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NATURAL PRODUCTS AS BIOAVAILABILITY ENHANCERS

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Abstract

With the development of advanced techniques of drug design, number of new molecules is being introduced as probable drug candidates every year. But many of them suffer from poor aqueous solubility, stability problems and poor bioavailability. Bioenhancers play significant role in improvement of the bioavailability of the drugs. The increase in bioavailability can lead to reduced dose and frequency of dosing, less side effects of the drugs minimizing the dose dependant toxicity of the drugs. This may reduce the cost of the treatment and thus will be beneficial to the patients. Number of natural products has been identified as potential bioenhancers and use of piperine as bioenhancer for antitubercular drug, rifampicin is approved. This review presents different aspects of bioenhancers and a short account on various natural products or phytoconstituents showing bioenhancing effect.

Keywords: Bioenhancers, natural bioenhancers, bioavailability, classification of bioenhancers, Piperine.

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INTRODUCTION

Plants play a significant role in maintaining human health and improving the quality of human life. Herbs have been used in many domains including medicines, nutraceuticals, cosmetics, flavours and fragrances, beverages, dyes and other industrial purposes. Since the prehistoric era, herbs have been the basis for nearly all medicinal therapies until synthetic drugs were developed in the nineteenth century. The phytoconstituents, belonging to different chemical classes, elicit different pharmacological effects. With rapid advances in drug design technologies, number of new drug candidates molecules introduced has increased dramatically. However, many of these molecules have suffered from low bioavailability upon oral administration due to poor permeation across the gastrointestinal epethelia, although they exhibit potential therapeutic effects. Drugs have low membrane permeability, probably because of their low lipophilicity and zwitterionic character at physiological pH, or because of poor water solubility or efflux by P- glycoprotein (P-gp) [1]. Bioavailability is the rate and extent to which a substance enters systemic circulation and becomes available at the required site of action [2]. Therefore, improving oral drug absorption and bioavailability of drugs has become an important issue within the pharmaceutical industries. There are numerous approaches to enhance the intestinal absorption. These approaches include the use of absorption enhancers, prodrugs and permeability enhancing dosage forms such as liposomes and emulsions. Recently, the application of P-gp inhibitors in improving per oral drug delivery has gained special interest [1].The concept of bioavailability enhancers is derived from the traditional age old system of Ayurveda (Science of life). Use of ayurvedic preparation "Trikatu", from the period between the 7thcentury B.C. and the 6th century A.D., which is a Sanskrit word meaning three acrids. It refers to a combination of black pepper (*Piper nigrum* Linn.), long pepper (*Piper longum* Linn.), and ginger (*Zingiber officinale* Rosc.), which contains active principle piperine, which enhances the bioavailability of drugs, nutrients, and vitamins [3-4]. The action of bioenhancers was first documented by Bose (1929) who described the action of long pepper increased the antihistaminic properties of *Adhatoda vasika* leaves. 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) who discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979 [3]. When a drug is administered orally, the bioavailability of the drug may be decreased due to incomplete absorption or first pass metabolism. Because of the low bioavailability, insufficient amount of

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drugs is reached in to the systemic circulation and unable to produce their therapeutic effects. This problem can be overcome by the use of bioenhancers [5].

Many synthetic and herbal drugs suffer from the problem of low bioavailability. Many natural compounds from medicinal plants have capacity to augment the bioavailability when co-administered with another drug. Thus bioenhancers are chemical entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit synergistic effect with the drug. Herbal bioenhancers play a crucial role in enhancing the bioavailability and bioefficacy of different classes of drugs, such as antihypertensives, anticancer, antiviral, antitubercular and antifungal drugs at low doses [6].

Ideal properties of the bioenhancers [5]**:**

1. Should be nontoxic, non-allergenic and non-irritating.
2. Should not produce own pharmacological effects.
3. Should be rapid-acting with predictable and reproducible activity.
4. Should be unidirectional in action.
5. Should be compatible with other active pharmaceutical ingredients.
6. Should be stable with time and environment.
7. Should be easily formulated into a various dosage form.
8. Should be easily available and cost effective.

Following the use of bioenhancers, the dose of the drug is reduced and risk of drug resistance is minimized. It also reduces the dose-dependent toxicity of the drug, especially of anticancer drugs [7].

NEED FOR BIOENHANCERS

The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms. Bioenhancers modulate one or more of these factors to enhance absorption and decrease the metabolism to reduce dose, toxicity, and cost of drugs. Need for bioenhancers arises for drugs which are poorly available, administered for long periods, toxic and expensive [8].

EFFECT OF BIOENHANCERS ON DRUGS

The dose of the drug is reduced and risk of drug resistance is minimized. There will be reduction in the dose-dependent toxicity and cost of the drug, especially of anti-tubercular drugs. Research

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have shown that bioenhancers enhanced bioavailability and bio-efficacy of different classes of drugs, such as anti-tubercular, antibiotics, antiviral, anti-fungal, and anticancer drugs at low doses [8].

MECHANISM OF ACTION OF BIOENHANCERS

The following are the chief mechanisms via which the various bioenhancers exert their bioavailability enhancing properties on the drug molecules:

1. Enhancing the absorption of orally administered drugs from gastrointestinal tract by increase in blood supply.
2. Modulating the active transporters located in various locations eg. P-glycoprotein(P-gp) is an efflux pump which pumps out drugs and prevent it from reaching the target site. Bioenhancers in such case act by inhibiting the P-gp.
3. Decreasing the elimination process thereby extending the sojourn of drug in the body.

a) Inhibiting the drug metabolizing enzymes like CYP 3A4,CYP1A1, CYP1B2, CYP2E1, in the liver, gut, lungs, and various other locations. This will in addition help to overcome the first pass effect of administered drugs.

b) Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibiting P-gp and facilitating passive tubular reabsorption. Sometimes biliary clearance is also affected by inhibiting the UDP glucuronyl transferase enzyme which conjugates and inactivates the drug.

In addition to the above mentioned mechanisms, few other postulated theories for herbal bioenhancers are:

- Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply,
- Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility,
- Modifications in GIT epithelial cell membrane permeability,
- Cholagogoue effect,
- Bioenergetics and thermogenic properties
- Suppression of first pass metabolism and inhibition of drug metabolizing enzymes and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids [7].

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CLASSIFICATION OF BIOENHANCERS [7-8]

1. Based on Origin
    - Plant Origin : Examples: Piperine, Niaziridin, *Carum carvi* (Caraway), Stevia, Glycyrrhizin, Ginger, Allicin, *Aloe vera*, Genestein, Quercetin, Curcumin, Naringin, Gallic acid, Ellagic acid, Ferulic acid, *Ammania multiflora*
    - Animal origin: Example: Cow urine distillate
2. Based on Mechanism of Action
    - Inhibitors of P-gp efflux pump and other efflux pumps
      Examples: Caraway, Genestein, Quercetin, Naringin, Sinomenine, *Cuminum cyminum* (Black cumin)
    - Suppressors of CYP-450 enzyme and its isozymes
      Examples: Naringin, Gallic acid and its esters, Quercetin
    - Regulators of GIT function to facilitate better absorption
      Examples: Aloe vera (Aloe), Niaziridin (Drumstick pods), *Zingiber officinale* (Ginger), Glycerrhyzin(Liquorice)

PHYTOCONSTITUENTS AND NATURAL PRODUCTS AS BIOAVAILABILITY ENHANCERS:

Piperine:

Piperine, the major plant alkaloid present in *Piper nigrum* Linn (Black pepper) and *Piper longum* Linn (Long pepper), has shown bioavailability enhancing activity for various drugs and nutritional substances. The bioenhancing dose of piperine is approximately 15 mg/person/day and not more than 20 mg/day in divided doses, which corresponds to from several thousands to up to 40,000 times less than the LD50 dose of piperine, as established in various experiments on rodents. The effective bioenhancing dose of piperine for drug compounds varies, but a dose of approximately 10% (w/w) of the active drug could be regarded as an appropriate bioenhancing dose for most drugs [9]. The bioenhancing property of piperine was first utilized in the treatment of tuberculosis in human. Piperine was found to increase the bioavailability of rifampicin by about 60% and hence reduce the dose of the drug from 450 to 200mg. This reduces dosage, cost and toxicity of rifampicin. Rifampicin considered to be a most potent anti-tubercular drug, is primarily metabolised in liver microsomal enzyme system. In human medicine piperine is approved to be combined with antitubercular drugs [7,10,11]. Piperine also showed enhanced bioavailability when combined with Nevirapine, a potent non-nucleoside inhibitor of HIV-1

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reverse transcriptase which is used in combination with other antiretroviral agents for the treatment of HIV-1 infection. Piperine also increases the bioavailability of curcumin, the active principle of *Curcuma longa* (turmeric). A 20 mg dose of piperine can increase the bioavailability of curcumin by 20 fold in humans. Several animal studies on piperine have shown promising results in bioenhancing capacity of piperine. Some of the drugs which are reported to be bioenhanced by piperine includes vasicine, pyrazinamide, phenytoin, propranolol, theophyllin, sulphadiazine, tetracycline, pentobarbitone, curcumin, nimesulide, indomethacin, oxyphenylbutazone, phenytoin, rifampicin, ciprofloxacin, amoxycillin trihydrate and cefotaxime and diclofenac sodium [12-15].

Quercetin

Quercetin is a plant derived flavonoid found in apples, onions, nuts, berries, and broccoli. It displays significant properties like anti-viral, anti-carcinogenic, anti-bacterial anti- inflammatory, anti-oxidant and free radical scavenging effects [16]. Quercetin is a dual inhibitor of CYP3A4 and P-gp. It influences the bioavailability of dilitiazem, paclitaxel, digoxin, doxorubicin and tamoxifen and also significantly increased the bioavailability of epigallocatechin gallate, a main anticancer component in green tea with poor bioavailability in rats and humans due to oxidation, metabolism and its effux [4, 9].

Curcumin

Turmeric (*Curcuma longa*) is a common household item used as remedy for various ailments. Curcumin, a flavonoid from turmeric suppresses drug metabolizing enzymes like CYP3A4 in liver and is also capable of inducing change in drug transporter P-gp and thus increased the bioavailability of celiprolol and midazolam in rats. The bioenhancer nature of curcumin is similar to piperine. Curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues. It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs [7].

Allicin

Allicin, the active bioenhancer phytomolecule in garlic (*Allium sativum*), enhances the fungicidal activity of amphotericin B against pathogenic fungi such as Candida Albicans, *Aspergillus fumigatus* and yeast *Saccharomyces cerevisiae* [17].

Naringin

Naringin is a major flavonoid found in grapefruits, sour oranges, onions, apples and tea. It exhibits various pharmacological effects such as anti-oxidant, anti-allergic, lowering blood lipid

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level and anti-carcinogenic. Naringin has shown inhibitory activity of several drug metabolizing enzymes such as CYP3A1, CYP3A2, and CYP3A4 and additionally modulates p-gp drug efflux pump. This mechanism of action made naringin to increase the bioavailability of drugs such as paclitaxel, verapamil, saquinavir and cyclosporine A, tamoxifen, doxorubicin and diltiazem [12,16].

Gingerol

Ginger has a powerful effect on GIT mucous membrane. Gingerol is the major pungent essential oil of ginger (*Zingiber officinale*). Gingerol increases the motility of the gastrointestinal tract and have analgesic, sedative, antipyretic, and antibacterial properties The chemo preventive potentials of gingerol presents a promising future alternative to expensive and toxic therapeutic agents [18]. Gingerol improves the absorption of several drugs by regulating the intestinal function to facilitate absorption of several drugs. Gingerol alone provides bio enhancing activity in the range of 30-75%, whereas piperine and gingerol combination provide the bioavailability of drugs in the range of 10–85%. The bioenhancing dosage of gingerol is in the range of 10–30 mg/kg body weight. To facilitate absorption it regulates the intestinal function. To facilitate absorption it regulates the intestinal function. The bioavailability of many antibiotics like azithromycin (85%), erythromycin (105%), cephalexin (85%),cefadroxil (65%), amoxycillin (90%) and cloxacillin (90%) is increased by using it [13,18,19].

Glycyrrhizin

Glycyrrhizin, the active principle present in Liquorice (*Glycyrrhiza glabra*), augments the inhibition of cell division with the core antineoplastic drugs. Studies have revealed its effect on taxol bioenhancement; this combination is used against breast cancer. Inhibition of cell growth by taxol with glycyrrhizin was higher than the taxol alone. The cell division inhibitory activity of anticancer drug `Taxol` was enhanced by 5 folds against the breast cancer cell lines development and multiplication. Studies also report its positive effects on transportation of antibiotics like rifampin, tetracycline, ampicillin and vitamins B_1 and B_{12} across the gut membrane [19,20].

Nitrile Glycoside

Nitrile Glycoside and its derivatives are components derived from the pods of *Moringa oleifera* L (Drumstick pods). They do not possess drug activity of their own but are reported to promote and augment the biological activity, bioavailability or the uptake of drugs in combination therapy. The nitrile glycoside (e.g. Niaziridin) has enhanced the absorption of commonly used antibiotics such as rifampicin, tetracycline and ampicillin, vitamins and nutrients [3].

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Caraway

Caraway/cumin which is a P-gp efflux pump inhibitor consists of the dried ripe fruits of *Carum carvi* of family *Umbelliferae*. It shows anti-oxidant, anti-microbial, diuretic and carminative. The main constituents are carvone and limonene. The effective dose of the bioenhancer extract is in the range of 5-100 mg/kg body weight. Percentage enhancement of bioavailability for rifampicin is 110%, for cycloserine is 75%, for ethionamide is 68%. Apart from the above bioenhancing effects, caraway also enhances the bioavailability of antibiotics (cefdinir – 89% and cloxacillin100%), anti-fungal (amphotericin b - 78%), anti-viral (zidovudine– 92%) and anti-cancer (5-fluorouracil – 90%) drugs at the dose of1-55 mg/kg body weight [7].

Black cumin

Black cumin (*Cuminum cyminum*) is a carminative, estrogenic, anti-nociceptive, anti-inflammatory, anti-oxidant and antimicrobial. The bioenhancer chemical constituent present in cumin is 3', 5-dihydroxyflavone-7-O-β-D-galactouronide-4'-β-O-Dglucopyranoside.The effective dose of the bioenhancer extract is in the range of 0.5-25 mg/kg body weight. Percentage enhancement of bioavailability for rifampicin is 250%, for cycloserine is 89%, for ethionamide is 78% [7].

EXAMPES OF DRUGS BIOENHANCED BY VARIOUS BIOENHANCERS

Extensive research has been published regarding bioenhacing effect of herbal products on modern drugs. Studies done in vitro, animals or humans has proved bioenhancing properties of bioenhancers along with drugs such as Macrolides (Azithromycin, Erythromycin, Roxithromycin), Cephalosporins (Cefalexin, Cefadroxil), Penicillins (Amoxycillin, Cloxacillin), Aminoglycosides (Kanamycin) Fluoroquinolones (Ciprofloxacin, Pefloxacin), Antifungal (Fluconazole, Ketoconazole), Antiviral (Acyclovir, Zidovudine), CNS acting drugs (Alprazolam), Anticancer (Methotrexate, 5-Fluorouracil, Doxorubicin, Cisplatin), Cardiovascular (Amlodipine, Propranolol, Lisinopril), Anti-inflammatory / Antiarthritic (Diclofenac, Nimesulide, Piroxicam), Antituberculosis / Antileprosy (Rifampicin, Dapsone, Ethionamide, Cycloserine), Antihistamines, Salbutamol, Theophylline, Bromhexine, Corticosteroids (Dexamethasone, Betamethasone), Immunosuppressant (Cyclosporin A, Tacrolimus), Antiulcer (Ranitidine, Cimetidine) Vitamins (Vitamin A, Vitamin E, Vitamin C, Folic acid, Anti-oxidants (β-Carotene, Silymar) [5].

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CONCLUSION

The concept of bioenhancers is innovative, which has been originated from Traditional System of Indian Medicine, Ayurveda. It provides a useful mean of enhancing bioavailability of several drugs. The natural bioenhancers are safe, free from side effects and are available easily. Use of bioenhancers shortens the duration of treatment and lowers the drug resistance and thus helps to reduce the cost of the treatment. Research and development of new bioenhancers from numerous unexploited plants and development of effective drug delivery system can lead to effective use of potential drugs with reduced dose and side effects as well as cost of the treatment.

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