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INTERPRETATION OF AYURVEDA THEORY OF "VIPAKA" V/S PHARMACOKINETICS: A REVIEW

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ABSTRACT

Ayurveda considers each human being as a distinct individual born with unique physiological/metabolic characteristics (most of which remain constant throughout life). These distinct characteristics, which contribute to the physical, physiological (metabolic) and psychological make-up of each individual, are described under the term Prakriti in Ayurveda. According to Ayurvedic pharmacology the drug action is attributed to certain principles/attributes namely Rasa, Guna, Virya, Vipaka and Prabhava of the active principles of the drug. Literally the term VIPAKA means - The final outcome of the biotransformation of the rasa of a given dravya through the action of jatharagni (digestive enzymes) i.e. end-product or the transformed state of ingested substance after digestion or metabolism is known as 'Vipaka'. As refers Ayurveda, there are 13 kinds of "*Agni*" (1 *Jatharagni* + 7 *Dhatvagni* + 5 *Bhootagni*), so it is important to understand first the meaning of the term - "*Agni*". *Agni* converts food in the form of energy, which is responsible for all the vital functions of our body. *Jatharagni Paka* (Gastro intestinal digestion) is described as *Avastha - paka* in Ayurveda. The process of vipaka starts in (dueodinum) *grahani*. The site (*Adhikaran*) of action of vipaka is described in text as: '*Antahkoshte pakwashaye madhyamamarge mutrashaye tatha dhatushu cha drushyate* '. Ayurveda refers that the assessment of Vipaka can be determined by the presumption. Thus it can be said that the Vipaka can be assessed by its (action performing) *karma* on body humors (*dosha*) , It can be interpreted that the Mechanical Digestion accomplishes in (Abdomen) *koshta* & Chemical digestion accomplishes at (formation of body tissues, starting from the lymph) *dhatu* level . The term "Pharmacokinetics' denotes to "What body does to the drug"? The various compartments that

the model is divided into are commonly referred to as the ADME scheme. The pharmacodynamic & kinetic actions of ayurvedic drugs (single & compound) are difficult to explain in terms of modern pharmacology. It is not the single chemical entity as in case allopathic drugs, acts as a receptor & elicits a response. Bio-availability of a drug (availability of biologically active drug) is defined as the amount or percentage of drug that is absorbed from a given dosage forms and reaches the systemic circulation following non-vascular administration. Nowadays with the advancement in the technology, novel drug delivery systems open the door towards the development of enhancing bioavailability of herbal drug delivery systems. There are several mechanisms of action by which herbal bioenhancers act. Different herbal bioenhancers may have same or different mechanism of action. The paper is an attempt to explore the facts and findings on VIPAKA for understanding and interpretation of the theory v/s Pharmacokinetics.

KEYWORDS: Ayurveda, Vipaka, Agni, Jatharagni, Bhootagni, Dhatvagni, ADME, Bioenhancer.

INTRODUCTION

The approach of Ayurveda to life and living is holistic and its range cosmic, while its application is universal and far-reaching, because it is based on certain eternal facts/principles that have not Changed with time. Ayurveda dates back approximately three to four thousand years. It is considered as an Upa-veda (a branch of Vedic Science).[1] Ayurveda considers each human being as a distinct individual born with unique physiological/metabolic characteristics (most of which remain constant throughout life). These distinct characteristics, which contribute to the physical, physiological (metabolic) and psychological make-up of each individual, are described under the term Prakriti in Ayurveda.[1]

In the modern pharmacology the drug action is quite often correlated with its chemical structure or active principle. But in Ayurvedic pharmacology the drug action is attributed to certain principles/attributes namely Rasa, Guna, Virya, Vipaka and Prabhava of the active principles of the drug. Rasa or taste of the drug indicates the general behaviour or effect of the drug on bodily or cellular components like Dosha (Vata, Pitta, Kapha), Dhatus (seven types of tissue components), Mala (metabolic debris), Srotas (channels/vessels) and Agni (energy useful to carryout digestion and metabolism of foods & drugs). In the modern pharmacology the modus operandi of the drug is explained through its drug molecule whereas Ayurveda attributes the mode of action of the drug to the five principles

(Rasapanchaka). Majority of the times these Gunas (attributes) may not be measurable but inferred through their pharmacological actions. The study of the biological and therapeutic effects of the drugs (what drug does to the body) are explained by these principles which can be identified as pharmacodynamic principles of Ayurvedic pharmacology. These pharmacodynamic principles also influence the pharmaco-kinetics (study of the absorption, metabolism and excretion of drugs and their relationship to the pharmacological response) of the drugs.[2]

VIPAKA: Literally the term VIPAKA in Ayurveda denotes to the Digestion & Metabolism with the absorption and bio-transformation, as refers Definition.

Meaning it by: The final outcome of the biotransformation of the rasa of a given dravya through the action of jatharagni (digestive enzymes) i.e. end-product or the transformed state of ingested substance after digestion or metabolism is known as 'Vipaka'.[3] It is only a literary meaning but the same definition covers a very vast area of the human body Physiology. Prior to exploring the detail meaning of this verse it is requires to understand the Vipaka and Digestion, Metabolism and Absorption vise-versa. As refers Ayurveda, there are 13 kinds of "*Agni*" (1 *Jatharagni* + 7 *Dhatvagni* + 5 *Bhootagni*) , so it is important to understand first the meaning of the term - "*Agni*".[4] The site of *Jatharagni* is said in the digestion system. Seven *Bhootagni* belong to 7 types of body tissue – *Rasa* (Lymph), *Rakta* (Blood), *Mansa* (Muscle), *Med* (Marrow), *Majja* (Fat), *Asthi* (Bone) and *Shukra* (Seamen). The *Bhootagni* corresponds to the five greater elements the *Pancha-mahabhotta*, i.e. – *Prithvi, Tej, Jal, Vayu* and *Akash*. *Jatharagni* . Among them all the *Jatharagni* is considered as prime *Agni*.[5]

Concept of Agni

Agni has been described as the one who carries everything, moves everywhere, which can metamorphoses substances, which can bring transformation in substances, assimilates, which gives and takes, which has the capacity to enter into minute channels, which burns, which glows etc., according to the *Vachaspatyam, Sabda kalpadruma, Unadikosha*,[6] (a,b,c) *Agni* converts food in the form of energy, which is responsible for all the vital functions of our body. Therefore, *Ayurveda* considers that *Dehagni* is the cause of life, complexion, strength, health, nourishment, lusture, *oja*, *teja* (energy) and *prana* (life energy).[7] *Agni* means it is a substance responsible for digestion and metabolism. All the 13 categories of *agni* are key factors in transformation of consumed *ahara* (diet) & *vihara* (Metabolic changes developed

from the Conducts – psychic behaviors released secretions) *dravya* (Substance) of *vijatiya* (Natural chemical constitution of in-taken origin from the source which is not acceptable by body) to convert into *sajatiya* nature (to accept for assimilation to body).[8]

Jatharagni Paka

Jatharagni Paka (Gastro intestinal digestion) is described as *Avastha - paka* in Ayurveda. *Avastha- paka* is the change in the state of food substance in the *amashaya* (Stomach) and *pakwashaya* (during passing food with reaction to *pancreatic and liver* secretions) in the course of digestive process. In *avastha - paka* , there are two phases called *prapaka* and *vipaka*. Prapaka phase contains three phases, Madhura Bhava, Amla Bhava and Katu Bhava.

Existence of Vipaka

The process of vipaka starts in (dueodinum) *grahani*. Charaka claims that *Vipaka works at koshtagni level i.e. doshas level*. It indicates his view of *kriya-sharir.*[9] Sushrut said that guru and laghu *Vipaka acts at dhatu level which is of clinical importance*.[10]

Role of Vipaka in the Mode of Action of Diet / Drug

According to Chakrapani, there are 2 types of dravyas viz. *Aahara dravya* (Diet) and *Aushadhi dravya* (Drugs) . *Aahara dravyas* are mainly *Rasapradhana.*[11] Here Rasa means Taste as well as denotes to the (Lymph) *Rasa dhatu* and (Metabolic procedure during the Absorption to the bio-transformation up to body tissue) *Dhatwagni* is responsible for its functioning. On the other hand, (Drugs) *Aushadh dravyas* are *Viryapradhana*.[12] As Virya is a gunatmaka entity, *bhutagni* helps in its functioning.[13] Therefore *Aaharadravyas* (Diet substances) mainly undergoes *Dhatwagnivyapara* and *aushadhadrvyas* undergoes *bhutagnivyapara*. From *jatharagni paka* to the *bhutagnivyapara* in the liver, there is functioning of rasa. After *bhutagnipaka* the process of vipaka starts and it ends with the bio-transformation of *rasa*.

Determination / Assessment of Vipaka

Ayurveda refers that the assessment of Vipaka can be determined by the presumption (Anuman).

Thus it can be said that the Vipaka can be assessed by its (action performing) *karma* on body humors (*dosha*) , It can be interpreted that the Mechanical Digestion accomplishes in (Abdomen) *koshta* & Chemical digestion accomplishes at (formation of body tissues, starting from the lymph) *dhatu* level .

1. *Bhoutikagni* (Chemical changes at the molecular level) helps in production of *doshas*.
2. *Jatharagni* i.e. *koshtagni* generates mala-mutra
3. Dhatwagni proliferates (body tissues) *dhatu*s upto (formation of finest body tissue which gives strength, stamina and strength to reproductive system) *shukra*. *Therefore it can be said that the Vipaka is a final transformative state achieved through all these agnis.*

Pharmacokinetics

The term "Pharmacokinetics' denotes to "What body does to the drug"? Pharmacokinetics, sometimes abbreviated as PK, (from Ancient Greek pharmakon "drug" and kinetikos "to do with motion"; see chemical kinetics) is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism.[15] (a,b)

A number of different models have been developed in order to simplify conceptualization of the many processes that take place in the interaction between an organism and a drug. One of these models, the multi-compartment model, gives the best approximation to reality, however, the complexity involved in using this type of model means that mono-compartmental models and above all two compartmental models are the most frequently used. The various compartments that the model is divided into are commonly referred to as the ADME scheme (also referred to as LADME if liberation is included as a separate step from absorption).[16]

Liberation - the process of release of a drug from the pharmaceutical formulation.[17]
Absorption - the process of a substance entering the blood circulation.
Distribution - the dispersion or dissemination of substances throughout the fluids and tissues of the body.

Metabolization (or biotransformation, or inactivation) – the recognition by the organism that a foreign substance is present and the irreversible transformation of parent compounds into daughter metabolites.
Excretion - the removal of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.[18]

The two phases of metabolism and excretion can also be grouped together under the title elimination. The study of these distinct phases involves the use and manipulation of basic concepts in order to understand the process dynamics. For this reason in order to fully

comprehend the kinetics of a drug it is necessary to have detailed knowledge of a number of factors such as: the properties of the substances that act as excipients, the characteristics of the appropriate biological membranes and the way that substances can cross them, or the characteristics of the enzyme reactions that inactivate the drug.

An Ayurveda View on Pharmacokinetics

The pharmacological , toxicological & clinical action '*Karma*' of a drug are attributed to 5 qualities of a drug broadly classified as *rasa* (Taste) , *guna* (Pharmacological Properties), *veerya* (Potency), *vipaka* (Digestion to the bio-transformation) & *prabhava* (Effect). After ingestion of bhukta dravya (Diet or drug) due to the action of *agni*, it alters in rupa and rasa; resulting in (Fraction of absorbable and excretal) *sara-kitta vibhajana*. *Sara bhaga* of bhukta dravya (Diet or drug) goes to *hrudaya* (heart through Lymph) ; there from circulates in all over body with the help of *vyan* vayu. Then this sara bhaga resides in all (body tissues) *dhatus* and get metabolized by the respective *dhatwagni*. (*Rasad Raktam…..*). This *aadyarasa* (initial metabolized fluid) and *rasadhatu* (plasma) combine causes *vruddhi* (growth) and *kshaya* (loss) of a particular body tissue (*dhatu*) due to *dhatuguna saamya* (General similarity in relation to respective body tissue) and *vishesha* (Specific similarity in relation to respective body tissue) , during the ***Dhatvagni- paka***.[19]

The pharmacodynamic & kinetic actions of ayurvedic drugs (single & compound) are difficult to explain in terms of modern pharmacology. It is not the single chemical entity as in case allopathic drugs, acts as a receptor & elicits a response. Moreover the drug therapy is not generalized as in the case of allopathic drugs. The drug selectivity is according to *doshas* (Body humors) and to see the *panchabhouthik* compatibility of the drug (Natural chemical constitution0 & individual (the patient). Classification of drugs into *mrudu* (mild), *madhyama* (moderate) & *teekshna* (high) is an eye-opener to modern therapeutics on the rationale of selection of drugs for the treatment of various diseases. A careful review of principles of Ayurvedic physiology and pharmacology indicates that *Ahara* (food substances) and *Aushadha* (drugs), the Dravya (substance) undergo for digestion and metabolism synthesizes nutritive and active principles along with *Kitta* (excreting material) formation. The substance material is like (Urine) *Mutra*, (Feces) *Purisha*, (Sweat) *Sweda* are the bi-products of drug metabolism and drug metabolites are excreted through them. The metabolism of drug usually tends to make the less polar, lipid soluble substances (*Guru Guna Dravyas*) as more polar and water soluble (*Laghu*) thus facilitating their excretion by kidneys. If a drug is already highly

polar and water soluble, then it may not get metabolized and may get excreted as such. Excretion of each and every herb was not studied and reported so far.

Understanding of Vipaka v/s Absorption &Bio-availability of a drug

Drug Absorption: According to Ayurveda, the stomach (*Amashaya*) is the site where (fatty /oily) snigdha, (cold) sheet, and (heavy) guru property holder contents are absorbed. Duodenum (*Grahani*) is the site for absorption of (light) *laghu* and (hot) *ushna* properties drugs. Colon (*Pakvashaya*) is site where the (dry) *ruksh*, (cold) *sheet* and (light) *laghu* properties drugs are absorbed. The site of absorption is termed in Ayurveda the "*Adhikaran*".

The route of administration largely determines the latent period between administration and onset of action. Poor absorption of the drug, inactivation in the gut or degradation of the drug during the first passage through the liver can be prevented by administration of (vehicle) *Anupanas* like honey, pepper, betel leaf juice etc. The particle size of the drug also affects the absorption. Fine powders of the herb quickly get absorbed than coarse particle *Churna*.

Metals in *Bhasma* (incinerated fine powder) form absorb quickly than coarse powder of metals or minerals. Acid drugs (i.e. Amalaki (*Phyllanthus embelica*) are rapidly absorbed, from the stomach. Basic drugs (containing *Ksharas* – the alakaline) are not absorbed until they reach alkaline environment of the small intestine (Eg. Apamarga (*Achranthus aspera*), Aswagandha (*Whythania somnifera*) , Shank Bhasma (incinerated fine powder of sea-shell) etc.) The alkaline environment, in which the major component of the drug exists in an unionized form, facilitates its absorption.[20]

Some fraction of the administered drug disappears (eliminated) from the body and is reflected in the rate of lowering of its plasma concentration (plasma half-life or biological half life). It is very difficult to calculate biological half-life for herbs as the plant contains many active principles and research to assess the concentration of the particular active principle by analyzing blood/plasma has not been so far developed. To study the total pharmaco-kinetics of the herb one has to administer it with radioisotopes and plot the journey of the drug which may facilitate also to identify the route of excretion of the drug.

Bioavailability of drugs

Bio-availability of a drug (availability of biologically active drug) is defined as the amount or percentage of drug that is absorbed from a given dosage forms and reaches the systemic

circulation following non-vascular administration. When the drug is given I.V., the bio-availability is 100%.[21] This may not be so after oral administration. Acharyas of Ayurveda preached and practiced the oral route of administration for majority of drugs. '*Anupana*' (substance administered either with the drug or after its administration) facilitates for better absorption of the drug and helps in achieving higher percentage of bio-availability of the drug.

1. Drugs are metabolised by the enzymes.
2. Drugs could change spontaneously into other substance without intervention of enzymes.
3. Drug could be excreted unchanged.

Nowadays with the advancement in the technology, novel drug delivery systems open the door towards the development of enhancing bioavailability of herbal drug delivery systems. For last one decade many novel carriers such as liposomes, microspheres, nanoparticles, transferosomes, ethosomes, lipid based systems etc. have been reported for successful modified delivery of various herbal drugs.[22]

Evidence based Ayurveda

Bioenhancers are phytomolecules development of which is based on ancient knowledge of Ayurveda. In ayurveda the concept of bioenhancers is being used since centuries and is called "Yogvahi" e.g. is the use of "Trikatu". Black pepper is supporting evidence where piperine was one of the ingredients as "*Yogvahi"*.[23] They augment the bioavailability or biological activity of drugs when administered at low doses. They reduce the dose; shorten the treatment period thus reducing drug-resistance problems. The treatment is made cost effective, minimizing drug toxicity and adverse reactions. When used in combination with number of drug classes such as antibiotics, antituberculosis, antiviral, antifungal and anticancerous drugs they are quite effective. Oral absorption of vitamins, minerals, herbal extracts, amino acids and other nutrients are improved by them. They act through several mechanisms which may affect mainly absorption process, drug metabolism or action on drug-target.[24]

Bioavailability and absorption enhancement through co-administration of drugs with naturally occurring compounds from plants are considered to be very simple and relatively safe. They increase the bioavailability and absorption of the co-administered drugs. Uses of bioenhancers are also applicable in veterinary practice since bioavailability of drugs and nutrients is of equal relevance to animals as to humans.[25]

Vipaka and Mechanisms of Action of Herbal Bioenhancers

There are several mechanisms of action by which herbal bioenhancers act. Different herbal bioenhancers may have same or different mechanism of action. Nutritional bioenhancers enhance absorption by acting on gastrointestinal tract. Antimicrobial bioenhancers mostly act on drug metabolism process. Among the various mechanisms of action postulated for herbal bioenhancers some are as follows

(a) Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply.[26]

(b) Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility.[27

(c) Modifications in GIT epithelial cell membrane permeability.[28]

(d) Cholagogous effect[29]

(e) Bioenergetics and thermogenic properties[30]

(f) Suppression of first pass metabolism and inhibition of drug metabolizing enzymes.[31]

(a,b,c) and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids.[32]

CONCLUSION

Thus, it can be concluded that the term *Vipaka* in Ayurveda covers a broad area that is not limited up to the metabolism, only. All kinds of Agni (*Jatharagni, Dhatvagni* and *Bhootagni*) works one by one on ingested diet or drug that helps to liberate the molecular substance from the chemical structure of ingested diet or drug and assimilate and absorbs in body at the site of action. Hence, to understand Ayurveda Pharmacokinetics, it requires to understand the *Jatharagni, Bhootagni and Dhatvagni Vyapar* (Chemical changes at metabolic level, at tissue level and finally at cellular and genetic level), that is why the Ayurveda quotes: *Anna eva Brhamam*, because ingested diet or drug works up to metabolic, tissue and cellular level. There is need to work on Ayurveda concept of Vipaka to understand the Pharmacokinetism of Ayurveda drugs.

REFERENCES

1. Wujast-Vk Dominik, The Roots Of Ayurveda (Revised Ed.), Penguin Books India, 2001.
2. Frawley, David, Ayurveda And The Mind – The Healing Of Consciousness, Motilal Banarasi Dass Publishers, Delhi, 1998; 11 – 38.
3. K. Nishteshwar, Basic-Concepts-of-Ayurvedic-Pharmacology, Chowkamba Sanskrit Series Office,Varanasi. 2007, available on:http://www.scribd.com/doc/24515020/, Retrieved on 3-12-2013.

4. Astanga Hridya Saram, Chandan Singh, Gulab Printers, Ujjain: 2010, p. 26
5. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Chikita Sthana 15/38, , Published by Chowkhamba Orientalia, Varanasi: 2007, p. 516-517.
6. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Chikitsa Sthana 15/16, Published by Chowkhamba Orientalia, Varanasi: 2007, p. 514.
7. (a) Vachaspatyam
   (b) Sabda kalpadruma
   ©. Unadikosha
8. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Chikita Sthana 15/3-4, , Published by Chowkhamba Orientalia, Varanasi: 2007, p. 512.
9. Vani and Prasad: Concept of Agni and Ahara Paka, International Ayurvedic Medical Journal ISSN: 2320 5091, p. 1-7.
10. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Chikitsa15/28, Published by Chowkhamba Orientalia, Varanasi: 2007, p. 515.
11. Sushruta, Sushruta Samhita(With the Nibandh Sangraha Commentary), Edited by Vaidya Jadavji Trikamji Acharya,Chowkhamba Orientalia, Varanasi. 2009, Sushurut sutra 40/10, p178.
12. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Sutrasthana2/17, , Published by Chowkhamba Orientalia, Varanasi: 2007, p. 25-26.
13. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Sutrasthana2/17, , Published by Chowkhamba Orientalia, Varanasi: 2007, p. 25-26.
14. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Sutrasthana2/17, , Published by Chowkhamba Orientalia, Varanasi: 2007, p. 25-26.
15. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Sutrasthana26/66, , Published by Chowkhamba Orientalia, Varanasi: 2007, p. 148.

16. (a) Pharmacokinetics. (2006). In Mosby's Dictionary of Medicine, Nursing, & Health Professions. Philadelphia, PA: Elsevier Health Sciences. Retrieved December 04, 2013, from http://www.credoreference.com.
    (b) Kathleen Knights; Bronwen Bryant (2002). Pharmacology for Health Professionals. Amsterdam: Elsevier. ISBN 0-7295-3664-5.
17. Milo Gibaldi, Donald Perrier. FarmacocinéticaReverté 1982 pages 1-10. ISBN 84-291-5535-X, 9788429155358.
18. Koch HP, Ritschel WA. "Liberation". Synopsis der Biopharmazie und Pharmakokinetik (in German). Landsberg, München: Ecomed: 1986, pp. 99–131.
19. Ruiz-Garcia A, Bermejo M, Moss A, Casabo VG (February 2008). "Pharmacokinetics in drug discovery". J Pharm Sci 97 (2): 654–90. doi:10.1002/jps.21009. PMID 17630642.
20. Charak Samhita,Ayurveda Dipika Commentary of Chakrapani Datta,Edited by Vaidya Jadavji Trikamji Acharya, Chikitsa15/36-38, Published by Chowkhamba Orientalia, Varanasi: 2007, p. 516.
21. K. Nishteshwar, Basic-Concepts-of-Ayurvedic-Pharmacology, Chowkamba Sanskrit Series Office,Varanasi. 2007, available on:http://www.scribd.com/doc/24515020/, Retrieved on 3-12-2013.
22. Michael E. Winter, Mary Anne Koda-Kimple, Lloyd Y. Young, Emilio Pol Yanguas Farmacocinética clínica básica Ediciones Díaz de Santos, 1994 pgs. 8-14 ISBN 84-7978-147-5, 9788479781477.
23. Kritika Kesarwani, Rajiv Gupta: Bioavailability enhancers of herbal origin: An overview, Asian Pac J Trop Biomed. 2013 April; 3(4): 253–266. doi: 10.1016/S2221-1691(13)60060-X.
24. Annamalai R, Manavalan R. Indian Drugs, 1990; 27: 595- 604.
25. Sushma Drabu, Smrfiti Khatri, Sheveta Babu, Pratush Lohani, Use of Herbal Bioenhancers to Increase the Bioavailability of Drugs, Research Journal of Pharmaceutical, Biological and Chemical Sciences, ISSN: 0975-8585, Volume 2 Issue 4 Page No. 107.
26. Ratndeep Singha, Sarita Devib, Jatin H Patela, Urvesh D Patela et al. Indian Herbal Bioenhancers: A Review, Phcog Rev 2009; 3(5): 80-82.
27. AR Annamalai, R Manavalan. Indian Drugs 1989; 27(12): 595-604.
28. S Bajad, KL Bedi, AK Singla, RK Johri. Planta Med 2001; 67: 176-179.
29. M Majeed, V Badmaev, R Rajendran. Use of piperine to increase the bioavailability of nutritional compounds. United States Patent, Number 5536506 (1995).

30. M Majeed, V Badmaev, R Rajendran. Use of piperine to increase the bioavailability of nutritional compounds. United States Patent, Number 5536506 (1995).
31. W Reanmongkol, W Janthasoot, W Wattanatorn, P Dhumma- Upakorn, P Chudapongse. Biochem Pharmacol 1988; 37(4): 753-757.
32. (a) CK Atal, RK Dubey, J Singh. J Pharmacol Exp Therap 1985; 232(1): 258-262.
(b) RK Reen, DS Jamwal, SC Taneja, JL Koul, RK Dubey, FJ Wiebel, J Singh. Biochem Pharmacol 1993; 46(2): 229-238.
©RK Bhardwaj, H Glaeser, L Becquemont, U Klotz, SK Gupta, MF Fromm. J Pharmacol Exp Ther 2002; 302(2): 645-650.
33. RK Johri, N Thusu, A Khajuria, U Zutshi. Biochem Pharmacol 1992; 43(7): 1401-1407.