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Review Article

Ayurvedic lipid based rasayans - A perspective on the preparation and pharmacological significance of lipids on the bioavailability of phytoconstituents

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ABSTRACT

For thousands of years, lipid based Ayurvedic formulations have been made in India, and the craft has survived down the millennia up to the present time. Some of these deliciously potent phytonutrient preparations are very popular and have sustained the test of time pertaining to their efficacy. Recent researches on the role of phytonutrients in promoting cardio-pulmonary, brain and immune health substantially buttress the philosophy underlying the use of lipids in preparing these emulsions, since a large number of these bioactives are lipophilic. Being lipoidic, they are absorbed through the lacteals in the small intestine, and are then transported through the thoracic duct directly to the heart, bypassing the liver. The formulations utilizing ghee (clarified butter) or sesame oil as the carrier lipid, either while frying the myrobalams or as *Anupana* (adjuvant), have special significance in modulating bodily immunity, since the immune system is housed in lymphatics which are lipid rich.

Amla and lipid based Ayurvedic rasayans (rejuvenating formulations) are a popular and highly palatable group of phytonutraceutical preparations. This group of polyherbal adaptogenic formulations is classified separately from other formulations in Ayurvedic therapeutics. Several of these health-promoting rasayans are suitable to be consumed by all age-groups in the recommended season and dose. Current research on endothelial and immune cell receptor mediated uptake of lipoidic molecules, together with the knowledge of lipid absorption pathways, lends credence to the usefulness of *rasayans* in targeting the cardio-pulmonary and immune systems. An attempt has been made in this paper to elucidate the mechanisms underpinning the complex interplay between lipid delivered hydrophobic phyto-molecules, systemic lymphatics and the Immune system.

1. Introduction

The emerging field of lipid based drug delivery systems (LBDDS) has been the cause of excitement in the pharmaceutical world [1]. The use of such systems to target drugs to the reticulo-endothelial systems and to cancerous cells is being explored in a big way [2]. An analysis of the lipid *based Ghrita* (medicated ghee), *Awaleha* (herbal confections) and *Rasayan* preparations of Ayurveda reveals that these too are incorporating several forms of LBDDS. A further analysis of the absorption pathways and systemic delivery of the phytonutrients, carried through the medium of these preparations, reveals their specific targeting of the cardiopulmonary and immune systems, and even to the brain. The very recent discovery of the presence of a *rich lymphatic system in the brain* has revealed a hitherto unknown pathway to deliver lipids to the brain [3].

Since a large number of phytonutrients present in herbs are lipophilic, their incorporation into lipoproteins especially *chylomicrons* is inevitable and has been substantiated [4]. The *chylomicrons* are taken up by the intestinal lacteals, and then carried into the lymphatic collecting system, to reach ultimately to the *thoracic duct* and empty into the large veins at the root of the neck [5]. Thus the phytonutrients saturated lipoproteins reach the heart directly *without undergoing metabolic degradation* in the liver, and the

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Abbreviations

Phyto	Phytochemical
LPL	Lipoprotein lipase
CM	Chylomicron
VLDL	Very low density lipoprotein
LDL	Low density lipoprotein
HDL	High density lipoprotein
CP	Chavanprash
TG	Triglyceride
CM	Chylomicron
GALT	Gut associated lymphatic tissue
MALT	Mucosa associated lymphatic tissue
LBDDS	Lipid based drug delivery systems
GPIHBP1	Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1
HSPG	Heparan Sulfate Proteoglycan
FDA	Food and Drug Administration, USA
TGL	Triglyceride rich lipoproteins
LCFA	Long chain fatty acids
FFA	Free fatty acids
FcR	Fragment crystallizable Receptor

unchanged phytochemicals can be taken up by cardio-myocytes and alveolar cells [6]. Also, while travelling through the lymph nodes and lymphatic vessels, the chylomicrons can interact with the lymphocytes and other immune cells, thereby delivering a part of their phytoactive payload to these cells of the immune system which are benefited by the anti-oxidant and adaptogenic effects of the bioactives.

2. Methods

Ancient Ayurvedic texts have described the varied poly-herbal formulations of Rasayans to be used under various circumstances, and for different health indications [7]. The art and craft of preparing Rasayans, as also the knowledge of herbs, has survived over the millennia leading to a knowledge based platform upon which modern research has been carried out over the past few decades [8]. With the discovery in the late twentieth century of the pharmacological effects of curcumin in turmeric, Indian herbology suddenly came of age, and since then pharmacological and biochemical research into Ayurveda has increased exponentially [9]. In scientific arena, the grounded theory of Ayurveda is now being seen in a new light, based on deductive reasoning.

Based on above established practices and researches, the authors embarked on their own methodical research in the methods of preparation of the rasayans and modes of ingestion [10,11]. Continued reflective inquiry and inductive reasoning based on current research into receptors mediating the uptake of lipoidic molecules by endothelial and immune cells, led to the designing of hypothesis articulated in present work.

3. Phytochemicals – types and bioavailability

3.1. Hydrophilic and hydrophobic phytoactives

Thousands of phytochemicals have been identified, and several dozens have been shown to have beneficial effects on the human body. These phytonutrients can be broadly divided into two groups: water soluble such as phenolics, polyphenols and water insoluble such as carotenoids, curcuminoids. This classification is important for appreciating the mode of delivery, and to obtain complete and proper absorption of the constituents of a fruit, vegetable or herb. The bioactive compounds can be either hydrophilic or lipophilic – i.e. soluble in either water or lipids respectively. Hence simply ingesting the powdered herb may not give the desired effect. For example, curcumin in turmeric requires some lipid for its absorption, and the turmeric drinks currently available in the market may not be able to deliver the desired benefits [12]. For complete absorption of all the phytoconstituents of the herb, both aqueous and lipid carriers are required.

3.2. Effect of heat treatment on bioavailability of phyto-constituents

As per Ayurvedic literature, the mode of processing before ingestion of a fruit, vegetable or cereal has an effect on the digestion and absorption of nutrients present in these foodstuffs. For instance, carrots can be eaten raw in salads, cooked as vegetable, pulped for juice or made into pudding. Carrot juice and raw carrots, if taken on empty stomach, would hardly deliver the carotenes available, since carotenes are lipid soluble and would be absorbed only sparingly in absence of lipids. But when consumed as carrot *halwa*, which is a dessert made of shredded carrots cooked in ghee and milk, the bioavailability of carotenes is vastly increased, because of milk fats. Another form of having carrots is in form of preserves prepared by boiling carrots in sugar syrup for long time, called *murabbas* [Fig. 1]. Boiling helps the release of nutrients which are otherwise packed inside thick walled cells [13]. Heat is required to disrupt the integrity of the pectin making up the cell walls and releasing the nutrients inside available for absorption. These *murabbas* are preserves prepared for consumptions in seasons when carrots will not be available. The bioavailability of carotenes in *murabbas* is superior compared to carrots eaten raw. This is because although mastication by teeth does cell wall disruption to some extent, boiling does a better job indegrading the cell walls.

3.3. Effect of emulsion systems on bioavailability

It has only just recently been acknowledged that many of the phytonutrients need to be in emulsion system to make them more bioavailable [14]. The significance of lipids as carriers of Phytonutrients has gained prominence only since 2010, and has led to the development of numerous lipid-based delivery systems [15]. Since lipophilic Phytonutrients are absorbed from the intestinal lumen only after emulsification and micellization, the first step is to extract the compounds from herbs and transfer them to mixed micelles. The efficiency of this step is only partial, and the fraction of fat-soluble phytochemicals that is made available for absorption is referred to as the bioaccessible fraction [16]. Bioactives like Phytosterols need an emulsion vehicle to diffuse in the aqueous lumen system of the gut and cross the lipid membrane of intestinal mucosal cells [17]. Even for phenolics, lipid-complex called phytosome is required to penetrate the gut lining and to enter in the circulation [18]. Several such leading edge studies conclude that lipid emulsions and other LBDDS are the future for delivering all the goodness of herbs in their entirety.

4. Use of lipids in Ayurvedic therapeutics

4.1. Types of lipid usage in a variety of formulations

Oils and fats are commonly used as drug delivery vehicles in Ayurvedic formulations, both for ingestion and local application. The most commonly used lipids are sesame oil and cow ghee, and these may either be employed as an integral part of the formulation, or be given alongwith powders (*churans*) and other formulations as bio-

Fig. 1. Three preparations of carrots: juice, preserve and pudding. Heating is essential to disrupt the thick plant cell wall, releasing the Phytosnutrients within the cells. Frying in ghee further enhances bioavailability by providing lipid, promoting the absorption of hydrophobic non-polar carotenoids.

enhancers or adjuncts (anupana). In general the use of lipids in Ayurveda may be classified into following three types:

1. Lipids used as adjunct (*anupana*) while administering herbal powders or other formulations. *Anupana* is a herb or food substance that is taken along with or after medicine. The use of proper *anupana* along with specific drug therapy is very important to cure the disease [19].
2. *Ghritas* (medicated clarified butter) and *Tailas* (medicated oils): These lipid preparations involve heating and cooking. *Ghritas* are prepared by mixing herbal paste, decoction and ghee and cooking all the three together. Similarly, medicated oils are prepared and which are mostly used for external application [20].
3. Use of lipids in *awalehas* and *rasayans*: *Awaleha* is a term that denotes a thick, semi-solid confection which can be licked while eating [21]. Being confections, *Awalehas* contain sugar or jaggery and most of the them utilize ghee or oil in the cooking process. Many popular *rasayans* are *awalehas*, for example Chavanprash awaleha, since they contain sugar. But all *rasayans* are not *awalehas*, since many *rasayans* do not contain sugar. Similarly, all *awalehas* are not *rasayans*, since they (the former) are formulated to cure specific diseases and may not fulfil the criteria of *Rasayan* as described below.

4.2. Lipid use in rasayans

Rasayans can be defined as rejuvenating formulations that help to maintain good health, increase healthy life-span and even restore youth [22]. Some *rasayans* are also designed as remedies for specific disorders, but even these perform the promotive functions (in addition to disease amelioration) mentioned above. While some *rasayans* are simply powdered herbs, most of them are either *ghritas* or *awalehas*.

The *Rasayana* formulations also employ ghee and oil in the following three ways:

a) as *anupana,*
b) as simple mixtures with herbal powders without cooking,
c) or the ghee/oil is used for cooking.

A detailed use of the three modalities is described in the following section:

a) An Ayurvedic formulation is recommended to be consumed with honey, ghee, butter-milk, curd or milk, etc. These are known as *Anupana* (adjunct) that increase the potency of the medicine and also direct its action towards the particular malady. Cow ghee is used as *anupana* while administering several rasayans like *Amalaka-ayasa Brahma Rasayana* or *Yastimadhu Churana* [23]. In most of the cases where ghee is used as *anupana*, honey is also employed with it. In fact, *Madhu-ghrita* (Honey-ghee) combination is a classic in Ayurveda.
b) In other *Rasayana* preparations like *Amalaka Avaleha* or *Dvitiya Brahma Rasayana*, ghee/oil is simply mixed with the powdered herbs and no cooking is done after adding the ghee.
c) The third method of employing ghee or sesame oil is by using these for frying or cooking while preparing the formulation. Some of these processes are complicated and intricate, and the lipid is used at some stage or even at multiple stages. Examples of *rasayans* utilizing lipids in the process of preparation are *Chavanprash* or *Agnitapi Brahma Rasayana.*

It is interesting to note that some *rasayans* utilize ghee in the cooking process and also as *anupana*, for example *Pippali Rasayana* and *Dwitheeya Haritakyadi Rasayana* [24].

4.3. Polyherbal lipid based rejuvenating formulations

Several hundred formulations using oils and ghee as a base are described in the ancient Indian medical texts. Most of these are *Awalehas* and *Rasayans* requiring long periods of preparation and cooking, utilizing several dozen herbs. Making these herbal confections is an art and a craft, and has to be learnt from an expert. In fact, the process of preparation is vital to ensure proper release of phytonutrients from the herbs and their incorporation into lipid particles, thereby optimizing absorption and bio-availability. Since taste is at the very root of Ayurvedic philosophy, the final product has to meet the requisite requirements of taste, flavour and texture. If properly cooked and dessicated, the *Rasayan awalehas* can stay for long without any need of preservatives.

4.4. Chavanprash rasayan

The most popular lipid based preparations in Ayurveda are the *Rasayans* (restoratives and revitalizers). Several rejuvenating formulations use pulp of Amla(E. officianalis) berries as the base and substrate for fabricating the *rasayana awaleha*, and ghee alongwith sesame oil as the lipid carrier for the herbal extracts. These poly-herbal Ayurvedic formulations can be considered as preparations, because making them is not simply about powdering the herbs and mixing them up. The craft of preparing these rasayans entails immense amounts of time, energy, effort and meticulous attention to detail. It may be stressed here that while the 'molecule' is of paramount importance in Western medicine, whatever be the process employed to manufacture it, in Ayurveda the 'process' is sacrosanct. As an illustration, the intricate process of preparing *Chavanprash*, a famous *awaleha* (semi solid herbal confection) *rasayan* is summarized below.

In brief, the *Amla* berries are suspended (tucked inside muslin cloth tote bags) in a huge cauldron containing dozens of herbs, and boiled for several hours until the fruit gets softened. Then the Amla berries which have been kept suspended in the boiling decoction are removed from the cauldron and mashed through muslin to separate the seeds and fibre and collect the pulp. The pulp is then fried in the mixture of ghee and sesame oil in equal amounts.

Simultaneously, the herbal decoction is sieved and made into thick syrup by adding sugar while heating. The fried *Amla* pulp and decoction syrup are then mixed together and again heated over low flame to obtain the final semi solid consistency of the *Awaleha*. At this stage, several powdered spices alongwith saffron, bamboo manna and honey are added as condiments. This mixture of powdered herbs and bamboo manna is known as *Prakshape*.

4.5. Rationale of the process of preparing chavanprash

At the outset, by immersing *amla* berries (containing Ascorbic acid) in water while preparing the poly-herbal decoction, the pH of the medium turns acidic and the acid soluble contents like alkaloids present in the herbs are released into solution, alongwith other water-soluble phytochemicals [25].

Alkaloids are water soluble under acidic conditions and lipid soluble under neutral and basic conditions, hence if the decoction were to be prepared without boiling the *Amla* berries therein, these alkaloids would not diffuse into the water [26]. Examples of such Alkaloids are vasicine and tinosporin. It would be pertinent to point out here that simply boiling a herb in water for a few minutes may not be sufficient to allow all its Phytonutrients to be released into the decoction. The herbs include several dried fruits having thick cover and barks of trees and intact stems that will require several hours of boiling to soften the cell walls enough in order for the bioactive compounds to be released from within the plant cells [27]. So the first stage of preparation of Chavanprash entails boiling the herbs for several hours to make the decoction.

During the boiling process, wherein the *Amla* berries are suspended in the herbal decoction, some of the lipid soluble components of the herbs which are released will associate with the oils present inside the *Amla* berries. After that, by frying the extracted *amla* pulp in ghee and sesame oil, we are loading these latter lipid molecules with phytonutrients in the *amla* pulp like gallic acid and quercitin [28]. Finally, by mixing the fried amla pulp and decoction syrup together accompanied with continued heating we are further permeating the ghee particles with lipid-soluble phytonutrients like Eugenol from the herbs, heat being the agent of conversion of the mixture into emulsion. At the end of this exacting and strenuous process, each ghee particle will have been fully loaded with several hydrophobic phytonutrients, and will be in emulsion form within the final semi-solid product.

4.6. Rationale of lipid use in ghrita and tailas

A close look at the methodology of preparing *ghritas* (where cow ghee is used as carrier) will illuminate the perfection of the technique in delivering the complete phytochemical profile of the herbs used. The *ghritas* are usually prepared from three components: ghee, herbal paste and fluid. Herbal paste is made by pulverising the powdered herb alongwith water to create a thick suspension. Fluid used can be one of following: water, curd, butter milk, herbal decoction, juice or meat broth. As a general principle, the proportion of herbal paste, ghee and fluid is 1:4:16 [29]. These three constituents are cooked together on medium heat to achieve semi-solid consistency, which of course, will require several hours of heating (to evaporate off all the surplus water).

When herbal decoction is the fluid used, a herbal paste of the same herbs used to prepare the decoction, is employed. The underlying philosophy is simple, yet intense. While the herbal decoction will contain the aqueous extract of the herbs, most of the hydrophobic Phytonutrients will not diffuse into it. When the herbal paste, consisting of a micronized suspension of the whole herb is added to the mixture composed of decoction and ghee, there is ample opportunity for the lipid soluble Phytonutrients to become associated with the lipid molecules. The cooking process takes time, so the tightly packed Phytonutrients inside the plant cells of the herb will also slowly permeate outside the cell walls when the latter disintegrates under the action of heat. The resulting *ghrita* (in emulsion form) will hence contain the entire water soluble and lipid soluble phytonutrient load of the herb. The full potential of the herbs will thus be realized.

4.7. Lipid based drug delivery systems (LBDDS) incorporated into the (awaleha) Rasayan

Poorly water soluble drugs pose a challenge to pharmacotherapeutics, in terms of their solubility and bioavailability after oral administration. It is because of this reason that LBDDS have gained significant attention in recent times. The most important example of using lipids to increase oral bioavailability is Cyclosporine, wherein the macro and micro emulsions increase the absorption many-fold as compared to the tablet form [30].

The Rasayan created by the process outlined in section 4.4 contains a mix of several LBDDS, which vastly increase the bioavailability of the poorly soluble phytochemicals present in the herbs. Firstly, the principal carriers ghee & sesame oil, alongwith the water in the decoction syrup form an oil-in-water emulsion under the action of heat [31]. These lipid carrier molecules also form bonds with several phyto-active molecules to form Phytosomes and Herbosomes [32]. Addition of the fried micronized particles of *amla* pulp to the decoction syrup, accompanied with heating and stirring, will form colloidosomes [33]. Sesame oil being rich in phospholipids, the latter alongwith cholesterol in the ghee will incorporate some hydrophilic bioactives to form liposome like vesicles [34]. Liposomes, Herbosome and Phytosomes are spherical vesicles made up of amphipathic lipids like phospholipids that can contain the hydrophobic molecules within them, in the centre.

Along with these emulsions and vesicular systems, finally when the *Prakshape* containing large amount of *Banslochan* (bamboo manna) which is composed primarily of finely powdered silica and silicon dioxide particles is added, there is formation of microparticles of SLH (silica lipid hybrid), which is one of the latest and most useful oral drug delivery system. The porous matrix of silica

particles allows for higher drug loading and stability, besides providing higher surface area for lipase activity in the intestinal digestive conditions, and enhanced lipid droplet digestion. This facilitates optimal formation of the mixed micellar phase composed of lipid digestion products which, along with the endogenous bile salts and phospholipids may preferentially sustain better solubilization of the lipophilic bioactive molecules [35]. Thus the bamboo manna in *Prakshape* increases the bioaccessible fraction and is a highly useful addition to further increase bioavailability and shelf life.

4.8. Lipid soluble bioactives present in traditional formulations

A number of lipid based *rasayan* rejuvenator formulations are used since ages. The most common herbs used in these preparations are Emblica Officianalis, *Zingiber officinale*, *Piper longum*, *Elettaria cardamomum*, *Cissampelos pareira*, Tinospora cordifolia, *Crocus sativus*, *Semecarpus anacardium*, *Terminalia chebula* and *Terminalia bellirica*. The important lipid soluble phyto-active ingredients present in these herbs are Polyphenols such as flavonoids and chebulinic acid, Essential oils such as eugenol and limonene, Ellagitannins such as phyllanemblinin, Alkaloids such as piperine, and Sesquiterpenes such as alpha-santanol and zingiberine [36]. Also present in Chavanprash are lipid soluble pterostilbenes, ergosterol and lactones [25]. Besides, the carrier sesame oil contains phytosterols such as sitosterol, daucosterol and sesamolin. Other lipid soluble anti-oxidants present in some of these formulations are carotenoids such as crocetin and phytofluene, and the tocopherols present in ghee and sesame oil [37].

5. Absorption pathways of the phytoactives

5.1. Diffusion and active transport

To understand how the various components of the *chavanprash awaleha* get absorbed, a brief summary of lipid digestion and absorption is given here. The water soluble molecules are simply absorbed by diffusion across the intestinal mucosa, and from here, the hydrophilic molecules enter the portal vein and reach the liver. But hydrophobic molecules require a different and more complex process. First, the ingested lipids are broken down into simpler molecules and transformed into micelles by action of pancreatic lipase and bile acids. These micelles reach the intestinal cells, and the fatty acids are absorbed into the cells by active transport. Receptor molecule CD36 (fatty acid translocase) is present in large amount in intestinal cells (enterocytes) and is involved in uptake of fatty acids, monoglycerides and fat-soluble vitamins A, D, E and K [16,38].

5.2. Synthesis of Chylomicron lipoproteins within enterocytes

The fatty acids alongwith other lipid molecules such as fat soluble vitamins are then packed into *chylomicrons* which are large lipoprotein assemblies [39]. Essentially being hydrophobic lipids cannot be transported in the blood, unless they are associated with hydrophilic proteins, this association enables them to be transported throughout the body. In the intestinal cells, this is achieved by associating the absorbed lipids with Apoproteins and the lipids and proteins assembly is called as lipoproteins. The chylomicron (CM) is the largest among the lipoproteins which is produced in the intestinal cells, and contains phospholipids, cholesterol, TG, vitamins A, D, E and K. The other lipoproteins are produced by the liver, namely high density lipproteins (HDL) and very low density lipoproteins (VLDL). VLDL contains Apoprotein B100 and carries lipids from the liver to the periphery where the adipose and muscle tissues take up the fatty acids in the lipoprorotein by the action of Lipoprotein lipase (LPL). The CM on the other hand contains Apo B48, is assembled in the intestines and contains dietary lipids including lipid soluble bioactives.

5.3. Uptake and transport of the chylomicrons in lymphatic fluid

The chylomicron particles are taken up by lacteals in intestinal walls, pass through mesenteric lymph channels and reach the axial lymphatic circulation. Travelling along the abdominal lymphatics, primarily the thoracic duct, the chylomicrons are ultimately emptied into the great veins at the root of the neck. Similarly, while the water soluble components in Chavanprash will reach the liver through the portal circulation, the *lipid soluble phytonutrients* will be absorbed by the lacteals and will then be transported by the thoracic duct, *bypassing the liver* [Fig. 2].

These lipid soluble phytochemicals are carried primarily by *chylomicrons and will directly reach the right atrium,* since the thoracic duct empties into left subclavian vein which then drains into right atrium through the SVC. From the right heart chambers, blood containing *phytonutrients will be pumped straight to the lungs, with the phytonutrients essentially unchanged*. This alternative route of absorption adopted by lipophilic compounds is significant for various reasons.

5.4. Significance of bypassing of liver by the chylomicrons

The bio-active compounds incorporated within chylomicron particles will reach the cardiopulmonary system and the immune system unchanged and in high concentrations. Unchanged, because they have bypassed the liver which is a metabolic factory, that chemically transforms all the substances passing through it. So some of these unchanged lipophilic phytochemicals can be absorbed into the heart tissues by the action of CD36, which is present on the endothelial cells [40]. The same CD 36 was also reported to be involved in uptake of fat soluble vitamins in the intestines. Thus the phytoactives are able to be taken up by cardiomyocytes and innervating neurons of the electrical conduction system of heart. The current concept of atherosclerosis is about it being an immune and inflammatory condition. Putative therapeutic strategies specifically targeting chronic inflammation in atherosclerosis include classic anti-inflammatory drugs, biological therapies targeting cytokines and chemokines, and small molecule enzyme inhibitors and receptor antagonists. Phytochemicals can mediate many of these immune responses. In the lungs, the uptake of fatty acids and other lipid molecules is due to action of LPL. The freshly released phytonutrients are taken up by alveolar cells and also the immune cells residing in MALT (mucosa associated lymphatic tissue) [41]. The lungs require lipids for efficient functioning and infection fighting capabilities. The lipid-soluble bioactives carried in the lipoprotein particles can prove greatly beneficial in enhancing these capabilities.

5.5. Phytochemicals carried by other lipoproteins and by albumin

The CM, after delivering TG and other lipid molecules to peripheral tissues, turn into CM remnants. These are taken up by liver cells and the constituent apoproteins and lipids (including lipoidic bioactives) are re-cycled. The VLDL secreted by liver and HDL carry the lipoidic phytochemicals from the liver to the blood-stream. Some of the lipoidic phytochemicals in the blood become bound to serum albumin for transport, since lipoidic molecules (being hydrophobic) by themselves cannot travel in blood. It is via all these carriers in blood that phytochemicals reach all the tissues of the body.

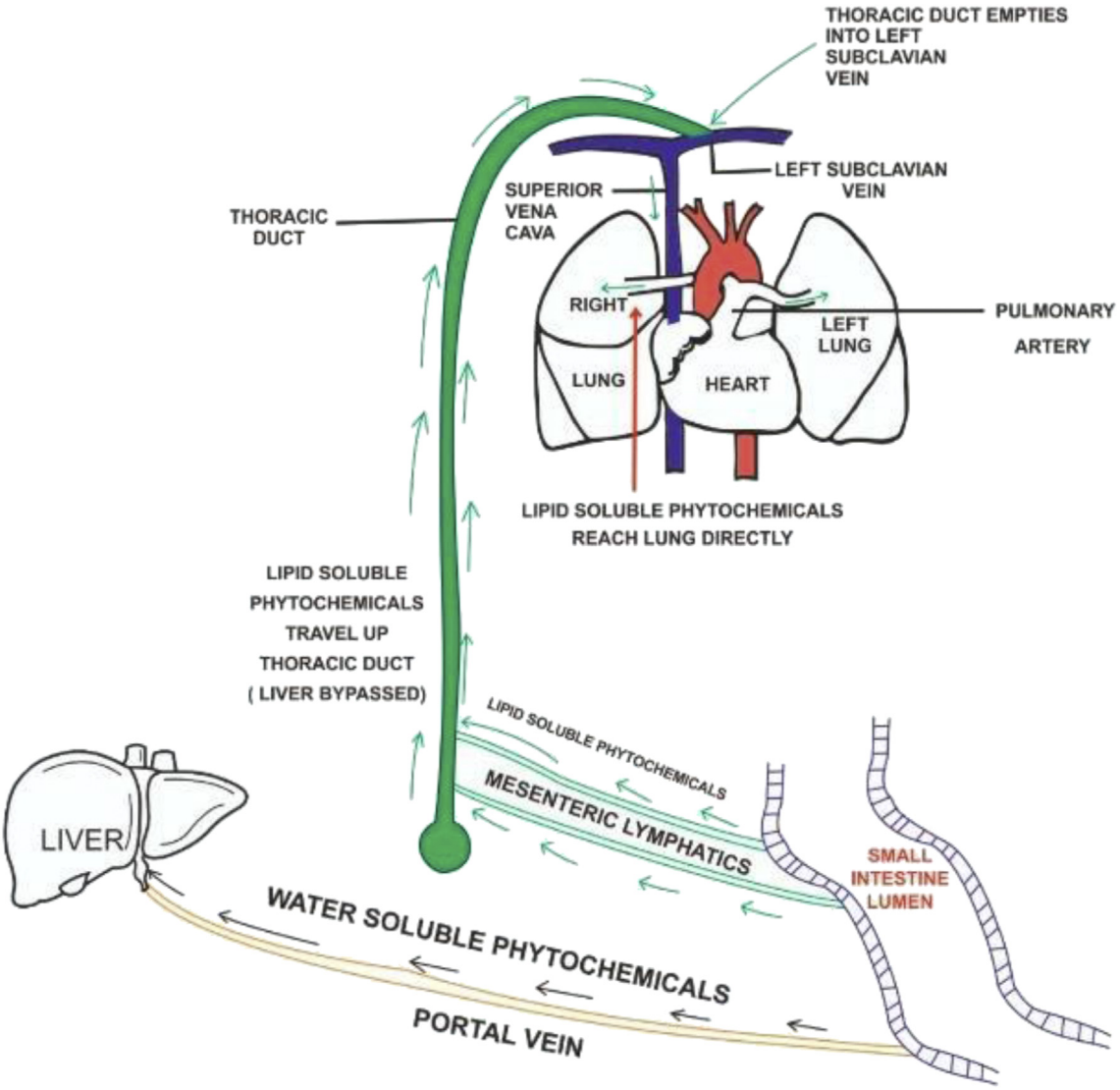

Fig. 2. Showing separate routes of absorption of water soluble and lipid soluble phytochemicals through the gut, and bypass of the lipophilic bioactives by metabolic degradation in the liver.

5.6. Impact on the immune system by interaction with and exchange of hydrophobic phytomolecules

The immune system of the human body is primarily housed in the lymphatics (Fig. 3) The lymphatic system, besides the spleen and bone marrow, mainly comprises GALT (gut associated lymphatic tissue), MALT and the lymph nodes. When the lipophilic bio-actives present within CM, associated with other lipid molecules reach the lymph vessels and bathe the immune cells, there is an opportunity to influence the immune reactivity. It is well known that lipoproteins exchange various lipid molecules amongst themselves. Lining endothelial cells also express several receptors like CD36 (alongwith helper molecules like Glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1 (GPIHBP1)and Heparan sulphate proteoglycans (HSPG) that facilitate action and binding of LPL) that help in uptake of fatty acids and other lipid molecules [42]. Blood and lymphatic vessels are all lined by the endothelium. Large number of receptors like CD32, present on surface of immune cells such as macrophages and lymphocytes, are also involved in lipid uptake [43]. Thus the relatively polar bioactive molecules present on surface of CM (the non-polar phytoactives would be in the core) have ample opportunity to be taken up by lymphocytes and other immune cells located in the lymphatics [44].

5.7. Endothelial receptors and receptors on immune cells involved in lipid uptake

CD 36 is a transmembrane glycoprotein that is expressed in microvascular endothelial cells, microglia, monocytes/macrophages, platelets, cardiac and skeletal muscles and adipocytes [45]. It is also known as Fatty Acid Translocase, it serves many functions in lipid metabolism and signaling. This immuno-metabolic receptor has a high affinity for long chain fatty acids (LCFA) which it takes from TGL and albumin. In the heart, this scavenger receptor is present on endothelium and cardiomyocytes where it is responsible for supplying Free fatty acids to myocardium [46].

CD 32 The CD 32 family of Leucocyte FcR (fragment crystallizable receptor) are integral membrane glycoproteins that are activating- Fc receptors [47]. They are present on neutrophils, monocytes, basophils, mast cells, platelets and Langerhans cells [48]. Though predominantly involved in internalization of anti-antibody complexes, they also have a role to play in phagocytosis

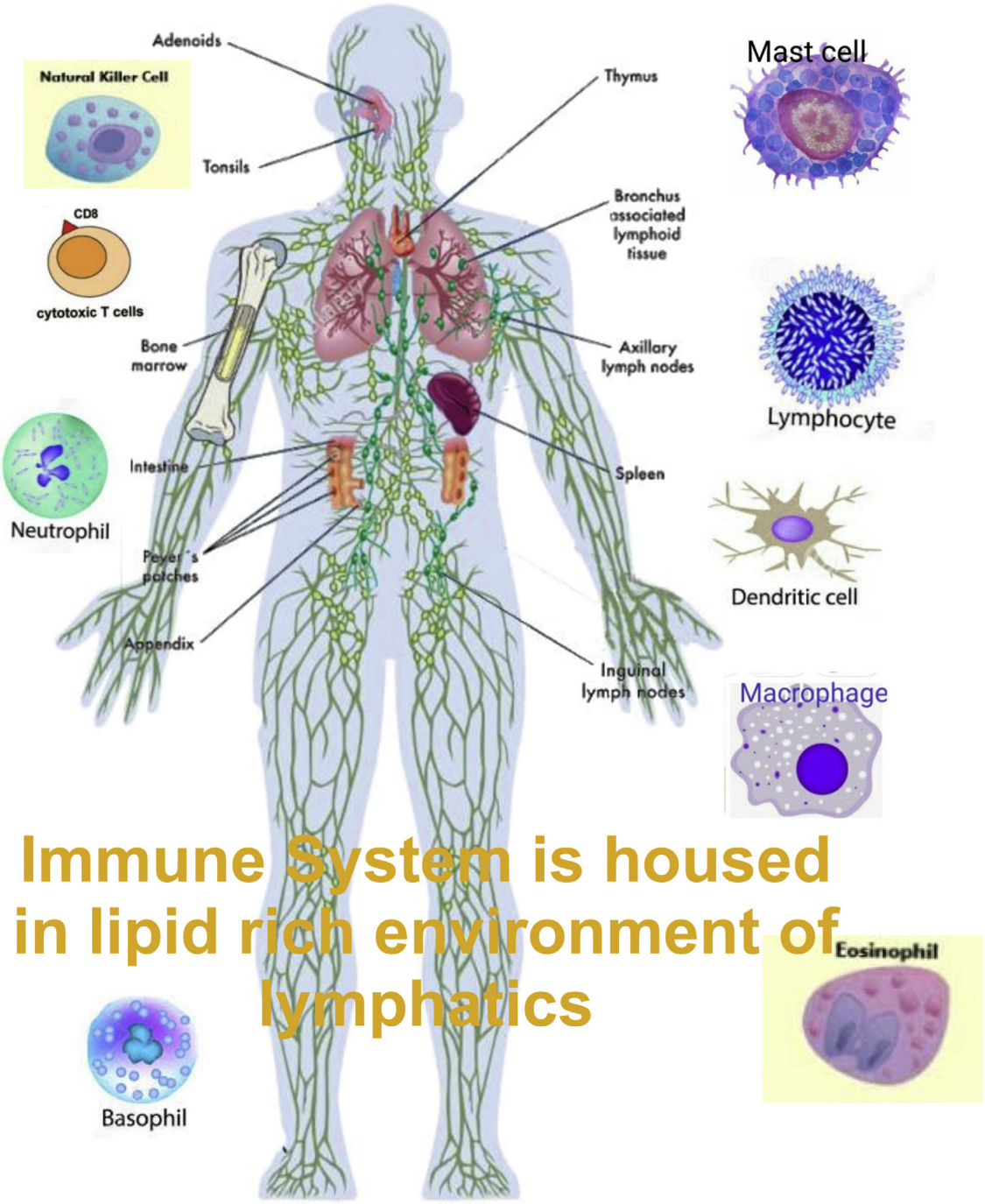

Fig. 3. The immune system of the human body: comprising of the thymus, spleen, bone marrow, adenoids, palatine tonsils, vermiform appendix and the entire lymphatic system including the lymph nodes. The scattered images are of the principal immune cells involved in innate and adaptive immunity.

of lipoproteins like LDL which are associated with C-reactive protein (CRP) in inflammatory conditions.

GPIHBP1 Glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1 is located on the luminal face of capillary endothelium. GPIHBP1 is highly expressed in the heart, lungs and adipose tissue, where it serves as an important platform for the LPL-mediated processing of chylomicrons in capillaries. The protein molecule binds both LPL and Chylomicrons and by playing a crucial role in lipolytic processing of TGL, these protein molecules play an important role in the delivery of lipid nutrients to cells [49].

HSPG Heparan sulphate proteoglycans are glycoproteins found at the cell surface and in the extracellular matrix. They act as receptors for growth factors, enzymes, chemokines and cell adhesion proteins, alongwith mediating the clearance of many lipoprotein subclasses. In particular, they play a crucial role in clearance of TG rich particles like CM [50].

5.8. Presence of communication between brain lymphatics and peripheral lymphatics

There is another important aspect to the intimate relationship between the lipid soluble compounds and the immune system residing in the lymphatics. This significant aspect is the connection between the systemic lymphatic system and brain lymphatics [51,52]. This rich communication can easily allow for the passage of phytochemical laden lipoproteins and lipophilic phytoactives to reach the brain, especially since the brain lymphatics do not have valves and can thus facilitate bi-directional flow.

The brain being composed primarily of lipids offers a natural high-affinity target for lipophilic phyto-molecules. The delivery of lipoidic bioactive molecules present in rasayanas to the brain via the lymphatic route opens up vast possibilities for drug delivery to CNS. Also, the modulation of immune activity in and around the brain tissue through the lymphatic route is also now a real possibility.

6. Conclusion and future prospectives

Traditional Indian Medicinal system has employed lipids in polyherbal formulations as phytochemical carriers for millenia. These complex formulations function as powerful immune modulators, restoratives and revitalizers. Though most of these formulations employing lipids have to be concocted taking into account the specific disorder and constitution of the patient, certain formulations like Chavanprash can in general be consumed by all to maintain good health. These lipid-based *rasayans* are able to deliver both water and lipid soluble phytonutrients effectively, and are mostly delicious and hence acceptable by children as well. Having a lipid carrier enables the formulation to target the nervous, immune and cardio-respiratory systems, for these systems modern medicine has hardly any preventive, promotive and restorative drugs.

Further studies are required to determine the bio-availability and uptake kinetics of lipid delivered and lipoidic phytochemicals by the intestinal cells, as well as by the mesenteric lymphatics. The concentrations achieved in the thoracic duct also need to be quantified. Such studies will lead to scientific validation of the absorption and transport pathways outlined here, and boost the herbal pharmaceutical industry, with great benefits to society.

Furthermore, the discovery of receptor mediated uptake of lipid molecules by endothelium and immune cells has opened up a whole new arena of pharmacological research. Confirmative experimental studies of such uptake of lipophilic phytoactive molecules would spawn the use of these molecules to specifically target the heart, lungs, bone marrow, immune system and the central nervous system. The addition of this vast armamentarium of lipoidic pharmaceutical formulations to the pharmacopoeia will greatly augment the present “limited” number of promotive and adaptive drugs. This will result in immense patient benefit to those suffering from hitherto incurable conditions like Alzheimer's disease, heart failure, chronic respiratory disorders, alongwith increasing resistance to repeated urinary and respiratory infections.

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Author contributions

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2021.09.004.

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