ORIGINAL RESEARCH PAPER

Pharma

REVIEW ON NATURAL BIOENHANCERS

KEY WORDS:

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1.Introduction:

Modern pharmaceutical research is concerned with all aspects of identifying new chemical substances with new modes of action. Particularly, economics of treatment linked to drug dosage has led to new drug development technologies. As a result, treatments are now becoming more affordable for wide sections of society, including the financially challenged One way to achieve reduction in drug dosage, and therefore drug toxicity and cost, is to increase drug bioavailability.

The infected individuals have to consume more amounts of antibiotics; this may be due to (1) Reduced absorption in gut membrane when taken orally, (2) restrictive uptake by target microbe, and (3) operation of efflux pump leading to indiscriminate extrusion of the antibiotics or therapeutic molecules. So, the major amount of the applied drug is wasted and only a minor amount is being targeted to the site of infection, the unutilized drug/antibiotics amount remains as a load in the body and environment acting as a selection pressure facilitating emergence of drug resistance, ultimately leading to failure of antibiotics against resistant infections, Herbal bioenhancer is an agent of herbal origin or any phytomolecule, which is capable of enhancing bioavailability and bioefficacy of a particular drug or nutrient with which it is combined, without any typical pharmacological activity of its own at the dose used. In the 1920's, Bose, an acknowledged author of "Pharmacographia Indica," reported an enhanced antiasthmatic effect of an Ayurvedic formula containing vasaka (Adhatoda vasica) when administered with long pepper 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) discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979.

The concept of bioenhancers of herbal origin can be tracked back from the ancient knowledge of Ayurveda system of medicine.Use of ayurvedic preparation "Trikatu" from the period between the 7th century 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 component piperine, which enhances the bioavailability of drugs, nutrients, and vitamins.

Bioavailability/Bioefficacy-Enhancing Activity

The term bioavailability or bio enhancing activity is defined as "a substance at a lower dosage level, which in combination with a drug or nutrient provides more availability of the drug by reducing the consumption of the drug or nutrient resulting in enhanced efficacy of the drugs. The great interests for the improvement of bioavailability of a large number of drugs are (1) poorly available, (2) administered for long periods, (3) toxic, and (4) expensive. Maximizing bioavailability is therapeutically important because the extent of bioavailability directly influences plasma concentrations and consequently therapeutic efficacy. Bioavailability enhancement can make the expensive drugs affordable and reduce the toxic effects by reducing the required dose of drugsPoorly bioavailable drugs remain sub therapeutic because a major portion of a dose never reaches the plasma or exerts its pharmacological effect unless and until very large doses are given which may lead to serious side effects. Any significant improvement in bioavailability will result in lowering the dose or the dose frequency of that particular drug. Inter subject variability is particularly of concern for a drug with a narrow safety margin. Incomplete oral bioavailability includes poor dissolution or low aqueous solubility, poor intestinal membrane permeation, degradation of the drug in gastric or intestinal fluids, and presystemic intestinal or hepatic metabolism. Many therapeutic treatments are also accompanied by loss of essential neutraceuticals in the course of therapy. The bioenhancers improve nutritional status by increasing bioavailability/bioefficacy of various neutraceuticals including metals and vitamins

2.Bioavailability enhancement can be done by the following [5].

(a) Promoting the absorption of the drugs from GIT.

(b) Inhibiting or reducing the rate of biotransformation of drugs in the liver or intestines.

(c) Modifying the immune system in such a way that the overall requirement of the drug is reduced substantially.

(d) Increasing the penetration or the entry into the pathogens even where they become persistors within the macrophages such as for Mycobacterium tuberculosis and such others. This eventually ensures the enhanced killing of these organisms is well secured within the places otherwise inaccessible to the active drug.

(e) Inhibiting the capability of pathogens or abnormal tissue to reject the drug, for example, efflux mechanisms frequently encountered with antimalarial, anticancer and antimicrobial drugs.

(f) Modifying the signaling process between host and pathogen ensuring increased accessibility of the drugs to the pathogens.

(g) Enhancing the binding of the drug with the target sites such as receptors, proteins, DNA, RNA, and the like in the pathogen, thus potentiating and prolonging its effect leading to enhanced antibiotic activity against pathogens.

(h) Besides above mode of action, the bioenhancer agents may also be useful for promoting the transport of nutrients and the drugs across the blood brain barrier, which could be of immense help in the control of diseases like cerebral infections, epilepsy, and other CNS problems.

Modern drug development processes achieve oral bioavailability enhancement by a number of approaches.

(a) Increasing the polarity of the drug through chemical modification.

(b) Salt preparation or complexation.
(c) Prodrug formation.
(d) Micronization and nanonization.
(e) Specific polymorphic form selection.
(f) Targeted delivery of the drug to the site of action.
(g) Controlled drug delivery through film coating.
(h) Sustained drug release through polymorphic matrices formation.
(i) Liposomal microencapsulation and so forth.
(j) Application of P-glycoprotein inhibitors

However, bioavailability enhancement through the supplementation of the main therapeutic agent with a secondary agent gained wide popularity since the traditional times. However, based on Ayurvedic literature, a new approach is increasing bioavailability of drugs including poorly bioavailable drugs by using herbal bioenhancers [5]. Major categories of drugs that have shown increased bioenhancement include cardiovascular, respiratory, CNS, GIT, antibiotics, and anticancerous. Some examples include tetracyclines, sulfadiazine, vasicine, rifampicin, pyrazinamide, ethambutol, phenytoin, phenobarbitone, carbamazepine, nimesulide, indomethacin β-carotene, coenzyme Q10, ciprofloxacin, curcumin, dapsone, amino acids, glucose, and several other classes of drugs.

3. Mechanisms of Action

Herbal bioenhancers act through several mechanisms of action. Different herbal bioenhancers may have same or different mechanisms of action. They increase bioavailability of neutraceuticals by acting on gastrointestinal tract to enhance absorption, whereas they increase bioavailability of drugs by acting on drug metabolism process. Various mechanisms of action postulated for herbal bioenhancers are They cause inhibition of gastric emptying (GE) of solids/liquids in rats and gastrointestinal transit (GT) in mice in a dose- and time-dependent manners was studied. It significantly inhibited GE of solids and GT at the doses extrapolated from humans (1 mg/kg and 1.3 mg/kg p.o.in rats and mice, resp.) However, at the same dose the effect was insignificant for GE of liquids. One-week oral treatment of 1 mg/kg and 1.3 mg/kg in rats and mice respectively did not produce a significant change in activity as compared to single-dose administration. GE inhibitory activity is independent of gastric acid and pepsin secretion [14]. Thermogenic and bioenergetic mechanisms are believed to be triggered by activation of thermoreceptors and release of catecholamines and/or direct action as beta 1, 2, 3-adrenoceptor agonist. Secretion of catecholamines can also be mediated by ATP via P2-type purinergic receptors an through a direct or indirect stimulation by the compositions of the invention of dopaminergic and serotinergic systems. It is known that stimulation of □-3 adrenoceptors results in increased thermogenesis, decrease in the amount of white adipose tissue without food intake being affected, increased levels of insulin receptors, and decreased levels of serum insulin and blood glucose. This may possess antiobesity and antidiabetic effects, which by themselves contribute to the mechanism of thermogenesis and the increase in lean body mass.

The thermogenic effect may also be mediated by an increase in the activity of thyroid peroxidase, an important enzyme in thyroid hormone synthesis, an increase in the plasma levels of triiodothyronine (T3) and thyroxine (T4) with simultaneous increase in tissue oxygen uptake, and increase in thermogenesis adipose tissue without food intake being affected, increased levels of insulin receptors, and decreased levels of serum insulin and blood glucose. This may possess antiobesity and antidiabetic effects, which by themselves contribute to the mechanism of thermogenesis and the increase in lean body mass. The thermogenic effect may also be mediated by an increase in the activity of thyroid peroxidase, an important enzyme in thyroid hormone synthesis, an increase in the plasma levels of triiodothyronine (T3) and thyroxine (T4) with simultaneous increase in tissue oxygen uptake, and increase in thermogenesis.

4.Herbal Bioenhancers:

Piperine. Piperine, the major plant alkaloid present in P. nigrum Linn (Black pepper) and P. longum Linn (Long 4 The Scientific World Journal pepper), has bioavailability enhancing activity for some nutritional substances and for some drugs. It has been used extensively as a condiment and flavoring for all types of savory dishes. Piper species have been used in folklore medicine for the treatment of various diseases, including seizure disorders. Piperine is known to exhibit a variety of biological activities which include anti-inflammatory activity, antipyretic activity, fertility enhancement , antifungal activity , antidiarrhoeal activity , antioxidant activity , antimetastatic activity , antithyroid activity , antimutagenic activity , antitumor activity , antidepressant activity, antiplatelet activity , analgesic activity , hepatoprotective activity , antihypertensive activity , and antiasthmatic activity . Piperine exhibits a toxic effect against hepatocytes and cultured hippocampal neurons, reproductive toxicity in swiss albino mice, and immunotoxicity Piperine reduces the aflatoxin B1-induced cytotoxicity and micronuclei formation in rat hepatoma cells in concentration-dependent manner. It is capable of counteracting aflatoxin B1 toxicity by suppressing cytochromes P450-mediated bioactivation of the mycotoxin. Inhibition of aflatoxin B1-induced cytotoxicity and genotoxicity in Chinese hamster cells by piperine was reported by Reen et al. A significant suppression (33.9–66.5%) in the micronuclei formation induced by benzo (a) pyrene and cyclophosphamide was reduced following oral administration of piperine at doses of 25, 50, and 75 mg/kg in mice

Other Bioenhancers

Quercetin: Quercetin is a plant-derived flavonoid found in fruits, vegetables, leaves, and grains. Quercetin has exhibited activities including antioxidant, radical scavenging, and antiinflammatory, antiatherosclerotic, anticancer, and antiviral effects. Quercetin is an inhibitor of CYP3A4 and a modulator of P-glycoprotein. It has been shown to decrease bioavailability of cyclosporin in pigs and rats. Wang et al. reported that coadministration of quercetin with digoxin leads to lethal effects in pigs.

Quercetin &Paclitaxel. The effect of quercetin on the bioavailability of paclitaxel was studied after oral administration in rats. Paclitaxel (40 mg/kg) and prodrug (280 mg/kg, 40 mg/kg as the paclitaxel) were administered orally to rats pretreated with quercetin (2, 10, 20 mg/kg). The Pharmacokinetic parameters that quercetin increases bioavailability of paclitaxel in rats Quercetin and Verapamil. Pharmacokinetic parameters of verapamil and norverapamil were determined after the oral administration of verapamil (10 mg/kg) to rabbits in the presence and absence of quercetin (5.0 and 15 mg/kg). While coadministration of quercetin concurrently was not effective to enhance the oral exposure of verapamil, pretreatment of quercetin 30 min before verapamil administration significantly altered the pharmacokinetics of verapamil. Compared with the control group, the Cmax and AUC of verapamil increased approximately 2-fold in the rabbits pretreated with 15 mg/kg quercetin. There was no significant change in tmax and t1/2 of verapamil in the presence of quercetin. Consequently, absolute and relative bioavailability values of verapamil in the rabbits pretreated with quercetin were significantly higher ($P < 0.05$) than those from the control group. In conclusion, pretreatment of quercetin significantly enhanced the oral exposure of verapamil.

Quercetin and Diltiazem: The effect of quercetin (2, 10, 20 mg/kg) /kg) pretreatment on the bioavailability of diltiazem

(15 mg/kg) was studied in rabbits after oral administration. The plasma concentrations of diltiazem in the rabbits pretreated with quercetin were increased significantly (P <0.05, at 2 mg/kg; P < 0.01, at 10 and 20 mg/kg) compared with the control, but the plasma concentrations of diltiazem coadministered with quercetin were not significant. The AUC and Cmax of the diltiazem in the rabbits pretreated with quercetin were significantly higher (P < 0.05, at 2 mg/kg; P < 0.01, at 10 and 20 mg/kg) than the control. The AB of diltiazem in the rabbits pretreated with quercetin was significantly (P < 0.05 at 2 mg/kg, P < 0.01 at 10 and 20 mg/kg) higher (9.10–12.81%) than the control (4.64%). The bioavailability of diltiazem in the rabbits pretreated with quercetin is increased significantly compared with the control, but not in the rabbits coadministered with quercetin.

Naringin: Naringin is the major flavonoid glycoside found in grapefruit, apples, onions, and tea. Naringin exerts a variety of pharmacological effects such as antioxidant activity, antiulcer activity, antiallergic activity and anticancer activity, and blood lipid lowering. Naringin has been reported as a CYP3A4 inhibitor as well as a Pglycoprotein modulator. Park et al. reported that naringin did not affect the in vivo pharmacokinetics of intravenously administered doxorubicin.

Naringin & Diltiazem. Pharmacokinetic parameters of diltiazem were determined in rats following an oral administration of diltiazem (15 mg/kg) to rats in the presence and absence of naringin (5 and 15 mg/kg). Compared to the control given diltiazem alone, the Cmax and AUC of diltiazem increased by 2-fold in rats pretreated with naringin, while there was no significant change in tmax and terminal t1/2 of diltiazem. Consequently, AB and RB values of diltiazem in the presence of naringin were significantly higher (P < 0.05) than those from the control group. Metabolite-parent AUC ratio in the presence of naringin decreased by 30% compared to the control group, implying that naringin could be effective to inhibit the metabolism of diltiazem. In conclusion, the concomitant use of naringin significantly enhanced the oral exposure of diltiazem in rats. 5.2.2. Naringin and Paclitaxel. The effect of oral naringin on the pharmacokinetics of intravenous paclitaxel was studied in rats. Oral naringin (3.3 and 10 mg/kg) was pretreated 30 min before intravenous (3 mg/kg) administration of paclitaxel. After intravenous administration of paclitaxel, the AUC was significantly greater (40.8% and 49.1% for naringin doses of 3.3 and 10 mg/kg, resp.), and ClB was significantly slower (29.0% and 33.0% decrease, resp.) than controls. The significantly greater AUC could be due mainly to an inhibition of metabolism of paclitaxel via CYP3A1/2 by oral naringin. The inhibition of hepatic P-glycoprotein by oral naringin could also contribute to the significantly greater AUC of intravenous paclitaxel by oral naringin.

Capmul: Capmul is a glyceryl caprate produced from edible fats and oils. It is commonly used in lip products. Cho et al. reported that capmul MCM C10 enhanced the bioavailability of ceftriaxone by 55–79% in rats.

Cow Urine Distillate: Cow urine distillate is more effective as bioenhancer than cow urine, to increase the effectiveness of antimicrobial, antifungal, and anticancer drugs. Cow urine has antitoxic activity against the cadmium chloride toxicity and it can be used as a bioenhancer of zinc. Mature male mice exposed to cadmium chloride only showed 0% fertility rate. However, the animals exposed to cadmium chloride cow urine distillate + zinc sulfate showed 90% fertility rate with 100% viability and lactation indices. Fertility index was also found to be 88% in group treated with cadmium chloride + cow urine distillate. Thus, these results indicate that cow urine distillate works as an antitoxic against the cadmium chloride toxicity and it can be used as a bioenhancer of zinc. Cow urine distillate increased the activity of rifampicin by about 5–7 times against Escherichia coli and 3–11 times against Gram-positive bacteria. It probably acts by enhancing the transport of antibiotics across the membrane of gastrointestinal tract. The enhancement in transport is approximately 2–7 times

Conclusions:

The effective formulation strategy for the optimization of the pharmacokinetic characteristics of dietary components is crucial to improve their in vivo performance and ultimately maximize their effectiveness as a bioavailability enhancer the available scientific research on bioenhancers has shown to produce significant enhancing effect on bioavailability when coadministered or pretreated with many drugs and nutraceuticals. These natural compounds include piperine, Zingiber officinale, niaziridin, glycyrrhizin, Cuminum, cyminum, Carum carvi, allicin, lysergol, Aloe vera, Stevia rebaudiana, curcumin, sinomenine, genistein, Ammannia, multiflora, capsaicin, quercetin, naringin, capmul and cow urine distillate. They reduce the dose, shorten treatment, and thus reduce drug-resistance and drug toxicity or adverse reactions. Due to dose economy, treatment is cost-effective. Bioenhancers are also found to decrease or having no effect or little effect on the bioavailability of some drugs The current paper discussed the enhancing effects of bioenhancers of drugs in animals and humans but these compounds have not been completely explored in experimental animals till date. However, these studies lack information on their exact mechanism of action, toxicity evaluation

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