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A Strategy to Enhance Bioavailability of Drug Candidates: Natural Bioenhancers

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ABSTRACT

Nowadays herbs are increasingly being used worldwide as therapeutic agents or in collaboration with minerals and vitamins in health supplements, teas etc. There are many advantages of herbalism over modern or conventional medicine such as the herbal/traditional systems of medicine causes lesser side effects than modern medicine; herbal medicine along with lifestyle modification enhances its potency by assisting and boosting the inborn self-healing mechanisms of the patient. Thus, the chronic disorder is not only cured but the possibilities of its recurrence are highly reduced. However, despite having great in-vitro potential, herbs or herbal extracts have demonstrated very less in-vivo activity due to insufficient lipid solubility and irregular molecular size. Thus, this led to poor absorption and poor bioavailability. With the advancement in science and technology, several trials are undergone to enhance the bioavailability of drugs via novel drug delivery systems such as microspheres, nanoparticles, liposomes, transferosomes, lipid-based systems, etc. Besides these novel approaches, there are certain compounds that exist in nature that are found to exhibit enhanced bioavailability rate such as piperine, curcumin, naringin, quercetin, genistein, etc. The objective of this review is to throw light on bioavailability enhancing effects of these natural bioenhancers of herbal origin, their characteristic features and mechanisms of action.

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INTRODUCTION

The utilization of plants for the medicinal objectives is from time immemorial. India is one amongst the many ancient civilisations which is famous for its rich heritage and also considered an abundant repository of plants used for therapeutic purposes. About 80 per cent of the population in the world still rely and use the plant-based medicines. About 25% of the drugs used in pharmacopoeias belong to plant origin. Medicinal plants are a major contribution towards traditional or alternative systems of medicines.

The application of herbal plants for medicinal purposes is since pre-historic period. In the last century, studies on pharmacological and chemical aspects of plant extracts are carried out to learn about their chemical composition and to validate the manifestations of traditional medicine.[1] Although the pharmacological and phytochemical studies have been accepted for the compositions, therapeutics and other health benefits of plant and plant products, there is a necessity for the bioavailability enhancement of the most of plants extracts and herbal drugs which have very less lipid solubility and are hence less bioavailable. [2]

Nowadays many herbs or herbal extracts have good potential in *in vitro* but they are not successful as they fail to exhibit significant *in vivo* activity due to poor absorption and bioavailability because of irregular molecular size or poor lipid solubility. [3]

Therefore, to sum up most of the synthetic and herbal drugs have the disadvantage of low bioavailability. The factors that contribute to low bioavailability are decreased membrane permeability which is the major cause, lower lipophilicity, ionic properties, poor water solubility or P-glycoprotein.

When drugs are administered via intravenous route of administration, the highest rate of bioavailability is attained. On the other hand, the drugs that are administered via oral route of administration are poorly bioavailable due to incomplete absorption and first pass metabolism. Such unutilised fraction of the drug in the body causes adverse effects and also drug resistance. Therefore, there is a necessity of molecules which by themselves have no same therapeutic activity but when given in combination of other drugs/molecules increase their bioavailability.

Mother Nature has provided several compounds from plant sources which when co-administered with other drug have the capacity to increase the bioavailability. Thus, bioenhancers are the chemical entities which boosts and promotes the bioavailability of the drugs when administered concomitantly and do not exhibit synergism. [4,5]

"The phenomenon of total availability increasing of any chemical entity in systematic circulation is called as bioenhancement or biopotentionation and the secondary agents which causes this augmentation of plasma concentration of principle ingredient are termed as Biopotentiers or Bioavailability Enhancers."[6]

The concept of bioavailability enhancers is acquired from the traditional 5000-year-old Alternative System of Ayurvedic Medicine. An Ayurvedic preparation, "Trikatu", has been popularly used between the period 700 BC and 600 AD. The term, "Trikatu" is a Sanskrit word which means three acrids. The term refers to amalgamation of three herbal ingredients, viz., *Piper nigrum* Linn. (black pepper), *Piper longum* Linn. (long pepper), and *Zingiber officianale* Rosc. (ginger). This preparation contains active principle piperine, which is responsible for the enhancement of the bioavailability of drugs, and other substances like vitamins and nutrients.[7-8] In 1929, the activity of bioenhancers was first reported by Bose who illustrated that the action of *Piper longum* increased the anti-histaminic properties of Adhatoda vasika leaves. The Scientists of India at the Regional Research Laboratory, Jammu (RRL, now recognised as the Indian Institute of Integrative Medicine) first coined the term, "Bioavailability Enhancer" and in 1979, also discovered piperine and scientifically approved it as the first bioavailability enhancer in the world [7].

CHARACTERISTICS OF BIOENHANCERS

Bioenhancers should have the following characteristic features [9]:

- Should be non-toxic, non-allergenic and non-irritating.
- Should not exhibit its own pharmacological effects.
- Should be fast-acting
- Should exhibit reproducible and predictable activity.
- Should be one-directional in action.
- Should be compatible with the active pharmaceutical ingredient (APIs).
- Should be stability with time and environment.
- Should be easily formulated into different forms of dosage.
- Should be easily available.
- Should be cost effective.

DRUG ABSORPTION BARRIERS

For the drug to exhibit its biological action, it is essential to cross the barrier of the intestinal mucosa made of epithelial cells so that it can be delivered into the systemic circulation from the lumen of the gut. The epithelial membrane has many barriers in terms of its anatomy and physiology, hence, the drugs intended for the purpose of oral administration must be able to pass through it .[10,11] The epithelial layer of the intestine is composed of many structures that cause hindrance to the drug transport from the lumen of gastrointestinal tract to the systemic circulation. The potential obstacle to the mechanism of drug absorption is an aqueous stationary layer overlying the apical membrane on account of its hydrophilic nature. Besides these, the apical and basolateral membranes having less permeability also act as possible barriers to the drug absorption. The cell membranes are lipid-bilayers composed of proteins such as receptors and carrier molecules. Drugs penetrate the cell membrane by means of passive diffusion or carrier-mediated transport involving the dissipation of the energy. There are aqueous channels within the protein molecules for the purpose of transport of small water-soluble molecules like ethanol. The drug molecules which are larger in size than 0.4nm cannot pass through these aqueous channels. [11]

MECHANISM OF ACTION OF BIOENHANCERS

The principal mechanisms by which bioenhancers exert their bioavailability enhancing property on the drugs are as follows:

1. By increasing the supply of blood which enhances the oral drug absorption from gastro-intestinal tract.
2. By regulation of the carrier molecules involved in the active transport mechanism. E.g. P-glycoprotein (P-gp) which is an ATP-dependent efflux pump that pumps foreign substances and drugs out of cells and block them from reaching the site of action. Thus, here the bioenhancers exert their action by inhibition of the P-gp.
3. By decreasing the elimination time of drug, thus, increasing the residence time of drug in the body.
   (a) Inhibition of the enzymes responsible for drug metabolism which include CYP 3A4, CYP 1A1, CYP 1B2, CYP2E1, in the liver, gut, lungs and other parts of the body which also

assist in controlling the first pass metabolism of orally administered drugs.

(b) Inhibition of the renal clearance by hindering glomerular filtration, active tubular secretion and assisting passive tubular reabsorption.

Besides the above-mentioned mechanisms, the other hypotheses for the action of bioenhancers include the following:

- Decrease in the secretion of Hydrochloric Acid and increase in gastro-intestinal blood supply.
- Inhibition of GI transit, gastric emptying time and intestinal motility.
- Regulation in permeability of epithelial cell membrane of GI tract.
- Cholagogoue effect.
- Bioenergetics and thermogenic properties.
- Prevention of first pass metabolism and inhibition of drug metabolising enzymes.
- Activation of gamma glutamyl transpeptidase (GGT) activity that promotes the consumption of amino acids .[12]

CLASSIFICATION OF BIOENHANCERS

Bioenhancers can be broadly classified based on their nature of origin and also based on their mechanism of action as follows: [13]

Classification of bioenhancers based on Origin:

- **Plant Origin:**

Piperine, Curcumin, Naringin, Quercetin, Niaziridin, Carum carvi, Capsaicin, Cuminum cyminum, Stevia, Lysergol, Glycyrrihizin, Ginger, Allicin, Aloe vera, Simomenine, Genistein, Peppermint oil, Gallic acid, Ellagic acid, Ferulic acid, 5-hydroxy hydnocarpin, Ammannia multiflora.

- **Animal origin:**

Cow urine distillate

Classification of Bioenhancers based on Mechanism of Action:

- **Inhibition of P-gp and other efflux pumps:**

e.g. *Carum carvi* (Caraway), Genistein, Sinomenine, *Cuminum cyminum* (Black cumin), Naringin, Quercetin.

- **Suppression of CYP-450 enzyme and its isoenzymes:**

e.g. Piperine, Naringin, Gallic acid and its esters, Quercetin.

- **Modulators of GI tract function to enhance absorption:**

e.g. *Aloe vera* (Aloe), Niaziridin (Drumstick pods), *Zingiber officinale* (Ginger), Glycyrrhizin (Liquorice)

Inhibition of P-gp

The objective of the inhibition of efflux pump is to enhance the transport of drugs. Generally, inhibition of P-gp occurs by three different mechanisms:

(i) Either competitive, non-competitive or allosteric inhibition of binding site of the drugs;
(ii) Interference with hydrolysis of ATP; and
(iii) Modification of the integrity of the lipids in the cell membrane. [14,15,16–18]

Classification of P-gp inhibitors: [14, 19, 20, 21-23]

P-gp inhibitors based on their specificity, affinity, and toxicity are classified into three generations.

- First Generation Inhibitors
- Second Generation Inhibitors
- Third Generation Inhibitors

- **First Generation Inhibitors:**

They are non-selective and have low binding affinities.

Examples: Reserpine, verapamil, quinidine, cyclosporin A, tamoxifen, yohimbine, and toremifene. First generation inhibitors are pharmacologically active. They are therapeutically employed for specific type of treatments but can also inhibit P-gp. Their use is limited on account of their high serum concentrations.[19, 24] They also act as substrates to other transporters and enzyme systems, that lead to pharmacokinetic interactions.

- **Second Generation Inhibitors:**

They exhibit higher specificity than first generation inhibitors but have the disadvantage of interaction with other systems. Examples: Dexniguldipine, dexverapamil, valspodar (PSC 833), and Dofequidar fumarate (MS-209)

Second generation inhibitors do not exhibit pharmacological actions but have higher P-gp affinity. They cause inhibition of the CYPA4 enzyme and other ABC transporters. Hence, metabolizing rate decreases and inhibition of two or more ABC transporters resulting in complicated pharmacokinetic interactions.

- **Third Generation Inhibitors:**

They exhibit highest specificity as they specifically and efficiently inhibit P-gp efflux.

Examples: Cyclopropyldibenzo suberane zosuquidar (LY335979), laniquidar (r101933), mitotane (NSC-38721), biricodar (vX-710), elacridar (GF120918/GG918), ONT-093, tariquidar (Xr9576), and hM30181

Third generation P-gp inhibitors are under clinical development phase with the objective to inhibit P-gp with higher specificity and lower toxicity. They are established using structure activity relationships (SARs). Most of them were known to be very specific and potent against P-gp with minimal toxicity. [20, 25, 26]

Suppression of CYP 450 enzyme and its isoenzymes

Herbal medicines are polyherbal formulations which consist of combination of biologically active compounds. The metabolism of these compounds may take place with the similar mechanism of the administered drug, thereby leading to interaction and eventually inhibition/increase of free drug metabolizing enzymes or transporters. The alteration in the expression of these proteins, or physical/chemical/ pharmacological competition, eventually effects the free drug/metabolite concentration and the pharmacokinetic parameters resulting in the altered pharmacological effects. Many herbs were found to interact with the cytochrome P450, the major microsomal enzyme for drug metabolism/detoxification, which has high polymorphisms in both human and companion animals. [27]

As the enzymes CYP and UDPs are essential for phase I metabolism of several substances such as drugs, nutrients, endogenous substances, and environmental toxins, the regulation of their expression contributes a great deal in the efficacy of the therapy or the progress of the toxicity. [28]

Inhibition will result in lesser drug molecules to be metabolized with an increased concentration of unchanged drug passing from gastro-intestinal tract into the systemic circulation. The important isoenzymes of CYPs which are responsible for the metabolism of drugs in humans are CYP3A4, 2D6 and 2C9 family. [29]

CONCLUSION

The progress of Natural Bioenhancers should be intended for the drugs that are poorly bioavailable, administered for longer duration of time, highly toxic, and costlier in price. The current research on bioenhancers has manifested to generate significant increase in bioavailability of drugs when co-administered with other drugs. Bioenhancers offer many advantages apart from increasing bioavailability such as they reduce the dose shorten the treatment duration and thus the drug resistance and drug toxicity. Ultimately it leads to cost-effective treatment.

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