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AN INSIGHTFUL OVERVIEW AND A COMPREHENSIVE CRITICAL ANALYSIS OF NASO HI SHIRASODWARAM

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ABSTRACT
The ancient Ayurvedic dictum, "Nasa is the doorway to Shira," underscores the significance of the nasal passages as a conduit for both sensory perception and therapeutic intervention. Considered one of the Panchagyanendriya, the nose plays a multifaceted role beyond olfaction and respiration, serving as a pathway for drug administration as well. In line with modern pharmacology, Ayurveda recognizes various routes of drug administration, with the nasal route proving particularly efficient for diseases above the supraclavicular region. Nasya Karma, the process of instilling medicated Taila, Swarasa, Churna through the nostrils, emerges as a key therapeutic modality in Ayurveda. This review article explores the probable mode of action of Nasya Karma, shedding light on its mechanisms in both Ayurvedic and modern contexts. Specifically, it delves into how Nasya Karma may act on vital points located in the brain and associated structures, offering insights into its therapeutic potential and reinforcing its relevance in contemporary medical practice with an understanding and addressing the nasal-head connection play a vital role in Ayurvedic approaches to wellness.

KEYWORDS: Nasa, Marmas, Pathways, Blood Brain Barrier, Intra Nasal Drug Delivery, Nasya Karmukata In Urdwajatru.

INTRODUCTION
The Acharyas have attributed prime importance to Shalakya Tantra, with Acharya Charaka emphasizing the significance of the shiras as the "Uttamanga," being the seat for all vital centers of living creatures and all senses. He compares the importance of the shiras to that of the roots of a tree, indicating that just as a tree without malformations in its roots grows properly, a human body without any peculiarities in the shiras can develop and survive better. Nasya, therefore, holds a pivotal role in this regard. The administration of medicine into the nostrils facilitates its spread through the shiras, aiding in the evacuation of doshas and thereby pacifying diseases. Nasya karma serves as the primary treatment for diseases above the clavicle, acting as the exclusive shodhanakarma for Urdhwanga. The drugs administered through the nostrils reach the shringataka marma (sira marma), spreading into the murdha (brain) via the Netra, Shrotra, Kanta, and Siramukha, thereby extracting morbid doshas from the uttamanga, resembling the removal of munja grass from its stem. Acharya illustrates this process by likening it to how a paintbrush absorbs colour through its bristles, indicating that the medicines administered are absorbed and spread throughout the shiras. Furthermore, the Ghranendriya, as one of the Pancha Gyanendriyas, has the nasa (nose) serving as the adhistana of Ghranendriya. Composed of Pruthvi mahabhuta, it is responsible for perceiving gandha (olfaction) among the five senses. This intricate connection highlights the profound role of the nasal passage not only in physical health but also in sensory perception and overall well-being.

AIMS AND OBJECTIVES OF STUDY
A literary review on Naso hi shirasodwaram aims to provide a comprehensive understanding of the anatomical structure and physiological significance and also explore the intricate details of this nasal region, elucidating its intricate connections to various bodily systems and its functions.

MATERIALS AND METODS

Various ayurvedic texts such as Brihattrayi, Laghutrayi, contemporary science textbooks etc medical journals, published articles were studied and all the relevant points have been explained in this study.

➢ **Marmas Related to Nasa**

❑ **Phana Marma (sira marma)**

➢ "घ्राणश्रोत्राक्षिजिह्वासन्तर्पणीनां सिराणां मध्ये सिरासन्निपातः शृङ्गाटकानि, तानि चत्वारि मर्माणि, तत्रापिसद्योमरणम।"(Su.Sha. 6/27)

- Are located at either side of nasal cavities
- Half angula in pramana
- 2 number
- Compared with Olfactory bulb with it's tract
- Injury to this marma leads to permanent loss of Gandhaagnyana(anosmia)

❑ **Sthapani Marma**

➢ भ्रुवोर्मध्ये स्थपनी नाम, तत्रोत्क्षेपवत्।

सिरामर्म अर्धांगुलं विशल्यघ्नं च।

स्थपनी पुनःभ्रुवोर्मध्ये नासिकाक्षि खचतुष्टय संगमे॥ su.sha.6/28

- It is a Sira marma
- Lies at roof of the nose and between the eyes
- ½ anguli in size
- Is a visalyaghna marma
- Is correlated with glabella

❑ **Shringantaka Marma**

➢ "घ्राणश्रोत्राक्षिजिह्वासन्तर्पणीनां सिराणां मध्ये सिरासन्निपातः शृङ्गाटकानि, तानि चत्वारि मर्माणि, तत्रापिसद्योमरणम।"(Su.Sha. 6/27)

- Shrungataka marma is situated within the confluence of Sira; nourishing the Ghrana(nose), Shrota (ear), Akshi(eye) & Jivha (tongue).
- These are four in number, incorporated under Sadyopranahara marma category, measures vicinity of four Angula (8cm)
- The corpus of this marma is made up of Sira or Dhamani (vascular entity). On injury of these marma, death will occur immediately or within the Seven days.
- The Nasya medicaments are going to reach in the shrungataka marma and the dosha residing in the region of oral cavity (Mukha), nose (nasa), eye (Akshi) & tongue (Jivha) are expelled out.
- Probably Shrigantaka marma is correlated with, base of the forebrain, limbic system, hypothalamus, cavernous sinus

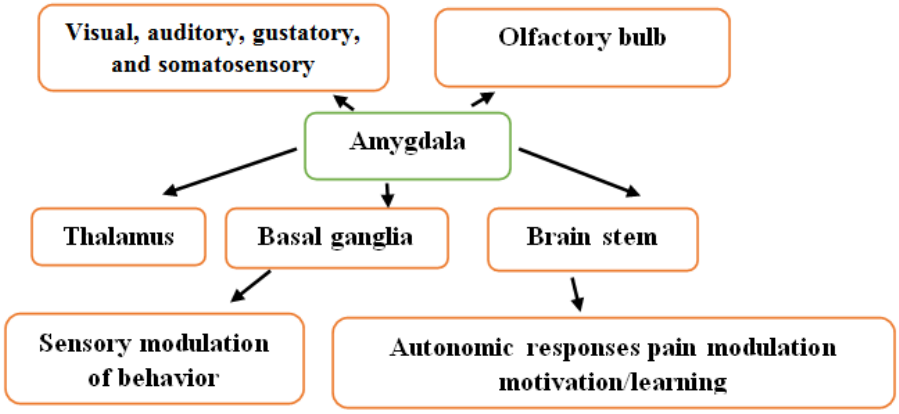
❖ **LIMBIC SYSTEM**

- The word "limbic" means "border." Originally, the term "limbic" was used to describe the border structures around the basal regions of the cerebrum
- The subcortical structures of the limbic system, includes the septum, the Paraolfactory area, the anterior nucleus of the thalamus, portions of the basal ganglia, the hippocampus, and the amygdala
- It controls emotional, behavior and motivational drives.

❖ **AMYGDALA**

- The amygdala is a complex of multiple small nuclei located immediately beneath the cerebral cortex of the medial anterior pole of each temporal lobe
- It has abundant bidirectional connections with the hypothalamus as well as with other areas of the limbic system

❖ **CONNECTIONS AND FUNCTIONS**



❖ **CAVERNOUS SINUS**

- Is a large venous plexus that lies on both sides of the body of the sphenoid bone which extends from the superior orbital fissure to the apex of the petrous temporal bone.
- Average length of 2cm and width of 1cm.
- The sphenoid air sinus and pituitary gland are medial to the cavernous sinus.

❖ **CONTENTS OF CAVERNOUS SINUS**

* Oculomotor nerve
* Ophthalmic nerve
* Trochlear nerve
* Internal Carotid artery
* Maxillary division of trigeminal nerve
* Abducent nerve

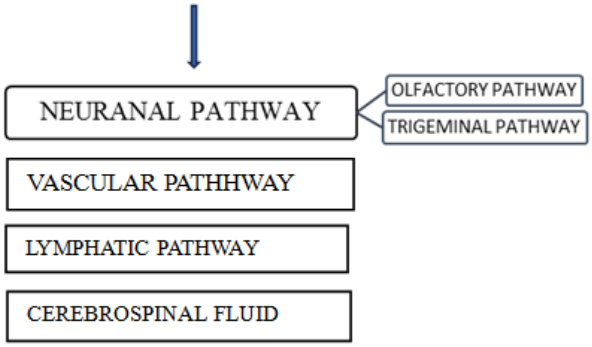
❖ **Tributaries Of Cavernous Sinus**

- Superior ophthalmic vein
- Inferior ophthalmic vein
- Superficial middle cerebral vein
- Inferior cerebral vein
- The central retinal vein and frontal tributary of the middle meningeal vein sometimes drains into it.

These tributaries drain into internal Juglar vein through the superior petrosal sinus

The drugs administrated intra nasally (nasya) stimulates the higher centers of brain via **4 main pathways**

NOSE TO BRAIN



OLFACTORY PATHWAY

The medicinal substance 1st diffuse into the mucus membrane of nose

⇓

Binds with receptor protein

⇓

Which activates the G protein complex

⇓

Activates the adenylyl cyclase inside the olfactory cell membrane, forms the cyclic AMP

⇓

Influx of Na+ takes place & generation of receptor potential

⇓

Olfactory nerves fibers pierces the cribriform plate of ethmoid

⇓

Olfactory bulb

⇓

Olfactory tract

⇓

olfactory cortex in the BRAIN

TRIGEMINAL NERVE PATHWAY

Internal and External nasal branches of the nasociliary nerve

⇓

(anterior part of septum, lateral wall nasal cavity and tip of nose)

⇓

cribriform plate of the ethmoid bone

⇓

cranium beneath the dura matter

VASCULAR PATHWAY

- Nose to brain route is utilized to deliver drug to the systemic circulation through absorption into the blood vessels underlying the nasal mucosa.
- Nose is supplied by both the external and internal carotid arteries, both on the septum and the lateral walls

a) **Nasal septum and Lateral wall** are supplied by the anterior and posterior ethmoidal artery.
b) **Nasal septum** is supplied by the sphenopalatine artery, septal branch of greater palatine artery, and septal branch of superior labial artery.
c) **Lateral wall** is supplied from sphenopalatine artery, greater palatine artery, nasal branch of anterior superior dental artery.
d) **Nasal vestibule** is supplied by the branches of facial artery.

- The relative density of the blood vessels is greater in the respiratory mucosa than the olfactory mucosa, making the former an ideal region for adsorption of drug into the systemic circulation.
- The respiratory region is the combination of the continuous and fenestrated endothelium that allows the exit of both small and large molecules of drug, into the blood subsequent transport cross the BBB of the brain.
- This is especially true for small lipophilic drugs which more easily enter to the blood stream and it can cross the BBB compared to large hydrophilic molecules.
- The intra nasal drug is distributed throughout the systemic circulation and it enter in the blood supply of the nasal cavity and get transferred to the brain via carotid artery.

CEREBROSPINAL FLUID PATHWAY

- This pathway is connected to the subarachnoid space containing CSF, perineural spaces encompassing olfactory nerves and the nasal lymphatics.
- The CSF circulation and drainage provide access for nose to brain administered medicines to the CSF and other areas of the brain.
- The medicines administered into the cerebral ventricles or subarachnoid space, drain to the olfactory bulbs into channels associated with olfactory nerves traversing the cribriform plate that reach the nasal lymphatic system and cervical lymph nodes. Hence CSF flows, along the olfactory sub mucosa in the roof of the nasal cavity.
- Nose to brain administration of drugs is a same pathway from the nasal cavity to CSF into the brain interstitial spaces and perivascular spaces for distribution throughout the brain.
- Therefore, nose to brain administration is demonstrated by the drugs gains direct access to the CSF from the nasal cavity followed by subsequent distribution to the brain.

LYMPHATIC PATHWAY

The nasal submucosal lymphatics
⇓
Via a perineural space route (cribriform plate)
⇓
subarachnoid space

➢ **BLOOD BRAIN BARRIER**

- The blood-brain barrier is the barrier between the cerebral capillary blood and the interstitial fluid of the brain.
- It is made up of capillary endothelial cells, basement membrane, neuroglial membrane, and glial podocytes, i.e. Projections of astrocytes.
- The BBB is playing a critical role in protecting the brain parenchyma from blood-borne agents and providing a significant obstacle to the entry of drugs and other exogenous compounds into the central nervous system.

➢ **FUNCTIONS OF BBB**

- The essential function of the BBB is the maintenance of brain homeostasis.
- This is achieved via tightly regulated ion and solute transport between the intravascular plasma and the CNS through molecular exchange pathways that transport molecules from blood-to-brain and brain-to-blood.
- However, not all molecules require transport mechanisms across the BBB. Gases such as carbon dioxide and oxygen, as well as lipophilic molecules with a molecular weight under 400 Da, can freely diffuse across the BBB.
- The diffusion of substances into the brain is achieved via paracellular or transcellular pathways. To a minor extent, small water-soluble molecules are able to use simple diffusion to travel through the tight junctions of the BBB.

➢ **TRANS NASAL DRUG DELIVERY**

1) Passage of drug through the mucus is the first step in the absorption from the nasal cavity.

2) Nasal route is easily accessible, convenient, and reliable with porous endothelial membrane and highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination.
3) Majority of Drugs are absorbed by passive diffusion
4) Literature shows that up to 1000dalton drug get easily absorbed without help of penetration enhancers.
5) Two mechanisms have been predominantly used for drug absorption

➢ **Paracellular transport**

- It is a Slow process and is an aqueous route of transport

➢ **Transcellular transport**

- Transport through lipoidal membrane
- Active transport occurs through carrier-mediated mechanism.

❖ **DIFFERENT FACTORS INFLUENCING NASAL DRUG ABSORPTION**

1. Biological factors
- Structural factors
- Biochemical changes

❖ **STRUCTURAL FACTORS**

RESPIRATORY MUCOSA	OLFACTORY MUCOSA
Ciliated & non ciliated	pseudostratified columnar epithelium
Columnar cells	supporting cells
Goblet cells	microvillar cells
Basal cells	olfactory receptors cells
low no.of neurosecretory cells	

❖ **BIO CHEMICAL CHANGES**

- Internasal administration of drugs avoids gastrointestinal and hepatic first pass effect.
- Drug may be metabolized in lumen of nasal cavity due to the presence of a broad range of metabolic enzymes in nasal tissues.
- Some examples of enzyme which may play role in enzymatic degradation of drugs are carboxyl esterase, aldehyde dehydrogenases, epoxide hydrolases, glutathione S transferases and Cytochrome P450 isoenzymes have been found in nasal epithelial cells.

❖ **PHYSIOLOGICAL FACTORS**

○ **Blood supply and neuronal regulation**

- Nasal mucosa is highly permeable site.
- The ramification of the vessels from a close plexiform network, beneath and in the mucous membrane makes an optimal location for drug absorption
- The blood flow rate influences significantly the systemic nasal absorption of drugs, so that as it enhances more drug passes through the membrane

○ **Nasal secretions**

- Nasal secretions are produced by anterior serous and seromucous glands.
- The permeability of drug through the nasal mucosa is affected by viscosity of nasal secretions.

○ **Mucociliary clearance (MCC) and ciliary beating**

- Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense
- Mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx.

2. Physiological factors
- Blood supply & neuronal regulation
- Nasal secretions
- MCC & ciliary beat frequency
- Pathological condition
- Environmental condition
- Membrane permeability

3. Physiochemical properties of drugs
- Molecular weight
- Particle size
- solubility
- lipophilicity
- Chemical form of drug
- Polymorphism
- Buffer capacity

4. Physiochemical properties of formulation
- PH
- Viscosity
- osmolarity

- Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MCC; Whereas, increased MCC decreases drug permeation.

- **Pathological conditions**
- Mucociliary misfunctioning, hypo or hypersecretions
- Irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

- **Environmental conditions**
- Moderate reduction in the rate of MCC occurs at the temperature of 24˚C, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.

- **Membrane permeability**
- Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor.
- The large molecular weight drugs and water-soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in fewer amounts

- **Physicochemical Properties of Drug**
- **Molecular Weight**
- A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da.
- Absorption decreases significantly if the molecular weight is greater than 1000 Dalton.
- Nasal delivery is expected to decrease with increasing molecular weight of the drug.

- **Particle size**
- It has been reported that particle sizes greater than 10µm are deposited in the nasal cavity
- Particles that are 2 to 10µm can be retained in the lungs, and particles of less than 1µm are exhaled.

- **Solubility of drug in nasal secretions**
- For permeation of drug solubility is necessary
- Drugs with poorly soluble in water may require high doses

- **Chemical form of drug**
- The form of a drug can be important in determining absorption.
- Example: Nasal absorption of carboxylic acid esters of L-Tyrosine significantly greater than that of L-Tyrosine.

- **Polymorphism**
- Polymorphism is known to affect the dissolution rate, solubility of drug and thus their absorption through biological membranes.
- It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and suspensions.

- **Lipophilicity**
- On increasing in lipophilicity, the permeation of the compound normally increases through nasal mucosa.
- Although the nasal mucosa was found to have some hydrophilic character,
- It appears that this mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes

- **Buffer Capacity**
- Nasal formulations are generally administered in small volumes ranging from 25 to 200µL.
- Hence, nasal secretions may alter the pH of the administrate dose.
- This can affect the concentration of unionized drug available for absorption

- **pH of nasal cavity**
- Variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants.
- pH of formulation should be between 4.5 to 6.5 for better absorption and also have good buffering capacity.

- **Osmolarity**
- Drug absorption can be affected by tonicity of formulation.
- Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions.
- Hypertonic saline solutions also inhibit or cease ciliary activity.
- Low pH has a similar effect as that of a hypertonic solution

- **Viscosity**
- ❖ A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation.
- ❖ At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs

❖ **Formulations based on Nasal Delivery System**

➢ **Liquid dosage forms**

○ **Nasal drops**

❖ Nasal drops are one of the most simple and convenient delivery systems among all formulations.

❖ The main disadvantage of this system is the lack of dose precision

○ **Nasal sprays**

❖ Both solution and suspension formulations can be formulated into nasal spray

❖ Due to the availability of metered dose pumps and actuators, a nasal spray can

❖ Deliver an exact dose anywhere from 25 -200 µL.

○ **Nasal emulsions, micro emulsions**

❖ Nasal emulsions offer the advantages for local application mainly due to the viscosity.

➢ **Semi-solid dosage forms**

❖ Semi-solid systems, for example gels, ointments and liquid systems containing polymers that gel at particular pH changes are usually employed for designing the nasal drug delivery systems.

○ **Nasal gels**

❖ Nasal gels are thickened solutions or suspensions, of high-viscosity.

❖ The advantages of a nasal gel include the reduction of post-nasal dripping due to its high viscosity,

❖ Reduction of the taste impact due to reduced swallowing, reduction of anterior leakage of the formulation

➢ **Solid dosage forms**

❖ Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications,

❖ since it can cover the vasculature within the epithelium of nasal mucosa.

○ **Nasal powders**

❖ Powder dosage forms may be developed if solution and suspension dosage forms cannot be developed, mainly due to lack of drug stability.

❖ The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation.

❖ However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients.

✓ **Novel drug formulations**

❖ Several claims have been made in favour of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery.

❑ **Liposomes**

❖ Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included.

❖ Liposomal drug delivery systems present various advantages such as

✓ The effective encapsulation of small and large molecules with a wide range of hydrophilicity.

✓ In fact, they have been found to enhance nasal absorption This has attributed to the increasing nasal retention.

✓ Protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption.

❑ **Microspheres**

❖ Microsphere technology has been widely applied in designing formulations for nasal drug delivery.

❖ Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery.

❖ Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect.

❑ **Nanoparticles**

❖ Nanoparticles are solid colloidal particles with diameters ranging from 1-1000 nm.

❖ They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached.

❖ Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity

❖ **ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM**

✓ Absorption of drug is rapid via highly vascularised mucosa.

✓ Availability of large nasal mucosal surface area for dose absorption.

✓ Onset of action is rapid.

✓ Non-invasive and easy for administration.

✓ Bypass the BBB.

✓ Degradation of drug observed in GIT is avoided.

✓ Hepatic first pass metabolism is absent.

- ✓ Nasal bioavailability of small drug molecules is good.
- ✓ Unsuitable drug candidates for oral route can be successfully given via nasal route.
- ✓ Convenient route for the patient on long term therapy.
- ✓ Side effects are reduced due to low dose.
- ✓ A self-administration is possible.
- ✓ Direct transport into systemic circulation and CNS is Possible.
- ✓ Offers lower risk of overdose
- ✓ Does not have any complex formulation requirement.

❑ LIMITATIONS OF NASAL DRUG DELIVERY SYSTEM

- ✓ Delivery volume in nasal cavity is restricted to 25–200 µL.
- ✓ High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa).
- ✓ Adversely affected by pathological conditions.
- ✓ Normal defense mechanisms like mucociliary Clearance and ciliary beating affects the permeability of drug.
- ✓ Smaller absorption surface compared with GIT.
- ✓ Possibility of nasal irritation hence inconvenient compared with oral route.

❖ DISCUSSION

- Nose is one among the Panchagyaanendriya, whose functions are not only limited to olfaction and respiration but also considered as a pathway for drug administration.
- As per our ayurvedic classics several treatment modalities have been explained for urdhwajathurgata vikaras but till date nasya is considered to be the prime treatment modality for all such conditions.
- दोषैर्विदग्धैरथवाऽपि जन्तोर्ललाटदेशेऽभिहतस्य तैस्तु ।
  नासा स्रवेत् पूयमसृग्विमिश्रं तं पूयरक्तं प्रवदन्ति रोगम् ॥ Su.utt.22/10
- Any injury to the lalata pradesha, causes the puya mishrita raktasrava from the nose here we may consider that there is a direct connection between the nose to brain.
- During nasya the drug administered through nose reaches to the brain and eliminates the morbid Doshas responsible for producing the diseases.
- कल्कक्काथादिभिश्चायं मधुपवासवैरपि II" A.H.SU.20/5
- The formulations for nasya encompass various forms such as ghrita (medicated ghee), taila (medicated oil), kalka (paste), churna (powder), and swarasa (juice). These can be analogously compared to the formulations used in intra-nasal drug therapy, where ghrita or taila represent lipophilic substances, swarasa signifies hydrophilic solutions, churna denotes powdered(nano particle) substances, and kalka represents semi-solid dosage forms. This analogy allows for a deeper understanding and comparison of the different forms of medication delivery in nasal therapy.
- The lipid - soluble part of this herbal drug enter into ghrita or taila and these ghrita or taila when used for nasya karma, this lipid soluble active ingredient enters in capillary network of the nasal mucosa. Being lipid - soluble it can also enter into CNS and reach the targeted areas.

CONCLUSION

- The meticulous attention to detail in the procedures, postures, and techniques of Nasya Karma plays a critical role in optimizing the absorption and distribution of medicinal substances within the body. This ancient practice aligns closely with the fundamental concept of "nasa hi shiraso dwaram," which underscores the nasal passage as a gateway to the head. By utilizing the inherent properties of the nasal mucosa, Nasya Karma facilitates the efficient absorption of therapeutic agents, offering significant advantages, particularly in treating conditions that afflict the upper body.

- One of the key benefits of Nasya Karma lies in its ability to deliver medications directly to the brain via the nasal route. As the nasal mucosa is highly vascularized and permeable, substances introduced through this pathway can rapidly enter the bloodstream and reach the brain. This direct access to the central nervous system allows Nasya-administered medicines to exert their influence on higher brain centers responsible for regulating a myriad of physiological processes, including neurological functions, hormonal balance, and blood circulation.

- This dual mechanism manifests both local and systemic effects. Consequently, this method of drug administration emerges as a promising alternative route, demonstrating efficacy for local, systemic, and central nervous system actions.

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