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Review Article

A Comprehensive Review on Pharmacotherapeutics of Herbal Bioenhancers

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A B S T R A C T

In India, Ayurveda has made a major contribution to the drug discovery process with new means of identifying active compounds. Recent advancement in bioavailability enhancement of drugs by compounds of herbal origin has produced a revolutionary shift in the way of therapeutics.

Thus, bibliographic investigation was carried out by analyzing classical text books and peer- reviewed papers, consulting worldwide-accepted scientific databases from last 30 years. Herbal bioenhancers have been shown to enhance bioavailability and bioefficacy of different classes of drugs, such as antibiotics, antituberculosis, antiviral, antifungal, and anticancerous drugs at low doses. They have also improved oral absorption of nutraceuticals like vitamins, minerals, amino acids, and certain herbal compounds. Their mechanism of action is mainly through absorption process, drug metabolism, and action on drug target. This paper clearly indicates that scientific researchers and pharmaceutical industries have to give emphasis on experimental studies to find out novel active principles from such a vast array of unexploited plants having a role as a bioavailability and bioefficacy enhancer. Also, the mechanisms of action by which bioenhancer compounds exert bioenhancing effects remain to be explored.

Keywords: Herbal Bioenhancers, Bioavailability, Pharmacokinetics, Piperine, Drug Absorption, Nutraceuticals, Synergism, Drug Metabolism, Plant-Based Adjuvants

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.[1] The consumption of antibiotics and drugs by man is increasing at an alarming rate. Out of the total drugs and chemicals, 20–50% of that use is unnecessary depending on the class of antibiotic. In addition, indiscriminate use of antibiotics promotes antibiotic resistance leading to multiple drug resistance and makes it difficult to control the diseases. The infected individuals have to consume more amount 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.[2]

In addition, 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. This is also responsible for side effects, illness, and reduction in life expectancy. One of the possible ways to reduce drug dosage is synergism between two therapeutic agents, that is, combination therapy. However, if both drugs used concurrently have antimicrobial property, the problem of selection pressure and drug toxicity will continue. Thus, there is need of molecules, which are not antimicrobial or target drugs but enhance activity and availability of main drugs in combination therapy, that is, bioenhancers. These molecules by their presence will not exert any selection pressure for mutants to emerge resistant against them and on that their ill effects can be minimized. The resistance development process will be substantially delayed, ultimately leading to enhanced life- span of the novel and existing antibiotics. Such drugs/molecule facilitators should have novel properties such as[1] nontoxic to humans or animals,[2] they should be effective at a very low concentration in a combination,[3] they should be easy to formulate, and[4] most importantly enhance uptake/absorption and activity of the drug molecules. This can lead to developing judicious and strategic concentrations of antibiotic with specific bioenhancers to improve availability of the drug for controlling the infectious organisms effectively.[2]

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.[3] 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.[4]

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.[2]

Bioavailability/Bioefficacy-Enhancing Activity

The term bioavailability or bioenhancing 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 drugs.

Poorly bioavailable drugs remain subtherapeutic 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. Intersubject 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 nutraceuticals in the course of therapy. The bioenhancers improve nutritional status by increasing bioavailability/bioefficacy of various nutraceuticals including metals and vitamins.[5]

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

1. Promoting the absorption of the drugs from GIT.
2. Inhibiting or reducing the rate of biotransformation of drugs in the liver or intestines.
3. Modifying the immune system in such a way that the overall requirement of the drug is reduced substantially.
4. 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.
5. Inhibiting the capability of pathogens or abnormal tissue to reject the drug, for example, efflux mechanisms frequently encountered with antimalarial, anticancer and antimicrobial drugs.
6. Modifying the signaling process between host and pathogen ensuring increased accessibility of the drugs to the pathogens.

7. 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.

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

1. Increasing the polarity of the drug through chemical modification.
2. Salt preparation or complexation.
3. Prodrug formation.
4. Micronization and nanonization.
5. Specific polymorphic form selection.
6. Targeted delivery of the drug to the site of action.
7. Controlled drug delivery through film coating.
8. Sustained drug release through polymorphic matrices formation.
9. Liposomal microencapsulation and so forth.
10. Application of P-glycoprotein inhibitors.[6, 7]

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 Q 10, ciprofloxacin, curcumin, dapsone, amino acids, glucose, and several other classes of drugs.[8]

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 nutraceuticals 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 .

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 and through a direct or indirect stimulation by the compositions of the invention of dopaminergic and serotinergic systems. It is known that stimulation of β-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.

Piperine mediated changes in the permeability of rat intestinal epithelial cells: the status of γ- glutamyl transpeptidase activity, uptake of amino acids, and lipid peroxidation was studied. The effect of piperine on the absorptive function of the intestine were studied. In vitro experiments showed that piperine (25–100 μM) 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.[12]

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 toxic-

ity 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 of extracts, and suitable combinations. Therefore, we have to focus on this area for further research on their active principles, mechanisms of actions, toxicity evaluation, and suitable combinations with other drugs. So we can explore novel principles with high bioenhancing ability and less toxic effects.

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