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BASTI KARMA - A NOVEL DRUG DELIVERY SYSTEM IN POSTERIOR SEGMENT DISEASES OF EYE

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ABSTRACT

Although topical therapies have been greatly developed and emphasised in ocular therapeutics in the form of Kriyakalpa in Ayurveda, but due to anatomical and physiological barriers like blood aqueous barrier and blood retinal barrier in Ophthalmic tissues, drug delivery poses a challenge towards drug permeability and bioavailability to the posterior segment of the eye. Posterior segment diseases like Diabetic retinopathy, Age related macular degeneration (ARMD), vascular and degenerative disorders of retina, Glaucoma and optic nerve disorders are emerging disorders of the twenty first century and posing a major challenge for ophthalmologist across the world and the treatment efficacy is dependent on the drug delivery to the target tissues of the eye for optimum therapeutic effect. Susruta, Vagbhata and Yogaratnakar had advocated Basti treatment in Timir chikitsa. Routes of drug administration that are currently used in contemporary medicine to treat posterior segment diseases are the intraocular (i.e., intravitreal injection) and periocular (i.e., sub-Tenon's injection) routes. However, intraocular drug delivery is the most invasive method often associated with many complications. In Ayurvedic therapeutics, Basti treatment is well established in vascular and neuronal disorders and often recommended in complicated and chronic disorders which also have systemic background. It has also been an established fact that high dosage is needed for drug delivery to posterior segment disorders which can be fulfilled through Basti chikitsa irrespective of the palatability. Hence an attempt has been made to study and explore another route of drug administration in the form of Basti

procedure for effective drug delivery to posterior segment diseases of eye for achieving optimum therapeutic effect.

KEYWORDS: ARMD, Basti, Diabetic Retinopathy, Drug delivery, Eye Diseases, Glaucoma, Posterior segment eye disorders.

INTRODUCTION

In the context of eye disorders, Kriyakalpa has been evolved to new dimensions and successfully established as the basis of ocular therapeutic system for anterior segment eye diseases, in modern day practice. Procedures like Panchakarma and Kriyakalpas are integral part of Ayurveda therapeutics. Irrespective of disease, the basic principle of Ayurveda treatment lies in Shodhana (purification therapy) followed by Shaman (palliative) therapy. Ocular therapeutics too followed the same and advocated purification before any Kriyakalpa procedure i.e. kayashirovirechana. Posterior segment of eye includes the structures beyond lens and includes choroid, retina, macula and optic nerve. The diseases associated with the posterior segment are mostly vascular and degenerative disorders of retina like diabetic retinopathy, central retinal vascular occlusion (CRVO), central retinal artery occlusion (CRAO), retinitis pigmentosa, ARMD, optic neuritis and optic neuropathy. Among these two major blinding diseases are diabetic retinopathy and ARMD. Apart from theses endophthalmitis, uveitis, and glaucoma are commonly combined disorders of anterior and posterior segment diseases which have an endpoint in retinal and optic nerve damage. Effective treatment of these posterior segment ophthalmic diseases is a formidable challenge for scientists and clinicians in the ophthalmic pharmaceutical field. Posterior segment drug delivery in eye is challenging, since the same anatomic, physiologic, and immune properties that effectively protect and nourish the healthy eye also hinder the efficient absorption of pharmaceutical drugs. The challenges include the anatomical and physiological barriers like blood aqueous barrier (BAB) and blood retinal barrier (BRB) that can reduce pharmacologically active levels of drug from reaching the targeted tissues inside the eye.[1]

All most all the diseases of posterior segment of eye comes under Timir and Dristigata vyadhi. Timir is described under Vatananatmaja vyadhi,[2] as Vata is prime factor for visual perception, which carries the visual impulse to the visual cortex in brain. As all the three doshas, saptadhatu and four internal patalas are involved in visual process in normal state and in pathological state also, all these structures gets affected adversely in Timir. The vitiated doshas follows the pitta dosha and spreads through Raktavaha Shirasrotas to reach to the

ocular tissues.[3] The initiating etiology behind any eye diseases is Shrioabhisyanda.[4] Vitiated pitta, rakta, kleda and kaphadosha causes obstruction in shirasrotas (microvesssels and cappilaries) in the eye which leads to srotas sanga (capillary occlusion) which reduces blood supply to posterior segment ocular tissues. When this occlusion continues for longer period, the retinal and macular tissue undergoes ischemia and hypoxic state. Hypoxia related retinal nerve fiber layer degeneration may be correlated to Dhatukshyaya stage of patalas in Dristi, as constitutional Dhatus of Dristiundergoes depletion stage due to nutritional arrest. Hypoxia related Dhatukshyaya causes axonal degeneration in retinal neurons resulting in optic neuritis and optic atrophy. Cleansing and nutritive action, special methods of preparation and drug contents of Basti may help in permeation of drug to ocular tissues. Pharmacological action of Basti, drug delivery to posterior segment ocular tissue and central nervous system (CNS) is discussed on the basis of different clinical, biochemical and experimental studies available online and all the Ayurvedic literatures were searched to establish the fact that Basti can be an effective route of drug administration in posterior segment diseases of eye.

BASTI KARMA IN NETRA ROGA CHIKITSA

Basti Karma is emphasized in Ayurveda as half of or whole treatment of any disease due to its wider application in almost all diseases. Though it is considered as the best treatment for VataDosha it is advised even for the treatment of Pitta Dosha, Kapha Dosha and Sarvadhatu AshritaVyadhi.[5] Basti Karma can be adopted in many diseases by using specific drugs prescribed for that particular condition. Further Dalhana says that Karma, Kala and Yoga Basti are Vata, Pitta and Kaphahara respectively. This procedure cures diseases of all Dosha of all the three Marga namely Shakha, Koshtha and Marma, Asthi, and SandhiAshrita. As Basti is given to Moolasthana of Vata Dosha and VataDosha is the predominant factor for the formation of all diseases hence Basti Chikitsa is considered as Ardhachikitsa and even Poorna Chikitsa by Ayurveda scholars.[6] In the context of Netraroga chikitsa, according to Sushruta both Timir and Adhimantha are among eye diseases which can be cured with BastiChikitsa.[7] While describing the importance of Basti Chikitsa, Acharya Sushruta has mentioned “Chakshyuhu Prinayati”.[8] It indicates that the pharmacological action of Basti can penetrate the blood retinal barrier and may result in vision improvement by alleviating Vatadosha, which is the prime dosha for normal vision process including all indriya karma. Pharmacologically Basti does both sodhana (purification) and shamana (alleviation) of vitiated doshas. Basti chikitsa is indicated in diseases of all the three dosha (Vata, pitta and

kapha). In general, in treatment of Timir, Vagbhatta mentioned Basti as one of the treatment procedure along with Murdhabasti, Tarpana, Alepana etc.[9] Again he had mentioned Niruha and Anuvasana Basti procedure for VatajaTimir.[10] Basti procedure may enhance drug permeation to the ocular tissues due to anatomical structure of colon, methods of preparation and drugs used in Basti. As Murdha (shira/head) is the seat of Pranavayu and Netra is the seat of Alochak pitta, the treatment of most of the diseases of dristi, have to be implemented on the line of Vata for Murdhasodhana and Pitta shamak chikitsa for pacification of Alochaka pitta.[11] An important step towards development of successful treatments for ophthalmic diseases is first based on understanding the pathogenesis or pathophysiology of these major ophthalmic diseases. These aspects are often best understood through proper evaluation of the diseases based on modern pathophysiology with Ayurvedic prospectives for effective selection of drug along with proper designing of treatment modalities.

Role of Bastikarma in Diabetic Retinopathy

Diabetic retinopathy is a disease of retinal microvasculature due to prolonged uncontrolled hyperglycemia. Jatharagni and Dhatwagnimandya are other factors implicated in madhumeha, which can be correlated with insulin deficiency or insulin resistance due to metabolic and endocrinal derangements.[12] Agnimandya causes many changes at a cellular and capillary level all over the body. Almost all the organs are affected by this and eye is not devoid of it. Agnimandya leads to Ama formation and ultimately Ama deranges the three doshas in their proportion in quantity and quality.

Ama causes Srotodusti and Siraabhisyandam, which is the main pathological process for initiation of eye diseases. Abhisyandam means oozing out, it means leakage from capillaries. In this context, Ama can be correlated with the formation of reactive oxygen species (ROS) and oxidative stress damage to endothelial cells of retinal capillaries. So the unified theory of Diabetic retinopathy (oxidative stress damage) by the scholars of modern medicine[13] can be correlated with Ama theory of Ayurveda.

Diabetic retinopathy basically a Dristipatalagata roga is mainly attributed to Sira Srotas Abhisyandam and Raktavaha Srotodusti due to a variety of Achakshyushy aahara and vihara karanas especially in Prameha patients.[14] Etiological factors of Madhumeha, Raktajavyadhi and endogenic eye diseases[15-17] are almost similar and are mainly Achakshyushya factors which vitiate Pitta and Rakta. This explains the logical approach towards the development of microvascular complications in diabetic retinopathy cases and manifested as symptoms of

Urdhwaga Raktapitta.

According to Vagbhata, Madhumeha is chronic progressive stage of prameha and of two types: Avaranajanya and Dhatukshayajanya.[18] Raktavriitavata and pranavrittavyana has implications in development of diabetic retinopathy symptoms. Symptoms of Rakatvritavata are: Twakmamsa antarajadaha and Raktayuktasotha mandala.[19] This type of symptoms can be correlated with general neuropathy; Raktayukta sothamandala can be correlated with splinter haemorrhages and IRMA as well as retinal edema in fundus picture of DR cases. Nevertheless Raktavriitavata stages can be correlated with rheological factors like leucocyte adhesion, inflammatory cytokinins, platelet and erythrocyte aggregation involved in pathology of DR. Treatment of Raktavritavata should be done as per Vatarakta chikitsa[19] to normalize the movement of obstructed Vatadosha. And Charak has mentioned Basti as the best treatment for Vatarakta.[20] Symptoms of Pranavrittavyana are: Sarvaindriya sunyata, smritikshaya and balakshaya and the treatment is UrdwaJatrugata cikitsa.[21] Thus in case of pranavrittavyana treatment of head region should be done and Basti, shirobasti, Nasya may be administered for treatment of different stages of Diabetic retinopathy. Acharya Sushruta, Vagbhata and Yogratnakar[22] mentioned Basti procedure for treatment of Timir. Madhumehajanya Timir is a complication of coexisting diabetes mellitus. Dosha involved in pathogenesis of diabetic retinopathy are Vatapitta predominant Kapha anubandha and main Dhatus vitiated are Rakta and Meda Dhatu. Srotas affected is Raktavahasrotas. Thus different types of Basti may be administered with chakshyusya drugs in different stages of diabetic retinopathy. Panchatikta Niruha Basti[23] can be administered in the initial stages of active shiroabhisyanda like mild to moderate non proliferative diabetic retinopathy (NPDR) stage of the disease. In Severe NPDR and proliferative diabetic retinopathy (PDR) cases Madhutailika Chaksyusya Basti[24] and in severe Dhatukshya stages of the disease Sthiradi Niruha Basti[25] or Mustadi Yapana Basti[26] can be administered for better visual improvement in diabetic retinopathy cases.

Role of Bastikarma in Glaucoma treatment

Timir is pain less loss of vision which may be sudden or gradual. Mostly painful loss of vision relates to Adhimantha in acute stage (acute angle closer glaucoma with severe visual field loss) but visual field loss due to established glaucomatous optic atrophy or primary open angle glaucoma (POAG) can be correlated with Timir. Timir is included in Vatajananatmaja vyadhi by Charak, as the end point of vision is done by Pranavayu (Indriyathasannikarsha).

Glaucoma is a group of disorder characterized by progressive optic neuropathy associated with raised intraocular pressure (IOP). Progressive optic neuropathy results from the death of retinal ganglion cells (RGCs) due to chronic ischemia and hypoxia. Mechanical compression due to raised IOP leads to ischemia and axonal degeneration, by altering blood flow to optic nerve head and retinal ganglion cells. As a result of this, supply of growth factors (neurotrophins) to retinal ganglion cells and optic nerve head (ONH) is reduced and RCGs undergo apoptosis. Factors affecting vascular perfusion of ONH like vasospasm, failure of auto regulatory mechanisms of blood flow, systemic hypotension and acute blood loss are various factors implicated in normal tension glaucoma (NTG).[27] Glaucomatous optic nerve changes can be interpreted as Pranavaha srotodushti. As the circulation of rasa-rakta (the vehicle of nutritional factors for dhatus, the structural elements) is impaired, Dhatukshaya (degeneration) can be considered as a component of pathogenesis of glaucoma.[28] This mechanism of pathogenesis can be interpreted in terms of Ayurveda as deposition of ama or mala in the drainage channels leading to increased resistance. Dhatukshya and rasa-raktavaha srotodusti are resultant effect of Vataprakopa due to achaksyusya ahara vihar mentioned in Ayurvedic classics. Vata can be aggravated by two ways i.e. Avarana and DhatuKshaya.[29] Both Dhatu Kshya and Avarana plays important role in reduction of vascular supply and nutrition to retina and optic nerve. For Srotosodhana (cleaning of microvessels) Panchatikta Niruha Basti may be administered before Brimhana (Nutritive) Basti such as YapanaBasti and Madhutailika Chakshyusya Basti. Anubasana Basti may be administered with Dasamoolataila or with other vatahara tailas to correct the dhatukshya related vataprakopa.

Role of Bastikarma in ARMD treatment

Age related macular degeneration (ARMD) is one of the leading causes of blindness in the world and presented in two forms: “dry” or atrophic and “wet” or exudative. The pathogenesis of ARMD revolves around oxidative and degenerative changes in retinal pigment epithelium (RPE) of macular region. ARMD is caused by sclerosis of the arteries that nourishes the retina.[30] This deprives the sensitive retinal tissue of oxygen and nutrients that it needs to function and thrive. Reactive oxygen species (ROS) such as hydrogen peroxide, singlet oxygen and superoxide anion which are byproduct of cellular metabolism can damage cell membranes. Retinal photoreceptors are extremely susceptible to damage by oxidative stress due to their high rate of metabolism and exposure to light. Oxidative damage by ROS of the cell membranes of RPE cells and photoreceptors among others is thought to be an initiator in the pathogenesis of ARMD.[31] A continuous decrease in the melanin content of

RPE cells occurs with age. Melanin protects the light sensitive structures in macula and absorbs free radicals. Loss of melanin and resultant accumulation of free radicals leads to atrophy and degenerative changes in macula in aging population. Geographical atrophy of the RPE involving the macula leads to vision loss in dry ARMD. Appearance of choroidal neovascular membrane (CNVM) in response to ischemic retinal tissue with sub retinal hemorrhages, yellowish deposits on Bruch's membrane (drusens), abnormal serous fluid, perimacular exudates and pigment disturbances are features of exudative ARMD. Hereditary factors, age, nutrition, smoking, hypertension, high cholesterol especially HDL and oxidized LDL and light exposure are all risk factors of ARMD.[31] On Ayurvedic interpretation of ARMD, some research scholars correlated it with Pitta Vidagdha Dristi, a Piitaja sadhya dristigataroga[32] described in Sushruta and other Ayurvedic literatures. Pitta VidagdhaDristi is a disease condition in which the vitiated pitta is confined to the third patala of the dristi. The third patala is directly confined to medadhatu, so when vitiated pitta affects the functional aspects of medodhatu, it manifests as pitta vidagdha dristi. In this condition the main function of Alochaka Pitta i.e. vision in presence of light is impaired. So the symptom like day blindness is a prominent feature of this disease. But after careful analysis it may be concluded that ARMD is nothing but Tritiya-Chaturtha Patalagata Timir caused mainly due to vitiation of Vata Pitta dosha, affecting Meda, Asthi and Majjadhatu of third and fourth Patala of Dristi. The line of treatment in ARMD cases should be Vata Pitta Shamaka, Srotas Shodhan and Rasayanachikitsa. A clinical study showed effectiveness of YapanaBasti with Vayasthapanagana Drugs, in this condition as it is age related degeneration.[33] Sthiradi Niruha Basti and Yapana Basti with anti oxidant, immunomodulator, anti-inflammatory and Rasayana drugs may be administered as effective therapy in ARMD.

Other disorders of posterior segment of eye such as central retinal artery occlusion (CRAO), central retinal vein occlusion (CRVO), optic neuropathy and optic neuritis followed similar pathogenesis either microvasular occlusion related ischemia or hemorrhagic features due to hypoxia related risk factors. The end point in all most all the posterior segment eye diseases are due to oxidative stress damage to endothelial cells in microvessels of retina or macula and reduction in supply of nutrition to the ocular tissue due to various etiologies. Sira Srotas Abhisyanda, DoshaAvarana, Dhatukshaya, and Rakttapitta are important factors which play significant role in pathogenesis of these posterior segment eye disorders. The causative processes involved are inflammation and immunology (observed in dry and wet AMD), neovascularization (DR and wet AMD), aging and oxidative damage (dry and wet AMD), and

genetic mutations (e.g., retinal degenerations, retinoblastoma, choroidal melanoma, and intraocular lymphoma).

PHARMACOLOGICAL ACTION OF BASTI

Pharmacological action of Basti can be explained on the basis of anatomical and biochemical pathways of drug delivery to posterior segment ocular tissues and advantages of colon specific drug delivery system. The retina is primarily a cellular central nervous system tissue with 15-to 20-nm wide intercellular spaces that do not contain tight junctions (TJs).Thus both small hydrophilic and lipophilic drugs can easily permeate the retina.[34] Physiochemical properties of drugs, such as the Molecular Weight, lipophilicity, ionic charge, and solubility, and their pharmacokinetic properties, such as the volume of distribution, bioavailability, and duration of action determines the therapeutic effect of Basti treatment. Following are some similes explained in Samhitas about the universal action of Basti from head to toes.

Basti administered into the Pakvasaya draws the Dosha or Mala from all over the body from the foot to the head by virtue of its Virya, just as the sun situated in the sky draws the moisture from the earth by virtue of its heat.[35] As trees irrigated in its roots yield branches with beautiful tender leaves, flowers and fruits in time and attain big stature in the same way Anuvasana Basti administered in the rectum yields significant results from head to toe.[36,37] Guda (Anus) is one of the Pranayatana, where all twelve Prana dwell predominantly. Guda (Anus) is a Mamsa Marma of Sadyapranahara type. Being a Marma it has roots of all four types of Sira embedded in it viz. Vatavaha, Pittavaha, Kaphavaha and Shonitavaha. Due to its Sadya pranahara nature, Guda (Anus) is highly sensitive. Even mild stimulation to it in the form of Basti drugs and procedure may sensitize the whole body by vigorous action of Vayu through all the Siras present in the body. This physiology confirms immediate and all pervasive action of Basti drugs and relation of Basti (colon) with central nervous system.

Pharmacokinetics of Basti Dravya with limitation to Blood Retinal Barrier (BRB)

Blood-retinal barrier (BRB) restricts drug transport from blood into the retina. BRB is composed of tight junctions of retinal capillary endothelial cells called, inner blood retinal barrier (iBRB) and RPE; called outer blood retinal barrier (oBRB) respectively. [38] The function of iBRB is supported by Müller cells and astrocytes. The retinal capillary endothelial cells are not fenestrated and have a paucity of vesicles. The function of these endothelial vesicles has been described as endocytosis or transcytosis that may be receptor mediated or fluid phase requiring adenosine triphosphate. A close spatial relationship exists between

Müller cells and retinal capillary vessels to maintain the iBRB in the uptake of nutrients and in the disposal of metabolites under normal conditions. Müller cells are known to support neuronal activity and maintain the proper functioning of the iBRB under normal conditions. They are involved in the control and homeostasis of K+ and other ions signaling molecules, and in the control of extracellular pH. Dysfunction of Müller cells may contribute to a breakdown of the iBRB in many pathological conditions, such as diabetes mellitus. Drug transport across the RPE takes place both by transcellular and paracellular routes.[38] The driving forces of outward transport of molecules from the subretinal spaces are hydrostatic and osmotic, and small molecules might transport through the paracellular inter-RPE cellular clefts and by active transport through the transcellular route. Small lipophilic drugs, however, can penetrate the oBRB and iBRB, achieving appreciable concentrations in the retina and vitreous humor after systemic administration. Larger doses of drugs are administered systemically to yield a sufficient concentration gradient in the choroid and retina. This need for a larger dose is true even for small, lipophilic drugs.[38] This explains the advantages of systemic administration of drugs in the form of Basti over oral route, as large doses in oral route may cause severe side effects and degradation of drugs by gastric enzymes, thus reducing drug concentration to the ocular tissues.

Saindhava

The cells of the intestinal mucosal membrane are so easily permeable for sodium chloride that hypotonic / isotonic solutions are absorbed almost as rapidly as pure water by enhancing temporary BRB disruption through temporary disruption of blood retinal barrier by Osmotic mechanism.[39]

Honey (Madhu)

Along with salts, honey makes homogenous solution (colloidal solution) and work as a prodrug, having properties to get penetrated easily and enhances bioavailability.

Taila (oily substance)/Ghee

Lipophilicity enhances the permeation of drugs through the outer BRB (RPE) through transecellular and paracellular route.

Kalka (Paste)

The drugs containing volatile properties which cannot be used in the form of decoction can be used in the form of Kalka. It can be correlated with carrier mediated drug delivery through

colon by modern pharmacologist.[39]

Kwatha (Decoction)

This is the main content of Basti Dravya. The drugs used for decoction are mainly according to the disease and the stage of the disease. Both water soluble and lipid soluble drugs can be used in this way. Lipophilic natures of emulsified drugs are better absorbed, as all the cellular structures of intestinal mucosa are also lipoprotein in nature. Even modern pharmacology established the fact that lipophilicity enhances the systemic absorption of drugs delivered through colon. However more lipophilic analogs becomes less soluble in the aqueous plasma and bind more readily to plasma proteins, leading to lower concentrations of drug available for diffusion into the CNS and the same is true for ocular tissue too. Hence, when a drug is delivered via the circulatory system for the treatment of CNS diseases, a delicate balance between cerebro-vascular permeability and plasma solubility is required.[39] This justifies why kwatha is used in Basti for optimal drug delivery to tissues.

Drug Absorption

Basti may be absorbed by: diffusion, filtration, osmosis or by adsorption depending upon the substances used in it. The rectum has rich blood & lymph supply. Basti drugs get absorbed via two routes: 1) Drug absorbed by upper haemorrhoidal vein goes into portal circulation.2) Drug absorbed by middle and inferior haemorrhoidal veins is always absorbed without reacting with digestive enzymes and acids.

Electrolyte absorption

The ions like sodium (Na+), calcium (Ca) and potassium are absorbed and are essential for the generation of action potential, which is the main functional unit of Nervous system. Here are the mechanisms show how they are absorbed from intestinal mucosa.Sodium (Na+) ions are absorbed by Diffusion & Active Transport. Chloride (Cl-) ions penetrates via Passive diffusion and facilitated by sodium absorption. Calcium (Ca) ions can be absorbed via Active Transport.

Influence on Bacterial Flora

Basti influences the normal bacterial flora in large intestine, thus it increases the endogenous synthesis of Vitamin B12, Vitamin K and production of Thiamine with the help of bacteria, which is necessary for nerve conduction. In this way Basti might be effective in checking haemorrhages and exudates in retina as well as repair retinal neurons.

Influence through ENS (Enteric Nervous System)

ENS (Enteric Nervous System) are substantial group of neurons and are capable of Autonomus reflex without influence of central nervous system. More than 500 million neurons are present in the ENS (Enteric Nervous System) and thus it's called "second brain". There are so many similarities between CNS-ENS regarding cellular structure, neuropeptide secretion and specific functions. And recent studies have shown that there is great influence of CNS and ENS (Enteric Nervous System) on each other. In this way, Basti may produce neuromuscular remodelling, pain modulation by influencing ENS (Enteric Nervous System) and thereby CNS (Central Nervous System)[40] and ocular tissue as well.

COLON SPECIFIC DRUG DELIVERY SYSTEM (CSDDS)[41]

The colon is a site where both local and systemic delivery of drugs can take place. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CSDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.

The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules. Thus colonic region of the gastrointestinal tract (GIT) has become an increasingly important site for drug delivery and absorption. CSDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes.

ANATOMICAL, PHYSIOLOGICAL & BIOCHEMICAL CHARACTERISTICS OF THE COLON[41]

The large intestine extends from the ileocaecal junction to the anus which is divided into three main parts colon, rectum and anal canal. The colon constitutes caecum, ascending

colon, hepatic flexture, transverse colon, splenic flexture, descending colon and sigmoid colon. The average size of colon is 1.5 m long; the transverse colon is the longest and most mobile part and has an average diameter of about 6.5 cm. The wall of colon is consisting of four layers namely the serosa, the muscularis externa, the submucosa and the mucosa. The serosa is the exterior coat of the large intestine. The muscularis externa is the major muscular coat of the large intestine which is composed of an inner circular layer of fibers surrounding the bowel and an outer longitudinal layer. The submucosa is the layer of connective tissue lies immediately beneath the mucosal lining the lumen of the colon. The mucosa has three parts epithelium, lamina propria and muscularis mucosae. The Anatomical and physiological features of small and large intestine are depicted in Table No.1.

Table No.1 Anatomical and physiological features of small and large intestine[41]

Sl. No	GIT Segment	Length (meter)	Surface Area	pH	Microorganism colony	Transit Time
1	Stomach	0.2	0.1	1.5	$\leq 10^2$	Variable
2 Small Intestine						
	Duodenum	0.3	0.1	6.9	≤ 10	2 hr
	Jejunum	3	6.0	6.9	$\leq 10^5$	1.5 hr
	Ilium	4	6.0	7.6	$\leq 10^7$	1.5 hr
3	Large Intestine	1.5	0.3	8	$\geq 10^{11}$	$\leq$ 48 hr

FACTORS AFFECTING DRUG ABSORPTION FROM COLON

The commonly used approaches of colon specific drug delivery system for systemic effect are:

1. pH dependent 2. Time dependent 3. Pressure dependent 4. Bacteria dependent. The colon specific drug delivery is primarily affected by two physiological factors; these are pH level and the transit time. The other factors which need to be considered are as follows:

1. Physical characteristic of drug (pKa, degree of ionization),
2. Colonic residence time as detected by gastrointestinal tract motility
3. Degradation by bacterial enzymes and byproducts.
4. Selective and non selective bindings to the mucus.
5. Local physiological actions of drug, disease state.
6. Use of chemical absorption enhancers e.g. a Prodrug like Honey in Ayurvedic Basti preparation.

The pH of gastrointestinal tract is subject to both inter- and intra subject variations. Diet, disease state and food intake influence the pH of the gastrointestinal fluid. The average pH

values and drug transit time in different region of human GIT are given in Table No. 2.

Table No. 2 Average pH and Drug Transit time in the GI tract[41]

Location	pH	Drug Transit time (hr)
Oral cavity	6.2 – 7.4	---
Oesophagus	5.0 – 6.0	---
Stomach	Fasted condition : 1.5 – 2.0 Fed condition : 3.0 – 5.0	< 1 (fasting) > 3 (fed)
Small intestine	Jejunum : 5.0 – 6.5 Ileum : 6.0 – 7.5	3 to 4
Large intestine	**Right colon : 6.4** **Mild colon and left colon : 6-7.6**	**20 to 30**

There is some evidence that the hepatic first-pass elimination of high clearance of drugs is partially avoided after rectal administration. This can be explained by the rectal venous blood supply: the upper part is connected with the portal system, whereas the lower part is directly connected with the systemic circulation. It is also likely those in the future novel drugs delivery systems with zero order release characteristics will be applied rectally. The rectal columns have a rich vascular bed and have their own arteries and veins. While the superior rectal vein drains via the inferior mesenteric vein into the portal vein, the inferior and middle rectal veins drain directly into the inferior vena cava via the internal pudendal vein and the internal iliac vein. This type of unique vascular supply of rectum helps in achievement of systemic drug effect. The Following reasons of therapeutic importance are quoted for preference of rectal administration of drugs which are as follows:

a) The presence of nausea and vomiting, or when the patient is unconscious.
b) The presence of diseases of the upper gastrointestinal tract which affect oral drug absorption.
c) An objectionable taste (a factor which may be particularly important in children).
d) The achievement of a rapid systemic effect by giving a drug in a suitable solution (suitable solution in the form of emulsification of both lipophilic and hydrophilic drugs)
e) Large doses of drug can be administered for optimum drug concentration and therapeutic effect for posterior segment delivery to ocular tissues.
f) Large surface area for better drug absorption.
g) Because of the rapid blood flow rate in the choroid and retinal vasculature, the duration of action of drugs are usually too brief to result in meaningful therapeutic effects. As the drug retention and transit time is more in Basti, the duration of drug action increases.
h) The rate of drug absorption is not influenced by food or the gastric emptying rate.

i) 'First-pass' elimination of high clearance drugs may be partly avoided.

j) Contact with digestive fluids of the upper gastrointestinal tract is avoided, thereby preventing some drugs from decomposition.

A Parallel analysis of modern system of CSDDS, CNS drug delivery and Basti procedure in Ayurveda is depicted in Table No.3.

Table No.3 Parallel analysis of modern system of CSDDS, CNS drug delivery and Basti procedure in Ayurveda[39-42]

Strategies for CNS drug delivery including eye.[39]	**Classical Basti procedure In Ayurveda**	**CSDDS[42] /Rectal drug Administration vis-à-vis Basti.**
Drug manipulation by Lipophilic Analogs	Snehadravya added during Basti preparation.	pH dependent: different Kasayas used in basti- like mridutiksnadravya etc.
Prodruglike amino acids, glucoronic acids, glucose, glactose, cellulose etc	Honey	Pressure dependant: procedure of basti karma like bastinetra and puta.
Carrier Mediated Drug Delivery	Kalka/Avapa used in Basti	Colloidal system: The emulsification prepared from honey, sneha, kalka and kwathadravyas in basti.
Disturbing the Blood-Brain Barrier - Osmotic Blood-Brain Barrier Disruption.	Sainadhavlavan used in Basti	Polysaccharide Based Delivery Systems/Prodrug delivery: parallel to honey based Basti preparation in ayurveda.

CNS- Central Nervous System, CSDDS- Colon Specific Drug Delivery System

CONCLUSION

Drug delivery to posterior segment of eye is challenging, due to its inherent anatomical, physiological and immunological properties to protect the eye in healthy conditions. Though Trans-scleral and other tropical routes are used for posterior segment drug delivery which have their own limitations such as blood aqueous barrier (BAB) and blood retinal barrier (BRB). Thus this drug delivery route has two major shortcomings, extremely poor bioavailability to the inner coat of the posterior segment and a short duration of action. Systemic oral route too has its limitations such as low doses of drug, certain degradation of drugs due to gastric enzymes and thus poor availability to the neural tissues including ocular tissue. So the routes of drug administration that are currently used in the contemporary medicine to treat posterior segment diseases effectively are the intraocular (i.e., intravitreal injection) and periocular (i.e., sub-Tenon's injection) routes. However, intraocular drug delivery is the most invasive, in that it involves penetrating the globe and thus is not free of

injection related complications. In this Context, Basti may prove to be a effective therapy to treat posterior segment diseases of eye as it has all the properties to increase drug permeation to CNS and ocular tissues. Drug ionization through proper emulsification, lipophilicity, and molecular weight, pH and transit time of drugs are the factors which influences drug absorption and bioavailability to the ocular tissues. Basti treatment meets all these properties along with unique anatomical characteristic of a large surface area which can deliver enormous drug to posterior segment of eye for effective therapeutic effect in the ocular conditions. Pathogenesis of major diseases of posterior segment of eye is caused by Sira Srotas Abhisyanda due to dosha avarana, dhatuksyaya with resultant of reduction of supply of nutrients to the ocular tissues. Basti does both Sodhana and Shamana along with enhancement of nutritional status of dhatus in the body which also applies to the dhatus or Patalas in Eye. Stimulation of autonomic nervous system could be the possible mechanism behind action of Basti. There is a close resemblance in the functioning of Vata Dosha and nervous system and Basti is prescribed as the best remedy for Vata. It again validates the efficacy of Basti karma on nervous system as well as in ocular disorders. There is a close resemblance between pharmacological actions of Basti, with colon specific drug delivery system (CSDDS) and strategies required for CNS drug delivery. Methods such as prodrug, carrier mediated drug delivery, drug manipulation by lipophilic analogs and osmotic blood brain barrier disruption or blood retinal barrier disruption strategies described by modern pharmacologists, completely compliments with classical methods of Basti procedure. Plasma concentration with biomarkers and CSF analysis data following rectal administration can give new dimension in future for Basti treatment in posterior segment disorders of eye like Diabetic retinopathy, ARMD, Optic nerve disorders, Glaucoma etc. Future studies may prove Basti as a novel route of drug delivery for posterior segment diseases of eye which have a limitation in contemporary science and Ayurveda paves a doorway for such disorders.

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