



# Role of Modern Biological Techniques in Evidence-Based Validation of Ayurvedic Herbometallic Preparations

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## Abstract

An alternative to synthetic drugs having severe side effects, the use of Ayurvedic preparations from natural sources like herbs, metals, and minerals may be efficient due to better activity profile to combat the harmful nature of the diseases. Ayurvedic therapy can treat those diseases better, which do not respond to the treatment by western medical practices. This preparation may have anticancer, antimicrobial, and immunomodulatory effect as evidenced earlier. Further, it may have a specific role in preventing cancer metastasis, neuro-diseases, diabetes, atherosclerosis, and many other chronic diseases. Modern biotechnology and molecular biology-based techniques have contributed to the identification of active components and mechanical effects of these preparations having ethnobiological importance. Treatment with Ayurvedic herbometallic preparations is practiced in India since 5000 BC to prevent, delay, or diminish the incidence of significant ailments. These are having a holistic approach as traditional medicine and have less toxicity and ignorable side effects. However, the experimental validity and nano-materialistic method of different Ayurvedic herbometallic preparations are not sufficiently acknowledged. An evidence-based validation of Ayurvedic herbometallic preparations, their mechanism of action in disease prevention or remedy is the main focus of this chapter. The information from the *in vitro* and *in vivo* studies on these preparations and mechanism-based analyses

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and challenges to evaluate its efficacy can add on therapy to improve the quality of life in patients.

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**Keywords**

Ayurveda · Herbometallic · Anticancer · Antimicrobial · Immunomodulatory

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**Abbreviations**

AAS	Atomic absorption spectroscopy
DCFHDA	2,7-Dichlorofluorescein diacetate
FTIR	Fourier-transform infrared spectroscopy
GSH	Glutathione
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SEM	Scanning electron microscopy
SOD	Superoxide dismutase
TEM	Transmission electron microscopy
TGA	Thermogravimetric analyses
XRD	X-ray diffraction

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**16.1 Introduction**

Ayurveda is a native ethnic medical system popularly practiced in India since time immemorial. The foremost strength of the system is its comprehensive approach toward health and disease using naturally occurring resources derived from medicinal plants and minerals. This system of medicine also emphasizes self-discipline and modest lifestyle and exercise in daily healthy livings.

In Ayurvedic medicine, minerals and metals used are mostly water as well as fat insoluble. The ancient researchers tried to transform these metals and minerals into nanoforms that they should have excellent bioavailability and therapeutic potentials, as mentioned in *Charaka Samhita* in 1500 B.C. These modified forms of the metals and minerals used in therapeutics of Ayurveda are known as Bhasma and Sindura. Most importantly, the Bhasmas and Sinduras are fine medicinal powders containing various elements, including carbon (C), hydrogen (H), and sulfur (S). The carbon particles formed in the Bhasma at a high temperature ( $>600^{\circ}\text{C}$ ) may be in the form of carbon nanotubes (fullerenes), help in targeted delivery of metal and mineral preparations, and can even cross the blood-brain barrier (BBB) (Kumar et al. 2007). In recent scenario, the Bhasmas are claimed to be bioprocessed nanoparticles, prescribed with several plant drugs and are taken along with milk, butter, honey, or ghee; thus, this makes these elements easily soluble, capable of being assimilated, eliminating their harmful effects and enhancing their biocompatibility (Sarkar and

Chaudhary 2010). Lauhadi Rasayana, an essential metallic preparation, as mentioned in *Charaka Samhita*, requires iron for its preparation. This iron is heated up to red hot and quenched in some liquid media immediately until the flakes of iron get transformed into fine powder form for medicinal use (Sharma and Dash 2000).

Again, one of the most effective Ayurveda preparations is Swarna Bhasma (gold ash). It deals with globular particles of gold with an average size of 56–57 nm using modern techniques, i.e., transmission electron microscopy (TEM) analysis. It indicates the high cell penetration possibilities for potential bioactivity (Brown et al. 2007). Again, comprehensive physicochemical characterization of Yashada Bhasma using modern techniques reveals that these particles are in the oxygen-deficient state and are identifiable for being nanometer in size. Therefore, these properties might contribute to the therapeutic possibility efficiently as biomedicine (Brown et al. 2007). Furthermore, the particle size of Rasa Sindura (preparation of mercury and sulfur) is 30 nm along with increasing milling time. From this observation, it concluded that further improvisation using modern techniques in these preparations might enhance the future possibilities in an active drug preparation according to requirements (Bhowmick et al. 2009).

Interestingly, the final form of the metals and minerals (Bhasma and Sindura) is nothing, but ethno-nanomedicine. It includes not only an ancient traditional medicine system but also the potential applications based on the physicochemical properties for treatment of various ailments. Therefore, it considered the medicinal system of Ayurveda as one of the pioneers for the implementation as biomedicine based on the proper scientific knowledge and validation. Herein, we have depicted overall possibilities of Ayurveda system as biomedicine based on medicinal potential and its future aspect regarding the growing attention followed by the advancement in various scientific techniques.

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## 16.2 Ayurveda: A System of Traditional Preparations

The Bhasma and Sindura are the most critical terms in preparation of metal and mineral-based constituents. A repeated levigation and incineration of metal or mineral with herbal extract or juice followed by sequential heating help to achieve those fractions. The compositions are prepared mostly by the following two different methods, i.e., Putapaka (incineration) and Kupipakwa (sublimation) method.

### 16.2.1 Putapaka Method

It is a complex process which includes four unit operations, i.e., Shodhana process, Jarana process, Bhavana process, and Marana process.

#### 16.2.1.1 Shodhana Process

In Ayurveda formulations, Shodhana means purification. After the procurement of raw metals or minerals, these are transformed into coarse powder by hammering.

Then, prior to the Shodhana process, the final fractions are repeatedly heated, melted, and quenched immediately in particular solvents for further refinements.

#### **16.2.1.2 Jarana Process**

This is an intermediate process in between Shodhana and Marana process, followed for some specific metals having low melting point. For the process, the metal is melted, mixed with some dried plant materials, and rubbed continuously until it becomes powder form in open air.

#### **16.2.1.3 Bhavana Process**

The Shodhita or Jarita materials are then subjected to Bhavana (levigation) process. Briefly, an incineration of Jarita material and specific drugs is simply specifying the Maraka Dravyas. These are further triturated with specified liquid media to make a doughy mass.

#### **16.2.1.4 Marana Process**

Followed by the Bhavana process, the levigated doughy mass transformed into pellets called Chakrika. Next, keep those in between two earthen crucibles facing each other after the sealing of junction by mud-smearred clothes which introduce the apparatus, called Sharava Samputa. It mainly works as an electric muffle furnace or traditional Puta (heating grade) for heating. A continuation of this heating process of materials is called Putapaka in the system of Ayurveda. After the completion of the heating process for a specified time, the apparatus (Sharava Samputa) is taken out and is made open to get the incinerated powder. Finally, the powder form of incinerated metal or Bhasma is ready for collection and storage after cooling.

### **16.2.2 Kupipakwa Method**

Herein, the finally prepared inorganic preparations are called Sindura or Kupipakwa Rasayana. It is called “Kupipakwa,” because here the medicine is prepared in a specially prepared glass bottle. The Kupipakwa method is carried out by including four different steps, Shodhana process, preparation of Kajjali, Bhavana process, and Kupipaka process.

#### **16.2.2.1 Shodhana Process**

In Sindura preparation, Shodhana process includes the purification of raw materials prior to Kajjali preparation in Ayurvedic validation.

#### **16.2.2.2 Preparation of Kajjali**

After the Shodhana process, the purified materials are called mostly Parada and Gandhaka. Next, a successive trituration of purified materials completes the Kajjali process for a long time to transform the mixture in a black, lusterless, fine, impalpable powder of uniform consistence. Again in Makaradhwaaja process, a mixture of Shuddha Parada and Shuddha Dhatu (metal like gold, etc.) is amalgamated prior to

titration for several hours in Kajjali preparation. Finally, the Kajjali preparations are ready to get further transformation through Bhavana process.

### **16.2.2.3 Bhavana Process**

In Bhavana process, the prepared “Kajjali” is then levigated by juice or decoction of some plant drugs for specific duration. It is then allowed to dry completely. After drying, again it is triturated to make powder.

### **16.2.2.4 Kupipaka Process**

After Bhavana processing of prepared Kajjali, the materials are transferred and filled into a specially prepared glass bottle (seven layers of mud-smeared clothes) up to 1/3 portion, then it is placed in a Valuka Yantra (sand bath), and the Valuka Yantra is heated. Here temperature is increased gradually and provided for specific duration. The final product is sublimed to deposit in the bottleneck inner side. Therefore, it completes the Kupipakwa Rasayana prior to self-cooling and collected by breaking the bottleneck.

## **16.2.3 Varna (Color)**

It indicates the color of the specific Bhasma. Different metals and minerals possess different colors in preparation of Bhasma. The specific color or Varna indicates the proper preparation of Bhasma, but changes in desired color suggest the inappropriate preparations.

## **16.2.4 Nishchandratvam**

In therapeutic application, the Bhasmas are prescribed to be lusterless, i.e., Nishchandratvam. In general, a luster or Chandratva is an important characteristic in metal, and it is not desired in Bhasma preparation because of insolubility and toxic effect. Therefore, metallic characters in Bhasma preparation should be checked properly. Nishchandratvam signify the transformation of the specific metallic luster to lusterless compound after incineration. For the confirmation of lusterless, Bhasma is checked under the sunlight for further incineration process if needed.

## **16.2.5 Varitara**

Varitara process includes the study of lightness and fineness of prepared Bhasma. It is a floating character of Bhasma based on the law of surface tension on stagnant water. In this process, the prepared Bhasma floats over the water surface without breaking the surface tension of stagnant water, and the final preparation is checked taking in between index finger and thumb followed by the sprinkling it on stagnant

surface water (Kulkarni 1998). Therefore, it signifies the quality of the Bhasma preparation.

### **16.2.6 Unama Test**

A fine-tuned Varitara process is further called Unama test. In this test, a rice grain is kept carefully on the floated layer of prepared Bhasma. Therefore, if the grain remains over the Bhasma layer without sinking, this indicates the excellent preparation, but sinking opposes its excellence (Kulkarni 1998).

### **16.2.7 Rekhapurnata**

The Rekhapurnata test is applied to investigate the size of the Bhasma particles for easy absorption and assimilation capacity in therapeutic purposes, as size barrier in cellular system plays one of the important parts for absorption and assimilation. In case of large size, the bio-system may not allow the particles to absorb and assimilate properly, thereby causing irritation in the gastrointestinal tract (Kulkarni 1998).

### **16.2.8 Slakshnatvam**

It is the tactile sensation produced by Bhasma by simple touch with finger tips. The properly incinerated Bhasma attains this quality. Slakshna Bhasma can be absorbed and assimilated in the body without producing any irritation to the mucous membrane of gastrointestinal tract.

### **16.2.9 Susukshma**

Susukshma includes the further fineness of the Bhasma following both Varitara and Rekhapurnata tests.

### **16.2.10 Anjana Sannibha**

Anjana (collyrium) is also a similar process like Slakshnatvam indicating smooth and fine character of Bhasma without any irritation whenever applied.

### **16.2.11 Particle Size**

Particle size of Bhasma is the most important characteristic for therapeutic purposes as mentioned in Rekhapurnata. In Ayurveda system, Churna (powder) form or

nanosize of the Bhasma particles are always favored which is mostly like pollen grains of *Pandanus odoratissimus* flower (*Ketaki Rajah*).

### 16.2.12 Gatarasatvam

Gatarasatvam indicates the specific taste of metallic preparations based on the taste perception. Some of the specified preparation also gets high attention by unique pharmaceutical procedure as every metal has its specific metallic taste.

### 16.2.13 Apunarbhavata

This process indicates the irreversible state of the prepared Bhasma which includes the inability to reform its original metallic form from transformed form. It also indicates the proper or improper incineration of Bhasma. A successive Apunarbhavata indicates the proper incineration of Bhasma (*Kulkarni 1998*).

### 16.2.14 Niruttha

Niruttha test is also similar to Apunarbhavata, but it emphasizes the ability of further physical condition to reform the previous stage. Briefly, a fixed weight of silver leaf and prepared Bhasma were further processed by Ayurveda system keeping in earthen pots with similar grade of heat. After cooling, the increase in silver leaf weight indicates the improper Bhasma preparations (*Kulkarni 1998*).

### 16.2.15 Inorganic Substance Processing

During Shodhana by the application of force in the form of heat, the tension in matter is increased, causing linear expansion. After heating, immediate cooling in liquid media leads to decrease in tension and increase in compression force. Repetition in heating and cooling causes disruption in compression tension equilibrium and leads to increased brittleness, reduction in hardness, and finally reduction in the particle size.

The applied force by the form of heat is initially taken on the high portion of the surface. As a result, high stress may be set up locally in the particles. The bonds at this place become weak, which may be responsible for creating flaws. The particle with the weakest flaw fractures most easily and produces largest possible pieces. The particle with the weakest flaw, fractures most easily and produces largest possible pieces. In the next step, another weak flaw fractures. In this way particle size is reduced.

It is very interesting to note that the same metal is processed (i.e., given Bhavana) with different sets of herbs, to be used for different therapeutic indications. In this

context, it is all the more interesting to study as to what changes the metal goes through during the different steps of Shodhana and subsequently during the process of Bhavana and the incineration (Marana) process that it acquires a nontoxic, therapeutically efficacious form. It has applied importance also, for example, Vanga (tin, Sn) Bhasma prepared by Jarana of Apamarga (*Achyranthes aspera*) or Palasa (*Butea monosperma*) should not be used for Vrishya (spermatogenesis) purpose, because Kshara has anti-Vrishya properties. The Apamarga (*A. aspera*) or Palasa (*B. monosperma*) Kshara present in the prepared Vanga Bhasma may affect the Vrishya property of Vanga. For Vrishya purpose, Vanga Bhasma prepared by Jarana of Shuddha Haritala (orpiment) should be used.

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### 16.3 Ingredients of Herbometallic Preparations and Their Importance in Biological System

A perfect balance between herbal and metallic components is a key requisite of Ayurvedic medicines. Gold (Au), silver (Ag), zinc (Zn), copper (Cu), iron (Fe), and tin (Sn) are frequently used in Ayurvedic drugs as “Bhasma” (the incinerated form of metal) (Sarkar, Das, Prajapati 2010). In Ayurvedic practice, the heavy metals like arsenic (As), chromium (Cr), mercury (Hg), lead (Pb), and many others are also in use but in a very low concentration and in an holistic approach (Kumar et al. 2006). These metals are then treated with herbal juice or decoction to blend properly (Pal et al. 2014).

The Ayurvedic preparations, namely, Swarna Bhasma (incinerated gold), Rajat Bhasma (silver ash), Hirak Bhasma (diamond ash), Tamra Bhasma (incinerated copper), Yashada Bhasma (zinc ash), Lauha Bhasma (incinerated iron), Vanga Bhasma (incinerated tin), and Naga Bhasma (incinerated lead), consist of one main metal component after which these are named. These key metals in the respective preparations play a central role for the cure of the ailments (Table 16.1) (Sarkar et al. 2010; Pal et al. 2014).

These Ayurvedic Bhasma preparations are suggested to consume with some specific adjuvants to enhance the drug activity. These adjuvants also complement the activity of the metal components of Bhasmas. Honey, jaggery, milk, sesame oil, and sugar are some common adjuvants prescribed with the herbometallic Ayurvedic drugs.

#### 16.3.1 Modern Techniques to Assess the Herbometallic Preparations

For a long time, the metal-based Ayurvedic drugs were in use, but the detailed concentration-based composition was not reported in the scientific proceedings. Thus, the mechanism of drug action was unknown which has been raising debates about the use of metals or even the heavy metals of these herbometallic drugs. With the aid of modern techniques, namely, atomic absorption spectroscopy (AAS) and X-ray diffraction (XRD), analysis researchers have now shown the presence of



**Table 16.1** The key metal elements of Ayurvedic herbometallic drugs, their importance, and use in respective diseases

Metals used in Ayurvedic preparation	Importance in biological system	Used in the disease
Gold	Cardiac stimulant, aphrodisiac, immunomodulator, to regain body potentiality and longevity, complexion, and to increase memory, intellect, and attentiveness	Tuberculosis, fever, dyspnea, cough, anorexia, ophthalmic disorders, and schizophrenia
Silver	Antiaging, immunomodulator, aphrodisiac, to increase potentiality and intellect	Diabetes, vitiligo, tuberculosis, anemia, dyspnea, cough, piles, etc.
Zinc	Immunomodulator, ophthalmic nourisher, to increase strength, potentiality, vitality, and intellect	Ulcer, emaciation, depression, tremor, ophthalmic disorder, diabetes, cough, dyspnea, anemia
Iron	Aphrodisiac, immunomodulatory, antiaging, emaciating agent, increases appetite and potentiality	Cachexia, obesity, bowel syndrome, hyperlipidemia, splenic disorder
Copper	Wound healer, emaciating agent, rejuvenator, and purgative	Anorexia, dyspepsia, abdominal tumor, liver disorder, ascites, piles, coughs, fever, and so on
Tin	Appetizer, rejuvenator, aphrodisiac, and immunomodulator. Increases vitality and intellect	Diabetes, hyperlipidemia, dyspnea, cough, emaciation, oligospermia
Arsenic	Antimicrobial, anticancer, immunomodulator	Sepsis, leukemia, skin diseases, psoriasis
Lead	Appetizer, aphrodisiac, immunomodulator	Rheumatoid arthritis, tetanus, cachexia, edema, ulcer, diarrhea
Mercury	Memory enhancer, antimicrobial, anticancer.	Syphilis, high fever, pneumonia, neurological disorders

metallic fraction along with their concentrations in such herbometallic preparations (Ruidas et al. 2019). XRD study revealed the crystalline nature of the Bhasmas. Also, the ratio of metallic and organic parts has been revealed via the thermogravimetric analyses (TGA) (Ruidas et al. 2019). The advanced spectroscopic techniques, namely, Fourier-transform infrared spectroscopy (FTIR) and Raman spectroscopy, have also appeared to be helpful for the detection of aromatic, aliphatic, or other organic functional groups (Balmain et al. 1999).

Pal has reported an elemental analysis of Swarna Bhasma (gold ash) via AAS study (Pal 2015). In 2016, R Sharma and colleagues reported the chemical characterization of Rajat Bhasma (silver ash) via inductively coupled plasma atomic emission spectroscopy (ICP-AES) and UV spectroscopy; also they detected the size and morphology through scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (Sharma et al. 2016) The ICP-AES and AAS studies of these Bhasmas profoundly suggest that the Bhasmas are a mixture of many metal components with one key element and thus explain their synergistic action on

specific target. Moreover, the results of TGA analyses suggest the higher fraction of organic material in Bhasmas is responsible to lower the toxicity of the heavy metals (Ruidas et al. 2019). Along with the progress of the new age, instrumental-based analyses of all these herbometallic compounds would bridge the lacking scientific evidences in the near future.

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## 16.4 Safety and Efficacy of Ayurvedic Herbometallic Preparations

As discussed above, Ayurveda uses various herbometallic preparations of diverse origins which contain many metals like in gold, silver, copper, zinc, tin, lead, mercury, etc. These metals have been complexed with herbal ingredients through a scrupulous preparation protocol, to form the unique complex formulation called Bhasmas (herb-mineral ashes). It has been estimated that most of the Ayurvedic preparations (near about 40%) among 6000 reported preparations contain at least 1 metal as an important therapeutic ingredient (Saper et al. 2004). Again, metallic formulation has gained high attention due to rapid and prolonged action in small dose (Parikh et al. 2012).

The assumption exists among the public that “natural” equates with “safe” and may believe that plant drugs are not toxic in any of the concentration. However, some findings suggest that the natural products can be toxic without proper medical supervision (Barakat and Fatma 2003; Harrison’s Internal Medicine n.d.; Ernst 1999; Rasheed et al. 2011). According to modern physicians, the addition of heavy metals with herbal medicine increases the toxic effects of herbal medicine at the lowest concentrations in the biological system (Desai et al. 1996). Any imbalance of essential substances in our body, whether excess or deficiency, can alter the normal activity of physiological function (Rasheed et al. 2011).

The efficacy and safety of an herbometallic preparation depend on its method of preparation, chemical nature, and therapeutic factors. The main purpose of herbometallic preparations is the transformation of starting elemental materials into an oxidized state which is the effective therapeutic ingredients of the preparation. Repeated heat treatment cycles are used to remove impurities and detoxify the harmful ingredients present in elemental materials. The effectiveness of nano-dimensional materials is greater than normal materials because their absorption, transport, and penetration into cells are relatively better (Desai et al. 1996; Rabinow 2004). The efficacy and safety of a drug depend on its pharmacokinetics parameters like digestion, absorption, metabolism, elimination, etc. These parameters are further attuned by the physicochemical properties of the herbometallic preparations. Without proper medical supervision, any drug can cause harmful effects to the body and even be life-threatening to a person. Long-term medication of any drug without proper scientific knowledge might be dangerous to health (Lucock 2004). Hence, an expert medical supervision is always welcome to overcome these backlogs.

Before the therapeutic use of modern medicine, many preclinical evaluations are done for its effectiveness, toxicity, dose-related information, etc. In the field of

Ayurvedic pharmacology, some special experiments are performed to assess the quality of metallic ingredients present in herbometallic preparation. The fineness of the metal in a Bhasma preparation can be tested by using a finger-based Rekhapoorva experiment. If the test sample settles in between the finger lines and it can be seen with a very narrow margin, then it is considered as a well-prepared Bhasma. A well-prepared Bhasma will lose its elementary nature, and monoxide metallic glaze is completely lost. The final form of metal cannot form an alloy with silver even at higher temperatures. This can be tested by the Nischandratwa test. The complete transformation of elemental metal to oxidized state is essential to its action; this is done by the Apunarbhava test. The density and surface energy of an herbometallic preparation depends on the oxidized state of metallic particles present in plasma. A properly calcined preparation tends to float on the water, rather than settling at the bottom (Nagarajan et al. 2012). Varitara test is done to determine the floating capability of Bhasma which is the indication of the density and surface energy of the preparation (Krishnamacharya et al. 2012).

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## 16.5 Important Factors in Determining Quality and Therapeutic Potency

Ayurveda means a science of life (*Ayur* = life, *Veda* = science or knowledge). According to Vedic culture in India, Ayurveda includes a 5000-year-old system having natural healing properties. Furthermore, Ayurveda has a strong root in the preparation of the traditional Chinese medicine and Tibetan medicine (Patwardhan et al. 2005; Vetrov and Sorokina 2012). Therefore Ayurveda has shown rejuvenation not only in its native palace but also throughout the world (WHO 2001; Ragozin 2016). Despite a broad range of activity, Ayurveda failed to achieve high importance due to lack of proper scientific evidences. In recent scenario, the drug development from Ayurvedic Bhasma has gained high attention due its overwhelming response against both microbes and cancer without any toxic effect in limited dose (Ruidas et al. 2019). The proper scientific knowledge and effective validation of Ayurveda Bhasma increases the possibilities as therapeutic drug nowadays. The advancement of new techniques including the introduction of more advanced extraction method (Soxhlet method) and quantification techniques (pharmacokinetics analysis) for effective assessment of Ayurveda drugs also intensified its acceptance as potential therapeutics.

Furthermore, analysis of molecular ingredients such as organic and inorganic fractions in traditional preparations having biological and medicinal functions is widely accepted in a defined dose as most of the molecules have an important role in biological system either individually or synergistically (Jungwrith et al. 2011; Nieboer and Richardson 1980). Again, both excessive and reduced amounts of molecular ingredients in biological system may show an adverse effect, thereby needing a balance system for active functioning of cellular system (Tchounwou et al. 2012). Majority of the diseases have shown an imbalance in molecular ingredients; therefore fixation of the imbalance might be a potential approach to encounter those

diseases (Dabrowiak 2017). Therefore identification of exact problem behind the disease progression and proper validation based on quality control and therapeutic potency are the most important parameters prior to the preparation of therapeutic drugs. Some of the major factors including high cost of new therapeutics, increased side effects of marketed novel drugs, and lack of effective remedial treatment for several chronic diseases, multidrug resistance of microbes, and other emerging diseases have enhanced the importance of traditional drug preparations. In ancient times, Ayurveda Bhasma has been used as therapeutic drug without proper scientific knowledge including proper medications and dose selection which also had increased the adverse side effects (Sarkar et al. 2010). In recent scenario the proper medication and dose selection including quality control, i.e., enhanced solubility, maintaining of biological pH 7.2–7.4, with minimal or without side effect, broad-spectrum activity range, low aggregation, high metabolism, etc. has gained the prime focus for Ayurveda Bhasma preparation for the enhancement of therapeutic potency. Therefore it will be worth declaring the drug prepared from Ayurveda Bhasma having high potential as therapeutic agent in the near future both quantitatively and qualitatively.

## 16.6 Antimicrobial Potential and Importance

Herbometallic compounds like Rasa Manikya, Hirak Bhasma, Swarna Bhasma, Parada, Yashada Bhasma, and so on possess antimicrobial potential. The key metal ingredients, namely, arsenic, diamond, gold, mercury, and zinc, respectively, of these compounds bring the microbicidal and/or microbistatic effect. Now, with the advancement in the modern scientific techniques, reports are coming very often

**Table 16.2** Antimicrobial property of ancient medicines

Ayurvedic preparations	Microbes affected	References
Swarna Bhasma	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Pal (2015)
Tamra Bhasma	Enteric pathogenic bacteria e.g., <i>E. coli</i> , <i>S. aureus</i> , <i>Enterobacter aerogenes</i> , <i>S. typhi</i> , etc.	Tambekar and Dahikar (2011)
Lauha Bhasma		
Mandura Bhasma		
Kashis Bhasma		
Rajata Bhasma	<i>S. aureus</i> , <i>Enterococcus faecalis</i> , <i>E. coli</i> , and <i>Pseudomonas aeruginosa</i>	Sharma et al. (2016)
Rasa Manikya	Pathological MRSA/MSSA strains of <i>E. coli</i> , <i>S. aureus</i> , <i>Enterobacter</i> sp.	Ruidas et al. (2019)
Hartala Bhasma (As <sub>2</sub> S <sub>3</sub> )	<i>S. aureus</i> , <i>P. aeruginosa</i> , <i>Streptococcus pneumoniae</i> , <i>Klebsiella pneumoniae</i>	Kumar et al. (2015)
Hartalagodanti Bhasma (CaSO <sub>4</sub> , 2H <sub>2</sub> O)		

with the emergence of scientific data proving the antimicrobial properties of these ancient medicines (Table 16.2).

Normally, in the herbometallic compounds, the metal ions are found in the oxygenated form, or bonded with carbon and nitrogen (e.g.,  $As_2O_3$ , of Rasa Manikya;  $C\equiv C$ ,  $C=C$  of Hirak Bhasma;  $HgO$  of Parada). In cellular metabolism, these oxygenated or nitrogenized metals act to release the cationic metals and eventually increase the reactive oxygen species (ROS) and/or reactive nitrogen species (RNS). This increased ROS and RNS level helps to acquire the primary defense of immunity against the pathogenic microbes. Moreover, these Ayurvedic preparations enact to regain the vitality in a sepsis condition by balancing the redox potential managing the glutathione (GSH) and superoxide dismutase (SOD) levels which reduce excessive ROS/RNS (Sharma et al. 2017). Apart from the ROS/RNS-mediated destruction of microbes, the herbometallic preparations exploit the ligand-receptor-based entry of microorganisms into the host body through metal chelation of receptor proteins. Microbes get entry inside the host body via receptor protein-mediated phagocytosis. Being the resource of cationic metals ( $Ca^{2+}$ ,  $Fe^{2+}/Fe^{3+}$ ,  $Zn^{2+}$ ,  $Mn^{2+}$ ,  $Mg^{2+}$ ,  $Cr^{3+}$ ,  $As^{3+}$ ), herbometallic compounds help in chelating the host receptor proteins so that microbes do not get an easy access to the host cells anymore (Bharti and Singh 2009).

## 16.6.1 Techniques Adapted to Prove Antimicrobial Activity of Herbometallic Preparations

### 16.6.1.1 Agar Well Diffusion/Disc Diffusion

For testing the antimicrobial activity of antibiotics, agar well diffusion and disc diffusion technique are a routine practice. Researchers have adapted this technique for documenting the antimicrobial potential of herbometallic Ayurvedic preparations (Table 16.2).

### 16.6.1.2 Minimal Inhibitory Concentration/Minimal Bactericidal Concentration

MIC and MBC determine the minimal concentrations of a drug to inhibit and kill a bacterial culture in solution, respectively. Though in Ayurveda the doses are predetermined following norms, the practice of this MIC and MBC determination would help in considering the dose scientifically and thus avoiding lethal toxicity for human being (Ruidas et al. 2019). This would also lessen the side effects.

### 16.6.1.3 Bacterial MTT Test

Besides MBC and well diffusion techniques, another test to confirm bactericidal effect of herbometallic preparations is a modified reduction test of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT assay) through which the percent bacterial cell viability can be counted after the treatment with targeted herbometallic drug with respect to the control study (Wang et al. 2010).

## 16.6.2 Antimicrobial Mechanism Revealing Techniques

### 16.6.2.1 Bacterial ROS/RNS Measurement

2,7-Dichlorofluorescein diacetate (DCFHDA) is used as an indicator of ROS generation. The change in fluorescence intensity after treating with DCFHDA indicates the presence of active microbial growth. By measuring the bacterial ROS level, the mechanism of antimicrobial drug can also be revealed (Su et al. 2009). Similarly, measurement of change in SOD, glutathione, and RNS level would be complementary to find out the oxidative stress and produce evidence against the drug mechanism of the herbometallic preparations.

### 16.6.3 Importance of Herbometallic Preparations in the Premise of Multidrug Resistance

To date, the antibiotics are considered most reliable fighting against pathogenic bacterial strains. However, an alarming bell has already rung due to the fast emergence of multidrug-resistant (MDR) bacterial strains. Reports have confirmed that we are thus far living in the post antibiotic era (Alanis 2005). Here lies the importance of the herbometallic compounds prescribed in Ayurveda. With the proven effectiveness of metal ions against bacteria, many metal-based nanoparticles (Ag, Au, Pt, etc.) are also tested as antibacterial agent, but they come up with high toxicity and other side effects. In herbometallic compounds the metal elements are blended with the organic decoction and thus cause almost no toxicity to the host. Moreover, the nanoformulation of the metals in these compounds functions as chelating agents and stimulator of ROS to combat with the MDR strains of bacteria and also helps to regain the vitality unlike the antibiotics which affect the good gut microflora. The growing scientific evidences for these Ayurvedic drugs (Table 16.2) present a glimpse of reconsidering the cost-effective traditional drugs as antimicrobial therapeutics.

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## 16.7 Anticancer Activity of Ayurvedic Herbometallic Preparations and Some Promising Drug Candidates

Based on the modern concepts for searching the anticancer drugs from natural resources, numerous researches have been conducted based on the information from folk and traditional medicines throughout the globe. Several anticancer drugs extracted from plant sources after purification are tested in both in vitro and in vivo models and then sent to clinical trials (Khazir et al. 2014). The substances of natural origin that exhibit antitumor or anticancer properties belong to various groups of compounds, such as alkaloids, diterpenes, lactonic sesquiterpene, peptides, cyclic depsipeptide, proteins, etc. (Subramaniam et al. 2019). Previous reports implied that on the basis of pharmacological activities and chemical structural information of natural compounds, antitumor or anticancer drugs have been synthetically

developed, viz., vincristine from *Catharanthus roseus* and paclitaxel and taxanes from the yew tree or *Taxus baccata* (Mukhtar et al. 2014). Some of the important active constituents present and isolated from the natural resources having anticancer activities are classified in (Lichota and Gwozdziński 2018) (Table 16.3).

Studies have shown that natural resource-derived compounds in combination with anticancer drugs have great potential to destroy tumor or cancer cells while not affecting normal cells such as lymphocytes and fibroblasts. The side effects of anticancer drugs may be reduced by using nanoparticle encapsulations to transport the drugs to their target sites. Drugs may also be administered in the form of liposomes, which serve as carriers for the drug. Considering the huge costs associated with the discovery and development of effective anticancer drugs, natural compounds can be an inexhaustible source in near future.

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## 16.8 Antidiabetic and Anti-inflammatory Role of Traditional Herbometallic Preparation

Chaturmukha Rasa has four metal constituents, viz., mercury, sulfur, iron and mica based Ayurvedic preparation. Recently, Sharma and colleagues extensively studied the antidiabetic role of Chaturmukha Rasa in streptozotocin-induced diabetic rat model (Sharma et al. 2019). Diabetes mellitus, the condition of hyperglycemia, can be treated with the approach to delay the digestion of carbohydrate. Through the inhibition of salivary amylase,  $\alpha$ -glucosidase, and sucrose, Sharma et al. have shown that Chaturmukha Rasa can lower down the carbohydrate digestion rate and thus combat hyperglycemia (Sharma et al. 2019). Earlier, in 1989 it was reported that the blood zinc level varies between diabetic and nondiabetic persons (Prasad and Sharma 1989). Also, Zn has been found in the alpha and beta cells of islet of Langerhans where it stabilizes the insulin being an integral part of insulin crystal. These findings indicate the role of Zn in diabetes mellitus. With the advancement in preclinical evaluation of the drugs, scientists now deserted the antidiabetic effect of Yashada Bhasma which contains Zn as the key metal ingredient (Rao et al. 1997). On the other hand, the anti-inflammatory role of copper and copper complexes has been known since long. Even the nonsteroidal anti-inflammatory drugs (NSAID) contain copper complexes which play the central role to heal inflammation (Bafna and Patil 2018). Bafna and Patil have reported a scientific evaluation of Tamra Bhasma in carrageenan, cotton pellet, and complete Freund's adjuvant (CFA) model (Bafna and Patil 2018). Here in this report, a significant reduction in carrageenan-induced paw edema, cotton pellet-induced granuloma, and CFA-induced arthritis has comprehensively demonstrated the anti-inflammatory action of Tamra Bhasma.

**Table 16.3** Anticancer activities of promising new molecules from natural resources

Active ingredients	Herbs/natural products' name	Information of anticancer activities	References
Camptothecin (quinoline alkaloids)	<i>Camptotheca acuminata</i>	Irinotecan and topotecan have been developed as semisynthetic compounds which have clinical efficacies on second-line lung cancer	Wagner (2015)
Combretastatin (stilbene derivative)	<i>Combretum caffrum</i>	Combretastatin A-1 has been synthesized and found in drugs targeting the microtubules similar to taxanes and <i>vinca</i> alkaloids	Zweifel et al. (2011)
Podophyllotoxin (toxin lignin)	<i>Podophyllum peltatum</i>	This compound is effective in lymphomas, brain tumors, gastrointestinal cancer, colon cancer, breast cancer, small-cell lung cancer, and testicular carcinomas	Zhang et al. (2018)
Geniposide (aglycone)	<i>Gardenia jasminoides</i>	Effective for lung cancer	Habtemariam and Lentini (2018)
Artesunate	<i>Artemisia annua</i>	Semisynthetic derivative of artemisinin is effective on pancreatic tumor and brain tumor	Konstat-Korzenny et al. (2018)
Homoharringtonine	<i>Omacetaxine mepesuccinate</i>	Effective in leukemia and breast cancer	Hansz (2000)
Salvicine (diterpenoquinone)	<i>Salvia prionitis</i>	Salvicine, chemical synthesized product acts as cytotoxic on nonintercalative topoisomerase II poisons	Deng et al. (2011)
Ellipticine (alkaloid)	<i>Ochrosia elliptica</i>	Synthetic ellipticine has antitumoral activity	Stiborova et al. (2011)
Roscovitrine	<i>Raphanus sativus</i>	Synthetic roscovitrine has efficacies on lung cancer and breast cancer	Cicenas et al. (2015)
Maytansine	<i>Maytenus serrata</i>	Synthetic maytansine is effective on metastatic breast cancer	Lopus et al. (2010)
Thapsigargin (sesquiterpene)	<i>Thapsia garganica</i>	Synthetic thapsigargin is effective on solid tumors	Ganley et al. (2011)
Curcumin	<i>Curcuma longa</i>	Effective on neck, head, oral, colon, pancreas, bladder, prostate, and breast cancers	Mohammadi et al. (2005)
Resveratrol (phytoalexin)	<i>Vitis vinifera</i>	Antileukemic activity	Sahpazidou et al. (2014)
Carnosol (diterpene)	<i>Rosmarinus officinalis</i>	Antitumor activities	Johnson et al. (2008)
Crocetin	<i>Crocus sativus</i>	Effective on lung, liver, pancreas, colon, and breast carcinoma	Aung et al. (2007)
Silibinin	<i>Silybum marianum</i>	Effective in colon, lung, prostate, and skin cancers	Ramasamy et al. (2011)
Withanolides	<i>Withania somnifera</i>	Effective in breast cancers and brain tumors	Samadi (2015)



## 16.9 Traditional Ayurvedic Herbometallic Preparations in Treatment of Neurological Disorders

According to several reports, the use of traditional Indian system of Ayurvedic herbometallic preparation is very common in treatment of several neurological ailments due to its easy accessibility, low cost, and minimal side effects. Ayurvedic herbometallic formulations refer to metal-based herbal remedies prescribed on the basis of traditional Asian system of medication. From time immemorial metals play a vital role in human physiology, and the deficiency in metals led to the occurrence of various diseases. In Indian Ayurvedic history, numerous metals like gold, silver, copper, iron, lead, zinc, tin, etc. are considered as important elements of body, but very few of them has got an effective role in treating neurological diseases. Therefore any imbalance in this metal content hampers the body metabolism. In this regard, metallic formulation Bhasmas are highly effective in prevention and treatment of various diseases (Lee et al. 2018). Generally, Bhasmas are metallic Ayurvedic preparations made up of herbal juices/fruits used in India from the seventh century B.C. and are widely used against chronic ailments.

### 16.9.1 Efficacy of Swarna Bhasma in Neurological Disorders

Gold along with other metals are therapeutically effective Ayurvedic medicine since ancient time. In the Vedic period, gold was used to increase the strength, potency, and longevity and also to combat aging in humans. Since the eighth century AD, by proper purification and incineration, gold was utilized as Bhasma (ash) which is referred to as Swarna Bhasma (gold ash) (Mitra et al. 2002). Several reports suggest that cognitive disorders such as dementia, delirium, amnesia, etc. can be characterized by various symptoms like memory impairment, and massive cognitive decline, gait disturbances, and language disturbances can be improved by Swarna Bhasma (Warad et al. 2014). This Swarna Bhasma acts as a nootropic agent and is primarily used to improve memory, behavior, and mood. Recently, a study evidenced the antioxidant/restorative property of Swarna Bhasma in cerebrovascular diseases (Singh and Chaudhary 2012). It has been demonstrated that the different enzymatic parameters were measured to assess ischemic brain damage, and the result showed significant restoration of altered values near normal level proving the efficacy of Swarna Bhasma in treatment for cerebrovascular disease. Not only cognitive and cerebrovascular disorder, but other neurological disorders also can be effectively treated by Swarna Bhasma. Alzheimer's disease (AD), the common form of age-related dementia, can be characterized by gradual deterioration of cognitive function specially functions related to memory. The main pathogenic hallmark of this disease is the gradual aggregation of misfolded protein like amyloid beta and tau. Currently, a study with Swarna Bhasma has been performed to illustrate the decrease in amyloid-beta aggregation. The study also paved the path of hope to treat AD if proper medication with Swarna Bhasma is initiated immediately after early diagnosis of AD (Agrawal 2010). Like AD, Parkinson's disease (PD) is also a

common geriatric disorder, and the initial manifestations may be tremor, rigidity, akinesia, slowness, and many others. The formulation of Swarna Bhasma plays a key role in the effective management of PD (Kaviya et al. 2016).

### **16.9.2 Efficacy of Raupya Bhasma in Neurological Disorders**

Raupya Bhasma also called Chandi Bhasma or calcined silver ash is an Ayurvedic herbometallic formulation used in eye diseases, jaundice, anemia, hysteria, epilepsy, and neurological disorders. This type of calcined silver ash possesses medicinal properties such as a potent cognitive enhancer as well as acts as an antidepressant, antianxiety, anti-stress, and neuroprotective agent. Generally, excessive use of the brain, insomnia, anxiety, fear, working on computers, etc. cause nervous aggravations in the body which lead to reduction in mental power and strength. Therefore, Raupya Bhasma works widely in all these conditions and can be effectively used in treating mental fatigue (<https://www.ayurtimes.com/rajat-bhasma-raupya-bhasma/#mental-fatigue>; 2014). Despite all these properties, very few evidences have been found regarding the successful use of Raupya Bhasma in treating neurological disorders.

### **16.9.3 Efficacy of Naga Bhasma in Neurological Disorders**

Naga Bhasma (incinerated lead) is the herbometallic preparation containing lead as the main ingredient. Manifestations of some extraordinary medical properties prove its therapeutic efficiency in treatment of various diseases. Nowadays, modern research revealed that in PD, APO-E 4/3 and 4/4 genotypes can excrete heavy metals in minimal amount. Those abundant APO-E proteins with this version of genotype in the cerebral spinal fluid surrounding the brain will have the highest affinity for becoming ill from exposure to neurotoxic heavy metals (Rajput and Patgiri 2013). This situation can be treated by Naga Bhasma due to its untoward side effects and responsive efficacy.

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## **16.10 Effective Medications Against Other Common Lifestyle Diseases**

In Ayurveda, the diseases associated with aging and cardiovascular diseases and many such diseases are correlated with obesity, food habits, and change in lifestyle. It is also considered that the normal physiology, metabolism, and the driven force of life are dependent on related state of metal ions and even a little imbalance in metal ions in body may lead to the irregular functioning of the biomolecules associated with those metal ions (Bharti and Singh 2009). Thus, it is prescribed in Ayurveda that these kinds of diseases can be treated following a common route. Virupaksha et al. have reviewed the works reflecting the success of Ayurvedic Bhasmas in treating the

lifestyle diseases, viz., type II diabetes, cardiac diseases, depression, obesity, stroke, and so on (Virupaksha et al. 2011). Similarly, Dr. Bhanu Priya and colleagues reported the evaluations of herbometallic compounds to achieve a state of well-being (Priya et al. 2018).

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### 16.11 Major Issues of Clinical Trials of Ayurvedic Medicine

The Department of AYUSH (Government of India) already has prescribed various clinical as well as preclinical trials for new herbal Ayurvedic drug formulations following proper evaluation methods to facilitate the development of regulation and registration in Ayurveda along with other traditional medicine systems. Presently, various reports evidenced the use of HMPs in lead toxicity. Thereafter, from early reports it has been evidenced that 65 cases of heavy metal intoxicity in adults and children have been found to be associated with Ayurvedic HMPs (Mishra and Gupta 2010). A report suggested that clinical trials with herbal medicine are a challenging phenomenon. For instance, the use of placebo group in evaluation of efficacy of herbal drugs leads to unethical issues as the patients are unaware of its use as an available therapy effective in treating the disastrous condition (Mishra and Gupta 2010). Recent reports suggested that there lie immense difficulties in estimation of active biomolecules in the pharmacokinetic study of drug discovery (Mishra and Gupta 2010). Another study reported that storage conditions generally alter the bioavailability of herbal medicines. This leads to loss of fungal or bacterial activity resulting into batch-to-batch variation (Mishra and Gupta 2010). On the other hand, dose selection is also a major issue. This dosage must be calculated on the basis of extractive value. Few herbal drugs have been immensely studied to prove their safety and efficacy. However, the clinical trials of *Ginkgo biloba* extract effective for treatment of CNS disorders and *Hypericum perforatum* effectively used as antidepressant evidenced the safety and efficacy of these drugs. Besides these two drugs, other herbal drugs include *Panax ginseng* (ginseng) effectively used as tonic, *Tanacetum parthenium* (feverfew) for headache and migraine, *Allium sativum* (garlic) for lowering cholesterol level, *Arnica montana* (arnica) to treat post-traumatic conditions, and *Serenoa repens* (saw palmetto) for the treatment of benign prostatic hyperplasia. Thus, all of these herbal medicines have been effectively evaluated in various clinical trials. However, well-organized and appropriate randomized clinical trials are still needed to be performed in order to prove their safety as well as efficacy.

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### 16.12 Status of Clinical Trials of Ayurvedic Medicine

Plants cannot be patented, due to insufficient research, and validation has been performed on plants as medicinal agents. The clinical trials on ancient Ayurvedic medicine need proper validation for betterment of treatment modalities by improving dose forms and side effects of any given drug. In the USA, it almost takes 15 years with an estimated cost of \$500 million for elucidating safety and efficacy of drug.

Due to the regulatory essentials regarding proof of safety, it turned out to be very uneconomical for private industry to carry out clinical trials regarding herbal Ayurvedic medicine. In this harsh condition, public funds are required in a huge amount to confirm the validity of herbal remedies, as this will help the pharmaceutical companies to earn meager incentive for development of an herbal drug against a patented drug. Owing to this fact, it is debated that there is a huge demand regarding a proper study, and unless and until it has been conducted on human subjects, no effective conclusion can be carried regarding the safety and efficacy of the drug.

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### 16.13 Future Scope

In a developing country, most of the rural people depend on herbal products for their health and used many medicinal plants without proper supervision. Traditional medicine is based on the universal principle like cold, heat, and five sense organs (Panchami elements). So in this modern era, our challenging issue is how we can change the form of Ayurveda without distorting its principal. The common people do not know the ingredients of these Ayurvedic preparations. They know the local names of this plant, but do not know the general name and scientific name. Many plants have some ingredients that work very well at low doses, but all of these ingredients can do a lot of harmful effect in high doses and long-term usage; even life-threatening events can happen if dose and duration of an herbometallic preparation is not adjusted. Only a small fraction of medicinal plants used worldwide has been tested rigorously in randomized control trials. If clinical trials of all herbal products are possible in the future and standardization of the ingredients can be done, then the efficacy, dose-related adverse effect, etc. can be predicted. Ayurveda is not only evolving, but it is also growing and changing day by day. At the same time, there are a lot of challenges being faced with Ayurveda. More specific experiments on animal models and also clinical trials are required to understand the exact molecular mechanisms of function of different ingredients present in herbometallic preparations. As traditional medicine is the first level of contact for rural people for their health system, it is necessary for the government to take immediate steps to introduce the use of traditional medicine to supplement Primary Health Care (PHC). All medicinal plants that have been reported in the rural area should be scientifically examined and detailed about their functional contents along with its pharmacokinetics. Health education should be given to the people concerning the use of the indigenous herbal product. PHC should impart education regarding the identification of various medicinal plants and their usage for the treatment of common diseases. The government should provide financial support to promote the potential role of traditional medicine in primary health care.

## 16.14 Conclusion

It is observed that most of the processed inorganic materials (Bhasma) have some common pharmacological properties like Rasayana, Yogavahi, Agni Deepana, Shighravaypti, Kshipram or Shighrakari, Alpamatra, and others (Mishra and Gupta 2010). The Rasayana exhibits immunomodulatory as well as antiaging properties, whereas Yogavahi shows ability of targeted drug delivery of the Bhasma. These ancient preparations are prescribed in very minute dose of 15–250 mg/day. Besides, other properties of these herbometallic preparations include that Bhasmas are readily absorbable, adaptable, and easily assimilable in the body and will be nontoxic in nature (Rasibhavan). Therefore, these features of Bhasma are comparable with the action of nanoparticles in the body as they are easily biodegradable as well as biocompatible and nonantigenic in nature. Besides, these nanoparticles are efficiently used to provide targeted drug delivery to specific site of action in the body including the blood-brain barrier. These can also be used to extend the bioavailability time and to protect the drug from chemical as well as enzymatic decomposition. However, these results in reduced peripheral side effect by decreasing the overall dose of drugs in the body.

In recent years, there has been concerted research regarding the potentiality of Ayurvedic medicines and its efforts to understand real-life treatment paradigm. Therefore, there is an immense need to interpret logic of Ayurveda while adopting modern scientific tools in development and validation of drugs. Hence, validation of Ayurvedic medicines using the latter approach may lead to evidence-based interdisciplinary study of modern Ayurvedic medicine. Further, owing to build better treatment opportunities, we ought to step beyond the realm of only drugs and attempt validation of comprehensive specific treatment package as per classical Ayurveda.

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