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Research Article

Prakshape condiment in Chavanprash: Harnessing Synergy of the Ages

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Abstract

Towards the conclusion of the tedious process of preparing chavanprash, a powdered herb combination known as *prakshape* is introduced. Many of these herbs have already been utilized in the initial stage of creating the decoction, which is the basis of chavanprash. The perplexing aspect is the necessity to incorporate the same herbs once more as *prakshape* during the final step, highlighting the intriguing nature of this addition and its associated benefits. The inclusion of prakshape proves to be ingenious for multiple reasons. Firstly, the incorporation of powdered herbs in prakshape ensures that the entire herb, along with all its phytochemical components, becomes part of the formulation. In contrast, the decoction process only extracts water - soluble components into the solution. This inclusion allows for a broader range of active compounds to be present in the final product. Secondly, the addition of prakshape serves to reintroduce volatile and heat-labile compounds that may have been lost during the extended heating process. Additionally, the inclusion of bamboo (Bambusa arundinacea) manna particles in prakshape contributes to an enhanced drug-delivery system. From a pharmacological standpoint, the incorporation of prakshape ingredients reinforces the therapeutic effects of the formulation and promotes synergy among the herbs. The principles underlying the use of prakshape can further be utilized for the development of new *awaleha* and ksheerpak formulations, potentially yielding more potent effects.

Keywords: *Prakshape*; *awaleha*; chawanprash; bamboo manna; silica lipid hybrid; essential oils

Abbreviations: SLH: silica lipid hybrid; LBDDS: lipid based drug development systems; ROS: reactive oxygen species; SCFA: short chain fatty acids; GIT: Gastro-intestinal tract; EO: essential oil; CEO: cardamom essential oil; PCM: paracetamol; MRSA: methicillin resistant Staphylococcus Aureus; MF: Messua ferrea; CFA: complete Freund's adjuvant

Introduction

Prakshape is a finely powdered mixture of herbs that is added to Ayurvedic preparations like decoction, paste or *awaleha* (semi-solid preparation) at the end of the manufacturing process, after the heating has been terminated [1]. In a typical 20 kg batch of Chavanprash, the prakashape spices consist of equal amounts (20 gm each) of *Dalchini* (Cinnamomum verum bark), *Tejpat* (Cinnamomum tamala), *Nagkesar* (Messua ferrea) and *Elaichi* (Elettaria cardamomum), along with 160 gm *Pippali* (Piper longum), all in powdered form [2]. These herbs have been used earlier in preparing the poly- herbal decoction [3]. This raises the question of why the same herbs/spices are reintroduced. In addition to these ingredients, some new components are also included in *prakshape*, such as bamboo manna (white concretions consisting mainly of silica, found in nodes of female Bambusa arundinacea stems), saffron (Crocus sativus) and honey (mellifluous) [1].

The decision to add these substances only after the heating process has been stopped holds significance for several reasons. While one reason aligns with Ayurvedic therapeutic principles, others can be explained by new research in phytochemical pharmacotherapeutics. The addition of honey at the very end, after the cooking process is complete and the *awaleha* has cooled down, follows Ayurvedic guidelines that prohibit heating honey [4]. One explanation for incorporating raw powdered spices as *prakshape* is to replenish the volatile aromatic essential oils that may have been lost during the prolonged heating process (section 3.5).

Another rationale for the addition of *prakshape* is its ability to synergistically increase the bioeffects of the formulation. This can be achieved through several mechanisms. Firstly, by adding *prakshape*, the absorption and bioavailability of the bioactive components present in the herbs can be enhanced, through the mechanisms of bio-potentiation and novel drug delivery systems. Secondly, Prakshape provides nutrients that support the growth of favourable gut flora which can contribute to overall gut health. Additionally, the inclusion of Prakshape can facilitate the sustained production of bioactives even after the formulation has been delivered, resulting in prolonged therapeutic effects. This is known as the holobiont effect. Furthermore, the direct synergism between the herbs in *prakshape* enhances the overall therapeutic effects of the formulation. Lastly, the use of Prakshape dravya (medicament) allows for the modification of taste and therapeutic effects according to individual preferences and requirements, offering versatility in adapting the formulation to specific needs.

Manufacturing process of awaleha rasayans:

The manufacturing process of *Awaleha Rasayans,* such as Chavanprash and *Kantakari Awaleha*, follows strict adherence to the procedure detailed in the ancient Ayurvedic texts. This is mandatory if the full therapeutic potentiality of the formulation is to be attained. The process is explained in Figure 1.

Significance of Adding *Prakshape*

Prakshape, in Sanskrit, means forcefully throwing something forwards [5]. In the traditional process of preparing Chavanprash, *prakshape* is incorporated by forcefully flinging the powdered herbs into a large cauldron [6]. Due to the highly viscous and intensely hot *awaleha* in the cauldron, the powdered *prakshape* needs to be swiftly thrown into the mixture and vigorously stirred without delay [7]. The forceful action is necessary since the cauldron contains a substantial amount of awaleha (about 20-30 kgs) with a glutinous consistency. This process ensures proper and uniform blending of the *prakshape dravya*, thereby justifying the name given to this powdered herbal condiment.

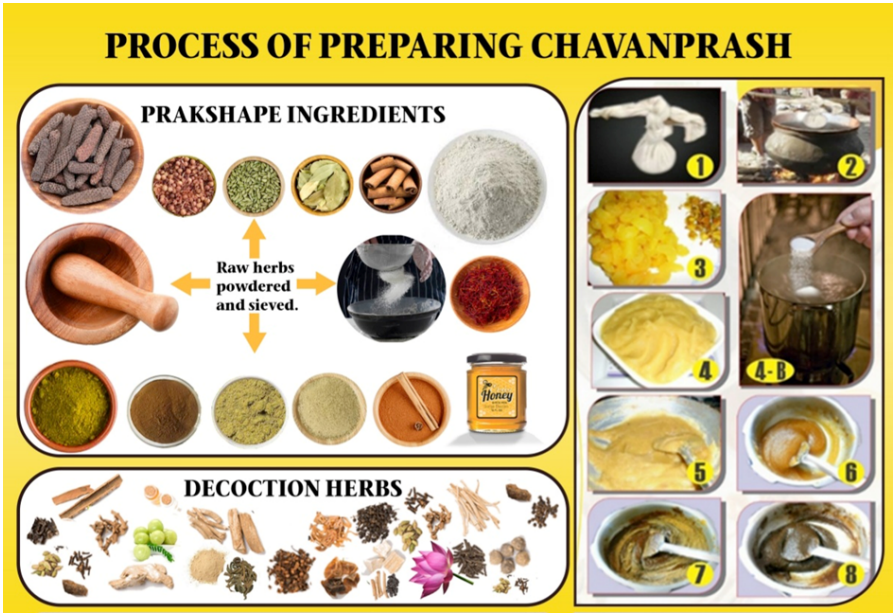

Figure 1: Crafting Chavanprash awaleha – A long and arduous process, requiring diligence and adroitness. The *prakshape* herbs are shown in the box on top left. Steps of the process are shown on the right, and comprise the following: 1) Amla berries are packed into a muslin tote bag. 2) Tote bag is suspended in a cauldron full of boiling water containing all the decoction herbs. 3) Seeds are extracted from boiled berries. 4) Amla pulp is sieved to remove tough fibre. 4B) Decoction is sieved through muslin and sugar is added. 5) Fine amla pulp is fried in ghee and sesame oil. 6) Decoction syrup is added to fried amla pulp and heated until semisolid. 7) Heating is stopped and prakshape is added with stirring. 8) Final product.

The addition of *prakshape* serves the following important functions:

(i) Formation of additional drug delivery systems like silica-lipid hybrid (SLH).

(ii) Fine tuning the taste and flavour of the product.

(iii) Supplementation by specific ingredients like *bhasmas* (calcined metals), honey and saffron.

(iv) Synbiotic and bio-enhancement effects, creating herbal synergy.

(v) Re-introduction of aromatic and volatile compounds lost in the cooking process

Each of these effects is explained below.

Formation of drug delivery systems

Many phytochemicals found in herbs exhibit limited solubility in water and are also susceptible to instability. They can be easily degraded by the acidic environment of the stomach and the enzymes present in both the stomach and duodenum [8,9]. The delivery of these phytochemicals in emulsion form, utilising lipids that play a vital role in solubilizing the hydrophobic phytochemicals, enhances their resistance to degradation by acids and enzymes. Additionally, this delivery method also improves their bioavailability [10]. A recent review has explained in detail the advantage of emulsion systems to make phytonutrients more bioaccessible [11].

Before the addition of *prakshape*, the formulation prepared according to the process outlined in Figure 1 (step 6) already contains various particles resembling lipid-based drug delivery systems (LBDDS). These particles play a role in enhancing the bioavailability of the phytochemicals present in the herbs [12,13]. One of the primary components is an oil-in-water emulsion formed when the fried Amla particles, cooked in a mixture of ghee & sesame oil, are dispersed in the decoction syrup under the application of heat. The lipid molecules in the cooking medium also bond with several phyto-active molecules, forming Phytosomes and Herbosomes [14]. Furthermore, the cooking of fried micronized particles of amla pulp with the decoction syrup results in the formation of colloidosomes [15]. The phospholipids present in sesame oil, along with the cholesterol in the ghee, incorporate certain bioactive molecules to form liposome like vesicles [16]. Liposomes, herbosomes and phytosomes are spherical vesicles made up of amphipathic lipids like phospholipids that can encapsulate the hydrophobic molecules, protecting the latter from acid attacks in the stomach [17].

Upon the addition of *prakshape* during the final stage of chavanprash preparation (step 7 in fig 1), which includes a significant amount of bamboo manna primarily composed of finely powdered silica and silicon dioxide particles, there is an additional formation of microparticles known as silica-lipid-hybrids (SLH) as depicted in figure 2. The lipoidic vesicular particles get adsorbed onto the surface of the silicon particles [18]. Furthermore, the inclusion of a large amount of silica particles (250 gm. in a 20 kg batch of Chavanprash) contributes to the stabilization of the emulsion by increasing the oil phase polarity through the adsorption of polar oil species and phytochemicals onto the negatively charged surface of the silica particles [19].

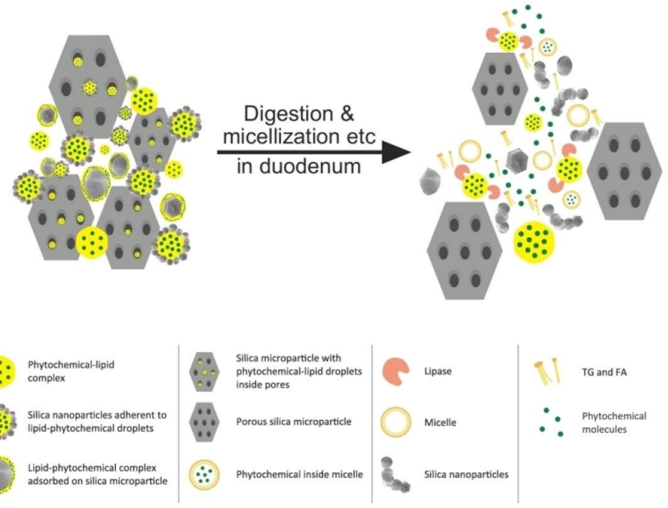

Figure 2: Formation of Silica-Lipid Hybrid particles upon addition of Bamboo Manna (250 gm in a typical batch of 20 kg Chavanprash). Bamboo manna is made up of both mesoporous and non-porous silicon particles, which are negatively charged and get linked to the polar vesicular lipid particles. There is considerable surface adsorption also. The left side of the figure shows the various types of SLH particles formed. The formation of these particles leads to higher drug loading, better stability, maximized surface area for lipase action (enhanced lipid droplet digestion) and increased solubilisation of phytochemical molecules. All these boosts the bioavailability of bioactives in the formulation.

Binks' research has demonstrated that the average drop diameter of oil-in-water emulsions, stabilized by hydrophilic silica particles, tends to increase as the particle size ranges between 5.5 and 34 nm [20]. Additionally, the greater surface adsorption capacity and porous matrix of silica particles contribute to augmented drug loading, and provide a greater surface area for lipase activity in the duodenum and small intestine (Figure 2). Consequently, this promotes improved digestion of lipid droplets and facilitates the optimal formation of the mixed micellar phase. In conjunction with endogenous bile salts and phospholipids, this may result in preferential solubilisation of the lipophilic bioactive

molecules [21]. Thus, the bamboo manna in *prakshape* enhances bioavailability by increasing the bio accessible fraction, and also increases shelf life by emulsion stabilization.

Role of silica in health. The role of silica in health is noteworthy. Silica found in Bamboo manna (known as *Banslochan* in vernacular) has been identified as a valuable health supplement [22]. It demonstrates beneficial effects on various aspects of health including bone formation, bone density, Alzheimer disease, immunodeficiency, improves state of skin, hair and nail conditions, as well as tumour growth suppression. Silica aids respiratory defence mechanisms by stimulating the immune system and promoting an increase in neutrophils, T- lymphocytes and NK cells [23]. In addition to its other effects, silica also plays a role in inducing the production of reactive oxygen species (ROS). This mechanism can be beneficial in promoting the pulmonary clearance of infectious agents [24-26]. Studies conducted on rats have shown that crystalline silica causes the proliferation and activation of CD8+ and CD4+ T cells. Furthermore, silica has demonstrated its usefulness in preventing atherosclerosis by preserving the ground substance and preventing the fragmentation of elastic fibres in arterial walls. This, in turn, leads to a reduction in the formation of atheromatous plaques [27,28]. The standardization of Bamboo Manna has been carried out by Parida et al [29].

The chemical form of ingested silica greatly influences its bioavailability and absorption. Generally, silica compounds are poorly absorbed by the body. It is worth noting that until recently, only synthetic silica gel crystals were available in the Indian market due to the ban on bamboo felling in India. However, with the relaxation of regulations regarding bamboo harvesting, genuine organic bamboo manna has become commercially available. The organic silica found in bamboo stems is superior to synthetic silica since it is an organic form that is well absorbed by the body. The fibre content in the ground spices of *prakshape* condiment is also a good source of absorbable silicon. The anti-atherogenic and antihyperlipidemic activity of many spices is partly due to the high content of silica in spice fibres [30].

Blending the taste and flavour of the product

Taste is a significant factor in Ayurvedic therapeutics, and can influence the physiological effects of the awaleha as detailed below. By adjusting the relative quantities of the condiments used in *prakshape*, such as cardamom and cinnamon, the taste and flavour of the *awaleha* can be modified. For instance, increasing the relative amount of cardamom in *prakshape* will result in a flavor that resembles cardamom more and, being one of the *Shwashar* (COPD) herbs, it will enhance the benefit for the lungs (section 5).

Ayurveda classifies taste, known as "*rasa"*, into six types. Each *rasa is* attributed to specific effects on various body systems and functions [31]. Blending the taste can thus be an important factor in modifying the constitutional effects of the *awaleha*. Cutting-edge research has now established that there are systemic responses to the different tastes through extra-sensory taste and smell receptors distant from the sensory organs [32]. These recent studies provide validation for the Ayurvedic concept of *rasa,* which emphasizes that the taste, flavour and aroma of food have an influence on the metabolic effects of the food substance. Interestingly, receptors for taste have been found in the airway, while light receptors for sight have been found in the blood vessels. Furthermore, olfactory receptors for smell have been identified in the sperms [33].

The taste and light receptors found in these extra-sensory locations cause smooth muscle relaxation upon stimulation, widening the airways and blood vessels, thus relieving bronchoconstriction in asthma and high blood pressure respectively [34,35]. Maberg and Hatt discovered in 2018 that when olfactory receptors in the nose are stimulated by specific aromas, similar receptors present at several extra-sensory sites in the body are also stimulated by them, exerting multifarious systemic effects. In the skin, these receptors increase the regeneration of skin cells and help speedy wound healing, while in the heart muscle cells, they function as metabolic regulators of heart functions [36]. The smell receptors in the liver, when activated, may even reduce the spread of cancer cells, while those in the immune system have been seen to promote the death of certain types of leukaemia cells [37].

Thus, bioactive molecules present in the *prakshape* spices exert their action not only after digestion and absorption in the gut, but begin acting even before swallowing, via the various taste and olfactory receptors present in the mucosa of the oral and nasal cavities. *Awalehas* by the nature of their consistency and traditional method of use, have to be slowly licked by tongue, and not swallowed all at once, hence providing time for the phytoactive principles to be savoured and absorbed by the highly vascular mucosa of the tongue. By altering the final taste and flavour of the *awaleha*, the pharmacological effects of the preparation can be fine-tuned towards specific desired therapeutic benefits, depending on the individual's requirements and physiological disorder.

Supplementation with specific ingredients like bhasmas, honey and saffron

Special substances like *bhasmas* and honey can be added to the prakshape during the final stage of preparation, based on the the specific requirements of an individual (patient). *Bhasmas* are calcined herbo-mineral preparations that offer significant benefits in various diseases and are also used for promotive purposes [38]. To incorporate the *bhasmas* into the *awaleha*, they are added at the semi-solid stage while it is still hot. Vigorous stirring is necessary to achieve a homogenous mixture. It is important to disperse the *bhasmas* properly in the *awaleha* because they can be toxic if used

in excessive amounts. Ensuring an even distribution of the bhasma guarantees that a specified quantity is delivered per dose of the awaleha.

Honey is commonly added to the *awalehas* due to its numerous health benefits. According to Ayurvedic principles, honey should not be heated. This is a logical practice because heating honey can denature the diverse range of antigens derived from pollen present in it [4]. Thus, honey is mandated to be added only after heating has been stopped, and the *awaleha* has cooled down. In practice, the powdered herbs of *prakshape* are added first, followed by the bamboo manna, and lastly, the honey and saffron.

Saffron (Crocus sativus), a very expensive herb/spice, is also only added after the *awaleha* has cooled down. This is because saffron contains several volatile and aromatic bioactives which may be volatilized if added to super-heated *awaleha*.

Synbiotic and bio-enhancement effects, producing herbal synergy

The spices constituting the *prakshape* have several synergistic effects, amplifying the beneficial effects of the individual herbs utilized in formulating the *awaleha*. These synergic effects are of four types, as detailed below.

Bio-enhancement or Bio-potentiation

Some constituents of the *Prakshape* are of pronounced importance due to their significant role in bio-potentiating the effects of several herbs used in the decoction (step 2 of Fig. 1). A bio-enhancer is an agent capable of augmenting bioavailability and bio-efficacy of a particular drug/phytochemical with which it is combined, without having any typical pharmacological activity of its own [39]. The benefits of adding a bio enhancer include reduced drug dosage, reduced cost of the drug, reduced incidence of drug resistance and reduced risk of adverse drug reaction/side effects. Another beneficial effect is the reduced requirement of raw (herb) material for drug manufacture, an important environmental factor in the commercial production of herbal formulations.

With the discovery of the first bioavailability enhancer piperine in 1979, a new class of drugs and a new concept was introduced to science. Piperine still remains the most effective bio-enhancer. Piperine is an important component of black pepper (Piper nigrum) and long pepper (P longum), and helps in bioenhancing a very wide variety of drugs. These include antibiotics like cefotaxime, amoxycillin, rifampicin and norfloxacin, chemotherapy agent docetaxel and the antiviral acyclovir. Used along with herbs, Piperine enhances absorption and bioavailability of curcumin (active ingredient of Curcuma longa), vasaka (Adhatoda vasica), ginger (Zingiber officinale), cardamom (Elettaria cardamomum), clove (Syzygium aromaticum) and carotene (a carotenoid), to name a few [40].

The mechanisms of action of bio-enhancers include reduction of hydrochloric acid secretion in the stomach, increase in blood supply to the gut, increase of gastrointestinal transit and gastric emptying times and inhibition of intestinal motility. They also exert the cholagogue effect, regulate modifications in GIT epithelial cell membrane permeability, exhibit bioenergetic and thermogenic properties, suppress first pass metabolism in liver, inhibit metabolizing enzymes and stimulate gamma glutamyl transpeptidase [41]. Since most phytochemicals are only feebly bio soluble and thus poorly bioavailable to the body, bioenhancers like piperine have a substantial role to play by increasing their bioavailability.

In the context of *prakshape* , Piper longum (pippali or long pepper) is a rich source of piperine and it is used in a large amount (160 gm in a typical 20 kg batch of Chavanprash). In fact, the amount of long pepper used is much more than any other herb, by as much as 8-10 times. This enhances the action of several of the herbs used in the decoction as well as in the *prakshape* itself. Another bio enhancer quercetin, present in the *prakshape* spices cardamom and cinnamon, which undergoes thermal degradation due to boiling while preparation of decoction, has been shown to increase the bioavailability, blood levels and efficacy of a number of drugs [42,43]. Besides bioenhancement, quercitin exhibits a wide range of beneficial biological activities including radical scavenging, anti-tumoral, anti-inflammatory, anti-atherosclerotic, and anti-viral effects [41].

Holobiont effect: Co-production of bioactives by endophytic fungi and bacteria

Holobiont is an assemblage of a host and the many other species (of microorganisms) living in or around it, which together form a discrete ecological unit [44]. The microbes (bacteria and fungi) living inside the plant parts are known as endophytes. In the context of *prakshape*," herb + endophytic microbe = Holobiont". The endophytes present in the five *prakshape* raw herbs *Dalchini* (Cinnamomum verum bark), *Tejpat* (Cinnamomum tamala), *Nagkesar* (Messua ferrea), *Elaichi* (Elettaria cardamomum) and *Pippali* (Piper longum) are capable of producing similar phytochemicals as the host/parent herb [45]. This recent discovery of holobiont effect proffers the prospect of utilizing the symbiotic microorganisms present in powdered spices as a source of added supply of herbal bioactives. In addition to producing similar phytochemicals, some endophytic fungi also produce metabolites that display antibiotic effects, for example, those present in *Syzygium aromaticum*, *Piper nigrum* and *Cinnamomum verum* [46]. Similarly, several endophytic bacteria produce novel antibiotics such as ecomycin, pseudomycin and kakadumycin [47]. Recent studies (given below) have demonstrated that the endophytic micro-organisms can survive in the intestines, and contribute to the microbiome.

Romero et al (2021) have provided data to support the endophytic origin of some gut bacteria in animals [48]. In humans, David et al showed that ingested bacteria may be metabolically active in human guts as revealed by gene transcripts from food-bacteria in guts [49]. In a recent study, Soto-Giron et al in 2021 highlighted the potential that plant microbes have when consumed as part of our diet and proposed these as transient contributors to the gut microbiome [50]. The human microbiome (defined as the community of microorganisms, such as fungi, bacteria and viruses, that exist in the human gut) is now recognized as a significant factor in human health and disease [51].

Recent studies on human gut microbiome have identified several species of bacteria that are common with plant endophytes, such as Bacillus species. Studies conducted by David and Giron (cited above) have made it apparent that plant bacterial endophytes can subsist in the human system after ingestion as foodstuffs [49,50]. These plant bacteria, surviving and colonizing in the milieu of human gastro-intestinal tract (GIT) can be considered as **probiotics**. The internationally endorsed definition of probiotics is live bacteria and fungi that, when administered in adequate amounts, confer a health benefit on the host [52]. As an example, Lactobacillus plantarum found in animal guts, plants and in fermented food is employed as a probiotic and helps defend animals against bacterial and viral infections [48]. Similarly, the endophytic bacteria in *prakshape* spices, by forming part of the gut microbiome, can contribute bioactive phytochemicals as detailed above.

The human mycobiome (fungal community in gut) is an important component of the gut microbiome. A proportion of this gut mycobiome is of dietary origin, as shown by Huseyin et al [53]. While most of these fungi survive only transiently in the human gut, emerging data indicates that ingestion of certain fungi-containing foods may provide an important source of inoculum of fungal species that can colonize the human gut [49,53]. Fungi of the Periconia genus have been documented to colonize the silkworm gut [54]. Piper longum fruits harbour this endophytic fungus Periconia, as also several endophytic bacteria, all of which produce piperine, the most important active principle in Piper *longum* [55]. After ingestion, these spice endophytes can meld with the existing gut microbiota and produce the same bioactives for varying periods of time, depending on their survival periods in the intestines. This leads to multiplication of the bioactive principle and resultant increased phyto-active drug action. Ingestion of raw Piper longum thus leads to increased therapeutic effects and also prolonged benefits, continuing for much longer time periods after ingesting the *awaleha* since the fungus will continue to reside in the gut. This is only possible if the raw *prakshape* is added towards the end of the manufacturing process when heating has ceased so as not to thermally destroy the endophytic fungi growing within the parts of the herb such as leaves, bark, dried berries and fruits.

Synbiotic effect of *prakshape* spices on gut flora

Synbiotics are a combination of prebiotics and probiotics that are believed to have a synergistic effect by inhibiting the growth of pathogenic bacteria and enhancing the growth of beneficial organisms in the gut [56]. Synbiotics can also be described as products having a mixture of pre and probiotics, in which the prebiotic compound selectively favours the growth of probiotics and their metabolite production [57].

Prebiotics are non-digestible carbohydrates that serve as food for the beneficial bacteria in the gut [58]. These include inulin-type fructans, oligosaccharides, isomaltooligosaccharides, xilooligosaccharides, arabinooligosaccharides, lactosucrose, lactobionic acid, resistant starch, psyllium and galactomannan [59,60]. All prebiotics are fibres, but not all fibres are prebiotics.

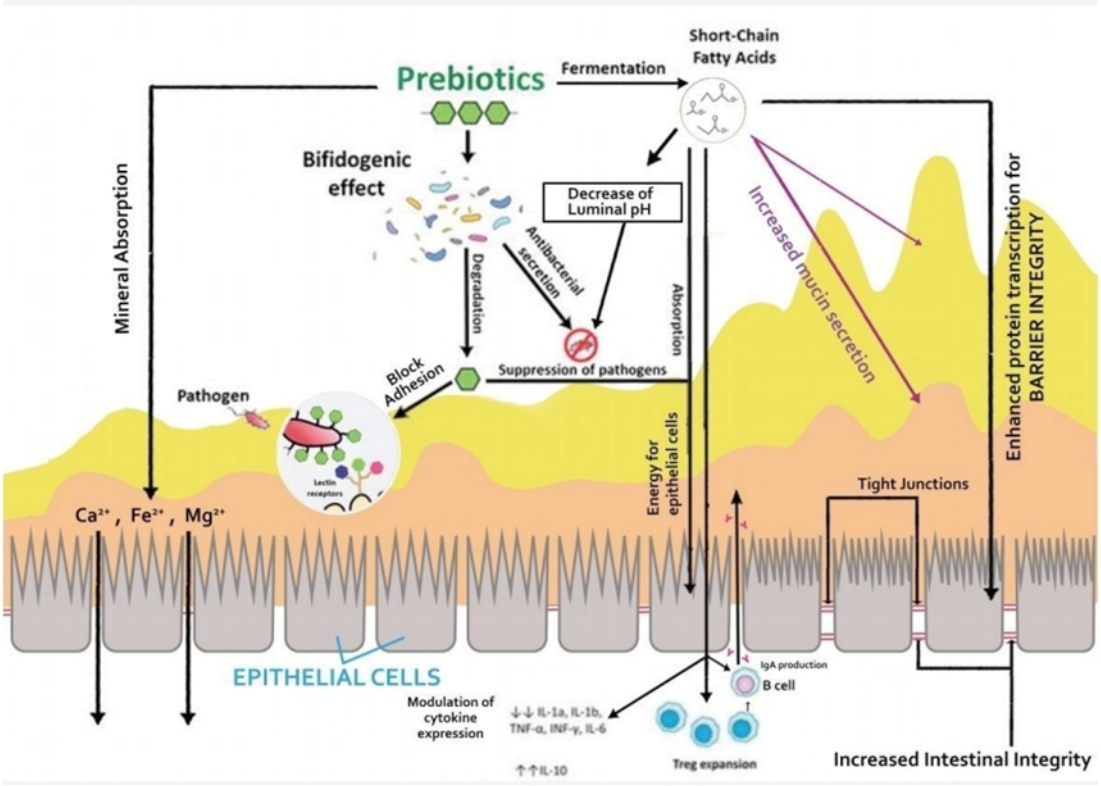

Figure 3: Mechanism of action of Prebiotics in prakshape. The figure represents part of the colonic lumen and epithelial lining, depicting from left to right the beneficial mechanisms of (i) Aiding mineral absorption, (ii) Pathogen suppression, (iii) Proliferation of beneficial microbes, (iv) Production of short chain fatty acids (SCFAs), (v) Increased secretion of protective mucin, (vi) Modulation of cytokine and lymphocyte expression, (vii) Tightening of inter-cellular junctions, and (viii) Enhancing mucosal integrity by increasing IgA secretion and decreasing permeability.

The spices that constitute the *Prakshape,* namely Cinnamomum verum (bark), Cinnamomum tamala, Messua ferrea, Elettaria cardamomum and Piper longum are utilized in their raw, powdered form. This is different from when these spices are included in the herbal mix to prepare the herbal decoction (aqueous extracts), when only the water-soluble phytochemicals present in these spices are dissolved into the decoction. In their whole (raw) form, these *prakshape* condiments provide natural fibre, volatile oils and lipophilic constituents also, which are all absent in the water-extracts of the decoction. The natural fibres are carbohydrates that act as prebiotics to promote the gut flora and hence enhance the microbiome [61]. Prebiotic effects include pathogen suppression, increased production of protective mucin and enhancement of mucosal integrity by tightening intercellular junctions and decreasing mucosal permeability [62]. The mechanisms underpinning these promotive effects are detailed in Figure 3.

Studies supporting the promotive effect of herbs and spices on the gut micro-flora have been carried out by Peterson et al 2019, and Lu et al 2017 [61,63]. The former observed that herb-supplemented cultures increased the relative abundance of a number of beneficial taxa including Eubacterium rectale, Gemmiger formicilis and Bacteroides thetaiotaomicron in human GIT. In particular, P. longum increased the relative abundance of Bacteroidaceae. Lu et al demonstrated that spice extracts like piperine, cinnamic acid, and cinnamaldehyde enhanced the growth of beneficial bacterial strains like Bifidobacterium spp. and Lactobacillus spp. All these spice extracts also exhibited inhibitory activity against harmful bacteria like Ruminococcus species. Cinnamon was also found to be active against selected Fusobacterium strains and against selected Clostridium spp [64]. These studies suggest the potential role of *prakshape* spices in the regulation of intestinal microbiota and the enhancement of gastrointestinal health. Thus, the prebiotic effects of the ground (powdered) spices along with the endophytes

of the holobiont as described above result in the prakshape spices acting like synbiotics.

Direct synergistic effects

Recent studies by Britto [65] and Diez [66] have established the synergistic antimicrobial effects of certain herbs in combination, while research conducted by Bag [67] and Mansour [68] has illustrated the synergistic antioxidant activity of herbs and spices. There are several herbs used in the *prakshape* that have synergistic effects. As an example, Majdalaweih has described the synergistic stimulatory effect of aqueous extracts of black pepper (Piper nigrum) and Cardamom (Elettaria cardamomum) on splenocyte proliferation [69]. He also found these two spices to be synergistically immunomodulary and anti-cancer. Since the most important active principle in both black pepper and long pepper (Piper longum) is Piperine, the synergism of cardamom and pepper is akin to that between cardamom and long pepper.

Britto has detailed the potent synergistic antibacterial effects of the extracts of the mixture of several spices, including cinnamon and cardamom with ginger (Zingiber officinale) and pepper [65]. Azzeh established that cinnamon and ginger work in synergy to reduce blood sugar [70]. In the above instances, it may be noted that the herbs working synergistically are cardamomum, cinnamon, (long) pepper and ginger. Whilst ginger is present in herbal decoction (step 2 of Fig 1), the addition of the former three in powdered raw form as *Prakshape*, is responsible for the synergistic effects.

Re-introduction of lost aromatic substances

The initial step of preparing Chavanprash involves the use of various spices, many of which (step 2 of Fig 1), contain volatile essential oils. Some of these spices are again used in the *prakshape*. Numerous studies conducted by researchers have clearly established the multifaceted health benefits associated with the essential oils present in the prakshape spices. However, due to the prolonged heating process, these beneficial aromatic oils can vaporize, resulting in their loss along with heat-labile phytoconstituents. It is crucial to restore these essential oils (EO) in the final awaleha formulation to ensure that the resulting chavanprash retains the aforementioned attributes. The addition of prakshape effectively replenishes the lost aromatic oils, thereby addressing this concern. These benefits include inhibiting microbial replication, modulating inflammatory and oxidative processes, and even exhibiting anti-neoplastic effects [71,72].

Behbahani et al., in their study conducted in 2020, analysed the composition and activity of **Cinnamomum** zeylanicum bark essential oil. They identified the major constituents as (E)-cinnamaldehyde (71.50%), linalool, β caryophyllene, eucalyptol, and eugenol [73]. The researchers, along with Jeong et al. in 2021, observed that Cinnamon essential oil exhibited antibacterial activity, particularly against Gram-positive bacteria, by disrupting the cell envelope and promoting the leakage of intracellular compounds [74]. Several studies have also demonstrated that C. zeylanicum essential oil contains significant levels of phenolic and bioactive compounds with remarkable free radical scavenging abilities, as well as the potential to inhibit lipid oxidation reactions [75]. Additionally, Behbahani et al also deduced that even at low concentrations, C. zeylanicum essential oil is capable of inducing the proliferation of Adipose Tissue Mesenchymal Stem Cells (AT-MSC), which can be beneficial for tissue regeneration purposes [76].

Cardamom essential oils (CEO) predominantly consist of ester α-terpinyl acetate, monoterpene 1,8-cineole, α-terpineol, linalool and α-pinene [77]. CEO has been identified as an intestinal smooth muscle relaxant, exhibiting antispasmodic and antidiarrheal activities [78,79]. These effects can be attributed primarily to the presence of 1,8 cineole [80,81]. Furthermore, CEO has demonstrated antibacterial effects against various Gram-negative bacteria, including E. coli and Pseudomonas aeruginosa, likely due to the presence of 1,8 cineole and α-terpinyl acetate [82,83]. In 2020, Cui et al. discovered that CEO is capable of scavenging methicillin-resistant Staphlyococcus aureus (MRSA) biofilm by inhibiting the metabolic activity of bacteria and the formation of extracellular polymers [84]. Additionally, in a study conducted by Khattab on paracetamol (PCM)-intoxicated rodents, the administration of CEO significantly improved hepato-renal profiles by elevating the total antioxidant capacity. The oil also offered protection against histopathological alterations in the liver and kidneys of rats exposed to paracetamol toxicity in PCM-intoxicated rats [85].

The inflorescences and fruit of Piper longum are rich in essential oils and contain the highly beneficial phytoactive alkaloid called piperine [86]. Piperine, being sparingly soluble in water and highly volatile, is mostly absent in the penultimate stage of the *awaleha* preparation, which corresponds to step 6 in Fig.1 [87]. However, it is vital for the awaleha to contain piperine, as it is the most valuable component of P longum and possesses a wide range of pharmacological actions [88]. Some notable pharmacological effects of piperine include its anti-asthmatic, anti-diabetic, anti-oxidant, anti-hyperlipidemic and anticarcinogenic properties [87]. Furthermore, piperine acts as an excellent bio-enhancer (as discussed in section 3.4.1) enhancing the absorption of nutrients from food.

The essential oil of P longum primarily consists of sesquiterpenes (50%) and monoterpenes, with notable compounds including β-caryophyllene, n-heptadecene, and n-heptadecane, 3-carene, eugenol, D-limonene, zingiberene, and cubenol [89,90]. Piper EOs have demonstrated several health benefits in various

studies. In 2021, Al-sayed demonstrated the promising inhibitory effects of piper essential oils on Helicobacter pylori, which are almost comparable to those of clarithromycin [90]. Singh et al observed the irreversible paralytic effect of P. longum essential oils on F. gigantica (liver fluke) in vitro [91]. Additionally separate studies conducted by Mamta Kumari and A Kumar revealed that the fruit oil of P longum significantly inhibited carrageenan-induced rat hind-paw edema indicating significant anti-inflammatory activity in rats [92,93]. Suresh Kumar's findings provided evidence of the high potential of Piper EOs in the treatment of diabetes mellitus and hyperlipidemia [94].

Messua ferrea (MF) is the only spice included in *prakshape* that is not added during the preparation of the decoction. The freshly ground seed powder of M ferrea is sifted through muslin and then incorporated into the hot awaleha as part of the *prakshape*. These seeds contain essential oils, xanthones and several 4-phenyl coumarin analogues, including mesuol, mammeign, mesuagin, mammeisin and mesuone [95,96]. The essential oil of M ferrea has as its major constituents trans-caryophyllene, caryophyllene oxide, humulene, cadinene, muurolene , selinene, germacrene D and bisabolene [97]. Many of these compounds have been the subject of investigations regarding their therapeutic actions, as outlined below.

Mesuol has demonstrated significant antioxidant and immunomodulatory activity in various models, including cellular immune response, in vivo humoral immune response, and cyclophosphamide induced myelosuppression [98]. The essential oil of M.ferrea has also been documented to possess antioxidant activity in certain studies, likely attributed to its high trans-Caryophyllene content, which is known for its antioxidant properties [99]. Furthermore, seed extracts of M.ferrea have exhibited beneficial effects on multiple pathological manifestations of formaldehyde and complete Freund's adjuvant CFA-induced arthritis in rodents. Jalalpure et al. suggested that these effects could be attributed to the xanthones present in the seeds [100].

The essential oil (EO) of M ferrea has displayed significant antibacterial activity against Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus [97,101]. Additionally, the EO has exhibited inhibitory effects on three human cancerous cell lines, including KB (oral cancer), MCF-7 (breast cancer) and NCIH187 (small lung cancer) cell lines [97]. Asif et al. demonstrated that the oleo gum resin extract of M ferrea EO possesses cytotoxic and antimetastatic activities against human colon cancer cell lines HCT 116 [102]. At the protein level, it down-regulated the expression of multiple pro-survival proteins such as survivin, xIAP, HSP27 and HSP60, while upregulating the expression of reactive oxygen species (ROS), caspase-3/7 and TRAIL-R2 in HCT 116 cells. Furthermore, a significant reduction in invasion, migration, and colony formation potential was observed.

The studies mentioned above highlight the crucial role of the volatile, heat labile and essential oil components of the spices reintroduced in *prakshape.* These components possess significant therapeutic properties, including anti-oxidant and anti-inflammatory effects, as well as anti-carcinogenic, anti-hyperlipidemic, anti-diabetic and anti-bacteria properties. The inclusion of these components ensures that the rejuvenating *awaleha* is fortified with their beneficial effects. Furthermore, the presence of the bioenhancing alkaloid piperine from Piper longum, which is heat labile, adds to the potency of the awaleha. Each component of the *prakshape* contributes to making every particle of the *awaleha* powerful and potent in its own way.

Materials and Methods

A comprehensive literature search was performed to identify recent articles that demonstrate the usefulness of silica-lipid hybrids as carriers for phytochemicals, the prebiotic effects of the *prakshape* spices, the bioenhancement properties of piperine and other phytochemicals, as well as the synergistic effects among *prakshape* spices. Various online databases, including Web of Science, Scopus and PubMed, were systematically queried. The following keywords were employed either individually or in combination as inclusion criteria for selecting relevant articles for this review: herb synergism, silica lipid hybrid phytochemicals, bioenhancement spices, prebiotic spices and honey benefits.

Upon conducting initial searches, approximately 250 results were obtained. The abstracts of these papers were thoroughly examined to confirm their relevance and applicability to the topic. Specifically, articles that provided details on the biopotentiation effects of piperine as well as those discussing Silica-lipid hybrids and the synergistic interactions among prakshape spices, were selected for further review. Additional exclusion criteria, such as non-English language, publications and manuscripts not available as full text, were also applied. As a result, a total of 140 papers were identified for further consideration.

Discussion

In Ayurveda, the inclusion of powdered herbs as adjuncts to specific decoctions or *awalehas* is a standard practice. Among the most commonly used herbal powders (*churans*) are pippali (Piper longum), saunth (dried ginger, Zingiber officinale), guggul (Commifora mukul), heeng (Ferula narthex) and pushkar moola (Inula racemose). Additionally, other substances such as ghee (clarified butter), castor oil (Ricinus communis) and shilajeet (Asphaltum punjabianum), are also added at the end of the preparation. These substances known as *prakshape*, serve as supplementary components in the preparation [1]. One of the most renowned *prakshapes* is the one utilized in the preparation

of Chavanprash awaleha. The formulation and preparation process of Chavanprash is given in various ancient Ayurvedic texts [103].

Several herbal powders used in *prakshape* of Chavanprash exhibit the properties of bioenhancement and synergy. Notably, pippali and ginger are recognized as bioenhancers, with piperine and gingerol identified as the bioenhancing compounds, respectively [40]. Piperine and gingerol enhance the effectiveness of various drug classes, including antibiotics, antihistamines, corticosteroids, anti-inflammatory drugs, immunosuppressants, and anti-cancer drugs [40]. Section 3.4.1 elaborates on some postulated mechanisms of action for herbal bio-enhancers. Additionally, these bioenhancers can act by inhibiting drug metabolizing enzymes and efflux pumps [104]. Moreover, some of the bio-enhancers also reduce renal clearance by impeding glomerular filtration and promoting passive tubular reabsorption. The P-glycoprotein 1 efflux pump functions to expel drugs from the intestinal epithelium, proximal tubule of kidneys, and the blood brain barrier, thereby preventing them from reaching their intended target sites [105]. However, bioenhancers can inhibit this pump, leading to increased plasma concentrations of drugs or enhanced entry into the brain. Piperine can modify the drug metabolizing process by reducing the endogenous UDP-glucuronic acid content, thereby decreasing the rate of glucuronidation [106]. Inhibition of other drug metabolizing enzymes such as CYP1A1, CYP1B2 and CYP2E1, in the liver, gut, lungs, and other locations, prolongs the presence of drugs in the body that are metabolized by these enzymes. This extended duration allows the drugs more time to exert their therapeutic effects [41].

Ayurvedic texts mention other substances that are added as adjuncts (prakshape) to herbal formulations, including honey, goat milk and cow urine. Cow urine distillate known as goumutra, has been found to contain a bioenhancer, for which US patents No. 6 896 907 and 6 410 059 were granted. Studies have revealed that Gomutra distillate enhances the bioavailability of antimicrobial, antifungal, and anticancer agents [107,108]. Additionally, some herbs used in prakshape contain phytochemicals that exhibit synergistic activity. Herbal synergy proves to be beneficial in amplifying the anti-oxidant, antibacterial, and anti-cancer effects of the herbs. For instance, combining dietary phytochemicals such as curcumin and cinnamaldehyde with antibiotics showed a synergistic effect against the bacteria Staphylococcus epidermidis [109].

Other phytochemicals demonstrating synergistic actions against oxidative stress include curcumin and resveratrol; quercetin dihydrate, rutin hydrate and resveratrol, as well as Osmanthus fragrans flowers (acteoside) and green tea (gallic acid) [110-112]. Ginger extract and its constituent biophenols (in particular, 6-gingerol) have shown significant synergistic anti-cancer activity against the proliferation of prostate cancer cells [113]. Hsieh et al 2008 discovered that a combination of three dietary phytochemicals, namely, -- epigallocatechin gallate, resveratrol, and gamma-tocotrienol, -- produced a synergistic effect in protecting against chemical-induced carcinogenesis in animal models [114]. This effect was attributed to the induction of quinone reductase NQO1, which enhances the important detoxification pathway by reducing electrophilic quinones [114]. Similarly, apple extracts and quercetin demonstrated significant synergism against the proliferation of MCF-7 human breast cancer cells [115]. Quercetin, a phytochemical, is present in several *prakshape* spices.

In Ayurveda, honey is regarded as *yogavahi*, which implies that it carries the qualities of the substance which it is combined or associated with [116]. Honey is a widely used ingredient in *prakshape*, and it is composed of approximately 200 unique components. It offers various health benefits, including antioxidant, anti-inflammatory, immunostimulatory, anticancer, and cardioprotective actions. Honey's antioxidant activity, mediated by phenolics such as vanillic and caffeic acids, as well as flavonoids, allows it to scavenge free radicals, reduce oxidative damage, and stimulate the body's antioxidant defence system [117,118]. The presence of flavonoids like quercetin and kaempferol in honey also contributes to its positive effects on cardiovascular health [118-120]**.**

Honey also plays a significant role in wound and tissue healing by promoting the production of immunological mediators and accelerating tissue regeneration, while simultaneously suppressing inflammation-associated molecules [118,119]. These immuno-modulatory properties, combined with honey's antimicrobial and antioxidant effects, contribute to its effectiveness in the tissue healing process [120,121]**.** In vitro studies have provided evidence that honey can effectively inhibit the development and progression of various cancer cell types through multiple mechanisms. These mechanisms include inducing apoptosis, modulation of oxidative stress, arresting the cell cycle, activating mitochondrial pathways, ameliorating inflammation, and inhibiting angiogenesis. Additionally, honey exhibits prebiotic properties due to its content of non-digestible oligosaccharides, selectively stimulating the growth of beneficial bacteria in the colon, including bifidobacteria and lactobacilli [118]. Adding honey to herbal formulations is thus a winning proposition.

The inclusion of silica, specifically bamboo manna, in the prakshape of Chavanprash is a remarkable addition. The challenge of low bioavailability of highly beneficial phytochemicals has prompted research into innovative delivery systems, including lipid based and particle-based systems like Silica Lipid Hybrids (SLHs). SLH formulations possess a distinctive nanostructured matrix that aims to improve the dissolution, absorption, and bioavailability of poorly water-soluble drugs and phytochemicals,

including curcumin [122]. Curcumin, in particular, faces challenges in application due to its low water solubility, weak stability, and poor bioaccessibility. In vitro simulated digestion tests have shown that curcumin-loaded nanoemulsions and SLH microparticles exhibit enhanced bioaccessibility compared to the control group. Moreover, SLH microparticles have demonstrated consistent storage stability across different temperatures over a period of six weeks [123]. Furthermore, innovative super-saturated SLH (super-SLH) formulations can increase drug loading capacity in cases of compounds having low potency [124]. The studies mentioned above provide strong evidence for the significant advantages offered by silica-lipid based systems in the delivery of phytochemicals. The incorporation of bamboo manna, which is primarily composed of silica, into the *prakshape* of Chavanprash represents an excellent approach to enhance the bioavailability of the numerous phytochemicals present in the formulation.

One additional reason for adding the (whole) powdered herbs at the end of process is to compensate for the loss of volatile and heat labile substances that occurs during the lengthy cooking procedures. The process of boiling the Amla and decoction herbs takes approximately 2-3 hours. After sieving, the decoction is reheated, and sugar is added to create the decoction syrup which takes around 1-2 hours. Subsequently, the fried Amla pulp and decoction-syrup are combined and heated for an additional 2-3 hours to achieve a semi-solid consistency. The total heating process spans approximately 6 to 8 hours. This prolonged heating is sufficient to evaporate volatile substances and degrade heat labile ones. By incorporating freshly powdered herbs at the end, these lost substances can be replenished.

These volatile and heat-labile compounds, including piperine, eugenol, linalool, 1,8, cineole, mesuol, and seaquiterpenes, alongwith many others, are important phyto-compounds found in spices such as long pepper, cinnamon, cardamom, and cobra saffron (Mesua ferrea). In numerous Ayurvedic formulations that involve prolonged heating, volatile elements may be lost to the environment. Adding them in powdered form at the end stage of preparation serves as a practical solution to replenish these compounds. It is worth noting that these proposed spices would be from among the original components of the formulation, and incorporating them would not alter the overall composition. For instance, the Charak decoction for chronic obstructive pulmonary disease (*shwashar*) consists of 10 herbs, including Hedychium spicatum (shati), Inula racemosa (pushkarmoola), Garcinia pedunculata (amlavetasa), Elettaria cardamomum (cardamom), Ferula narthex (Hing), Aquilaria agallocha (agaru), Ocimum sanctum (surasa), Phyllanthus niruri (tamalaki), Leptadenia reticulata (jivanti) and Angelica glauca (chanda) [125]. By adding powdered cardamom after preparing the decoction, the volatile oils in cardamom lost during the heating process can be restored without affecting the formulation itself.

Conclusion and future perspectives

The incorporation of powdered condiments called *Prakshape* is a pharmacologically potent modality to enhance the action of the herbs. It is based on sound principles of synergy engineered by several mechanisms, most of which have been discovered only recently. These include bio-potentiation, holobiont interplay, prebiotic spin offs and enhanced drug delivery systems. The ingenious method of creating such modalities by the simple addition of *prakshape* magnifies the phytochemical drug action, which helps to reduce the required quantity of herbs, resulting in huge cost savings and environmental benefits.

The principles underlying the various modalities of augmenting and potentiating phytochemical drug action effectuated by *prakshape* can also prove to be stepping stones for further developments in herbal therapeutics. Using the mechanisms of synergy and drug delivery elucidated herein, other herbal and even non-herbal formulations can be similarly potentiated and crafted to meet specific needs. In traditional Ayurvedic formulations, use of the same ingredients in their raw or unprocessed form, known as "*prakshape"* can enhance the efficacy of the formulation. This is because processing methods like boiling or frying can lead to the loss of volatile compounds in the ingredients, which may impact their therapeutic properties. An example mentioned in section 4 is the use of cardamom as *prakshape* in a classical decoction for breathlessness (*shwashar*). By using cardamom in its raw form, the volatile compounds lost during processing can be replaced, thus increasing the efficacy of the formulation.

Another possibile use of prakshape in traditional Ayurvedic formulation is in *Kashmaryadi ksheerpak*, a milk-based preparation for intrauterine growth retardation [126]. This formulation includes three herbs boiled in milk: Gmelina arborea, Glycyrrhiza glabra and Saccharum officinarum. Glycyrrhiza glabra, also known as liquorice, contains volatile components, such as linalool oxide, geraniol, α-terpineol, pentanol, hexanol, terpinen-4-ol, and tetramethyl pyrazine, along with essential oils. During the long heating process involved in preparing Kashmaryadi ksheerpak, some of these volatile compounds may be lost. To enhance the therapeutic effect and address the loss experienced, an approach to consider is the addition of a *prakshape* of powdered liquorice to the milk emulsion. This addition would replace the volatile compounds that were lost during the heating process. By incorporating powdered liquorice as *prakshape*, the overall formulation's therapeutic efficacy can be significantly improved, while maintaining the fundamental composition of the milk emulsion.

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