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Review Article

An Overview: Natural Bio-enhancer's in Formulation Development

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ABSTRACT

Bioenhancers are chemical entities that are obtained from synthetic as well as natural sources. They are mainly used in formulation development to enhance the bioavailability of poorly solubilized drug molecule. The ideal characteristic of bioenhancers includes inertness, nontoxic, cost effective and decrease the dose of active constituents. There are lots of natural bioenhancers available such as piperine quercetin niaziridin, genistein, glycyrrhizin, curcumin. The review focus on plant based bioenhancers and their active principle that produces those effects. There is a need of extensive study on natural bioenhancers which can be utilized in formulation development.

Keywords: bioenhancer, bioavailability, piperine, curcumin

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INTRODUCTION

Drugs that are administered orally go through a dissolution process and then permeation across the gastric membrane before they can appear in the blood stream (1). The amount of drug that goes into the bloodstream from its site of administration is defined as its bioavailability (2). Solubility is defined as the property of a substance to dissolve itself into a solid, liquid or a gaseous solvent to form a homogeneous solution of it. Solubility of a drug in gastric media is an essential requirement for an orally administered drug to be absorbed adequately (3). The majority of factors that affect the bioavailability of a drug other than solubility and permeability include the dissolution rate of the drug, first-pass effect, pre-systemic metabolism of the drug in any other organ and susceptibility to efflux mechanisms(4). Solubility in the gastric media is a major problem associated with orally administered drugs that leads to erratic bioavailability and possible toxicity in the living system; making solubility of new drug molecules one of the crucial challenges for formulation scientists(3). In spite of these issues, the oral route of drug administration has been the most sought after route due to its ease of administration, high patient compliance, cost-effectiveness, least need for maintenance of sterile conditions, and flexibility in design of the dosage form(5).

The use of bio enhancers is a promising approach to overcome the issues related to bioavailability. A bioenhancer

enhances the bioavailability of a drug molecule without causing any pharmacological activity of its own(6). Bio enhancers of herbal origin have gained interest recently and many herbal compounds including quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside have proved their efficacy in increasing the bioavailability of the drugs with which they are combined(7).

BARRIERS TO DRUG ABSORPTION

For a drug to exert its biological actions, it is essential for it to reach to the systemic circulation (7). However, the drug has to cross various biological barriers before it reaches to the bloodstream. The epithelium of intestine consists of several physiological barriers to the absorption of drug. Solubility and permeability of a drug are important barriers to its absorption(8). The aqueous layer present on the intestinal epithelium serves as a crucial barrier for the absorption of drugs due to their hydrophilic nature (9). Generally, drugs with size more than 0.4 nm seldom pass through the aqueous channels(7). Results from recent investigations have also revealed that P-glycoprotein, a type of energy dependent efflux pump plays important roles in preventing the entry of drug into systemic circulation(10). The presence of both Cytochrome P450 (CYP) 3A and P-glycoprotein and their combined action on the enterocytes is also assumed to be a limiting factor in oral drug absorption (11). Importantly, the inhibition of these

proteins have shown enhanced bioavailability of drug in clinical studies (12). Moreover, the thick cytoplasm of the cells responsible for the absorption is also acts as a potential barrier to the transfer of drug from the site of absorption to the systemic circulation (9).

BIOENHANCERS

A herbal bioenhancer is an agent of herbal origin that has the capability to enhance that bioavailability of a drug with which it is combined, without causing any pharmacological activity of its own (13). Adding a bioenhancer to a drug helps to reduce drug dosage, drug cost, incidences of drug resistance and risks of adverse drug reaction. Most importantly, a bioenhancer improves the efficacy of a drug by enhancing its bioavailability. In addition, adding a bioenhancer also reduces raw material requirement during pharmaceutical manufacturing (14). Major categories of drugs that have shown increased bioenhancement include the drugs acting on cardiovascular system (CVS), respiratory system, central nervous system (CNS), gastrointestinal tract (GIT), antibiotics and anticancer agents. Some examples where addition of bioenhancers have significantly improved the drug efficacy include tetracyclines, sulfadiazine, vasicine, rifampicin, isoniazid, pyrazinamide, ethambutol, phenytoin, phenobarbitone, carbamazepine, nimesulide, indomethacin beta-carotene, coenzyme Q10 (CoQ10), ciprofloxacin, curcumin, dapson, amino acids, glucose and several other classes of drugs (6).

MECHANISM OF BIOENHANCER ACTION

Bioenhancers are known to act through several mechanisms of action. Generally a bioenhancer increases the bioavailability of the accompanied drug by acting on gastrointestinal tract to enhance its absorption or by acting on drug metabolism process either by inhibiting or reducing the rate of biotransformation of drugs in the liver or intestines. A bioenhancer may also additionally modify the signaling processes between host and pathogen by increasing the accessibility of the drugs to the pathogens or by inhibiting the active transporters located in various locations such as 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 efflux mechanisms that are frequently observed in case of antimalarials, anticancers and antimicrobials (15). In a study carried out on a natural bioenhancer molecule, Piperine, to evaluate the bioenhancer mediated changes in the permeability of rat intestinal epithelial cells, the status of γ -glutamyl transpeptidase activity, uptake of amino acids, and lipid peroxidation, piperine (25–100 M) significantly stimulated γ -glutamyl transpeptidase activity, enhanced the uptake of radiolabelled l-leucine, l-isoleucine, and l-valine, and increased lipid peroxidation in freshly isolated epithelial cells of rat jejunum. In the presence of benzyl alcohol, an enhanced γ -glutamyl transpeptidase activity due to piperine was maintained. These results suggested that piperine may interact with the lipid environment to produce effects which lead to increased permeability of the intestinal cells (13).

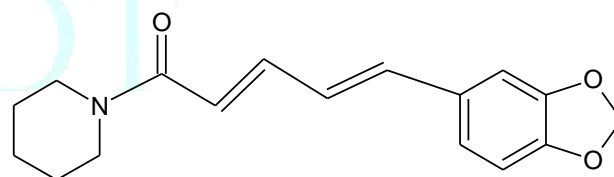
A bioenhancer may also act by decreasing the elimination process in the body thereby extending the residence time of drug in the body or by inhibiting the drug metabolizing enzymes like CYP 3A4, CYP1A1, CYP1B2, CYP2E1, in the liver, gut, lungs, and various other locations. Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibiting P-gp and facilitating passive tubular reabsorption can also be an employed mechanism of a bioenhancer molecule (16, 17).

NATURAL BIOENHANCERS

Natural bioenhancers of both plant and animal origins such as piperine, quercetin, genistein, naringin, sinomenine, glycyrrhizin, curcumin, lysergol, allicin, niiaziridinetc. have been investigated and reported to possess bioenhancer activities. Several mechanisms of actions for the bioavailability enhancement of these bioenhancers have been proposed including, but not limited to, modification of acid secretion and blood supply to the GIT, modification of bile acid secretion, modification of gastric emptying time, GIT motility and transit, modification of GIT membrane permeability, inhibition of drug metabolizing enzymes (DMEs) in gut wall and liver, stimulation of specific enzymes and/or transporters, etc. However, predominant mechanisms of action of these bioenhancers are enhancing the absorption by increased blood supply of the GIT and reducing biotransformation and efflux by modulation of DMEs and efflux drug transporters (EDTs) respectively (18). Some of the natural bioenhancers that are employed frequently in pharmaceutical manufacturing are discussed in this review.

Piperine

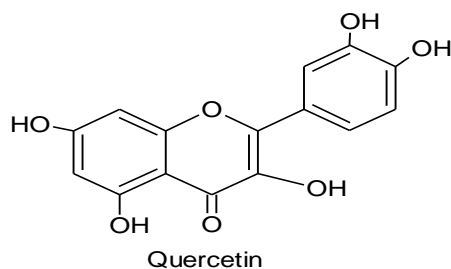
Piperine is the most intensively investigated bioenhancer. It is an alkaloid obtained from black and long peppers (*P. nigrum* Linn and *P. longum* Linn). Piperine has been reported to enhance the bioavailability of various drugs and nutraceuticals. Piperine act is through multiple mechanisms including the inhibition of DMEs, EDTs, stimulation of gut amino acid transporters, increased intestinal glucuronic acid secretion etc. Piperine is found to inhibit DMEs that include arylhydrocarbon hydroxylase (AHH), uridine diphosphate-glucuronyl transferase (UDP-GT), ethylmorphine-Ndemethylase, 7-ethoxycoumarin-O-deethylase, 3-hydroxy-benzopyrene glucuronidation, UDP-glucose dehydrogenase (UDP-GDH), 5-lipoxygenase, cyclooxygenase-1, and cytochrome P450. Most importantly, piperine inhibits P-gp and CYP3A4 that are expressed in enterocytes of the gut wall and hepatocytes of the liver that contribute to a major extent of pre-systemic elimination of many drugs resulting in poor bioavailability.



Piperine

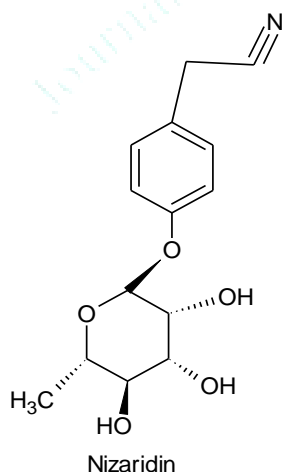
Quercetin

Quercetin is a plant derived flavonoid that is 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, antiatherosclerotic, anticancer, and antiviral effects. Quercetin has been reported to enhance the bioavailability of various drugs including, pioglitazone, diltiazem, digoxin, paclitaxel, tamoxifen, verapamil, etoposide and epigallocatechin-3-gallate (EGCG). Quercetin is an inhibitor of CYP3A4 and a modulator of P-glycoproteins and MDR transporters (13, 16, 18).



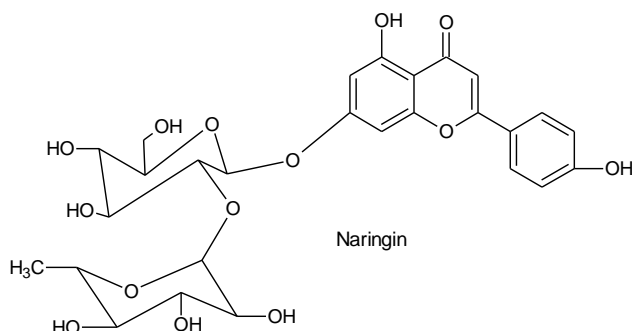
Niaziridin

Niaziridin is reported to enhance the bioavailability of a number of antibiotics. These include rifampicin, ampicillin, tetracycline, nalidixic acid etc. against both gram-ve and gram +ve bacteria. Niaziridin has resulted in enhanced bioavailability of antibiotics against gram-ve bacteria *E. Coli*. Moreover, combining Niaziridin with antibiotics has also increased the spectrum of the latter against various gram+ve bacteria that include *M. smegmatis* and *Bacillus subtilis* most importantly. It is reported to enhance the activity of rifampicin, ampicillin, tetracycline, and nalidixic acids by 1.2–19-fold against the Gram-positive strains and the activity of azole antifungal drugs such as clotrimazole against *Candida albicans* by 5–6-fold. However, the antifungal activity enhancement by Niaziridin is possible at relatively higher concentration (10 µg/mL) of the compound. Niaziridin is also known to facilitate the uptake of nutrients like Vitamin B₁₂ through the intestinal gut membrane in combination (18, 19).



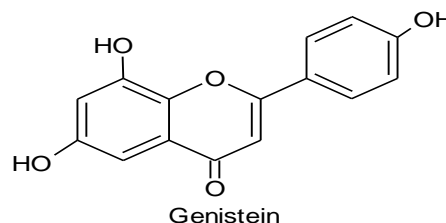
Naringin

Naringin is a flavonoid glycoside isolated mainly from grapefruit, apples, onions and tea. 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. These include diltiazem, verapamil, paclitaxel etc.



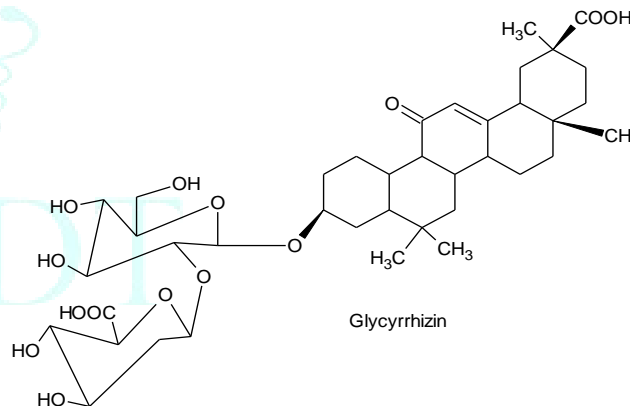
Genistein

Genistein is a phytoestrogen and an isoflavone flavonoid found in dietary plants such as soybean and kudzu (*Glycine max* and *Pueraria lobata*). It exhibits its bioenhancing properties on various drugs including paclitaxel and EGCG through the inhibition of CYP3A, P-gp, MRP2, and BCRP transporters. Although genistein 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.



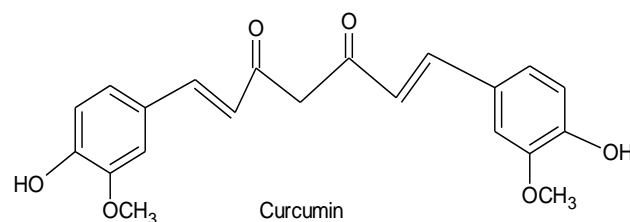
Glycyrrhizin

Glycyrrhizin is a triterpenoid saponin glycoside isolated from liquorice (*Glycyrrhiza galbra L.*). Glycyrrhizin has demonstrated bioenhancing activity when combined with various antimicrobial agents including rifampicin, tetracycline, nalidixic acid, etc. The anticancer activity of Paclitaxel increases manifold when it combines with glycyrrhizin. Glycyrrhizin is also reported to enhance (2 to 6 fold) transport of vitamins B1 and B12 across the gut membrane. 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 (16, 20).



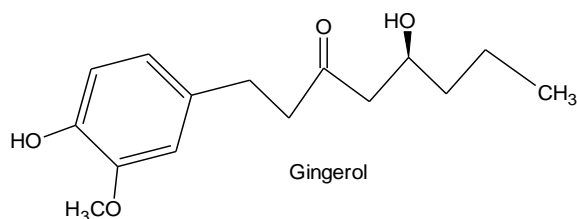
Curcumin

Curcumin is a curcuminoid obtained from turmeric (*Curcuma longa*). 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 (13, 21).



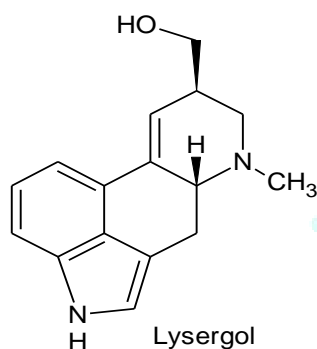
ZingiberOfficinale(Ginger)

One of the most useful dietary ingredients, a spice common in Indian Kitchen Zingiber officinalis (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 as fluoroquinolones, penicillins, cephalosporins; antifungals such as fluconazole, ketoconazole, acyclovir, zidovudine; anticancer drugs such as methotrexate, 5- fluorouracil; cardiovascular drugs such as amlodipine, lisinopril and anti-histaminic salbutamol(22, 23).



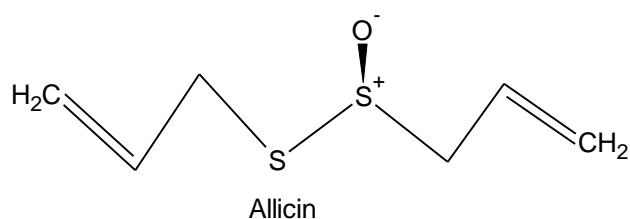
Lysergol

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*, *M. smegmatis* and other similar microbes. In another study, lysergol improved the bioavailability of berberine after oral administration in Sprague-Dawley rats (13, 24).



Allicin

Allicin is an allyl sulphur compound obtained from garlic (*Allium sativum*). Allicin is reported to be an enhancer of the fungicidal activity of Amphotericin B against pathogenic fungi including *Candida albicans*, *Aspergillusumigatus* and yeast *Saccharomyces cerevisiae*. Allicin enhances Amphotericin B induced vacuole membrane damage by inhibiting ergosterol accumulation from the plasma membrane to the vacuole membrane(16, 23, 25).



Aloevera (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, concomitant use of *Aloe vera* and pantoprazole for the gastroesophageal reflux symptoms in mustard gas victims were found to be improved compared to single treatments. (26).

DISCUSSION AND CONCLUSION

The origin of bioenhancers is based on traditional system of Indian medicine. The earliest use of bioenhancers is mentioned in Charaka, Sushruta and other apothecaries in traditional system of medicine. The concept of bioenhancement is useful in curbing the rising drug cost, toxicity, and other adverse effects, and thus may ultimately have a positive influence on the national economy. It satisfies all necessary criteria to be considered as an ideal drug excipient. It is safe, effective, economical, easily procured, non-addictive, and has a widely-based effect on several classes of drug. Hence, it has been proved that novel drug delivery system of herbal as well as of chemical origin can be used to increase the bioavailability of the compounds or their respective constituents (in case of herbal extracts).

Medicinal plants with bioenhancing potentials require extensive exploration to improve the current approaches of drug delivery. Bioenhancers are efficient tools that to reduce the dose of the drugs as well as and the duration of the treatment which is especially important for economic outcomes and health outcomes in humans. Bioenhancers also attenuate the drug resistance or related adverse reactions which are of prime importance in case of cancer treatment. Eventhough, the major known herbal bioenhancers are discussed in this review, various phytoactive compounds and plant extracts are further required yet to be exploited with their mechanism of action and complex drug interactions.

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