Herbomineral Formulations - A Review

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ABSTRACT

Ayurveda has earth-shattering in audience of worldwide on virtue of its holistic approach of life and its fewer side effects. Ayurvedic herbal and herbo-mineral preparations are used for the treatment of chronic and degenerative diseases without any side-effect. Herbo mineral formulation uses the metals and minerals for chronic disorders in different combinations, dosage forms and at various levels of purities. Hence it is very essential to prepare it in a proper way. As per the reported data, there are so many herbo-mineral formulations available in market which is useful in anaemia, diabetes, cancer, liver diseases, skin diseases etc. This review is an attempt to emphasis on the benefits and problems associated with it.

Keyword: Cumulative toxicity, Ayurveda, Bhasma, Heavy metals, Herbo-mineral

I. INTRODUCTION

Ayurveda is the science of life which deals with maintenance of health of healthy persons and cure of ailing humanity as its main ambition. Ayurvedic doctrine of treatment is based on Hetu, (etiological factor) linga (symptom/manifestation) and Aushadh (medicine) and all these stand on concept of Tridosha (three fundamental humours), Panchamahabhuta (five basic of existence of cosmos), saptadhatu (seven vital functionaries of human physiology). Ayurvedic physicians put into practice these all factor with excellence of their individual skill to find out understanding of Dosha-Dushaya-Samurchana (aetiology and pathology of disease) and SampraptiVighattan (breaking of pathology of diseaseto get healthy state of functions). Ayurveda viewed health as a state of many-sided equilibrium, and disease as its reversal. Ayurvedic practice of medicine aimed at the restoration of equilibrium and, in that process, represented more than the sum of dietary regimen, procedures and medications.

Rasaushadhis (Herbo-bio-mineral metallic preparation).

Rasashastra may be defined as a branch of Ayurveda which deals with the various pharmaceutical processes of Shodhana (purification/potentiation), Marana (incineration/calcinations), Jarana (polling), Murchana (a procedure by which substances specially mercury istransformed for therapeutic application) and other detailed description of metals, minerals, poisonous herbal drugs and animal products used therapeutically in practice of Ayurveda.[04]. The innate qualities of Rasaushadhis like quick action, lesser dose, tastelessness, prolonged self-life, better action, lesser dose, tastelessness, prolonged self-life, better as pharmaceutical proprietors. [05].

II. METHODS AND MATERIAL

A. Herbomineral Formulations

Rasayana Tantra

The word Rasayana is composed of two words, rasa and Ayana. Rasa means dhatus responsible for sustenance of life. Ayana means specific measures uses for obtaining rasa and responsible for longevity. Rasayana is a well-developed concept in Ayurveda. Rasayana means the augmentation of rasa, the vital fluid produced by the
digestion of flood, which sustains the body through the strengthening of the dhatus [6].

In modern term, the study and practice of Rasayana is referred as rasavidya (alchemy). Rasa ausadhis are known as metallic preparation which includes Bhasma and sindoora. Metals like gold, silver, copper, lead, tin and iron, sand, lime and minerals like red arsenic, germs, salts and red chalk are indicated as drugs in Ayurveda. There are more than 200 plants mentioned in Rasashastra which uses mineral and metals as medicinal plant or a desirable chemical property [6].

B. The Aim and Types of Rasayan

Rasayana therapy enriches rasa with nutrients to help one attain longevity, memory, intelligence, health, youthfulness, excellence of luster, complexion and voice, optimum development of physique and sense organs, mastery over phonetics, respectability and brilliance.

Types of Rasayana[7]

1. Kamya Rasayanas are promoters of normal health.
   These boost body energy levels, immunity and general health.
   o Pranakamya – Promoter of vitality and longevity
   o Medhakamya – Promoter of intelligence.
   o Srikamya – Promoter of complexion.
   o NaimitikaRasayanas help to fight a specific disease.

In pursuit of these matters, herbal prescriptions with many herbal substances, preserved in ghee and honey are given. Chyawanprasha is one of the traditional rasayanas.

Specific adaptogenic herbs are also included in rasayanas including amla, shilajit, ashwaganda, holy basil, guduchi and shatavari. Several rasayana herbs have been tested for adaptogenic properties:

The whole, aqueous, standardized extracts of selected plants (Tinosporacordifolia, Asparagus racemosus, Emblicaofficinalis, Withaniasomnifera, Piper longum and Terminaliachebula) were administered orally to experimental animals, in a dose extrapolated from the human dose, following which they were exposed to a variety of biological, physical and chemical stressors. These plants were found to offer protection against these stressors, as judged by using markers of stress responses and objective parameters for stress manifestations. Using a model of cisplatin induced alterations in gastrointestinal motility; the ability of these plants to exert a normalizing effect, irrespective of direction of pathological change was tested.... All the plant drugs were found to be safe in both acute and sub-acute toxicity studies. Studies on the mechanisms of action of the plants revealed that they all produced immunostimulation. The protection offered by Tinosporacordifolia against stress induced gastric mucosal damage was lost if macrophage activity was blocked. Emblicaofficinalis strengthened the defence mechanisms against free radical damage induced during stress. The effect of Emblicaofficinalis appeared to depend on the ability of target tissues to synthesize prostaglandins. Recent data obtained with Tinosporacordifolia have led researchers to suggest that it may induce genotypic adaptation, further opening the arena for more research and experimentation.[8]

C. Rasayana Formulae

Puri [9] has given detailed account of Classical formulations such as AmritRasayana, Brahmrasayana, JawaharMohra, KamudgdhaRas, Lakami Vilas Ras, Lakman Vilas Ras, MadanodayModak, Makrdhawajvati, ManmathRas, MuktapanchamritRasayana, NariKalyan Pak, NavjeevanRas, NavratnaRas, NavratnakalpAmrit, PancamritRas, ParadRas, RamchuramniRas, Rattivalbh Pak, ShukarAmritVati, SmritisagarRas, SuvarnMaliniVasant, Suvarn VasantMalti, Swapmanehtank, VasantKusmakarRas, VishaRasaayana, VrihdaVangeshwar Rasa.

These classical Rasayan formulas, contain a large number of ingredients, including minerals, pearl, coral and gems, and include a specially processed (samskara) mercury (the word Ras indicates mercury as an ingredient). Because of negative publicity and cost factor, the use of the classical rasayana formulas has declined considerably, and most of the preparations available now have herbal ingredients with a couple of mineral and animal products. The non-availability and wild life protection act has made the use of musk, amber, and parts of wild-life animals nearly impossible. The current Rasayan formulas are based on such
ingredients as amla (Emblica officinalis which has very high stable Vitamin C, Vitamin E, and proteins), Terminalia belerica, Terminalia chebula, Shilajit (a mineral exudate high in fulvic acid), Long pepper, Black pepper, Ginger, processed Guggul, Guduchi, Ashwagandha, Shatavari and similar ingredients.

Rasayan has meanings beyond healthful substances. Rasayan Shastra in Ancient India was much less developed than today. Nevertheless, the use and practice of Rasayan was widespread in Ancient India, and some examples of applied rasayan include paints used in the caves of Ajanta and Ellora, Maharashtra state, the steel of Vishnustambha (literal meaning: the tower of Vishnu), and a processed wood sample in the Kondivade caves near the Rajmachi fort in Maharashtra.

D. Rasayana (Fruit Squash or Juice)

In many Indian homes, Fruit squash, juices are prepared and served as drink, desert or as accompaniment to meals. In Tulunadu region of India, Banana and Mango Rasayana are made by mixing of fruit pulp with cow's milk or water with thick consistency. This rasayana may be drunk as juice by diluting with water or milk. With thick consistency it is used as accompaniment to Dosa, Chapati or meals. Rasayana is also known as lassi. Many believe this rasayana helps to beat the heat of Indian summer.

E. Bhasma

Bhasma is an ash obtained by calcinations of metals. It is a unique preparation of Ayurveda with extracts of herbs and metals in combination which functions best when converted from their original metals to metal oxide forms.[10]. It is prepared by calcinations of metals in a closed crucible in pits and with cow dung cakes (puta).

Bhasmas are biologically produced nano-particles and are taken along with milk, butter, honey or ghee which makes these elements easily assailable, eliminating their toxic effects and enhancing their biocompatibility.[11]

F. Preparation of BHASMA[12]

It is prepared from purified minerals, metals, marine and animal products. The process of purification is called Shodhana. It is aimed to remove harmful impurities present in the drug or sometimes modification of undesirable physical properties of the drugs. It helps in enhancement of the therapeutic action and thereby increases the potency of drug. Shodhana is of two – Samanya Shodhana applicable to a large number of metals or minerals and Visesa Shodhana applicable to certain drugs and in certain preparation. After Shodhana, second stage is the Marana which means metals and minerals are made into paste with various drugs and juices. It is essentially the burning process or calcination. It is subjected to fire treatment in a measured manner for reducing them to ashes. The objective of doing Marana Process is to reduce the size of the drug to its finest particles so that it absorbs easily into the system and produce their desired effects without producing harmful side effects.

G. Types of BHASMAS[13]

Bhasmas are classified based on their colour and appearance. Scientifically they are classified based on their dominant metal and mineral groups, such as rajata bhasma (silver), tamra bhasma (copper), loha bhasma (iron), pravala bhasma (shells) etc. Bhasmas are generally yellowish, black, dark, white, grey, reddish black and red, depending upon the predominant drug as well as the other drugs used in the process of marara. They are stored in air tight container (glass or earthen) and maintain their potency indefinitely.
3. Varitara – Small quantity is spread on cold and still water, it should float on the surface. 4. Apurnabhava
   It should not revert to the original state.

I. SINDOORA[12]

It is more potent preparation then bhasma and prepared by the elaborate process of sublimation. The preparation of sindoora process is called kupipakwavidhi in which sublimed mineral obtained on the neck of the sublimation glass flask is called sindoora. Characteristics and preparation of sindoora is similar to Bhasma.

J. SHODHANA

It is a process of purification and detoxification by which physical and chemical blemishes and toxic materials are eliminated and substances are subjected for further processings[16][17]

Procedures of Shodhana:
Following procedures are performed for the purpose of shodhana as per physico-chemical characters of substances.

1. Abhisheka (sprinkling) e.g. Mandura (Iron oxide) Shodhana

2. Achushana (absorption) e.g. Bhallataka (Semicarpusanaocardium) Shodhana.

3. Atapa/Agni Shoshana (drying) e.g. Shilajatu (Black bitumen) Shodhana.

4. Bharjana (frying or roasting) e.g. Gairika (Ochre) shodhana.

5. Bhavana (levigation) e.g. Hingula (Cinnebar) Shodhana.

6. Nirjalikarana (evaporation of water) e.g. Sphatika (Alum) Shodhana.

7. Mardana (trituration e.g. Parada (Mercury) Shodhana

K. MARANA

The process which converts the purified metals and minerals into Bhasma (fine powder) after subjecting them to levigation and incineration is called as Marana.

L. BHAVANA

Required amount of substances and liquid media are levigated smoothly for specific period and is shaped as requirement, often in flat shape and if pressed between finger tips it should be soft to touch, this is considered as indication of proper completion of process.

Herbomineral Formulations

<table>
<thead>
<tr>
<th>Compound name</th>
<th>Reference</th>
<th>Mineral ingredients</th>
<th>Sneha dravya, Madhura dravya and Drava Dravya for Bhavana</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashadashanga Lauha (Kiratai Mandura)</td>
<td>BR-Pandu 12/34-76</td>
<td>LB (50%)</td>
<td>Honey, Cow’s Ghee</td>
</tr>
<tr>
<td>Yograja</td>
<td>BR-Pandu 12/100-35</td>
<td>LB (50%), SMB, Rajata Maksika Bh, Shilajit</td>
<td>Sugar candy, Honey</td>
</tr>
<tr>
<td>Maha Shwashari Lauha</td>
<td>BR (Plika Shiwas)</td>
<td>LB (55%), AB, Vamsalochana</td>
<td>Sugar candy, Honey</td>
</tr>
<tr>
<td>4*Saptarshita Lauha</td>
<td>BR (Shula) 30/130</td>
<td>LB (50%)</td>
<td>Honey, Cow’s Ghee</td>
</tr>
<tr>
<td>Yakshmari Lauha</td>
<td>BR (Rajayaksha) 16/83</td>
<td>LB (50%), SMB, Shilajit</td>
<td>Cow’s Ghee</td>
</tr>
<tr>
<td>Shularaja Lauha</td>
<td>BR (Shula) 30/131-36</td>
<td>KLB (5.4%), AB</td>
<td>Sugar candy, Honey</td>
</tr>
<tr>
<td>Triktrayadi Lauha</td>
<td>BR (Pandu) 12/98-43</td>
<td>KLB (9%), MB</td>
<td>Honey, Cow’s Ghee, five types of Shankara (sugars)</td>
</tr>
<tr>
<td>4*Pippalyadi Lauha-1</td>
<td>BR (Tikhakshwas) 16/4-3</td>
<td>LB (50%)</td>
<td>Honey, water</td>
</tr>
<tr>
<td>Sarvatobhadra Lauha</td>
<td>BR (Amlapitta) 50/4-3</td>
<td>LB (20%), TB, AB, Kajalai (Dviguna), SMB, Marahshila, Shilajit</td>
<td>Honey, Cow’s Ghee</td>
</tr>
</tbody>
</table>

M. VIBHUTI

In certain circumstances Bhasma, ‘Vibhuti’ (Sanskrit) and ‘Thiruneeru’ (Tamil) are synonymous.

Toxicity

Modern medical science finds that mercury is inherently toxic, and that its toxicity is not due to the presence of
impurities. While mercury does have anti-microbial properties, and formerly was widely used in Western medicine, its toxicity does not warrant the risk of using it as a health product in most circumstances. The Centers for Disease Control and Prevention have also reported a number of cases of lead and mercury poisoning associated with rasa shastra containing Ayurvedic medicines.

III. RESULT AND DISCUSSION

A. Advantages of Herbomineral Formulations

Herbo mineral formulation uses the metals and minerals for chronic disorders in different combinations, dosage forms and at various levels of purities. Hence, it is very essential to prepare it in a proper way. As per the reported data, there are so many herbo-mineral formulations available in market which is useful in anaemia, diabetes, cancer, liver diseases, skin diseases etc. Table-5 shows the list of herbo-mineral formulation and its uses in common diseases as per WHO guidelines. Traditional medicines in Asia [18] Prakash et al [19] reported Prak-20 (judicious combination of nineteen herbs and MandoorBhasma) that is a potent hepatoprotective herbo- mineral formulation used in treatment of liver ailments in CCl4 induced toxicity in rats. Prak-20 treated animals had minimum necrotic changes after seven day treatment and further studies are required to understand its mechanism of action. Chronic urticaria (Refractory skin diseases) often creates a therapeutic challenge. Herbal treatment is gaining popularity in the treatment of chronic urticaria. Azad Hussain et al [20] has reported that Unaniherbo-mineral formulation is effective and safe for the treatment of chronic urticarial. It has produced significant effect on itching, wheals, and erythema without causing any untoward effect or adverse reactions. Scabies (Skin diseases) is very common skin disease found in urban population of Gadap town area or Karachi, Pakistan. Sultan Ayaz et al [21] has explained the safety and efficacy of herbal coded medicine, ScaNeem (Herbal coded medicine), for the treatment of scabies. The test drug was found to be an economical, safe and effective in treatment of scabies. Infertility is a very common medical problem associated with male person. Rajeev Kumar et al [22] has reported the use of herbo- mineral supplement – Addyzoa® (Charak Pharmaceuticals, Mumbai India contains Withaniasomnifera and Emblicaofficinalis as its principal constituent) in men with idiopathic oligoasthenoteratospermia (iOATs). The study concluded that treatment with Addyzoa is effective in improving the semen quality by increasing the sperm count and sperm motility in men with iOATs after 3 months of therapy. There was no change in the sperm concentrations, ROS, DFI or TAD levels. Ajitvaze [23] has described the use of Addyzoaherbo-mineral formulation in oligospermia in comparison with Ubiquinone (COENZYME Q 10). A double-blind, randomized controlled trial was conducted and study concluded that treatment with Addyzoa is effective in improving semen quality by increasing the sperm count and sperm motility. The results are comparable with that of Ubiquinone on semen parameters. Lauhabhasma is the most widely used herbo-mineral formulation used in iron deficiency anaemia. Verma P. R. P. and Prasad [24] have reported the use of Lauha bhasma in anaemia. It is better absorbed in GIT and devoid of the usual side effects associated with administration of the allopathic iron preparation. Pattonder R. K. et al [25] has reported the standardization and quality control of herbo-mineral drug AgnimanthaBhavitaShilajatu- ABS (contains Agnimantha and Shilajatu) and TrivritYuktaNavakaGuggulu- TYNG (contains Shunthi, Maricha, Pippali, Haritaki, Vibhitaki, Amalaki, Chitrak, Nagarmotha, Vayavidanga, Siddha Guggul and Trivia). Both ABS and TYNG were prepared using authentic raw materials and subjected for physicochemical analysis which provides objective parameters to fix up the standards for quality control of finished drugs. Pawar R. K. and et al [26] has reported the physico-chemical standardization and development of HPTLC method for the determination of Plumbagin in KalmeghNavayasaLoha. The proposed HPLC method is simple, rapid, accurate, reproducible, selective and economic and can be used for routine quality control analysis of KalmeghNavayasaLoha. The powder. Herbo-mineral formulation showed remarkable improvement in quality of life of various cancer patients who have been found to be refractory or poor responders to modern chemotherapy and radiation treatment. Jayawardhane N. D. N. et al [27] has stated herbo-mineral treatment as an adjuvant in the treatment of Hepatocellular carcinoma (HCC) patient. Herbo- mineral formulations (Hemabhraka, TamraSindoora, Vanda Bhasma, and Manikyapistie) are safe, cheap and effective in management of HCC and have developed a new clinical application in treatment of Cancer. Saba Sheikh et al
Ayurveda is one of the world’s oldest traditional medicinal systems and is experiencing revitalization among the consumers throughout the world. However the major drawback associated with Ayurveda is the lack of evidence based on its standard profile and quality and safety aspects of Ayurvedic formulations. There is a lack of data supporting the efficacy of clinical trials in traditional medicines. Other major problem associated with Ayurvedic formulation is the loss of genetic biodiversity or risk of annihilation [33]. Heavy metal (HM) toxicity is a major safety issue in Ayurvedic formulations and it is essential to evaluate them for their content. Table-1 provides data of Ayurvedic formulations containing heavy metals (Lead, Mercury, and/or Arsenic) [34]. Ayurvedic literature emphasizes the use of heavy metals in their formulation due to their particular biological properties for curing. Ayurveda has described specific physiochemical processes like sublimation, heating etc to detoxify the metals and to avoid its toxicity Heavy metals in Ayurvedic medicines include not only lead and mercury but other metals such as chromium, iron, zinc, nickel, cadmium, arsenic and tungsten. Amount of heavy metals and trace elements in Ayurvedic preparation depends on the geographical location, varying according to the quality of the soil, water or air pollution [35]. The American medical research community has sounded a heavy metal warning against Ayurvedic cures. Herbal products from the Indian system of medicine sold in the US contain dangerous levels of lead, mercury & arsenic [36]. Environmental impact of heavy metals [37, 38] such as Cd, Pb, Hg and as it causes serious concern on the health of individuals. In Japan, Itai-itai disease [39] and Mina Mata disease [40] are caused due to the consumption of rice containing Cd and eating methyl mercury contaminated fish respectively. Table-2 gives information about most important disaster occurred with heavy metals [41]. Current levels of toxic metals in some environmental compartments may be high enough to constitute a threat to human health. Table-3 provides data of global emission of trace metals into atmosphere, water and soil. Environmental exposure to low levels of lead has been allied with a wide range of metabolic disorders and neuropsychological deficiencies. Toxicity of lead at metabolic and cellular level in asymptomatic children include - Impairments in haemoglobin, vitamin
D and red blood cell nucleotide metabolism, - Trepidations of calcium homeostasis in the hepatocytes, bone cells and brain cells, - Neurological damage Dangerous level of cadmium in environment leads to intoxication of the kidney like tubular proteinuria ad renal dysfunction. High amount of arsenic in environment contaminates drinking water and causes skin cancer, peripheral vascular disorders (known as black foot disease), hyper-pigmentation and keratosis [42]. Table-4 provides data of most commonly used metals, its toxic effect on human and their treatment [43]. Medicinal plants grows in nature can accumulate heavy metals at certain extent which depends on its individual properties and the concentration of HM in soil, air and water [44]. Heavy metal contamination is due to accidental contamination during manufacturing process such as grinding, use of lead releasing equipment’s or other manufacturing utensils [45]. Due to its hazardous effect, heavy metal content in plants and foodstuff must be limited and GMPs procedures should be implemented during manufacturing of Ayurvedic formulation [46]. Environment factors can be controlled by implementing standard operating procedures (SOP) leading to Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), Good Supply Practice (GSP) and Good Manufacturing Practice (GMP) for producing medicinal products from herbal or natural sources. The public belief that herbal and natural products are safer than synthetic medicines can only be ascertained by imposing regulatory standards on herbal products that should be manufactured using good practises. [47].

C. Cumulative Toxicity: Caused In Herbomineral Formulations [48]

Most of the Ayurvedic preparations prescribed contain herbal, minerals and metals. These preparations are believed to be fast acting and disease specific. Non purified heavy metals have been known for their toxicity. The possible heavy metal related toxicity arising from the use of herbo mineral preparation is the subject of interest. Historically there is no consensus on a scientifically validation. Regarding toxic effect of heavy metals used in herbomineral preparation. There is a layman tendency, unsupported by facts to assume that all the so called heavy metal and their compounds are highly toxic or have eco-toxic properties. The confusion keeps on increasing, when you find the most referred book on toxicology. All metals are present in earth’s crust and enter our bodies continuously at lower levels. The multimillion ayurvedic drug industries are attracting so many pharmaceutical companies and thousands of products are being marketed per year. Unfortunately, none of them have given emphasis on the toxic effect of herbomineral preparation. This lead to decrease in the projected efficacy, even though they are combination or modification of classical formulations. This may be due to following reasons: improper purification of heavy metals used in herbomineral preparation. The selected formulation may not be suitable for a specified clinical condition of that person .inappropriate form for the finished product. Method of modification for a classical drug or method of preparation of new drug may be incorrect. Failure of determining the accurate dose. Out of the above said factors the improper purification plays a key role in developing toxicity in formulations containing mineral drugs. The incidence of cumulative toxicity is related to the concentration of toxic chemicals in the body. In the living organism, local, systemic, short term, delayed, reversible or irreversible toxicity may be precipitated. Many chemicals are toxic because they are bio transformed into more toxic chemicals. In this situation effective measures should be taken to inhibit biotransformation, to de-crease the toxicity of compound preparations.

D. Causes of Toxicity In Herbomineral Preparations

1. Improper identification of crude drugs- Ayurvedic products most commonly has multiple ingredients. Before taking any crude drug to a formulation they should properly get identified. If the drug is wrongly identified then this may lead to unwanted effects.

2. Adulteration/ substitution-This is another serious problem associated with Ayurvedic formulation. Most of the Ayurvedic manufacturers are purchasing the crude drugs from commercial suppliers. Some times the price of crude drug may be very high. It is here, that the profit motive commercial suppliers may increase the bulk of the drug by adding adulterants or sometimes entirely re-placing the crude drug with some other substances.

3. Manufacturing under unhygienic conditions- In India apart from few big companies most of the Ayurvedic manufacturers are from small scale unit. The hygienic conditions of these units
are very poor. Many times the store rooms are the thriving areas of many rodents and they will make the raw material further unhygienic.

4. **Lack of technically qualified persons**-like other manufacturing industries Ayurvedic manufacturing units also require technically qualified persons, un- fortunately not so common in India.

5. **Improper quality control checks**- At least at the state level of government laboratory should be established for the exclusive testing of Ayurvedic drugs.

6. **Inadequacy of the present laws**- The laws relating to manufacturing of Ayurvedic products are very weak and it enables a simple way to get license for their manufacturing. These laws should be made strict so that no product should be marketed without proper standardization.

**E. Factors of Cumulative Toxicity**

The cumulative toxicity is attributed to the drug due to some extrinsic and intrinsic factors

**Extrinsic factors:**

Pesticide residue e.g. Agro chemicals. Fumigants e.g. Methyl bromide Adulteration of accidental mixing with more toxic plant

**Intrinsic factors:**

Chemical constituents such as toxalbumin, Hydrocyanic acid, certain alkaloid, saponins, glycosides etc. Compound preparation mostly causes cumulative toxicity. The toxicity of medicines not only arises by combination but by antagonistic surroundings namely: Drug growth in different seasons (Kaa laviruddha). Discrepancies in its collection (Sampathvirudha) Blemishes on its processing (Samskaravirudha and paakaviruddha). Faults in dose fixation (Matraavirudha). Deficiency in preservation (Sampath virudha)

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