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Exploring natural bioenhancers to enhancing bioavailability: An Overview

Arpita Singh*, Bimal Kumar Verma and Swarnima Pandey

Department of Pharmacy, Goel Institute of Pharmacy and Sciences, Lucknow (U.P.) - India

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Abstract

Bioenhancers are such agents, which by themselves are not therapeutic entities but when combined with an active drug lead to the potentiation of the pharmacologic effect of the drug. Such formulations have been found to increase the bioavailability / bioefficacy of a number of drugs even when reduced doses of drugs are present in such formulations. Evidence have been obtained for such classes of drugs which are (a) poorly bioavailable and/or efficacious, (b) require prolonged therapy, and (c) are highly toxic and expensive. These are phytomolecules development of which is based on ancient knowledge of Ayurveda. They augment the bioavailability or biological activity of drugs when administered at low doses. They reduce the dose; shorten the treatment period thus reducing drug-resistance problems. The treatment is made cost effective, minimizing drug toxicity and adverse reactions.

When used in combination with number of drug classes such as antibiotics, antituberculosis, antiviral, antifungal and anticancerous drugs they are quite effective. Oral absorption of vitamins, minerals, herbal extracts, amino acids and other nutrients are improved by them. They act through several mechanisms which may affect mainly absorption process, drug metabolism or action on drug-target.

Key words: Bioenhancers, Bioavailability, Ayurveda, Herbal plants

Introduction

Plant based medicines is used by about 60% of the world population and most of the third world countries still depend on herbal medicines. Almost 25% drugs in the modern pharmacopoeias too contain drugs of plant origin [1, 2]. Advances in drug design technologies have lead to a large no of drug gable compounds being introduced. But many of these molecules have suffered due to low bioavailability upon oral administration due to poor permeation across the gastrointestinal epithelia [3], inspite of possessing potential therapeutic effects. Low lipophilicity and zwitterionic character at physiological pH [4] poor water solubility or efflux by P-glycoprotein (P-gp) [5] probably are the reasons for the drugs having low membrane permeability. Therefore, improving oral drug absorption and bioavailability of drugs is a major issue with the pharmaceutical industries and a number of approaches to enhance the intestinal absorption of drugs have been taken up [6] which include the use of absorption enhancers, prodrugs and permeability enhancing dosage forms such as liposomes and emulsions. The application of P-gp inhibitors in improving peroral drug delivery has been of special interest to the scientists [7]. In ayurveda the concept of bioenhancers is being used since centuries and is called "Yogvahi" e.g. is the use of "Trikatu". Black pepper is supporting evidence where piperine was one of the ingredients as "*Yogvahi"* [8, 9]. They were prescribed routinely for a variety of diseases as part of multidrug formulations [10].

***Corresponding Author**
E.mail: arpitmohan2010@gmail.com

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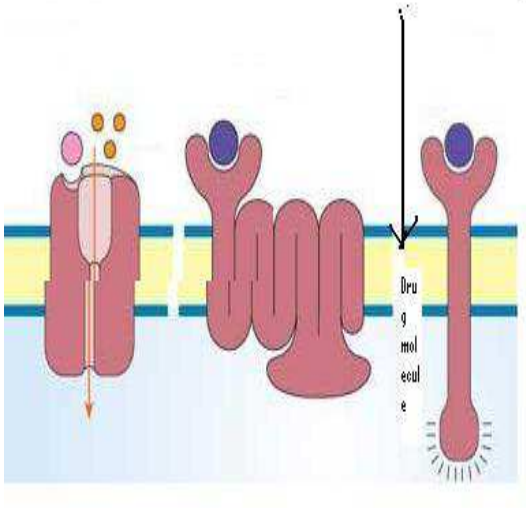
Bioavailability and absorption enhancement through co-administration of drugs with naturally occurring compounds from plants are considered to be very simple and relatively safe. They increase the bioavailability and absorption of the co-administered drugs. Uses of bioenhancers are also applicable in veterinary practice since bioavailability of drugs and nutrients is of equal relevance to animals as to humans [11].

Drug absorption barriers

The drug must cross the epithelial barrier of the intestinal mucosa for it to be transported 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 epitheial membrane [12, 13]. There are many structures in the intestinal epithelium which serve as barriers to the transfer of drugs from the gastrointestinal track to the systemic circulation. An aqueous stagnant layer due its hydrophilic nature is potential barrier to the absorption of drugs. 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 [13].



Recent work has shown that drug efflux pumps like Pgp possess very important role inhibiting efficient drug entry into the systemic circulation [14]. P-gp is a type of ATPase and an energy dependent trans membrane drug efflux pump it belongs to members of ABC transporters. It has a molecular weight of -170 kDa and has 1280 amino acid residues [15]. Since P-gp is gaining importance in absorption enhancement much work has still been made about its modulation due to its substrate selectivity and distribution at the site of drug absorption.

Methods in use for enhancement of absorption of orally administered drugs

There have been many approaches in use to enhance the intestinal absorption of poorly absorbed drugs. These approaches are as follows:

Absorption Enhancers

Many of the absorption enhancers are effective in improving the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers [16, 17]. Chitosan, particularly trimethylated chitosan, increases the drug absorption via paracellular route by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions. Bile, bile salts and fatty acids are surfactants which act as absorption enhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Calcium chelators such as EGTA and EDTA enhances absorption by reducing the extracellular calcium concentration, leading to the disruption of cell-cell contacts [18].

Prodrugs

To enhance the drug absorption and bioavailability chemical modification of drugs to produce prodrugs and more permeable analogues has been widely studied as a useful approach. Various ampicillin derivatives are one of the well-known examples of increasing the lipophilicity of agents to enhance absorption of a polar drug by prodrug strategy [19]. Ampicillin due to its hydrophilic nature is only 30 - 40% absorbed from the gastrointestinal tract. By esterification of carboxyl group of ampicillin the produgs of ampicillin such as pivampicilline, bacampicilln and talampicillin were synthesized These produgs were more lipophilic than the parent compound

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following oral administration and they showed higher bioavailability in comparison with ampicillin.

Dosage Form and Other Pharmaceutical Approaches

Utilization of permeability-enhancing dosage forms is one of the most practical approaches to improve the intestinal absorption of poorly absorbed drugs. Various dosage formulations such as liposomes [20] and emulsions [21] enhanced the intestinal absorption of insoluble drugs. Particle size reduction such as micronization, nanoparticular carriers, complexation and liquid crystalline phases also maximize drug absorption [22, 23].

P-glycoprotein Inhibitors

The application of P-gp inhibitors in improving peroral drug delivery has gained special interest. Several studies to enhance oral bioavailability have demonstrated the possible use of P-gp inhibitors that reverse P-gp-mediated efflux in an attempt to improve the efficiency of drug transport across the epithelia. P-gp inhibitors influences metabolism, absorption, distribution, and elimination of P-gp substrates in the process of modulating pharmacokinetics [24].

Mechanisms of Action of Herbal Bioenhancers

There are several mechanisms of action by which herbal bioenhancers act. Different herbal bioenhancers may have same or different mechanism of action. Nutritional bioenhancers enhance absorption by acting on gastrointestinal tract. Antimicrobial bioenhancers mostly act on drug metabolism process. Among the various mechanisms of action postulated for herbal bioenhancers some are as follows: (a) Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply [25], (b) Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility [25, 26], (c) Modifications in GIT epithelial cell membrane permeability [27, 28], (d) Cholagogous effect [27], (e) Bioenergetics and thermogenic properties [27, 29] (f) Suppression of first pass metabolism and inhibition of drug metabolizing enzymes. [30-32] and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids [33].

Medicinal plants and their compounds as drug bioavailability enhancer Piperine

Piperine (1-piperoyl piperidine) is a pioneer alkaloidal component of *Piper nigrum* Linn. or *Piper longum* Linn. Piperine, or mixtures containing piperine, increases the bioavailability, blood levels and efficacy of a number of drugs including ingredients of vasaka leaves, vasicine, sparteine, rifampicin, phenytoin, sulfadiazine and propranolol [34,35,36].

Ginger

Ginger (*Zingiber officinale*)has a powerful effect on GIT mucous membrane. It regulates the intestinal function to facilitate absorption. Ginger is used in the range of 10-30 mg/kg body weight as bioenhancer. The bioavailability of different antibiotics like Azithromycin (85%), Erythromycin (105%), Cephalexin (85%), Cefadroxil (65%), Amoxycillin (90%) and Cloxacillin (90%) are increased by it [37].

Drumstick Pods (*Moringa oleifera*)

Niaziridin a nitrile glycoside is isolated from the pods of Moringa oleifera which enhances bioactivity of commonly used antibiotics against gram-positive bacteria like Myobacterium smegmatis, Bacillus subtilis and gram-negative bacteria like Escherichia coli. It enhances activity of rifampicin, ampicillin, nalidixic acid by 1.2 - 19 folds against the gram-positive strains [22], also enhances the activity of azole antifungal drugs such as clotrimazole against Candida albicans by 5 - 6 folds. Increases the absorption of Vitamin B12 [38].

Liquorice *(Glycyrrhiza glabra)*

Bioenhancing activity of liquorice is due to its active component Glycyrrhizin. It enhances cell division inhibitory activity of anticancerous drug `Taxol` by 5 folds against the growth and multiplication of breast cancer cell line. Inhibition of cancerous cell growth by Taxol in presence of glycyrrhizin was higher than treatment with taxol alone [39]. It is reported that glycyrrhizin enchances the transport of antibiotics like rifampicin, tetracycline, nalidixic acid, ampicillin and vitamins B1 and B12 across the gut membrane [39]. At the same concentration Glycyrrhizin shows a more potent absorption enhancing activity than caproic acid [40].

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Absorption enhancing activity obtained from the simultaneous treatment of sodium deoxycholate and dipotassium-glycyyrihizin was much greater than sodium deoxycholate alone in Caco-2 cell monolayers [41].

Black cumin *(Cuminum cyminum)*

Bioactive fraction of Cuminum cyminum enhances the bioavailability of Erythromycin, Cephalexin, Amoxycillin, Fluconazole, Ketoconazole, Zidovudine and 5-Fluorouracil (42). The doses responsible for the bioavailability enhancement activity ranged from 0.5 to 25 mg/kg body weight. It in itself is an effective gastric stimulant, carminative and anthelmintic. It has been used therapeutically as an anti-diarrheal, galactagogue, diuretic and also beneficial in hoarseness of voice [43]. Bioavailability/bioefficacy activity of Cuminum cyminum was attributed to various volatile oils, luteolin and other flavonoids. Luteolin especially has been demonstrated to be a potent P-gp inhibitor in literature [44]. Cumin/Caraway (Carum carvi) seeds enhance the bioavailability of antibiotics, antifungal, antiviral and anticancerous drugs. The effective dose for the Carum carvi bioactive fraction as bioenhancer is in the range of 1-55 mg/kg body weight. They have carminative, mild stomachic, aromatic and diuretic actions. It shows greater bioenhancing effect when used in combination with bioenhancer from Zingiber officinale and piperine [54, 55].

Garlic *(Allium sativum)*

Allicin, the active bioenhancer phytomolecule in garlic 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 [45].

Quercetin

Quercetin is shown to increase bioavailability, blood levels and efficacy of a number of drugs including dilitazem, digoxin and epigallocatechin gallate. It was found that increased amount of quercetin administered along with epigallocatechin gallate increased absorption of epigallocatechin gallate from the intestine.

Morning glory plant *(Ipomoea spp.)*

Lysergol, a phytomolecule, is isolated from higher plants like Rivea corymbosa, Ipomoea violacea and Ipomoea muricata. It enhances the killing activities of different antibiotics on bacteria and is a promising herbal bioenhancer [46].

Indian Aloe (Aloe vera)

The results of two different Aloe vera preparations i.e. whole leaf extract and inner filled gel indicate that the aloes improve the absorption of both the vitamin C and E. The absorption is slower and vitamins last longer in the plasma with aloes, this increases bioavailability of Vitamin C and E in human [47]. Aloe vera is a very promising future nutritional herbal bioenhancer.

Genistein

Genistein is reported to be able to inhibit P-gp, BCRP and MRP-22 efflux function. When co-administered with Genistein the intestional absorption of paclitaxel, a substrate for efflux transports such as P-gp [48] and MRP2 [49] was dramatically increased.

Sinomenium acutum

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 [50]. Co-administrated sinomenine an alkaloid extracted from *Sinomenium acutum* Thunb.) [51], dramatically altered the pharmacokinetic behaviors of paeoniflorin in rats [52]. The mechanism underlying the increase in bioavailability of paeoniflorin is explained as sinomenine could decrease the efflux transport of paeoniflorin by P-gp in the small intestine [53].

Recent Advances of bioenhancers

Atal et al worked on biochemical basis of enhanced drug bioavailability by piperine. The study was aimed at understanding the interaction of piperine with enzymatic drug biotransforming reactions in hepatic tissue. They found that piperine shows little discrimination between different cytochrome P-450 forms and is a non-specific inhibitor of drug metabolism. Piperine strongly inhibited the hepatic AHH and UDP-glucuronyltransferase activities when orally administered to rats. The results of the experiment demonstrated that piperine is a potent inhibitor of

drug metabolism [56]. Singh et al reviewed the Indian Herbal Bioenhancers . They found Piperine in both Long Pepper and Black Pepper as the potent bioenhancer. Rifampicin transcription activity is augmented several fold by piperine against M*ycobacterium smegmatis.* Even at higher concentration of 50 microgram/ml, piperine alone shows no inhibitory effect for the growth of *M. smegmatis* but increases the inhibitory potential of rifampicin when given with it in ratio of 24:1 at the lower concentration of 0.125-0.5 microgram/ml. The binding ability of rifampicin to RNA polymerase is enhanced by piperine [57, 58]. Navin et al reviewed the concept of bioenhancers to reduce treatment costs by increasing the bioavailability of the drug. The Indian scientists discovered and scientifically validated Piperine as the world's first bioavailability enhancer [59]. DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump are the different mechanisms proposed for the bioenhancer activity of piperine. [60, 61, 62]. They found that Piperine is added in a dose of 10mg irrespective of the dose of active combination in all formulations. Their work concluded piperine as a novel bioenhancer because it is effective, safe, economical, non-addictive, easily procured, and has a widely based effect on several classes of drugs [63].

Chanda et al carried the acute and sub-acute toxicity study and chemical characterization of trikatu in Charles Foster rats for safety profiling. Their studies showed that in acute toxicity experiment Trikatu was well tolerated by the animals under study and no significant changes were observed in morbidity, mortality, gross pathology, vital organ weight, gain in weight, haemotological count and other necessary parameters [64]. Karan et al studied the effect of trikatu on the pharmacokinetic profile of indomethacin in rabbits. The results showed that TRIKATU enhanced the absorption of indomethacin which was supposed to be the result of an increase in the gastrointestinal blood flow and an increased rate of transport across gastrointestinal mucosa [65]. Bhat et al carried studies on the metabolism of piperine. They observed that the highest concentration in the stomach and the small intestine was attained at 6hours. Traces of piperine were detected in the spleen, kidney and serum from ½ hour to 24 hour [66]. Singh et al studied the alteration of pharmacokinetics of oxytetracycline following oral administration of *Piper longum* in hens. Their studies revealed that the prior administration of P.*longum* increases total duration of antimicrobial action and enhances the therapeutic efficacy of oxytetracycline in poultry birds. There was reduction in loading and maintenance dose and thus the subsequent side effects [55]. Kang et al studied the bioavailability enhancing activities of natural compounds from medicinal plants. They found Trikatu as an essential ingredient of many ancient prescriptions and formulations and that it played an important role in increasing drug bioavailability when given orally [34]. They concluded that co-administration of natural compounds is one of the promising approaches for increasing bioavailability of drugs [13]. Dama et al worked on the effect of Trikatu pretreatment on the pharmacokinetics of pefloxacin administered orally in mountain Gaddi goats. They found that the trikatu treated animals showed a better penetration of the drug and the trikatu administration enhanced the duration of antimicrobial action by about 22%. There was an enhanced bioavailability due to suppression of drug metabolizing activities and not because of increased absorption [55]. Pattanaik et al. evaluated the effect of simultaneous administration of piperine on plasma concentration of carbamazepine twice daily in epileptic patients undergoing carbamazepine monotherapy. They observed that Piperine could significantly enhance the oral bioavailability of carbamazepine. The mechanism of action was possibly by decreasing the elimination or by increasing its absorption. They concluded that piperine significantly increased the mean plasma Concentrations of carbamazepine in both dose groups [67].

Bhutani et al. investigated antidepressant effect of curcumin with piperine. They concluded that the combination of piperine with curcumin showed quite significantpotentiation of its anti-immobility, neurotransmitter enhancing (serotonin and dopamine) and monoamine oxidase inhibitory effects as compared to curcumin effect [68]. Kulkarni et al. found that there was potentiation of

antidepressant activities when piperine was administered simultaneously with curcumin. This approach was useful in the management of depression [69]. Nirala et al. Evaluated the effect of piperine individually and in combination with tiferron against beryllium induced biochemical alteration and oxidative stress. They found that the combination of tiferron with piperine could reverse all the variables significantly towards the control [70]. Zhao et al. Studies concluded that gallic acid exerts a synergistic effect when administered with piperine . This provided a more pronounced therapeutic potential in reducing beryllium-induced hepatorenal dysfunction and oxidative stress consequences. They observed that individual administration of gallic acid and piperine moderately reversed the altered biochemical variables. On the other hand the combination of these was found to completely reverse the beryllium-induced biochemical alterations and oxidative stress consequences [71]. Kasibhatta et al. studied the Influence of piperine on the pharmacokinetics of nevirapine under fasting conditions. The study was randomized, crossover and placebo controlled. They administered piperine or placebo to healthy adult males for 6 day. On day 7 piperine or placebo was administered with nevirapine. Blood samples were collected post-dose. The results of the study showed that there was an enhanced bioavailability of nevirapine when administered with piperine [72]. Durgaprasad et al. evaluated the effect of oral curcumin (500 mg) with piperine (5 mg) on the pain, and the markers of oxidative stress in patients with tropical pancreatitis for 6 wks. There was a significant reduction in the erythrocyte malonyldialdeyde levels following curcumin therapy in comparison to placebo administration , with a significant increase in glutathione levels [73]. Lambert et al reported that piperine coadministered with (-)-Epigallocatechin-3-gallate to male CF-1 mice increased the plasma C(max) and area under the curve by 1.3-fold compared to mice treated with Epigallocatechin-3-gallate only. The results appeared such due to inhibiting glucuronidation and gastrointestinal transit [74].
Vladimir et al. Studied the relative bioavailability of different doses of coenzyme Q10 simultaneous administered with piperine or placebo in healthy adult male volunteers. The results were studied for single-dose experiment or in separate experiments for 14 and 21 days. When compared with coenzyme Q10 plus placebo the result of single and the 14th day dose study indicated smaller, but no significant increase in plasma concentration. Compared to coenzyme Q10 plus placebo supplementation of higher dose coenzyme Q10 with piperine for 21st days produces a statistically different approximately 30% greater, area under the plasma curve [75]. Vladimir et al., 1999 studied the effect of simultaneous administration of piperine on serum concentration of β-carotene in healthy volunteers for 14-days. The results of the study indicated a significant increase in serum β-carotene concentration when supplemented with piperine in comparison to β-carotene plus placebo, respectively. They found that there was 60% increase in area under curve of β-carotene plus piperine when compared with β -carotene plus placebo [76].

Conclusion

In developing countries like India cost of treatment is the major concern for modern medicines. Systematic innovative means are needed to reduce these costs. New chemical substances with new modes of action are what modern pharmaceutical research is all about. New drug development technologies are concerned about the economics of drug development. Drug discovery process has been highly aided by Ayurveda through reverse pharmacology with new means of identifying active compounds and reduction of drug development cost. The researchs are now aimed at methods of reduction of drug dosage and thus drug treatment cost making treatment available to a wider section of the society including the financially challenged.

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