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Mini-review article

Importance of *Srotas* (channels of circulation) in pharmacokinetics

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ABSTRACT

Pharmacokinetics refers to what happens to a drug from entrance into the body until the exit of all traces. Four processes encompass it namely absorption, distribution, metabolism and excretion. In pharmacokinetics, the *Srotas* (channels and pathways) has a crucial role. The aim of this study is to critically review the role of *Srotas* in the pharmacokinetics of drug as per Ayurvedic as well as modern perspective. The most relevant literature based on the *Srotas* was accessed from the online scientific database as well as from the Ayurvedic classical texts. The literature revealed that the pharmacokinetics is described in Ayurveda as *Vipaka*, which involves thirteen types of *Agni* (fire) together with various *Srotas*. This review comprised of the mechanism based role of *Srotas* in pharmacokinetics with the main emphasis on absorption, distribution, metabolism and excretion.

INTRODUCTION

Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. It determines the route of administration, dose, the latency of onset, time of peak action, duration of action and frequency of administration of the drug (Tripathi, 2008). It involves ADME steps i.e. absorption, distribution, metabolism and excretion of the drug in/ from the body (Doogue and Polasek, 2013).

The living body is a channel system and/ or is comprised of innumerable channels which are designed as an inner transport system for divergent functions, gross and subtle biological and energetic as proclaimed by Ayurvedic classics- '*Srotomayam hi Shariram*' (Verma and Gehlot, 2014). Term *Srotas* has been used to mean minute individual cells and also to mean different individual organ systems (Patwardhan, 2008). The numbers of *Srotas* are as many as the number of life factors operating in life process- '*Yavantah Purushe Murtimanto Bhava vishesah Tavantevasmin Srotasam Prakara visheshah* (Sharma, 2010). Synonyms of *Srotas* are *Sira* (vein), *Dhamani* (arteries), *Rasayani* (lymphatics), *Rasavahini* (capillaries), *Nadi* (tubular conduits), *Path* (passage), *Sthan* (site, locus), *Ashaya* (repositories), *Niketa* (resorts), *Marga* (pathways/tract), *Samvrita Asamvrita* (open or blind passages), *Sharir chhidra* (body orifice or openings), etc. (Sharma, 2010). This signifies that term *Srotas* indicates all the macro and micro-channels and pathways operating in living organisms (Swarnkar et al., 2014). These are the channels or systems in which some tissue is formed; some material is metabolized, secreted or transported. Sushruta and Vagbhata both have compared *Srotas* to the extremely fine passages and pores present in the lotus stem, through which *Rasadi poshya dhatus* circulate all over the body and provide nutrition to the body (Srikanthamurthy, 2017).

MATERIALS AND METHODS

This article centralizes on published research articles in the MEDLINE, PubMed, Google Scholar, Science direct, ASL and Scopus besides various Ayurvedic classics (especially *Brihattrayi*) and books related to pharmacology. Study criteria based on research articles and publications related to *Srotas* and Pharmacokinetics, scientific explanations related to *Srotas*.

RESULTS

Srotas in body

There are innumerable *sukshma Srotas* and numerable *Sthula Srotas* [9 Bahirmukh (11 in

female) and 13 Antarmukh *Srotas* (11 pairs according to Sushruta)] (Srikanthamurthy, 2017). Thirteen gross *Srotas* simulate the major physiological systems of the body as known in conventional modern science. In addition to these, Manovaha *Srotas* carries impulse of thoughts and emotions (Sharma, 2010).

Srotas serves as a conduit through which both Prasad (nutrient) dhatu, as well as Mala dhatu (waste product or product of degradation), are transported, as a structure through the pores of which nutrients and waste product pass to and from the *Sthayi Dhatu*.

All the *dosha, dhatu* and *Mala* are dependent on *Srotas* for their formation, transportation and destruction. These are not only the passage or channels for flow of various substances but also are specific in their function. Each *Srotas* provide their nutrition to respective dhatu only with requisite quantities, not others (Sharma, 2010).

ADME

ADME is an abbreviation in pharmacokinetics for absorption, distribution, metabolism and excretion and describes the disposition of a pharmaceutical compound within an organism. These four criteria influence the drug level and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug (Sakai, 2008).

Relationship between *Srotas* and ADME

Srotas involves at each step of the pharmacokinetics of the drug compound i.e. from the administration of the drug to its excretion. The drug is administered in a *Srotas* like in buccal cavity (oral & sublingual route), rectum (rectal route), nostrils (nasal route), veins (intravenous route). Further, the administered drug spreads all over the body through various *Srotas*, viz. if the drug has been administered via oral route it will pass through *Annavaha Srotas* (alimentary canal) followed by *Rasavaha Srotas* (assimilatory canals) then in *Raktvaha Srotas* (capillaries and veins) then to all over the body through various *Srotas*.

Absorption

It is a movement of drug from its site of administration into the circulation. The drug must be absorbed before any medicinal effect can take place. Pharmacokinetic profile of a drug can be easily and significantly changed by adjusting factors that affect absorption like concentration, the area of the absorbing surface, vascularity of absorbing surface, etc. (Tripathi, 2008). Thus this is the type and nature of *Srotas* which determines the area and vascularity of absorbing surface.

The filtrate is the passage of drugs through aqueous pores in the membrane or through paracellular spaces. Majority of the cells have very small pores ($4A^0$) and drugs with molecular weight more than 200 are not able to penetrate. However capillaries (except those in brains) have large paracellular spaces ($40A^0$) and most drugs can filter through these (Tripathi, 2008). These aqueous pores in membranes and paracellular spaces are also *Srotas* which determines the pharmacokinetics of drug by affecting the absorption. Besides, the role of vesicles (a *Srotas*) is quite significant in Pinocytosis which contributes little to transport of most drugs. Channels in the membrane which controls the active transport and facilitated diffusion are also the *Srotas*.

Distribution

The extent of distribution of drug depends on its dissolution, lipid solubility, ionization at physiological pH, the extent of binding to plasma and tissue proteins, the presence of tissue-specific transporters and differences in regional blood flow. The rate of dissolution depends upon surface area (Noyes- Whitney equation), which in turn increased by reducing the particle size of the drug. Intercellular pores between endothelial cells present in capillaries (except in brain capillaries) which provides transport to lipid insoluble polar drugs. Crystalline and hydrated forms dissolve slower than amorphous forms. The rate of transport is proportional to the lipid-water coefficient of the drug because lipid soluble drugs diffuse by dissolving in a lipoidal matrix of the membrane. This is due to the unique arrangement of protein and lipid in the membrane. Distribution of drug is done by different vessels involving paracellular and intracellular spaces as well; these all are *Srotas*.

Metabolism

It is a chemical alteration of the drug in the body needed to render nonpolar (lipid soluble) compounds into polar (lipid insoluble) so that they are not reabsorbed in the renal tubules and are excreted. Sites for drug metabolism are liver, kidney, intestine, lungs and plasma. Smooth endoplasmic reticulum of the liver is the principal organ of drug metabolism although every biological tissue has some ability to metabolize drugs. The liver has a very high concentrate of most drug metabolizing enzyme system relative to other organs. The enterohepatic circulation affects the drug metabolism (Williams et al., 1965). This enterohepatic circulation, a site for enzymatic release & activities within the organs are the *Srotas* again.

Excretion

It is the process of passing out systematically absorbed drugs. Drugs and their metabolites are

excreted in urine, faeces, exhaled air, saliva, sweat & milk. The most important channel of excretion for the majority of drugs are kidneys. Net renal excretion is the sum total of glomerular filtration, tubular reabsorption and tubular secretion. These whole process takes place in nephron and finally it is excreted through various *Srotas* of body chiefly Mutravaha *Srotas*.

DISCUSSION

In Ayurveda, digestion & metabolism with the absorption and biotransformation is denoted by *Vipaka* (Sharma and Singh, 2015). The final outcome of biotransformation of rasa of a given *dravya* through the action of *jatharagni* i.e. end product or the transformed state of ingested substance after digestion or metabolism is known as Vipaka. As refers to Ayurveda there are 13 kinds of *Agni* (1 *Jatharagni*+ 7 *Dhatvagni*+ 5 *Bhootagni*). All kinds of *Agni* work one by one on an ingested drug that helps to liberate the molecular substance from the chemical structure of the ingested drug and assimilate and absorb in the body at the site of action. The site of jatharagni is said in the *Annavaha Srotas*. Seven *Dhatvagni* belongs to seven types of body tissues (Dhatus) which further resides in their respective *Srotas*. *Bhootagni* corresponds to the five greater elements of the Panch-mahabhoot i.e. *Akash, Vayu, Agni, Jala & Prithvi. Akash* mahabhoot in the body almost denotes *Srotas* as "Kha" is the synonym for both *Srotas* and *Akash*. Pathways, channels and other all sites involved in ADME steps of pharmacokinetics are *Srotas*. Thus *Srotas* has a foremost and paramount role in the pharmacokinetics of the drug from both views Ayurvedic as well as contemporary modern science.

CONCLUSION

From the vivid discussion, we may conclude that *Srotas* are present in every nook and corner of the body and they are responsible for carrying out each and every functional activity of the human body. *Srotamsi* indicates all macro, micro level descriptions pertaining to exchange, transportation and excretion. They crucially take part in pharmacokinetics (ADME) of drug according to Ayurvedic as well as modern pharmacology. Lesser particle size, amorphous & anhydrous molecules have a comparatively higher rate of absorption and distribution in the tissues. This fact also advocates the lesser need of dose and quick action of *Rasaushadhis* as compared to herbal drugs as mentioned in Ayurveda.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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