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Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

J P P Journal of Pharmacognosy and Phytochemistry

ISSN 2278-4136
ISSN 2349-8234
JPP 2013; 2 (3): 55-60

Received: 19-7-2013
Accepted: 09-8-2013

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Natural Bioenhancers: An overview

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ABSTRACT

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. The need for bioenhancers arises due to drugs which are poorly available, administered for long periods, toxic and expensive. Bioenhancers can be classified based on their natural origin as well as based on the various mechanisms elicited by them when in combination with drugs to improve their bioavailability. The various bioenhancers available are piperine, garlic, *Carum carvi*, *Cuminum cyminum*, lysergol, naringin, quercetin, niaziridin, glycyrrhizin, stevia, cow urine distillate ginger. Out of these, *Cuminum cyminum* and niaziridin are the potential bioenhancers of future. Therefore, the need of the hour is to carry out extensive research on these bioenhancers so that they could be utilised in the drug formulations.

Keywords: Bioenhancers, Classification, Piperine, *Cuminum cyminum.*

1. Introduction

Plant based medicines are used by a majority of the world's population. Our Ayurvedic texts have a mention of thousands of herbal drugs for various diseases including the rare ones. Almost 25% of modern pharmacopoeias too contain drugs of plant origin [1].

Many synthetic and herbal drugs suffer from the problem of low bioavailability. Bioavailability is the rate and extent to which a substance enters systemic circulation and becomes available at the required site of action [2].

Maximum bioavailability is attained by drugs administered via intravenous route, whereas drugs administered orally are poorly bioavailable as they readily undergo first pass metabolism and incomplete absorption. Such unutilized drug in the body may lead to adverse effects and also drug resistance. Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs/molecules enhance their 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 [3.4].

Bioenhancers should have novel properties such as:

- Nontoxic to humans or animals,
- Should be effective at a very low concentration in a combination,
- Should be easy to formulate, and
- Most importantly, enhance uptake/absorption and activity of the drug molecules [5].

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.

1.1 Drug Absorption Barriers

The drug must cross the epithelial barrier of the intestinal mucosa for its transportation from the lumen of the gut into the systemic circulation and exert its biological actions. There are many anatomical and biological barriers for the oral drug delivery system to penetrate the epithelial membrane [6, 7]. There are many structures in the intestinal epithelium which act as barriers to the transfer of drugs from the gastrointestinal track to the systemic circulation. The membranes around cells are lipid bilayers containing proteins such as receptors and carrier molecules.

Drugs cross the lipid membrane by passive diffusion or carrier-mediated transport which involves the spending of energy. For the passage of small water-soluble molecules such as ethanol there are aqueous channels within the proteins. The drug molecules larger than about 0.4 nm face difficulty in passing through these aqueous channels [6].

Drug efflux pumps like Pgp have been proven to have a very important role in inhibiting efficient drug entry into the systemic circulation [8]. P-gp is a type of ATPase and an energy dependent transmembrane drug efflux pump it belongs to members of ABC transporters. It has a molecular weight of -170 kDa and has 1280 amino acid residues [9]. A lot of bioenhancers work by inhibiting this efflux pump.

2. 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. By enhancing the absorption of orally administered drugs from gastrointestinal tract by increase in blood supply.
2. By 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 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 [10].

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 [11].

3. Hurdles with Bioenhancers

Although bio-enhancers in drug delivery have been successful, not all approaches have met with the same success.

New bio-enhancers being developed come with challenges which have to be surmounted. One of the challenges is to improve on properties of drug formulations such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site-specific targeting.

Another challenge of research and development of herbal bioenhancers is large scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. The challenges of scaling up include low concentration of nanomaterials, agglomeration and the chemistry process; it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale.

Advances in herbal bio-enhancers also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products [11].

Classification of Bioenhancers

The use of bioenhancers is familiar concept in Ayurveda as 'Yogavahi' which was used to enhance bioavailability, tissue distribution and efficacy of drugs especially those with poor availability. One such example is 'trikatu' which is a mixture of *Piper longum* (long pepper), *Piper nigrum* (black pepper) and *Zingiber officinale* (ginger).

Bose, in 1929, first reported the application of bioenhancer long pepper to increase the antiasthmatic effect of vasaka [12,13].

Bioenhancers can be classified based on origin and mechanism of action (Table 1 and 2).

Table 1: Classification of Bioenhancers Based on Origin

PLANT ORIGIN		ANIMAL ORIGIN
Niaziridin	Capsaicin	Cow urine distillate (*Kamdhenu ark*)
Cuminum cyminum	Quercetin	
Carum carvi	Curcumin	
Stevia	Naringin	
Lysergol	Capmul	
Glycyrrhizin	Peppermint oil	
Ginger	Gallic acid	
Allicin	Ellagic acid	
Aloe vera	Ferulic acid	
Simomenine		
Genistein		
5'-methoxy hydnocarpin		
Ammannia multiflora		

Table 2: Classification of Bioenhancers Based on Mechanism of Action

• **Inhibitors of P-gp efflux pump and other efflux pumps:** Examples: *Carum carvi* (Caraway), Genistein, Sinomenine, *Cuminum cyminum* (Black cumin), Naringin, Quercetin
• **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), Glycyrrhizin (Liquorice)

A detailed description of some of the bioenhancers based on the above classification system is as follows:

4.1 Piperine

Piperine (1-piperoyl piperidine) is an amide alkaloid found in plants of Piperaceae family like *Piper longum* (long pepper), *Piper nigrum* (blackpepper). 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 from 450 to 200mg [14]. In human medicine piperine is approved to be combined with antitubercular drugs. Piperine also showed enhanced bioavailability when combined with Nevirapine, a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase which is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.[15] 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.[16]Several animal studies on piperine have shown promising results in bioenhancing capacity of piperine for various drugs [13, 17, 18].

4.2 Turmeric

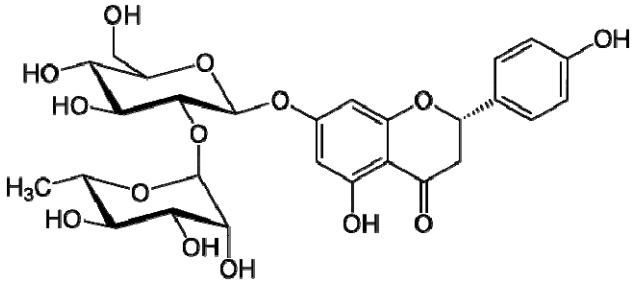
Turmeric (Curcuma longa) is a common household item used as remedy for various ailments. Curcumin, a flavonoid from turmeric suppresses drug metabolizing enzymes like CYP3A4 in liver and is also capable of inducing change in drug transporter P-gp and thus increased the bioavailability of celiprolol and midazolam in rats [19]. The bioenhancer nature of curcumin is similar to piperine [13]. Curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues [20]. It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs.

4.3 Allicin

It is an allyl sulphur compound obtained from garlic (*Allium sativum*).Allicin 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 *S. cerevisiae* [11].

4.4 Naringin [5, 10, 21]

Naringin is the major flavonoid glycoside found in grapefruit, apples, onions and tea.



4.4.1 Naringin

It exhibits pharmacological actions like anti-oxidant, anti-ulcer, anti-allergic and blood lipid lowering. Naringin is capable of inhibiting intestinal CYP3A4, CYP3A1, CYP3A2, P-gp and thus acts as a bioenhancer. Pretreatment with oral ingestion of naringin @ 3.3 and 10mg/kg improves the AUC for intravenous paclitaxel (3 mg/kg) in a dose dependent manner [21]. Naringin at 3.3-10 mg/kg body weight dose enhances the bioavailability of paclitaxel. Other drugs bioenhanced are diltiazem, verapamil, saquinavir and cyclosporine A.

4.5 Quercetin [5, 10, 21]

Quercetin is a flavonoid; an aglycone form of a number of other flavonoid glycosides found in citrus fruits. It exhibits anti-oxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic activities. It works by inhibiting CYP3A4 and P-gp efflux pump. Quercetin has been shown to increase bioavailability, blood levels

and efficacy of a number of drugs including diltiazem, digoxin, verapamil, etoposide, and paclitaxel.

4.6 Genistein [5, 10, 21]

Genistein is a phytoestrogen belongs to the isoflavone class of flavonoids found in a number of dietary plants like soyabean (*Glycine max*) and kudzu (*Pueraria lobata*). It is a P-gp and BCRP efflux pump inhibitor. The presence of genistein (10 mg/kg) causes an increase in AUC by 54.7% and a decrease in total plasma clearance by 35.2% after oral administration of paclitaxel at dose of 30 mg/kg.

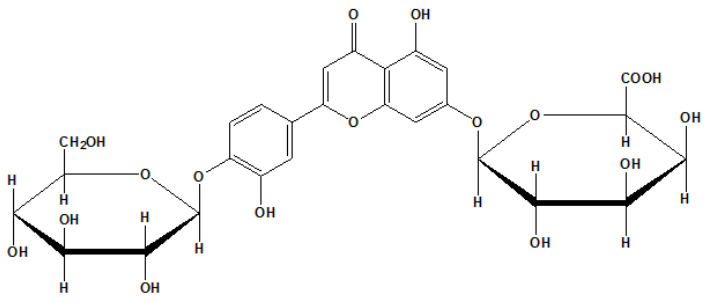
4.7 Caraway [22]

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 anti-biotics (Cefdinir – 89% and Cloxacillin – 100%), anti-fungal (Amphotericin B – 78%), anti-viral (Zidovudine – 92%) and anti-cancer (5-fluorouracil – 90%) drugs at the dose of 1-55 mg/kg body weight.

4.8 Black cumin [23, 24]

Black cumin (*Cuminum cyminum*) is a carminative, estrogenic, anti-nociceptive, anti-inflammatory, anti-oxidant and anti-microbial. The Bioenhancer chemical constituent present in cumin is 3', 5-dihydroxyflavone-7-O-β-D-galactouronide-4'-β-O-D-glucopyranoside.



3',5-dihydroxyflavone-7-O-β-D-galactouronide-4'-β-O-D-glucopyranoside

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%.

Sachin *et al*. studied the enhancement of rifampicin levels in rat plasma by 3', 5-dihydroxyflavone-7-O-β-D-galactouronide-4'-β-O-D-glucopyranoside. The results obtained revealed that the C_{max} of rifampicin was enhanced by 35% and the AUC was enhanced by 53%.[25]

Apart from the above bioenhancing effects, black cumin also enhances the bioavailability of anti-biotics (Cefadroxil – 90% and Cloxacillin – 94%), anti-fungal (Fluconazole – 170%), anti-viral (Zidovudine – 330%) and anti-cancer (5-fluorouracil – 335%) drugs.

4.9 Drumstick pods[26]

It contains niaziridin, a nitrile glycoside which is a powerful bioenhancer. It regulates GIT functions to facilitate better absorption. It enhances the bioavailability of rifampicin by 38.8 folds at 1.0 μg/ml. It also enhances the bioavailability of Clotrimazole by 5-6 folds.

An *in-vitro* study of active fraction of *M. oleifera pods* against *Mycobacterium tuberculosis* (H37Ra) exhibited no anti-tuberculosis activity at the concentration at which it enhanced the anti-tubercular activity of rifampicin [27].

Khanuja *et al*. performed a pre-clinical study to evaluate the influence of *M. oleifera* (MoAF) on pharmacokinetic disposition of rifampicin using HPLC-PDA method.[26] They orally administered to Swiss albino mice a dose of 20 mg/kg body weight of rifampicin alongwith a dose of 0.1 mg/kg body weight of the active fraction of *M. oleifera* (*viz*. Niaziridin). They observed the bioavailability pattern shown in the following figure thereby proving the success of Niaziridin as an effective bioenhancer for rifampicin [27].

4.10 Morning glory plant [10]

It is a source of lysergol that enhances the bioavailability of rifampicin by 4.5-6 folds at 0.2 μg/ml concentration. It also enhances the bioavailability of antibiotics in the range of 2-12 folds. It's mechanism of bioenhancer action is not yet clearly known.

4.11 Liquorice [28]

Liquorice consists of dried, peeled or unpeeled, root and stolon of *Glycyrrhiza glabra* and exhibits anti-hepatotoxic, anti-fertility, anti-inflammatory, expectorant and anti-oxidant activity. It contains glycyrrhizin which enhances the bioavailability of rifampicin by 6.5 fold at the concentration of 1 μg/ml. It also enhances the bioavailability of taxol by 5 fold at the concentration

of 1 μg/ml.

4.12 Ginger [29]

It contains Gingerol which facilitates better absorption by regulating GI tract function.

The effective dose of the bioenhancer extract is in the range of 10-30 mg/kg body weight.

It enhances the bioavailability of rifampicin by 65% and ethionamide by 56%. It also enhances the bioavailability of antibiotics (Azithromycin – 78%), anti-fungal (Ketoconazole – 125%), anti-viral (Zidovudine – 105%) and anti-cancer (5-fluorouracil – 110%) drugs.

4.13 *Stevia* (Honey leaf) [30]

Stevia is anti-hypertensive agent and also promotes insulin secretion. The bioenhancing chemical constituent present in *Stevia* is stevioside.

Though the mechanism of action is not known, it enhances the bioavailability of anti-tubercular, anti-leprotic, anti-cancer, anti-fungal and anti-viral drugs.

The effective dose of the bioenhancer extract is in the range of 0.01-50 mg/kg body weight.

4.14 Peppermint oil [31]

Peppermint oil significantly improves the oral bioavailability of cyclosporine. Co-administration of 100 mg/kg peppermint oil almost tripled the C_{max} and AUC of cyclosporine. It exerts its mechanism of action probably by CYP3A inhibition.

4.15 *Aloe vera* [32]

Aloe is an important source of phytochemicals and increases the absorption of vitamins C and E.

4.16 *Sinomenium acutum*

Sinomenine is an alkaloid extracted from *Sinomenium acutum* [33]. It is found to increase the bioavailability of paeoniflorin by inhibition of P-gp efflux pumps. Paeoniflorin is used in the treatment of inflammation and arthritic conditions but has a poor absorption rate and thus a very low bioavailability (3 – 4%) when administered orally [34].

4.17 Gallic acid

Gallic acid exerts a synergistic effect when administered with piperine and provides a more pronounced therapeutic potential in reducing beryllium-induced hepatorenal dysfunction and oxidative stress consequences [35].

Gallic acid esters like propyl gallate, octyl gallate, aluryl gallate etc. have been found to enhance bioavailability of several drugs like nifedipine [36].

4.18 Capsaicin

It is an active component of *Capsicum annum* and other chilli species. It enhances the bioavailability of theophylline [37].

4.19 Capmul

Capmul MCM C10, a glyceryl monocaprate, is produced from edible fats and oils. In a study in rats, antibiotic ceftriaxone when given concomitantly with capmul, increased the bioavailability of ceftriaxone by 80% [38].

4.20 *Ammoniac multiflora*

The methanolic extract of *Ammannia multiflora* (Lythraceae) showed significant bioenhancing activity with the antibiotic nalidixic acid. *A. multiflora* contains a novel compound ammonia along with other compounds. The methanolic extract of *Ammannia multiflora* bioenhancing activity in combination with nalidixic acid against the two strains, CA8000 and DH5a of Escherichia coli [39].

4.21 Cow urine distillate: (Kamdhenu ark) [40]

Cow urine distillate is more effective as a bioenhancer than cow urine. It enhances the transport of antibiotics like rifampicin, tetracycline and ampicillin across the gut wall by 2-7 folds [40]. It also enhances the potency of taxol against MCF-7 cell lines [41]. It enhances the bioavailability of rifampicin by 80 fold in 0.05 μg/ml concentration, ampicillin by 11.6 fold in 0.05 μg/ml concentration and clotrimazole by 5 fold in 0.88 μg/ml concentration. Cow urine also has antitoxic activity against the cadmium chloride toxicity and it can be used as a bioenhancer of zinc [12]. The bioenhancing ability is by facilitating absorption of drugs across the cell membrane.

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