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CONCEPT OF SIGNIFICANCE OF BIOENHANCER IN TRADITIONAL INDIAN MEDICINE

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ABSTRACT

The concept of 'bioavailability enhancers' appears to be originated from the ancient traditional medical system i.e. *Ayurveda*. A 'Bioenhancer' is an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used. The objective of this review is to explore the concept and significance of Bioenhancer in Indian medicine. The literary review to understand the "Concept of significance of Bioenhancer in Indian medicine" was carried out from classical ayurvedic and contemporary texts and published research articles and various other sources. In this review, several bioavailability enhancing agents of natural origin and some methods for increasing bioavailability are discussed.

KEYWORDS: Bioenhancer, Bioavailability, *Mardana, Bhavana.*

INTRODUCTION

Oral drug delivery is the most common, widely used and appropriate route of administration as it offers advantages like painless administration, safety, non-invasive nature, and patient compliance as compared to other routes.[1]

Intravenous administration of drugs achieves maximum bioavailability whereas oral administration of drugs offers low bioavailability. The drugs with reduced bioavailability are unable to reach the minimum effective concentration to exhibit therapeutic action. Several therapeutics bears the issue of low bioavailability upon oral administration because of poor

absorption and undergo first pass metabolism. The poorly absorbed drugs remain in the physiological system and lead to several adverse effects such as drug toxicity, adverse drug reactions and drug resistance.[2]

Modern researchers are increasingly showing interest toward the improvement of bioavailability of a large number of drugs by addition of various herbs with bio-enhancing properties. The promising approaches being used are absorption enhancers, prodrugs, micronization, and manufacturing of delayed release, timed release, sustained release capsules and spansules, and permeability-enhancing dosage forms, such as liposomes and emulsions, etc.[3]

Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.[4]

The concept of bioenhancers or biopotentiators is new to the modern science but when we look towards historical traces regarding the concept of 'bioavailability enhancers', it appears to be originated from the ancient traditional medical system i.e. *Ayurveda*. Many scholars of *Ayurveda* opined that the term *yogvahi* can be correlated to the term bioenhancer. According to *Acharya Charka* and *Sushruta Madhu* (Honey) is opined to be the ideal *Yogvahi Dravya*.

The herbs such as *Shunthi* (*Zingiber officinale*) *Maricha* (*Piper nigrum* L.), *Pipalli* (*Piper longum* L.) collectively known as "Trikatu". In sanskrit "Trikatu" means three acrid are known for its bioenhanching property.[5] The action of bioenhancers was first documented by Bose (1929) who described the action of long pepper to *Vasa* leaves increased the antiasthamatic properties of *Adhatoda vasica* Nees leaves.[6]

AIMS AND OBJECTIVE

Present article aims towards reviewing the concept and significance of Bioenhancer in Indian medicine.

MATERIAL AND METHODS

Present article is a literary review to understand the Concept of significance of bioenhancer in Indian medicine with the help of data collected from classical ayurvedic and contemporary texts and published research articles and various sources from internet.

Definition of 'Bioavailability enhancers'

'Bioavailability enhancers' are drug facilitators, they are the molecules which by themselves do not show typical drug activity but when used in combination they enhance the activity of drug molecule in several ways including increasing bioavailability of the drug across the membrane, potentiating the drug molecule by conformational interaction, acting as receptors for drug molecule and making target cells more receptive to drugs. A 'bioenhancer' is an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used. These are also termed as 'absorption enhancers' which are functional excipients included in formulations to improve the absorption of a pharmacologically active drug.[5]

History of bioenhancers

The term 'bioavailability enhancer' was first coined by Indian scientists at the Regional Research Laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine, Jammu), who discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979.[10] C. K. Atal, the Director of the institute scrutinized a list of ancient Indian Ayurvedic formulations used in the treatment of a wide range of diseases. He observed that a majority of Ayurvedic formulations contained either *Trikatu* or else one of the ingredients of *Trikatu*, namely *Piper longum* (*P. longum*) (210 formulations out of 370 reviewed) which is used in a large variety of diseases.[5,8]

Mechanism of action

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

a) Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply,
b) Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility,
c) Modifications in GIT epithelial cell membrane permeability,
d) Cholagogous effect,
e) Bioenergetics and thermogenic properties and
f) Suppression of first pass metabolism and inhibition of drug metabolizing enzymes,

Stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids. Mechanism of action of piperine Different mechanisms for the bioenhancer activity of piperine have been proposed including DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump.[5,8]

Extensive research during the past decades has revealed that bioenhancing approach has attracted considerable attention as regards of its many potential advantages. It offers comfortable, convenient, and noninvasive way to administer drugs due to following advantages of it:-

1. Dose reduction
2. Minimization of drug resistance
3. Minimization of drug (especially true in case of anticancer drug like taxol).
4. Ecological benefit.
5. Safety of the environment

Ideal properties of the bioenhancers[6,7]

The contribution of bioenhancers have been reviewed which states that the ideal bioenhancers

a) Should be nontoxic, non-allergenic and non-irritating.
b) Should not produce own pharmacological effects.
c) Should be rapid-acting with predictable and reproducible activity.
d) Should be unidirectional in action.
e) Should be compatible with other active pharmaceutical ingredients.
f) Should be stable with time and environment.
g) Should be easily formulated into a various dosage form.
h) Should be easily available and cost effective.

Reasearches regarding natural bioenhancer[3,5,7,9,10]

Piperine:- Piperine is an alkaloid obtained from black and long peppers (*P. nigrum* Linn and *P. longum* Linn). It is the most intensively investigated bioenhancer. Piperine has been reported to enhance the bioavailability of various drugs and nutraceuticals. The action of Piperine is through diverse mechanisms including the inhibition of DMEs, EDTs, stimulation of gut amino acid transporters, increased intestinal glucoronic acid secretion etc.

Quercetin: Quercetin is a flavonoid, that derived from plants. This type of flavonoid found mainly in citrus fruits, vegetables, leaves, and grains. Quercetin is known for diverse set of biological properties that include antioxidant, radical scavenging, anti-inflammatory, anti-

atherosclerotic, anti-cancer, and anti-viral effects. It has been reported to enhance the bioavailability of various drugs including, pioglitazone, diltiazem, digoxin, paclitaxel, tamoxifen, ranolazine, valsaratan verapamil and epigallocatechin-3-gallate (EGCG). Quercetin is an inhibitor of CYP3A4 and a modulator of P-glycoproteins and MDR transporters.

Nitrile glycoside: Nitrile Glycoside is a bioenhancer that obtained from drum stick pods. Contains two active principles niaziridin and niazirin. They acts by enhancing penetration into pathogen and by enhancing absorption. Rifampicin, tetracycline, INH, amphicillin, vitamin B12, clotrimazol, nalidixic acid can be used to improve bioavailability by using nitrile glycosides.

Genistein: Genistein is a phytoestrogen and an isoflavone flavonoid found in dietary plants such as soybean and kudzu (*Glycine max* (L.) Merr. and *Pueraria lobata*). It exhibits its bioenhancing properties on various drugs like paclitaxel through the inhibition of CYP3A, P-gp, MRP2, and BCRP transporters. Although gensitein is known to inhibit various efflux transporters and metabolizing enzymes, its use is restricted due to its tumor promoting effects that are evident from in vivo reports.

Glycyrrhizin: Glycyrrhizin is a triterpenoid saponin glycoside isolated from liquorice (*Glycyrrhiza galbra* L.). Glycyrrhizin exhibited bioenhancing activity when combined with various antimicrobial agents including rifampicin, tetracycline, nalidixic acid, etc. Glycyrrhiza also reported to increase the anticancer activity of Paclitaxel, enchance transport of vitamins B1 and B12 across the gut membrane to manifold. It especially acts through the inhibition of intestinal P-gp transporters.

Naringin: Naringin is a flavonoid glycoside isolated mainly from onions, tea, grapefruit and apples. It acts as a bioenhancer by inhibiting the metabolizing enzymes such as CYP3A4 and CYP3A1/2. It is also reported to act through the inhibition of efflux pump P-gp. Naringin is reported to efficiently enhance the bioavailability of a number of drugs, which results in decreased drug dose and increased plasma drug concentration. These include diltiazem, verapamil, paclitaxel etc.

Glycyrrhizin: Glycyrrhizin is a triterpenoid saponin glycoside isolated from liquorice (*Glycyrrhiza galbra* L.). Glycyrrhizin has demonstrated bioenhancing activity when combined with various antimicrobial agents including rifampicin, tetracycline, nalidixic acid, etc. The anticancer activity of Paclitaxel increases manifolds when it combines with glycyrrhizin. It majorly acts through the inhibition of intestinal P-gp transporters. However,

the major determinant of its action is the rate and extent of biotransformation of glycyrrhizin to glycyrrhizic acid by intestinal β glucuronidase.

Curcumin: Curcumin is obtained from turmeric (*Curcuma longa* L.). It is an efficient bioenhancer for antimicrobial and anticancer drugs such as norfloxacin, docetaxel etc. Curcumin inhibits the actions of metabolizing enzymes CYP3A4 in the liver. However, curcumin also inhibits drug metabolizing enzymes (DMEs) non-specifically. It is also reported to inhibit the P- glycoproteins (P-gp) in the gut walls.

Black cumin: Black cumin is called as *Cuminum cyminum* Linn., which is a small and thin annual herb. It is an effective gastric stimulant, beneficial in abdominal lump and flatulence. It has therapeutically been used as an diuretic, anti-diarrheal, galactagogue. It enhances bioavailability of rifampicin, cyclosporin, ethionamide, cefadroxil, cloxacillin, flucanazol, zidovudine, 5- FU, erythromycin, cephalexin, amoxicillin, Ketoconazole, toconazol etc.

Gingerol: It is one of the most useful dietary ingredients obtained from *Zingiber officinale* (Zingiberaceae) has shown effective bio-enhancement. A patent invention suggested that ginger extract helps to enhance bioavailability of several drugs. It has significant bioenhancing capabilities with a number of drugs that includes antibiotics such penicillins, cephalosporins; antifungals such as fluconazole, ketoconazole; anticancer drugs such as methotrexate, 5- fluorouracil; cardiovascular drugs such as amlodipine, lisinopril and anti-histaminic salbutamol.

Garlic: Allicin, the active bioenhancer phytomolecule in garlic (*Allium sativum* L.) enhances the fungicidal activity of amphotericin B against pathogenic fungi such as Candida albicans, Aspergillus fumigatus and yeast Saccharomyces cerevisiae. Amphotericin B when given along with allicin exhibited enhanced antifungal activity against the common yeast known as Saccharomyces cerevisiae.

Lysergol: Lysergol is alkaloidal phytoconstituent obtained from Morning Glory Plant (Ipomoea spp.). It is reported to enhance bacteriocidal effects of different antibiotics against bacteria and is a promising herbal bioenhancer. It is also isolated from higher plants including Riveacorymbosa, *Ipomoea violacea*, and *Ipomoea muricata*. In various other studies, lysergol is reported to enhance the bioavailability of different drugs like rifampicin, tetracycline and ampicillin. It is found effective against broad spectrum microbes, Gram-positive and Gram-negative, consisting E. coli, B. subtilis and other similar microbes. In another study, lysergol improved the bioavailability of berberine after oral administration in Sprague-Dawley rats.

Aloe vera (Aloe): Aloe, a perennial and succulent xerophyte consist of several phytoconstituents' that is widely used in both human and veterinary medicine for its

immunomodulatory, wound and burn healing, hypoglycemic, anticancer, gastro-protective, antifungal, and anti-inflammatory effects. The ethanolic extract of Aloe vera is found to augment the hypoglycemic effect of glipizide in streptozotocin induced diabetic rats. Due to its cytoprotective effects on gastric mucosa through induction of endogenous prostaglandin production, concominant use of Aloe vera and pantoprazole for the gastroesophageal reflux symptoms in mustard gas victims were found to be improved compared to single treatments.

Processes act as bioenhancer[11,12,13,14]

1. ***Shodhana*:** This process is intended to lessen external and internal impurities in addition to enhancement of its original medicinal properties. It changes physicochemical structure of purified drug up to some extent. The prime objective of these physico-chemical changes of the material is to reinforce its biological availability. Reduction in particle size helps in absorption, smoothness leads to non-irritability and all chemical changes make the material body friendly. The process of *Shodhana* insist to enhance the efficacy and reduce the toxicity of crude drugs by alteration of their pharmaco-dynamics properties. During purification process herbal drugs not only nullify the toxicity & modify the active principles, but also bring organic qualities, which is highly necessary for clinical drug administration.
2. ***Mardana*:** There is a quote mentioned as *"Mardanam Guna Vardhanam"*, which means that if more *Mardana* (grinding) is done the more *Guna* (property) will be ingested in the drug. The process of grinding reduces the particle size that in turn will increase the surface area of the drug. The *Nirendriya Parada* turns into *Sendriya* by the addition of organic properties to mercury done in the process of *Mardana* or *Bhavana*. Thus the benefits of *Mardana* can be addressed as follows: In the context of *Mardana Samskara* (process) that comes under the *Asthadasha Samskaras* of *Parada* (eighteen processes of Mercury), *Mardana* is done to remove the external impurities of mercury. In *Satvapatana* (extraction) process: Firstly, the process of grinding reduces the particle size. Secondly, it helps in uniform mixing of the drug.
3. ***Bhavana:*** *Bhavana* is the process in which powdered drug is impregnated with liquid media such as decoctions, juices etc. by triturating till it become dry. Liquid media should be added in such a quantity so that powdered drug is quenched enough for pestle movements. Impregnation of properties of media to the drug material which lead to unique and suitable physiochemical changes helping in incorporation of organic properties to inorganic substances. It is asystematic procedure of enhancing therapeutic

qualities in individual drug and in formulations. The interaction of liquids of same drug or different drug in *Bhavana* process may give leads for development of newer pharmaco-kinetic-dynamic potent molecules. *Bhavana* plays a vital role in enhancing the efficacy of drug by making desirable changes while processing through various types of *Bhavanadravyas* which act as catalyst.

4. ***Marana*:** The process of making the metals/minerals into a fine powder by applying required quantum of heat is known as *Marana*. It is the conversion of metal/mineral into fine nano particles which herbo-mineral, organo-metallic nature and therapeutic potency. The metals and minerals are not bio-assimilable in their natural forms. They needed to be converted into such fine form which can be easily assimilable in human body and able to cure various illnesses and did not cause any harmful effect.

The objective of *Marana* is to bring physico-chemical changes of material to increase its biological availability, i.e. to potentiate its biological efficacy. There is reduction in particle size, which helps in absorption, smoothness leads to non-irritability. The vegetable drugs which are used in the form of decoction or juice have their own therapeutic properties, imported with *Marana*, the drug become non-toxic, easily digestible and absorbable, suitable for metabolic changes, assimmilable by tissue cells and become therapeutic potent.

DISCUSSION AND CONCLUSION

According to the above said The term *yogvahi* can be opined as a substance which adopts the properties of the formulation or drug with which it is added. Apart from its synergistic action it acts as a vehicle to transport the desired medicine to reach its site of action. In other word helps in *Vahana* of the medicine (*Yogam Vahyatiti*, Sha. K. Dru., *Yogena Vahati*, Vach.). Furthermore although the properties of bioenhancer and *Yogvahi* are same but it can not be said as coin term because of the diverse nature of Sanskrit terminology. e.g. The word *Yogvahi* is also synonymous to *Parda* and A special type of *Kshara*.

The primitive use of bioenhancers is indicated in ancient texts of traditional medical system. The bioenhancing activity in traditional medicines was incorporated by several methods. The main is to increase bioavailability. Bioenhancers are systematic tools to control the increasing cost of drugs, to reduce dose, reduce drug resistance and also to reduce duration of treatment. This concept of bioenhancement might be helpful to control adverse effects of drugs, the rising drug cost, toxicity, and other adverse effects, and thus may ultimately have a positive

influence on the national economy. There is need to further explore this activity of bioenhancement. It is safe, effective and easily acquired.

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