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Original Article

Herbal Ingredients for Sleep Disease Management: Using Vitex Negundo, Chamomile An Comprehensive Review

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ABSTRACT

Insomnia, a prevalent sleep disorder characterized by difficulty in initiating and maintaining sleep, adversely affects physical, mental, and emotional well-being. Conventional pharmacological treatments, although effective, are often associated with adverse effects, dependency, and tolerance. These limitations necessitate the development of safer, alternative therapeutic strategies. Nasal drug delivery systems have emerged as a promising approach due to their non-invasive nature, rapid onset of action, and direct access to the central nervous system, bypassing the hepatic first-pass metabolism. This study focuses on the of Vitex negundo and chamomile extracts, both renowned for their sedative and anxiolytic properties. Vitex negundo is rich in flavonoids and essential oils known for their sleep-inducing effects, while chamomile contains apigenin, a bioactive compound that binds to benzodiazepine receptors in the brain, promoting relaxation and sleep. The synergistic combination of these herbal extracts aims to provide a natural and effective solution for insomnia management without the risks associated with synthetic hypnotic. The results revealed optimal physicochemical characteristics suitable for nasal administration, ensuring sustained drug release and prolonged therapeutic effects. Pharmacological evaluations further demonstrated significant sedative activity, supporting the formulation's potential as an effective herbal remedy for insomnia.

Keywords: Insominia, Blood Brain Barrier,Nanotechnology, Vitex negundo,Chamomile

INTRODUCTION

Insomnia Disease

Insomnia is a common sleep disorder characterized by difficulty falling asleep, staying asleep, or waking up too early and not being able to return to sleep. It often leads to inadequate sleep, which can affect daily functioning, mood, and overall health.

Types of Insomnia

- **Acute Insomnia**: Short-term, usually caused by stress, a significant life event, or environmental factors.
- **Chronic Insomnia**: Lasts for a month or more, often associated with underlying health issues or persistent stress.
- **Comorbid Insomnia**: Occurs alongside other conditions such as depression, anxiety, or chronic pain.
- **Onset Insomnia**: Difficulty initiating sleep.
- **Maintenance Insomnia**: Difficulty staying asleep throughout the night.

Causes

- **Lifestyle Factors**: Irregular sleep schedules, excessive caffeine or alcohol intake, lack of physical activity.
- **Medical Conditions**: Chronic pain, asthma, acid reflux, neurological disorders, or hormonal changes (e.g., menopause).
- **Psychological Conditions**: Stress, anxiety, depression.
- **Medications**: Certain drugs for hypertension, asthma, or depression.
- **Environmental Factors**: Noise, light, uncomfortable bedding, or temperature.

Symptoms

- Difficulty falling asleep or staying asleep.
- Waking up frequently during the night.
- Feeling tired or fatigued despite sufficient time in bed.
- Mood disturbances, irritability, or anxiety.
- Reduced concentration and memory problems.
- Decreased performance at work or school.

Pathophysiology

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The pathophysiology of insomnia involves multiple complex interactions between the brain's sleep-wake regulatory mechanisms, psychological factors, and environmental influences. Insomnia can arise from hyperarousal, dysregulation of circadian rhythms, and disruptions in the neurotransmitters and hormones that control sleep.

Pathophysiological Mechanisms:

Hyperarousal:

- Insomnia is often associated with an increased state of physiological and psychological arousal, even at night.
- Hyperarousal may involve increased brain metabolic activity, elevated levels of stress hormones (e.g., cortisol), and sympathetic nervous system activation.

Neurotransmitter Imbalance

- Sleep is regulated by a balance between sleep-promoting and wake-promoting neurotransmitters.
- **Wake-promoting neurotransmitters**: Dopamine, norepinephrine, serotonin, and orexin.
- **Sleep-promoting neurotransmitters**: GABA (gamma-aminobutyric acid), adenosine.

Insomnia, a prevalent sleep disorder, is often caused by an imbalance in neurotransmitters that regulate the sleep-wake cycle. These chemical messengers in the brain play a crucial role in maintaining proper sleep patterns by either promoting wakefulness or inducing sleep. One of the primary neurotransmitters involved is Gamma-Aminobutyric Acid (GABA), the brain's main inhibitory neurotransmitter that helps calm neural activity. A deficiency in GABA can lead to heightened brain activity, resulting in difficulty falling or staying asleep. Another key neurotransmitter is Serotonin, which influences mood and sleep onset. Serotonin also serves as a precursor to Melatonin**,** the hormone responsible for regulating the circadian rhythm. Low levels of serotonin can impair melatonin production, disrupting the sleep-wake cycle and contributing to insomnia.Additionally, Dopamine, a neurotransmitter associated with wakefulness and arousal, when present in high levels at night, can cause restlessness and sleep disturbances. Norepinephrine, which plays a role in the body's stress response and alertness, can lead to hyperarousal if overactive, making it hard to stay asleep. Orexin (Hypocretin) is another neurotransmitter that promotes wakefulness; its increased activity has been linked to insomnia as it keeps the brain alert. Lastly, Glutamate, the main excitatory neurotransmitter, when excessively active, results in heightened brain activity, making relaxation and sleep initiation difficult.

The pathological mechanisms of insomnia:

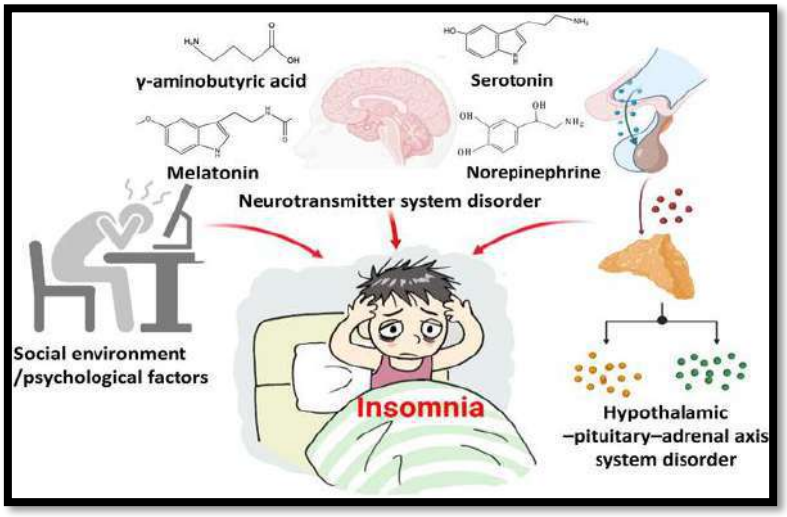

Figure No.- 1 Pathological mechanism of Insomnia

Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation

Chronic stress activates the HPA axis, increasing the release of cortisol, which can disrupt sleep by prolonging wakefulness and reducing deep sleep stages.

Circadian Rhythm Disturbance

The circadian rhythm, controlled by the suprachiasmatic nucleus (SCN) in the hypothalamus, regulates the sleep-wake cycle.

Misalignment of circadian rhythms (e.g., due to shift work or jet lag) can lead to insomnia.

Sleep-Wake Dysregulation

The two-process model of sleep regulation includes:

Process S: Sleep homeostasis, driven by the buildup of sleep pressure (adenosine) during wakefulness.

Process C: Circadian rhythms, which promote alertness during the day and sleepiness at night.

In insomnia, these processes may be out of sync or disrupted.

Risk Factors for Insomnia

Insomnia can be influenced by a variety of biological, psychological, environmental, and lifestyle-related factors. Understanding these risk factors helps identify vulnerable populations and guide preventive measures.

1. Psychological Factors:

Stress: Work pressure, financial worries, relationship issues, or traumatic events.

Mental Health Disorders: Anxiety, depression, and post-traumatic stress disorder (PTSD) significantly increase the risk.

Cognitive Hyperarousal: Excessive worrying or overthinking about sleep.

2. Medical Conditions:

- **Chronic Pain**: Conditions like arthritis, fibromyalgia, or back pain disrupt sleep.
- **Neurological Disorders**: Alzheimer's disease, Parkinson's disease, and restless leg syndrome.
- **Respiratory Issues**: Asthma, chronic obstructive pulmonary disease (COPD), or sleep apnea.
- **Gastrointestinal Problems**: Acid reflux or irritable bowel syndrome (IBS).
- **Endocrine Disorders**: Thyroid disorders or menopause-related hormonal changes.

3. Lifestyle and Behavioral Factors

- **Irregular Sleep Schedules**: Shift work, frequent travel, or irregular bedtimes.
- **Substance Use**: Excessive caffeine, nicotine, or alcohol consumption.
- **Screen Time**: Using electronic devices before bed exposes the brain to blue light, suppressing melatonin production.
- **Lack of Physical Activity**: Sedentary lifestyle affects overall sleep quality.

4. Environmental Factors

- **Disruptive Sleep Environment**: Noise, bright lights, uncomfortable bedding, or extreme temperatures.
- **Urbanization**: Living in areas with high noise or light pollution.

5. Demographic Factors

Age: Older adults are more prone due to changes in circadian rhythms and increased prevalence of medical conditions.

Gender: Women are more likely to experience insomnia, especially during hormonal changes (e.g., pregnancy, menopause).

Genetics: Family history of insomnia may increase susceptibility.

6. Medications

- **Stimulants**: Drugs containing caffeine or other stimulants.
- **Antidepressants**: Certain classes (e.g., selective serotonin reuptake inhibitors).
- **Steroids**: Corticosteroids like prednisone.
- **Beta-blockers**: Used for hypertension or heart conditions, which can interfere with sleep.

Nasal Route of Drug Delivery

The nasal route of drug delivery involves the administration of medications through the nostrils, where they are absorbed by the mucous membranes of the nasal cavity. This method has gained increasing attention in recent years due to its ability to provide both **local** and **systemic** therapeutic effects with several benefits over traditional routes like oral or injectable administration.

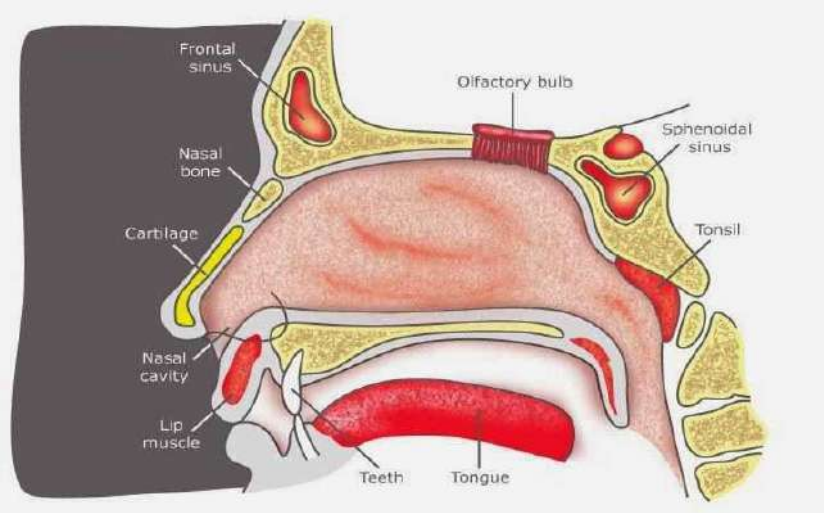

Figure No-2 Anatomy of nasal cavity

Advantages of Nasal Drug Delivery

- **Rapid Onset of Action**: Due to the rich vascularization of the nasal mucosa, drugs administered through the nasal route can be absorbed quickly, leading to a rapid onset of action compared to oral administration.
- **Bypassing the Gastrointestinal Tract**: Nasal administration avoids the gastrointestinal system and first-pass metabolism in the liver, leading to higher bioavailability for certain drugs.
- **Direct Delivery to the Brain**: The **nose-to-brain** pathway allows for targeted drug delivery to the central nervous system, which is beneficial for treating neurological disorders that require brain-specific action.
- **Convenience**: Nasal drug delivery is non-invasive, easy to self-administer, and suitable for acute conditions, such as allergies, pain management, and respiratory infections.
- **Avoids Needles**: Unlike injectable routes, the nasal route is needle-free, reducing the risk of infections and other complications associated with injections.

Applications of Nasal Drug Delivery

Nasal drug delivery is used for a wide variety of therapeutic purposes, including:

- **Treatment of Nasal and Respiratory Conditions**: Nasal sprays are commonly used to treat nasal congestion, allergic rhinitis, and sinusitis through decongestants, antihistamines, and corticosteroids.
- **Vaccines**: The nasal route is an ideal method for delivering vaccines, especially for respiratory diseases like the flu. Vaccines delivered nasally can stimulate both systemic and mucosal immunity.
- **Pain Management**: Nasal sprays are increasingly used for rapid pain relief, such as nasal administration of drugs like **fentanyl** for breakthrough cancer pain.
- **Neurological Disorders**: The ability of certain drugs to cross directly into the brain via the **nose-to-brain** pathway makes nasal delivery a promising approach for treating conditions like Alzheimer's disease, Parkinson's disease, and migraines.

Working & Mechanism of Nasal to Brain route

The **nasal-to-brain route** refers to the direct pathway through which drugs or other therapeutic agents are delivered from the nasal cavity to the brain, bypassing the blood-brain barrier (BBB). This route holds significant potential for targeting central nervous system (CNS) disorders, as it allows drugs to reach the brain quickly and efficiently. The mechanism behind this route involves complex anatomical and physiological processes that facilitate the transport of drugs from the nose to the brain, primarily via two key pathways: the **olfactory** and **trigeminal** nerve pathways.

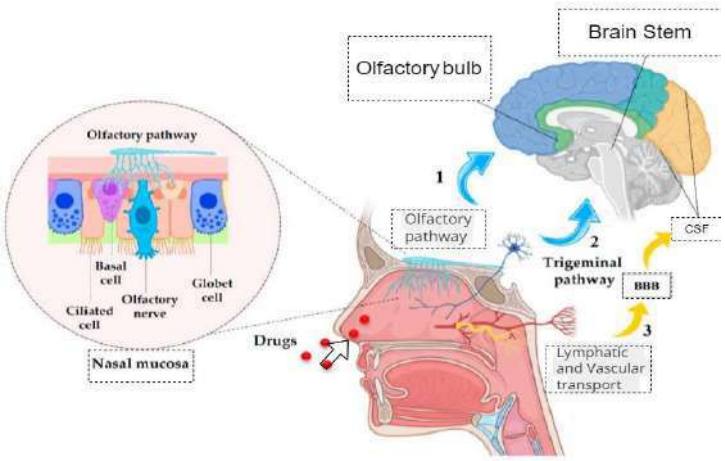

Figure No-3 Intranasal mechanism of nose-to-brain delivery's

1. Olfactory Nerve Pathway

The **olfactory nerve pathway** is the most well-known and studied mechanism for nasal-to-brain drug delivery. The process occurs as follows:

1. **Drug Administration**: When a drug is administered through the nose (e.g., via a nasal spray or nasal drop), it comes into contact with the olfactory epithelium, which is located at the roof of the nasal cavity. The olfactory epithelium is directly connected to the olfactory bulb in the brain.
2. **Absorption into Olfactory Nerve Endings**: The olfactory epithelium contains sensory receptors that detect odor molecules. These receptors are located on the olfactory nerve endings, which extend from the olfactory bulb. The drug particles can penetrate the mucosa and come into contact with these sensory nerve endings.
3. **Travel Along the Olfactory Nerve**: Once the drug interacts with the olfactory nerve endings, it is transported along the olfactory nerve fibers through the **cribriform plate**, a bony structure separating the nasal cavity from the brain. The cribriform plate has small openings (foramina) that allow the nerve fibers to pass through and connect to the olfactory bulb.
4. **Direct Access to the Brain**: From the olfactory bulb, the drug molecules travel along the olfactory tract to various brain regions, including the limbic system (which is involved in memory, emotion, and learning). This direct pathway bypasses the blood-brain barrier and allows for rapid drug delivery to the brain.

- **Advantage**: This route is beneficial because the olfactory pathway is not protected by the blood-brain barrier at the olfactory bulb, allowing drugs to reach the brain without the constraints of BBB permeability.

2. Trigeminal Nerve Pathway

The **trigeminal nerve pathway** is another important mechanism for nasal-to-brain drug delivery. This pathway involves the trigeminal nerve, which is responsible for sensory and motor functions in the face, including the nasal mucosa.

1. **Drug Absorption in the Nasal Cavity**: After the drug is administered through the nasal cavity, it can also be absorbed through the nasal mucosa and interact with the sensory nerve endings of the **trigeminal nerve**. The trigeminal nerve innervates the nasal mucosa and provides sensory information from the face to the brain.
2. **Transport Through the Trigeminal Nerve**: The trigeminal nerve fibers travel from the nasal cavity to the **trigeminal ganglion**, which is located near the brainstem. From there, the sensory information, along with the absorbed drug, is transported to the brainstem and other regions of the brain.
3. **Bypassing the Blood-Brain Barrier**: Like the olfactory pathway, the trigeminal nerve pathway bypasses the blood-brain barrier, allowing drugs to reach various regions of the brain, including the brainstem, hypothalamus, and cerebral cortex.

Advantage: The trigeminal nerve pathway offers a complementary route for delivering drugs to the brain, particularly when the olfactory pathway may not be as effective or suitable for certain types of drugs.

3. Mucosal Absorption and Transport

Once a drug enters the nasal cavity, the drug molecules are absorbed through the **nasal mucosa** (the inner lining of the nasal passages). The mucosa is highly vascularized, which enables efficient

absorption of drugs into the bloodstream. However, for the nasal-to-brain route, the focus is on the **direct transport** of the drug molecules through the nerve pathways (olfactory and trigeminal), bypassing systemic circulation and the blood-brain barrier.

1. **Transport Across the Mucosa**: The drug crosses the epithelial cells in the nasal mucosa, which is rich in blood vessels, and enters the underlying tissues. The absorption is facilitated by the thin mucosal layer and the high vascularity of the nasal cavity, which allows drugs to quickly reach the nerve fibers.
2. **Direct Interaction with Nerve Fibers**: After absorption into the mucosa, drugs can directly interact with the olfactory or trigeminal nerve endings located in the nasal cavity, enabling the rapid transport of the drug to the brain.

Drug used in Insominia:

Vitex negundo Linn:commonly known as the Chinese chaste tree, Lagundi, or the five-leaved chaste tree, is a medicinal plant belonging to the *Lamiaceae* family. The biological source of this plant is its leaves, which are widely used for their therapeutic properties. Typically, *Vitex negundo* grows to a height of 1–3 meters and is characterized by opposite, palmate leaves with serrated edges. The plant produces small purple or blue flowers arranged in spikes, which attract various pollinators.

Taxonomical study .

- Kingdom: Plantae
- Division (Phylum): Angiosperms
- Class: Dicotyledons
- Order: Lamiales
- Family: Verbenaceae
- Genus: Vitex
- Species: Vitex negundo

Figure No-4 Vitex negundo Linn

Pharmacologically, *Vitex negundo* exhibits a wide range of beneficial properties. It has notable **anti-inflammatory** effects, making it useful in managing arthritis and other inflammatory conditions. Its **antioxidant** properties help protect the body against oxidative stress, thereby supporting overall cellular health. Additionally, the plant has **sedative** effects that promote relaxation and enhance sleep quality, potentially by influencing GABA activity. As a **hormonal modulator**, it plays a role in balancing hormones, offering relief from menstrual and menopausal symptoms. Moreover, *Vitex negundo* demonstrates **antimicrobial** activity, exhibiting effectiveness against various bacteria and fungi. Lastly, its **analgesic** properties provide pain relief, particularly for headaches and muscle aches, making it a versatile plant in traditional and modern medicine.

Chamomile:

scientifically known as *Matricaria chamomilla* (German chamomile) and *Chamaemelum nobile* (Roman chamomile), belongs to the *Asteraceae* family. The flowers of the plant are primarily used for their medicinal properties. Chamomile contains several active constituents, including flavonoids such as apigenin, luteolin, and quercetin, along with terpenoids, bisabolol, and chamazulene. It is also known by various synonyms, including Camomilla, Ground Apple, and *Babune ka Phal*.

Figure No-5 Chamomile

Pharmacologically, chamomile is renowned for its wide range of therapeutic effects. It acts as a **mild sedative**, promoting relaxation and aiding in the treatment of **insomnia** and **anxiety**. For **skin conditions**, chamomile is effective in treating eczema, dermatitis, and minor burns due to its soothing and anti-inflammatory properties. In terms of **digestive health**, it helps alleviate issues such as indigestion, bloating, and stomach cramps. Chamomile also supports **wound healing**, accelerating the recovery of cuts and abrasions.

Additionally, it exhibits **anti-allergic** properties, helping to reduce symptoms associated with allergic reactions, making it a versatile and widely used medicinal herb.

Taxonomical Classification:

- **Kingdom**: Plantae
- **Clade**: Angiosperms
- **Order**: Asterales
- **Family**: Asteraceae
- **Genus**: Matricaria
- **Species**: *Matricaria chamomilla*

DISCUSSION:

The use of the nasal route for drug delivery in treating insomnia presents a promising therapeutic approach, particularly due to its potential for direct nose-to-brain drug transport. This bypasses the blood-brain barrier (BBB), enhancing the efficacy of treatments aimed at the central nervous system (CNS). Traditional oral medications for insomnia often face challenges such as first-pass metabolism, leading to reduced bioavailability and delayed onset of action. In contrast, nasal delivery offers rapid onset, higher bioavailability, and non-invasiveness, which significantly improve patient compliance.The anatomy of the nasal cavity, especially the olfactory region, plays a critical role in facilitating direct drug transport to the brain. This route minimizes systemic exposure, potentially reducing adverse effects commonly associated with systemic sedatives and hypnotics. Moreover, the nasal route's ability to bypass hepatic metabolism may allow for lower dosages, reducing toxicity risks.However, several limitations must be considered. The nasal mucosa's enzymatic activity can degrade some drugs, affecting their therapeutic potential. Variability in absorption d ue to individual anatomical and physiological differences can also influence treatment outcomes. Additionally, chronic use of intranasal formulations may lead to mucosal irritation, which could compromise patient adherence.In terms of insomnia's pathophysiology, hyperarousal and neurotransmitter imbalances, especially involving GABA, serotonin, and orexin, are key contributors. Nasal delivery systems targeting these pathways can provide rapid and efficient symptom relief. The role of the hypothalamic-pituitary-adrenal (HPA) axis in insomnia also highlights the potential of nasal delivery for drugs modulating stress-related hormonal pathways.

CONCLUSION:

Nasal drug delivery represents a highly promising alternative for managing insomnia, offering rapid onset of action, improved bioavailability, and enhanced patient compliance due to its non-invasive nature. By leveraging direct nose-to-brain pathways, this method provides an efficient approach to targeting the CNS, potentially overcoming limitations associated with oral and injectable formulations.While the advantages are significant, careful consideration of formulation stability, mucosal compatibility, and long-term safety is essential. Future research should focus on optimizing drug formulations to minimize mucosal irritation, improve absorption consistency, and enhance targeting of specific neurotransmitter systems involved in sleep regulation. Overall, nasal delivery systems have the potential to revolutionize insomnia management, especially when combined with advancements in nanotechnology and personalized medicine. Further clinical studies are warranted to validate their efficacy and safety, paving the way for innovative, patient-friendly treatment options for insomnia.

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