.

This pathway is also responsible for transmitting sensory information from the nasal cavity, oral cavity, eyelids, cornea, and meninges to the brain⁴⁰.

Drug transport through the trigeminal route may occur *via* axonal transport or perineural diffusion, similar to the olfactory pathway. Importantly, this route enables delivery to deeper structures such as the pons, brainstem, and hindbrain, making it highly valuable for CNS therapeutics that require distribution beyond the forebrain⁴¹. This pathway has been successfully exploited for the delivery of various bioactive molecules and neuropeptides, including insulin, IGF-1, and interferon- β , to the central nervous system (CNS), highlighting its translational potential for targeted drug delivery systems such as intranasal nanoemulsion-based formulations⁴². The mechanisms involved in intranasal nose- to- brain transport of nanoemulsion are illustrated in **Fig. 3**.

Advantages of Intranasal Delivery in Migraine:

Intranasal drug delivery offers several distinct advantages in the management of migraine, particularly for achieving rapid therapeutic action and effective brain targeting. Migraines are characterized by the sudden onset of symptoms and involvement of central neurovascular pathways; therefore, a delivery route that ensures fast and efficient drug transport to the brain is highly desirable.

One of the key benefits of the intranasal route is that it bypasses the blood–brain barrier, allowing for direct nose-to-brain transit via the olfactory and trigeminal nerve pathways. This approach enhances the brain bioavailability of therapeutic agents and reduces the requirement for higher systemic doses, thereby minimizing systemic side effects. Intranasal administration provides a rapid onset of action, which is crucial during acute migraine attacks. Drugs delivered through the nasal cavity can reach the brain within minutes, offering faster relief compared to oral formulations, which are affected by delayed gastric emptying and poor gastrointestinal absorption during migraine episodes. Another significant advantage is improved patient compliance. Migraine attacks are frequently accompanied by nausea and vomiting, which limit the effectiveness of oral medications.

Intranasal delivery overcomes these limitations by offering a non-invasive, painless, and patient-friendly alternative to parenteral administration.

Moreover, the intranasal route bypasses first-pass hepatic metabolism, resulting in enhanced drug bioavailability and more predictable pharmacokinetic profiles. This advantage is especially significant for drugs that are extensively metabolized in the liver following oral administration. Additionally, intranasal delivery enables reduced systemic exposure, which lowers the risk of adverse effects associated with conventional anti-migraine therapies, such as cardiovascular complications and medication-overuse headache. This makes intranasal formulations suitable for both acute and long-term management of migraine.

When combined with advanced drug delivery systems such as nanoemulsions, intranasal delivery further enhances drug solubility, stability, and mucosal permeability. Nanoemulsions can prolong nasal residence time and protect bioactive compounds from enzymatic degradation, thereby improving therapeutic efficacy.

Overall, intranasal drug delivery represents a promising approach for migraine management, offering rapid therapeutic effects, targeted brain delivery, enhanced safety, and improved patient compliance. These advantages address several unmet clinical needs associated with conventional migraine therapies^{3, 43, 44, 45}.

Limitations and Safety Considerations of Intranasal Drug Delivery in Migraine Therapy:

Despite several advantages, intranasal drug delivery also has certain limitations and safety concerns. One of the primary limitations is the limited surface area available for drug absorption in the nasal cavity. The small surface area and short residence time can reduce the amount of drug reaching the brain. Another significant restriction is mucociliary clearance. The nasal mucosa constantly eliminates foreign particles, which can cause the drug to be quickly removed. This lowers drug contact time with the nasal epithelium and influences drug absorption. Variations in nasal physiology, such as nasal congestion, inflammation, or pathological conditions, can

influence drug absorption and lead to inconsistent therapeutic effects. In migraine patients, nasal irritation and sensitivity may further affect intranasal drug administration. Safety concerns include possible irritation or damage to the nasal mucosa due to repeated drug administration. Certain excipients, preservatives, or surfactants used in formulations may cause local toxicity or discomfort if not properly chosen^{46, 47}. In nanoemulsion-based intranasal systems, factors such as particle size, surfactant concentration, and formulation composition should be carefully optimized to ensure safety. Furthermore, long-term safety assessment should include evaluation of nasal ciliotoxicity, as repeated exposure to surfactants, preservatives, and bioactive compounds may impair normal ciliary function and mucociliary transport. Histopathological examination of nasal tissues is also important to identify any epithelial damage, inflammation, or structural alterations following repeated intranasal administration. Since the olfactory epithelium plays a crucial role in nose-to-brain transport, potential effects on olfactory function should also be considered during safety evaluation. In addition, formulation parameters such as pH, osmolality, viscosity, and excipient concentration should be carefully optimized to maintain nasal compatibility, minimize irritation, and improve patient acceptability. Intranasal nanoformulations must be thoroughly evaluated for long-term use to prevent toxicity and guarantee biocompatibility. Therefore, proper formulation design, safety evaluation, and clinical studies are essential to minimize risks and ensure the safe and effective use of intranasal drug delivery systems for migraine therapy^{48, 33}.

Nanoemulsion Drug Delivery Systems:

Nanoemulsions are transparent or slightly translucent systems and are suitable for delivering both hydrophilic and lipophilic drugs. They are widely used in pharmaceutical applications due to their ability to improve bioavailability and therapeutic efficacy. Nanoemulsions are especially effective in delivering poorly water-soluble drugs, including herbal bioactive compounds. Many herbal drugs exhibit low bioavailability and instability when administered in conventional dosage forms. Nanoemulsion systems protect bioactive compounds while enhancing their solubility and permeability⁴⁹.

Nanoemulsions offer significant advantages for intranasal administration, as their nanosized droplets promote efficient penetration across the nasal mucosa. This, in turn, facilitates direct transport to the brain through the olfactory and trigeminal nerve pathways. Nanoemulsions can also be formulated with mucoadhesive polymers to increase nasal residence time and reduce mucociliary clearance. This results in improved drug retention and enhanced brain targeting⁵⁰. Intranasal nanoemulsion-based drug delivery systems offer a rapid onset of action, improved therapeutic efficacy, and reduced systemic side effects in the management of migraine. As a result, nanoemulsions offer a promising strategy for efficient brain-targeted drug delivery⁵¹.

Classification of Nanoemulsions: Nanoemulsions can be classified based on their internal and external phases:

Oil-in-Water (O/W) Nanoemulsions: In this type, oil droplets are homogeneously distributed in a continuous aqueous phase. O/W nanoemulsions are commonly used for delivering lipophilic drugs and are suitable for intranasal and oral drug delivery.

Water-in-Oil (W/O) Nanoemulsions: In W/O nanoemulsions, water droplets are homogeneously distributed in a continuous oil phase. These systems are primarily employed for the delivery of hydrophilic drugs and for achieving sustained drug release⁵².

Bi-continuous Nanoemulsions: Bi-continuous nanoemulsions consist of interpenetrating oil and water phases stabilized by surfactants. Both oil and water phases are continuous in this system, allowing simultaneous delivery of hydrophilic and lipophilic drugs⁵³. Among these O/W systems more favourable for intranasal delivery due to their better compatibility with the aqueous nasal environment and enhanced absorption properties.

Formulation Strategies for Polyherbal Nano Emulsions:

Oil Phase: Poor aqueous solubility of novel molecules is a significant obstacle in the field of drug discovery due to its influence on such critical characteristics of the drug's efficacy as pharmacokinetics and pharmacodynamics.

Therefore, oils are incorporated into NE formulations to improve drug solubility⁵⁴. Oil lipophilicity is proportional to its ability to dissolve drugs in the following order: vegetable oils > medium-chain triglycerides > medium-chain mono- and diglycerides⁵⁵. Furthermore, total solubility of drugs relies on the quantity of oils used in NE. Increased oil concentration results in the formation of larger globules, thus reducing the ability of drugs to permeate through the nasal mucosa⁵⁶.

There exist certain oils, which facilitate absorption of specific drugs only. For example, linolenic acid, polyunsaturated and omega-6 fatty acids, as well as pinolenic acid, are absorbed exclusively⁵⁷. It was found that while oleic acid, which possesses only one cis-double bond, is not able to penetrate the BBB, linoleic acid with two cis-double bonds and 18-carbon monocarboxylic acids readily penetrate the BBB after the nasal route⁵⁸.

Surfactants: The process of surfactant adsorption occurs on the boundary of the dispersion medium and droplets, creating a flexible monolayer film, which results in a reduction in the surface tension (γ) and surface free energy of nanoemulsions (NEs), thus preventing their coalescence⁵⁹. Furthermore, surfactants can affect the structure of mucosa, so the right choice of surfactant concentration is important while preparing nanoemulsions intended for brain targeting. Surfactants are the components of NE formulation, which have a significant effect on reducing surface tension. The surfactants help in stabilizing NEs by avoiding phase separation and globule fusion. Furthermore, surfactants enhance drug solubilization and increase penetration through the nasal mucosa by altering membrane fluidity and disrupting the tight junctions of epithelial layers⁶⁰. Studies indicate that increasing the concentration of surfactants leads to a decrease in the globule size of NEs. Smaller globule sizes result in improved permeation and higher drug levels in the brain. However, it is important to carefully select surfactant concentrations, as excessive amounts can compromise the structural integrity of the nasal mucosa, posing safety concerns⁶¹.

Cosurfactants: Surfactants cannot lower the surface tension sufficiently due to the fact that the surfactants employed for the preparation of the NE

formulation are usually of the single-chain surfactants⁶². Cosurfactants have the capability of increasing fluidity and hence facilitating emulsification through the decrease in interfacial tensions. For a successful preparation of NE, proper selection of surfactant and cosurfactant is necessary. Ternary phase diagrams are commonly used to determine the optimum working concentrations of oil, surfactant, and cosurfactant. An increase in the concentration of cosurfactant normally results in small globules of the nanoemulsion and hence high drug loading and increased drug concentration. The commonly applied cosurfactants for intranasal nanoemulsion formulations are Transcutol P, butan-1-ol, chirality alcohols, sorbitol, and polyethylene glycol⁵⁵.

Aqueous Phase: The aqueous phase typically consists of distilled or deionized water and may be supplemented with humectants or buffering agents to maintain a pH within the physiological nasal limits (5.5–6.5). The choice of the aqueous phase further influences important formulation characteristics, including droplet size, viscosity, and zeta potential.

Construction of Pseudo-Ternary Phase Diagram: The identification of the area of formation of nanoemulsions and the determination of the ideal concentration of oil, surfactants, and cosurfactants can be made using the pseudo-ternary phase diagram based on the titration technique⁶³.

In the proposed polyherbal nanoemulsion system, formulation development should also consider the physicochemical characteristics of the selected bioactive constituents. Thymoquinone and menthol are predominantly lipophilic compounds and may be incorporated into the oil phase, whereas withanolides also exhibit limited aqueous solubility and may require suitable lipid-based solubilization strategies. Therefore, the selection of oil phase, surfactant, and cosurfactant should be based on their solubilization capacity, compatibility, stability, and suitability for intranasal administration. Furthermore, analytical methods capable of simultaneous quantification of thymoquinone, withanolides, and menthol would be required during formulation development and evaluation.

Preparation Methods of Nanoemulsion:

Nanoemulsions can be prepared using high-energy or low-energy methods. The choice of method depends on the drug, formulation components, and the desired droplet size^{49, 50}.

High-Energy Methods: The preparation of nanoemulsions is achieved through the utilization of high-energy approaches. High-energy approaches utilize mechanical energy in large quantities to create disruptive forces that disintegrate large-sized droplets in an emulsion into small-size droplets, thus creating kinetically stable nanoemulsions. The disruption force can be created by the use of machines such as ultrasonication, microfluidization, and high-pressure homogenizers. In high energy processes, one can easily control the size of droplets by properly choosing the formulation composition. Moreover, such approaches give better control on factors such as emulsion stability, rheology, and overall appearance. In addition, for the food and biologically active substances, high-energy processes are beneficial as they reduce the chances of microbial contamination and destruction of sensitive substances without altering food safety and its nutritional and sensory qualities.

High-Pressure Homogenization: The high-pressure homogenizer generates considerable mechanical energy by forcing the material under regulated flow rates, which leads to the production of nanoemulsions with uniform and minute droplet sizes. High-pressure homogenizers are commonly used for nanoemulsion formulation due to their effectiveness, efficiency, and accuracy. Nanoemulsion formation occurs when the coarse emulsion passes through a nozzle with a narrow opening at a very high pressure of 500 to 5,000 pounds per square inch. At the same time, various forces like turbulence, hydraulic shear, and cavitation act on the system. Therefore, nanoscale droplets are formed from the large-sized droplets⁶⁴.

Microfluidization: Microfluidization is a high-energy mixing technique that employs a specialized device called a microfluidizer to reduce droplet size to the nanoscale. In this process, fluids are forced through microchannels under high pressure, typically ranging from 500 to 20,000 psi, allowing efficient mixing at the microscale. Initially, the oil

and aqueous phases are combined to form a coarse emulsion. This macroemulsion is then pumped through the microfluidizer, where it passes through narrow microchannels and is directed into an interaction chamber. Within this chamber, two high-velocity streams of the emulsion collide with each other. The resulting shear forces, cavitation, and impact lead to the formation of stable nanoemulsions with small and uniform droplet sizes⁶⁵.

Ultrasonication: Ultrasonication is considered an efficient high-energy method due to its simple operation and ease of cleaning. In this technique, ultrasonic waves generate acoustic cavitation, which breaks coarse emulsions into nanosized droplets. Ultrasonicators consist of a probe that emits high-frequency sound waves into the emulsion system. By adjusting the ultrasonic power and processing time, nanoemulsions with the desired droplet size and stability can be obtained. The implosion of cavitation bubbles generates intense shear forces and turbulence, which facilitate the formation of stable nanoemulsions⁶⁶.

Ultrasonic irradiation of an oil–water system generates cavitation forces that supply sufficient energy for the formation of new interfaces, resulting in the production of nanosized emulsion droplets. Nanoemulsions can be prepared using ultrasonication even in the absence of surfactants, depending on the specific formulation conditions. The efficiency of ultrasonic emulsification mainly depends on ultrasound intensity, processing time, and the nature of the surfactant. Ultrasonication has been widely employed for the preparation of nanoemulsions containing pharmaceutical drugs and food ingredients. Food-grade nanoemulsions produced by ultrasonication generally exhibit smaller droplet sizes, improved stability, and require lower energy input compared to other high-energy methods⁶⁷.

Low-Energy Methods: Low energy technique uses little external energy for nanoemulsion formation. This method is said to be energy-efficient as it makes use of internal energy of the system through chemistry and involves only mild stirring. Methods used in low energy technique are phase inversion, emulsification, and self-emulsification. Nonetheless, these methods are

unsuitable for production of food grade nanoemulsions since it requires large amounts of surfactants⁶⁸.

Phase Inversion Emulsification Method: Phase inversion emulsification relies on changes in the spontaneous curvature of surfactants, which trigger phase transitions during the emulsification process. Such changes can be achieved by altering parameters such as temperature or formulation composition. Phase inversion methods are broadly classified into transitional phase inversion (TPI) methods, including phase inversion temperature (PIT) and phase inversion composition (PIC), and catastrophic phase inversion (CPI) methods, which involve the emulsion inversion point (EIP)⁶⁹.

Phase Inversion Temperature (PIT) Method: The Phase Inversion Temperature (PIT) method is a low-energy technique for preparing nanoemulsions, relying on temperature-induced changes in surfactant affinity. In this approach, the solubility of non-ionic surfactants changes in response to variations in temperature. At a specific temperature, known as the PIT, the surfactant shows equal affinity toward both oil and water phases, resulting in minimal interfacial tension. Upon rapid cooling or heating through this temperature, the system undergoes phase inversion, leading to the formation of fine nanosized droplets⁷⁰.

Phase Inversion Composition (PIC) Method: Phase Inversion Composition (PIC) technique depends upon variation in the composition of the mixture rather than temperature variations. In this process, a phase (generally aqueous phase) is incrementally added to the oil-surfactant system while stirring. With the variation in composition, the surfactant curvature undergoes a change leading to the phase inversion. This process is helpful in producing nanoemulsions^{71, 72}.

Evaluation and Characterization of Polyherbal Nanoemulsion: Proper evaluation of nanoemulsions is essential to ensure stability, efficacy, and suitability for intranasal delivery. The main parameters include⁷³:

Droplet Size and Polydispersity Index (PDI): The droplet size is determined by DLS technique. Nanoemulsions with droplet sizes <200 nm is

preferred for better nasal absorption and brain targeting. PDI indicates size distribution; a value <0.3 shows uniform droplets.

Zeta Potential: Zeta potential indicates the droplet's surface charge. The higher zeta potential (>±30 mV) implies electrostatic stability that prevents aggregation of droplets.

pH and Viscosity: pH is adjusted to match the nasal mucosa (usually 5.5–6.5) to avoid irritation. Viscosity is optimized for proper nasal retention and ease of administration.

Drug Content and Entrapment Efficiency (EE%): The total amount of polyherbal bioactives in the nanoemulsion is measured. Entrapment efficiency indicates the proportion of the drug successfully encapsulated within the nanosized droplets.

In-vitro Drug Release: Release studies determine the rate and extent of drug release from the nanoemulsion. Comparison with conventional formulations demonstrates improved solubility and sustained release^{74, 75}.

Osmolality: Osmolality is an important parameter for intranasal formulations, as it influences nasal tolerability and patient comfort. Formulations with osmolality close to physiological nasal conditions are generally preferred to minimize irritation and maintain normal mucosal function³.

Mucoadhesive Properties: Mucoadhesive studies are performed to evaluate the ability of the formulation to adhere to the nasal mucosa. Enhanced mucoadhesion may prolong residence time in the nasal cavity, thereby increasing the opportunity for drug absorption.

Storage Stability: Storage stability studies are essential to assess the physical and chemical stability of nanoemulsions during storage. Parameters such as droplet size, phase separation, drug content, and appearance are typically monitored under different storage conditions.

Ex-vivo Nasal Permeation Study: Ex-vivo nasal permeation studies are commonly used to evaluate drug transport across excised nasal mucosal tissues. These studies provide preliminary information

regarding the permeability and absorption potential of intranasal formulations.

Pharmacokinetic and Biodistribution Studies:

Pharmacokinetic studies help determine the absorption, distribution, and elimination profile of the administered formulation. Biodistribution studies provide information regarding the extent of drug distribution to the brain and other organs following intranasal administration.

Pharmacodynamic Studies: Pharmacodynamic evaluation is important to assess the therapeutic efficacy of the formulation. Migraine-relevant experimental models may be used to investigate the potential effects of the formulation on neuroinflammation, pain signaling, and related pathological mechanisms^{3, 27, 28, 75}.

Herbal Actives for Migraine:

Bioactive Constituents of *Nigella sativa* in Migraine Therapy: Black cumin, or *Nigella sativa*, is a well-known medicinal herb from the Ranunculaceae family that has long been used for its neuroprotective, analgesic, anti-inflammatory, and antioxidant properties. Numerous bioactive components, including thymoquinone (TQ), nigellone, carvacrol, α -hederin, and p-cymene, are found in its seeds; among these, thymoquinone is the primary pharmacologically active substance. These phytoconstituents are essential for controlling inflammatory signaling, oxidative stress, and neural excitability all of which are key processes in the pathogenesis of migraines^{76, 77}. Neurogenic inflammation, trigeminovascular system activation, and elevated production of inflammatory mediators such as CGRP, prostaglandins, and nitric oxide are hallmarks of migraine⁷⁸. Thymoquinone, the major bioactive constituent of *Nigella sativa*, has demonstrated antioxidant, anti-inflammatory, and neuroprotective activities in several experimental studies. These pharmacological properties may be relevant to migraine pathophysiology, which involves neuroinflammation, oxidative stress, trigeminovascular activation, and altered neuronal excitability. Studies have reported that thymoquinone can inhibit cyclooxygenase, lipoxygenase, and inducible nitric oxide synthase pathways, thereby reducing the production of inflammatory mediators. In addition, thymoquinone

has been shown to modulate NF- κ B and MAPK signaling pathways and decrease the expression of pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6. Although direct evidence in migraine-specific clinical studies remains limited, these findings suggest the potential utility of thymoquinone in migraine management^{79, 80}.

Bioactive Constituents of *Withania somnifera* in Migraine Therapy:

Withania somnifera (Ashwagandha), a member of the Solanaceae family, is one of the most extensively used medicinal herbs in Ayurveda and is well known for its neuroprotective, adaptogenic, antioxidant, and anti-inflammatory properties. The major bioactive constituents of Ashwagandha are withanolides, a group of naturally occurring steroidal lactones that have demonstrated diverse pharmacological activities. Other constituents, including alkaloids, flavonoids, and saponins, may also contribute to its biological effects^{81, 82}.

Migraine pathophysiology involves multiple mechanisms, including oxidative stress, neuroinflammation, mitochondrial dysfunction, altered neuronal excitability, and dysregulation of stress-related pathways. Several studies have reported that withanolides possess antioxidant and anti-inflammatory activities that may be relevant to these pathological processes. Withaferin A and other withanolides have been shown to modulate inflammatory signaling pathways, including NF- κ B, leading to reduced expression of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. These mediators are known to play important roles in neuroinflammatory responses associated with migraine.

In addition, Ashwagandha has been reported to enhance endogenous antioxidant defense systems by increasing the activity of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby protecting neuronal cells from oxidative damage. Experimental studies have also demonstrated adaptogenic effects through modulation of the hypothalamic–pituitary–adrenal (HPA) axis, which may help regulate stress-related physiological responses. Since psychological stress is a common trigger for migraine attacks, these effects may have potential relevance in migraine management.

Furthermore, neuroprotective effects of Ashwagandha have been observed in several experimental models, where withanolides were found to support neuronal survival, improve mitochondrial function, and maintain neuronal homeostasis. These pharmacological activities suggest that *Withania somnifera* may influence biological pathways implicated in migraine pathogenesis. However, it is important to note that most available evidence is derived from experimental studies investigating neuroprotection, oxidative stress, inflammation, and stress-related disorders rather than migraine-specific clinical studies. Therefore, the potential role of Ashwagandha and its bioactive constituents in migraine management remains largely exploratory and requires further migraine-specific preclinical and clinical investigations to establish therapeutic efficacy^{83, 84, 85, 86, 87, 88}.

Bioactive Constituents of *Mentha piperita* in Migraine Therapy: *Mentha piperita* (peppermint), a member of the Lamiaceae family, has been widely used in traditional medicine for the management of headache and various pain-related conditions. The major bioactive constituents of peppermint include menthol, menthone, menthyl acetate, limonene, pulegone, and cineole, which contribute to its cooling, analgesic, and anti-inflammatory properties. Among these constituents, menthol is considered the principal compound responsible for many of the reported pharmacological effects⁸⁹. The potential relevance of menthol to migraine is primarily attributed to its

ability to activate transient receptor potential melastatin-8 (TRPM8) ion channels located on sensory neurons, producing a cooling sensation and modulating pain perception. Experimental studies have suggested that menthol may influence calcitonin gene-related peptide (CGRP)-associated signaling pathways and neurogenic inflammatory responses, which are implicated in migraine pathophysiology. In addition, menthol has demonstrated analgesic, anti-inflammatory, and antioxidant activities in several experimental models^{90, 91}. Peppermint oil and menthol preparations have also been investigated for their potential effects on headache symptoms. Some studies have reported reductions in headache intensity and associated discomfort following topical application of menthol-containing formulations. Furthermore, experimental evidence suggests that peppermint constituents may reduce the production of pro-inflammatory mediators and enhance endogenous antioxidant defenses, thereby protecting neuronal tissues from oxidative stress. However, it is important to note that much of the available evidence is derived from topical headache preparations, experimental studies, and non-migraine headache models rather than direct investigations of intranasal menthol-based therapy for migraine. Therefore, although menthol exhibits pharmacological activities that may be relevant to migraine pathophysiology, further migraine-specific preclinical and clinical studies are required to establish its efficacy and safety in intranasal migraine therapy^{92, 93, 94}.

TABLE 1: HERBAL BIOACTIVE COMPOUNDS AND THEIR MECHANISM IN MIGRAINE^{95, 88, 90}

S. no.	Herbal source	Bioactive Compound	Evidence type	Experimental model	Mechanism	Reference
1	<i>Nigella sativa</i>	thymoquinone	Direct migraine evidence(preclinical)	GTN-induced migraine rat model	CGRP modulation, anti-neuroinflammatory activity, mast cell stabilization	Kilinc <i>et al.</i> , 2020
2	<i>Withania somnifera</i>	withanolides	Indirect mechanistic evidence	Neurological disorder and stress-related models	Neuroprotection, anti-inflammatory activity, antioxidant effects, mitochondrial protection, and modulation of neuronal signaling pathways	Anees A Syed <i>et al.</i> , 2021
3	<i>Mentha piperita</i>	menthol	Direct migraine evidence(preclinical)	Migraine-like responses in female rats	Analgesic activity, sensory pathway modulation, anti-inflammatory effects Activates TRPM8 receptors and provides rapid pain relief	Laura de Oliveira Koren <i>et al.</i> , 2024

Polyherbal Nanoemulsion for Migraine Therapy: In this conceptual review, the term “polyherbal nanoemulsion” refers to a nanoemulsion system containing bioactive phytoconstituents derived from multiple medicinal plants, namely thymoquinone from *Nigella sativa*, withanolides from *Withania somnifera*, and menthol from *Mentha piperita*. These phytoconstituents were selected based on their reported pharmacological activities relevant to migraine pathophysiology, including anti-inflammatory, antioxidant, neuroprotective, and analgesic effects.

Migraine is a multifactorial neurological disorder involving neuroinflammation, oxidative stress, and neurotransmitter imbalance. Single-drug therapies often target only one pathway and may not provide complete relief. Therefore, a polyherbal approach is considered more effective due to its multi-target action¹.

Polyherbal formulations combine two or more herbal constituents with diverse pharmacological activities that may be relevant to migraine management. The selection of thymoquinone, withanolides, and menthol in the present review is based on their reported antioxidant, anti-inflammatory, neuroprotective, and analgesic properties. However, the therapeutic advantages of this specific combination have not yet been established through dedicated experimental or clinical studies and therefore require further investigation⁴.

Many herbal bioactive compounds exhibit poor aqueous solubility, limited stability, and low bioavailability, which may restrict their therapeutic application. Incorporation into nanoemulsion systems may help overcome some of these limitations by improving solubility, protecting sensitive constituents, and enhancing absorption. Intranasal nanoemulsions have also been investigated as a potential approach for facilitating drug transport through nasal pathways while avoiding certain limitations associated with conventional administration routes. Furthermore, the use of mucoadhesive polymers may increase nasal residence time and improve formulation retention within the nasal cavity^{96, 28}. Therefore, intranasal polyherbal nanoemulsion-based delivery

represents a promising conceptual approach for migraine management. Nevertheless, further formulation development, pharmacokinetic evaluation, safety assessment, and efficacy studies are required to establish its clinical utility.

Recent Advances in Intranasal Nanoemulsion for Brain Targeting: Recent developments in medication delivery systems based on intranasal nanoemulsions have shown great promise for efficient brain targeting. By avoiding the blood–brain barrier and increasing medication bioavailability, this method permits the direct delivery of therapeutic substances from the nasal cavity to the brain via olfactory and trigeminal pathways. The creation of nanoemulsion formulations for intranasal delivery to enhance the therapeutic efficacy of medications used in neurological illnesses, particularly migraine, has been the subject of various studies in recent years. Nanoemulsions nanoscale droplet size improves medication solubility, permeability, and retention in the nasal mucosa, leading to a quick beginning of action and better brain absorption.

Furthermore, the stability and performance of nanoemulsion systems have been further enhanced by developments in formulation tactics, such as the use of biocompatible surfactants, mucoadhesive agents, and optimised preparation techniques. These advancements lead to fewer systemic adverse effects and more effective drug administration.

Research on polyherbal nanoemulsion systems for intranasal brain targeting is still scarce, despite the fact that many experiments employing synthetic medicines have been published. This emphasises the need for more research on polyherbal formulations, which may provide enhanced safety profiles and synergistic medicinal advantages. Most studies summarized in **Table 2** were designed to evaluate formulation performance, nasal permeation, and CNS delivery rather than migraine-specific efficacy. Nevertheless, these studies collectively support the feasibility of intranasal nanoemulsion platforms. Direct investigations involving polyherbal intranasal nanoemulsions for migraine remain limited, highlighting an important research gap^{97, 98, 99, 100}.

TABLE 2: REPRESENTATIVE STUDIES DEMONSTRATING THE FEASIBILITY OF INTRANASAL NANOEMULSION-BASED DELIVERY SYSTEMS FOR CNS APPLICATIONS

Author	Year	Drug	Delivery system	Route	Key findings
Hadi AS	2022	Rizatriptan	Nanoemulsion	Intranasal	Enhance permeation and residence time and increase patient compliance.
Fatima AR <i>et al.</i>	2026	Sumatriptan	Nanoemulsion	Intranasal	Rapid drug release and improved permeation
Maryam H.	2023	Lomustine	Nanoemulsion	Intranasal	Promising potential drug delivery system may deliver the drug quickly and directly to brain as safe
Ebtsam M <i>et al.</i>	2017	Zolmitriptan	Nanoemulsion	Intranasal	Enhance the residence time.

Challenges and Future Prospects: Migraine therapy presents several challenges, primarily ensuring that drugs effectively reach the central nervous system (CNS), the key site of migraine pathology. The blood-brain barrier (BBB) remains a major obstacle, restricting the transport of many therapeutic agents to the brain parenchyma and thereby reducing their efficacy. Developing nanoformulations capable of penetrating the BBB and delivering drugs to specific CNS targets requires innovative design strategies to maximize brain penetration while minimizing off-target effects¹⁰¹.

A significant consideration for successful clinical translation is ensuring the safety, stability, and biocompatibility of these nanoformulations. Researchers must rigorously evaluate the toxicity, biodegradability, and pharmacokinetics of nanocarriers and their degradation products to guarantee patient safety¹⁰². Equally important are issues of cost-effectiveness, reproducibility, and quality control, which remain critical barriers to scaling up nanoformulations from the laboratory to industrial production. Standardized protocols and Quality-by-Design (QbD) strategies are crucial for ensuring consistent formulation quality and optimal therapeutic performance¹⁰³.

Additionally, the choice of manufacturing methods and optimization of formulation parameters significantly influence the stability and efficacy of nanoemulsions. Achieving regulatory approval poses another hurdle due to the novelty and complexity of nanocarrier systems. Establishing bioequivalence, assessing immunogenicity, and evaluating biodistribution are critical steps for successful clinical translation. Moreover, the high production cost of nanomaterials and the need for specialized equipment can limit accessibility, particularly in low-resource settings. Regulatory

compliance and safety assessments further add to development costs.

Therefore, maximizing manufacturing efficiency, reducing production expenses, and streamlining regulatory processes are crucial for ensuring that advanced nanoformulations, including polyherbal nanoemulsions, become affordable, scalable, and globally accessible. Moving forward, the integration of computational modeling, green synthesis, and advanced characterization techniques is expected to improve formulation predictability and safety. With continued interdisciplinary efforts, polyherbal nanoemulsion-based intranasal systems hold immense potential for the safe, effective, and non-invasive management of migraine and other CNS disorders¹⁰⁴.

CONCLUSIONS: Polyherbal nanoemulsions represent a novel and promising approach for brain-targeted drug delivery, particularly via the intranasal route. By combining the synergistic therapeutic potential of multiple herbal actives with the enhanced permeability and bioavailability offered by nanoemulsion systems, these formulations can effectively overcome the limitations of conventional CNS therapies. The intranasal route bypasses the blood-brain barrier, allowing rapid drug transport to the brain via the olfactory and trigeminal pathways, making it an excellent alternative to systemic delivery. Despite these advantages, issues such as formulation stability, scalability, regulatory compliance, and limited clinical translation continue to restrict their widespread application. Future research should focus on optimizing nanoemulsion composition, developing standardized polyherbal combinations, ensuring long-term safety, and advancing preclinical studies to clinical translation. With continued interdisciplinary efforts,

polyherbals nanoemulsions hold great promise as a sustainable, biocompatible, and effective therapeutic strategy for managing complex neurological disorders.

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