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Review Article

EMERGING NEED OF PHARMACOKINETICS IN DEMYSTIFICATION OF HERBO-MINERAL COMPOUNDS

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ABSTRACT

Ayurveda has its own way of processing herbal, mineral, metallic and animal origin materials to prepare therapeutic dosage forms. Pharmacology is the science of drugs including their origin, composition, pharmacokinetics, therapeutic use, and toxicology. Pharmacology is the base of research and development in all medical sciences which utilizes natural or synthetic materials for therapeutic purposes and such materials as known as medicines. **Importance of Pharmacokinetics in Ayurveda:** It is evident that understanding of pharmacokinetic characteristic especially bioavailability of Ayurveda drug compounds is needed while planning as well as interpreting the result of experimental/clinical studies**. Challenges to Herbo-mineral compounds:** Several experiments as well as clinical researches regarding safety profile of *Rasoushadhi* have been conducted at various Ayurveda institutes at graduate and post graduate level, however these researches have not attracted the attention on global platform. **Conclusion:** Pharmacokinetic studies will be helpful in discovery of Ayurveda drug action, organ involved, safety studies, dose determination, ADME of AYUSH medicines, information of bioavailability, mode of action, identifing differences in Ayurveda drugs having similar chemical composition.

KEYWORDS: Emerging Need of Pharmacokinetics, Demystification of Herbo-Mineral Compounds.

INTRODUCTION

India is one of the 12 mega biodiversity zone covering 2.4% of world's area but with 8% of global biodiversity. It includes 15 agro-climatic zones containing about 47,000 plant species including nearly 15,000 medicinal plants[1]. Experimentation is the stepping stone for the advancement of science. Over the last 25 years, Pharmacokinetics has emerged as an integral part of drug development especially when identifying a drug's biological properties. The term thereby implies the time course and fate of drug in the body. Bio availability captures two essential features, namely how fast does the drug enter the systemic circulation (rate of absorption) and how much of the nominal strength enters the body (extend of absorption). Given that the therapeutic effect is a function of the drug concentration, the above properties of non intravenous dosage forms are there for important in identifying the response to a drug dose[2]. Bio availability following oral doses may vary due to patient related or dosage form related factors. The dosage form related factors include the chemical form of the drug, its physical properties and manufacturing variables. Generally herbomineral formulations are multi component mixtures, containing plant and animal– derived products, minerals and metals. Ancient's texts like '*Rig Veda'*, *Atharva Veda*, and Official compendia like Ayurvedic Pharmacopoeia, Ayurvedic Formulary show dominance of plant and mineral derived products.[3] More than 25000 single or poly herbal formulations are used by the tribal and rural population in India[4]. Export – Imports bank reports reveals that the global trade of plant derived and plant originated products is of around US $62 billion (with growth of 7% per annum) where India holds stake US $1billion.[5] There is an urgent need to cherish these in both the national and international perspectives for benefit of mankind. Apart from healthcare, medicinal plant trade is an important alternative income generating source for under-privileged communities. As far as Ayurvedic formulations are concerned the concept of drug action and absorption is designed on the basis of the *Panchamahabhuta* theory, *Agni, Rasa*, *Guna, Virya, Vipaka* etc of the drug. Pharmacokinetics studies supports the studies of preclinical toxicology

in animals (toxicokinetics) because the drug levels in plasma or tissues are often more predictive than the dose to extrapolate the toxicity data to man. To go for the bio availability of the Ayurvedic formulations especially Herbo minerals is a daunting task but they provide strong evidence base to the safety and efficacy of herbo mineral formulations.

International market scenario of Indian medicinal plants

Global market of herbal industry shares about US $62 Billion.[6] The value of botanical related trade in India is about US $10 billion per annum with annual export of US $1.1 billion[7] while China's annual herb drug production is worth US $48 billion with export of US $3.6 billion[8]. India seems to be lagging behind and is ranked third in the herbal medicine category, with less than 2% global market share. According to an Ayurveda expert, Chinese herbal medicines, which rarely contain 10% scientific base when compared with the Indian Ayurvedic system, are doing better than India by 50-fold[9,10]. India had failed to make an impact in the global share market with Ayurvedic system of medicine and the gap between Indian and other countries is extending rapidly in the herbomineral field. The export of herbal medicine from India is insignificant despite the fact that country has a rich traditional knowledge and heritage of herbal medicine. The constant challenges for herbomineral medicine are lack of standardization, quality control and pharmacokinetic profile of bioactive molecules. Although the herbalmineral medicines have been used for thousands of years, basic research programmers need to be focused on the quality assurance. To overcome contaminations from pesticide residues and heavy metals there should be a control measures to implement necessary Standard Operating Procedures (SOP) at source. Good laboratory practices (GLP), Good Agricultural practices (GAP) and Good Manufacturing practices (GMP) are needed to produce good quality medicinal products. Also scientific based complete pharmacological data is required for the Ayurvedic system of medicine. Without all these measures, it is impossible to realize the dream of having a major share of herbal drug industry despite having goldmine of well documented and well-practiced knowledge of traditional herbal medicines. Both India and China having great traditional systems of medicines with strong philosophical basis and could play an important role in new therapies, drug discovery and development process.[11]

Challenges to Herbomineral Compounds

Although herbomineral medicines are widely used for the prevention, diagnosis, treatment and management of diseases, quality control and proper regulation worldwide are still a big challenge as shown in Figure 1. Widespread and growing use of botanicals has created a global challenge in terms of quality, safety and efficacy. Scientific validation and standardization of herbal medicines is needed for the future advancement of traditional medicine. Proper use of products of assured quality could also do much to reduce any risks associated with herbal medicine. However, regulation and legislation of herbal medicines has been enacted in very few countries. Most of the countries do not have any proper regulation on botanicals and the quality of herbal products sold is generally not guaranteed. [12,13].

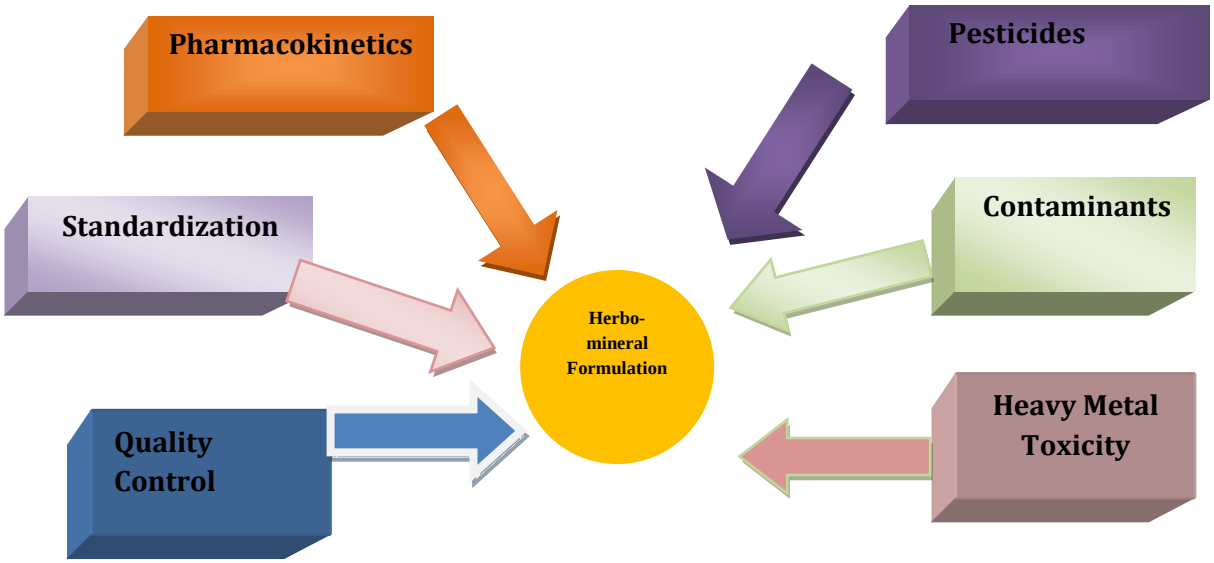

Figure 1: Constant challenges for Herbo-mineral medicine

Establishing the pharmacological basis of efficacy of herbomineral products is constant challenge due to their complex composition and the ever-increasing list of their putatively active constituents. *In vitro* assays normally are cheap and relatively easy to perform, but the relevance of the findings is based on a sufficient concentration of active constituents at the site of action. Of particular interest is the question of bioavailability to assess to what degree and how fast compounds are absorbed after oral administration of herbo-mineral products. Of further interest are the elucidation of metabolic pathways which yields potentially new active compounds and the assessment of elimination route and their kinetics. Thus the pharmacokinetic data will become an important link data from pharmacological assays and clinical effects.

There is usually detailed information available about the pharmacokinetics and bio pharmaceutics of chemical active pharmaceutical ingredients but it is absolutely lacking in the case of herbo-mineral medicine. The reason for that lies in the complexity of extracts as multi component mixtures and lack of knowledge of the active principles. With increasing knowledge of putatively active compounds and availability of highly selective and sensitive analytical methods pharmacokinetics can be evaluated for the Herbo-mineral formulations.

Pharmacokinetics: A missing critical step in the Validatation of Herbo-mineral medicine

Pharmacokinetics of the new drug entity is one of the regulatory requirements for an investigational new drug approval. However, for the majority of Herbo-mineral formulations used in the traditional or conventional medical practice, data on their disposition and biological fate in human are lacking. It is vital in the drug development process to understand the absorption, distribution, metabolism and excretion (ADME) of an active molecule from these formulations and how they interact with conventional drugs before their launch in the market in order to ensure the rational use of herbo-mineral medicines. Pharmacokinetics in the Ayurvedic system are largely ignored due to the rigor, cost and time consumption of the drug development process. One of the major reasons is that for most of these multi component mixtures their active ingredients are not known. In addition, there is a difficulty of measuring the quantities of the active constituents in systemic circulations due to very low concentrations, arising from the very small amount per dose in the final product. These challenges have led to the situation that most herb-drug interaction studies and case reports in the literature only evaluate the outcome of adding an herbal product to an existing conventional drug therapy and monitoring changes in pharmacokinetics and clinical response on the traditional drug[14]. The metabolism of a drug can be altered by another drug or foreign chemical; such interactions are significant in clinical effects. Cytochrome P450 enzymes, a super family of enzymes found mainly in the liver are involved in numerous interactions between drugs food, herbs and other drugs. The observed induction and inhibition of the CYP enzymes by natural products in the presence of prescribed drug has led to the general acceptance that natural therapies can have adverse effects contrary to the popular beliefs in countries where there is an active practice of traditional medicine. Majority of the classes of conventional drugs have been shown to be affected by different types of herbo-mineral preparations leading to various consequences, including treatment failure, adverse / toxic effects and even death. In order to improve the safety of Herbo-mineral medicine, use alongside conventional therapies in public healthcare, it is necessary to know that how the herbal drugs interact with conventional drug, early in the drug development. It is also necessary to predict early so as to eliminate regulatory obstacles and avoid market pressure for recalls that may have been induced by adverse effects linked to interactions. Therefore a better understanding of the pharmacokinetics of Herbo-mineral formulations is needed to support the predictability of herb– mineral interactions.

Non-compartmental approach to pharmacokinetic analysis of Herbo-mineral formulations

Theoretically when the drug is rapidly distributed to all parts of the body, the body behaves as one compartment and the drug profile in the body can be described as one compartment pharmacokinetic model. On the other hand when the distribution of the drug in a group of tissues or organs is faster than its distribution to other tissues or organs, the body behaves as two different compartments and the drug profile in the body can be described by a two compartment pharmacokinetic model. The body can also behaves as multiple compartments when the drug is distributed to different group of tissues at different rates. The compartmental approach in data analysis sometimes is faced with some difficulties such as when the drug concentration-time profile after intravenous administration is described by a two compartment pharmacokinetic model, but after oral administration of the same drug, the profile is similar to that of the one compartmental model because the rate of absorption and distribution process are not

distinctively different. To avoid these difficulties, a different approach, known as the non-compartmental approach, may be used for data analysis which can be examined without the need to assume a certain compartmental model[15]. The non-compartmental approach in pharmacokinetic data analysis is based on the statistical moment theory, which has been utilizes in chemical engineering. This theory views the drug molecules in the body as randomly distributed and each molecule has certain probability to be eliminated at certain time t. So, according to this theory, the time course for the drug concentration in plasma can be regarded as probability density function. This probability density function multiplied by time raised to certain power (0, 1 or 2) and integrated over time yields the area under the moment curve.

Mean residence time

The drug molecules are distributed throughout the body after drug administration. Some drug molecules are eliminated from the body faster than other molecules, which stay longer despite the fact that all the molecules are similar. The difference in the residence time for each molecule in the body occurs by chance according to statistical moment theory. The MRT is defined as the average time for the residence of all the drug molecules in the body. MRT can be calculated from the area under zero and first moment curve according to equation.

$$MRT = \frac{AUMC}{AUC}$$

Where AUMC is the area under the first moment – time curve and AUC is the area under the zero moment time curve or the area under the plasma concentration-time curve. The MRT has units of time.

The absolute bioavailability is determined from the ratio of AUC after oral and IV administration as in equation.

$$F_{Absolute} = \frac{AUC_{Oral}}{AUC_{iv}}$$

and the relative bioavailability of two products is determined from the ratio of AUC for the two different oral products as in the equation.

$$F_{Relative} = \frac{AUC_{Product\ A}}{AUC_{Product\ B}}$$

CONCLUSION

Recognition of the medical and health benefits of Herbo-mineral medicine with health claims is growing worldwide. Pharmaceutical research must go beyond focusing on pharmacological efficacy of Herbo-mineral formulations mainly in studies that improves their effectiveness in order to fully benefit humanity from their inherent therapeutic potentials. With advance in instrumentation like AAS and ICP-MS as increasing number of components are being identified from starting material used for preparation of those products. India needs a clear policy for such integration without compromise on the strategies that are science based. Efforts are needed to establish and validate pharmaco-epidemiological evidence regarding safety and practice of Herbo-mineral medicines. Pharmacokinetic data of biomarkers contribute considerably to the scientific assessment of the various claims of herbo-mineral products, which are increasingly marketed with curative claims worldwide. While a registration process reviewing quality, safety and efficacy of herbo-mineral products is established in curtained European countries and also the FDA is considering to review certain botanicals via the IND/NDA (Investigational New Drug/New Drug Application) process. In summary Indian alchemial preparations having great traditional with strong philosophical basis and could play an important role in new therapies, drug discovery and development process. Herbo-mineral system of medicine with strong scientific evidence will be top leader in the global market.

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