Review Article

Growing impact of Herbal Bioenhancers in Pharmaceutical Industries: A Comprehensive Review

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Running Title: Herbal bioenhancers in pharmaceutical industries

Received: 15 March, 2015; Revised: 10 May, 2015; Accepted: 25 May, 2015

Abstract

Bioenhancers are the drug facilitators which are combined with some drug in order to increase the activity of a drug molecule without affecting its properties and making it biologically available across the membrane for target cells to be used. They are an efficient source to reduce the drug dosage and toxicity, major causes of drug resistance, and ultimately play a vital role in the treatment of various disorders. They have shown to increase the bioefficacy in combination with antibiotics, antiviral, antifungal, anticancer and antituberculosis drugs at lower doses. When they come from any herbal origin, they are known as herbal bioenhancers. Many herbal compounds e.g. quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin, nitrile glycoside, allicin, gallic acid and capsaicin etc. have been established to illustrate bioenhancing activity of various drugs. Herbal Bioenhancers are safe, effective, economical and easily procurable molecules with a broad-spectrum impact. However regarding their mechanism of action the exact mechanism still needs to be elucidated but current literature suggests their mechanism of action is mainly through absorption, drug metabolism and dose reduction. In conclusion their application may ultimately have a positive influence on the national economy of a country.

Keywords: Bioenhancers, Quercetin, Antibiotics, prodrug.

Introduction

Treatment cost is a major concern of today’s medicine in developing countries for which systematic innovations are needed to get them reduced [1]. Modern pharmaceutical research has resulted in the affordable treatments of diseases that are now easily available for even financially challenged sections of the society. However, this easy access has also resulted in an unnecessary and indiscriminate use of antibiotics and drugs at an alarming rate (20–50%). When taken orally, they result in reduced absorption inside the gut membrane due to first-pass metabolism [1] thus a major amount of the applied drug goes waste, leaving a minor amount for the target site. Sometimes, these drugs/antibiotics remain as a load in the body and act as a selection pressure thus facilitating the emergence of drug resistance and making the diseases difficult to be controlled over time and finally there are numerous side effects with reduced life expectancy [2].

Bioenhancers

One possible way to reduce this drug dosage and toxicity is to increase the drug bioavailability; the rate at which a therapeutically active substance enters the systemic circulation and becomes available at the required site of action [1]. This improvement can be brought about by using combination therapy; synergizing two therapeutic agents for an improved result. However, both of the drugs used concurrently should not have antimicrobial properties, otherwise the problem of selection pressure and toxicity would persist. Hence, there is need of those molecules, which are not antimicrobial or target drugs but they just enhance the activity and availability of the main drugs, such molecules are called bioenhancers [2].
Bioavailability enhancers are actually the drug facilitators which do not show typical drug activity by themselves but when used in combination, enhance the activity of drug molecule by increasing bioavailability and making it biologically available across the membrane, potentiating it by conformational interaction, acting as receptors for drug molecule and making target cells more receptive to drugs [3].

**Background**

The term bioavailability enhancer/ bioenhancer was initially coined when Indian Scientists at the Regional Research Laboratory, Jammu discovered and scientifically validated piperine as the world’s first bioavailability enhancer in 1979 [2]. C.K. Atal, the Director of the institute analyzed a list of ancient Indian Ayurveda formulations and formed the working hypothesis that Trikatu increases the efficacy of formulations. Trikatu has three ingredients: black pepper (Piper nigrum), long pepper (Piper longum) and ginger (Zingiber officinale). Based upon this hypothesis, one of the ingredients, ‘Piper longum’ was found to increase the bioavailability of many drugs. Hence, it was found that trikatu contains piperin and piperin is a bioenhancer [1].

**Role of Bioenhancers**

Latest development on advent of enhancing drugs bioavailability idea has produced a dramatic shift in the way medicines are administered [3]. These bioenhancing molecules do not exert any selection pressure for mutants rather they maximize the bioavailability of main drug by directly influencing the plasma concentrations and consequently their therapeutic efficacy. They can also make the expensive drugs affordable and reduce the toxic effects by reducing the required dose of drugs. Thus development of resistance slows down leading to enhanced life-span of the drugs/ antibiotics [2].

**Herbal Bioenhancers**

Preferably, herbal sources as treatment are used at very high rate due to their lower risk to benefit ratio in comparison to the modern allopathic medicines [4]. Hence, the use of herbal medicine has recently increased all over the world owing to their remarkable therapeutic effects and fewer side effects. However, many herbal drugs show less or negligible in-vivo activity as compared to their in-vitro findings due to their poor bioavailability. This can be improved by using them with a herbal bioenhancers [3]. Herbal bioenhancer is an agent of herbal origin which has the ability to enhance bioavailability and bioefficacy of a particular drug or nutrient when combined, without any typical pharmacological activity of itself at the dose used [2].

**Mode of Action**

There are several mechanisms by which different herbal bioenhancers act in same or either different way. For example, nutritional bioenhancers enhance gastrointestinal absorption, antimicrobial bioenhancers target the drug metabolism processes. Some are involved in reduction in hydrochloric acid secretion, increase in gastrointestinal blood supply, inhibition of gastrointestinal transit, intestinal motility, bioenergetics, thermogenic properties, suppression of first pass metabolism and inhibition of drug metabolizing enzymes etc. [3].
Some Examples of Herbal Bioenhancers

Many herbal compounds like quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside have been reported to demonstrate the capability to enhance bioavailability of different drugs. Some of them are mentioned below as:

Piperine is the major plant alkaloid present in *P. nigrum* (Black pepper) and the active ingredient of *Piper longum* which was isolated and reported for its bioavailability enhancing action. It was found to increase the bioavailability of different drugs ranging from 30 to 200%. Piperine acts as a bioenhancer by inhibiting hepatic and intestinal biotransformation processes [5]. Subsequent research has shown that it also increases curcumin bioavailability by ten-fold [1].

Glycyrrhizin is a triterpenoid saponin that is found in *Glycyrrhiza glabra* (Fabaceae). It has been reported to show a more potent absorption enhancing activity that was increased by presence of the other absorption enhancers [9]. It enhances bioactivity of rifampicin, ampicillin, tetracycline, and nalidixic acids against Gram-positive bacteria e.g. *M. smegmatis* and *Bacillus subtilis* and Gram-negative bacteria like *E. coli*. It also enhances the activity of azole antifungal drugs such as clotrimazole against *Candida albicans* [10, 11].

Sinomenine is an alkaloid extracted from *Sinomenium acutum* Thunb. Paeoniflorin is a bioactive monoterpene glucoside, which has a poor absorption rate hence a very low bioavailability (3-4%) when administered orally. Co-administration of paeoniflorin with sinomenine was informed to get enhanced by more than 12 times in rats. The mechanism underlying is that sinomenine could decrease the efflux transport of paeoniflorin by P-glycoprotein in the small intestine [13].

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Quercetin is a flavonoid found in the citrus fruits. It has been proved to inhibit both CYP3A4 and P-gp [7]. It also increases bioavailability, blood levels and efficacy of many drugs like diltiazem, digoxin, Calcium channel blockers (verapamil, dilitazem), antineoplastics (paclitaxel, doxorubicin) and epigallocatechin gallaate from the gastrointestinal tract [7]. It also exhibits a wide range of beneficial biological activities including antioxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic, anti-tumor and anti-viral effects.

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<td>Structure of Quercetin (2-(3, 4-dihydroxyphenyl)-3, 5, 7-trihydroxy-4Hchromen-4-one) [8]</td>
<td>Structure of Sinomenin (7, 8-didehydro-4-hydroxy-3, 7-dimethoxy-17-methylmor phinan-6-one) [11]</td>
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Genistein (5, 7-Dihydroxy-3-(4-hydroxyphenyl) chromen-4-one) is an iso-flavone also known as phytoestrogen. It has been reported to inhibit P-glycoprotein (efflux transporters), BCRP and MRP2 efflux function. The inhibition of the efflux transporters by genistein also contributes to the improvement of systemic exposure of paclitaxel [14].

![Structure of Genistein (5, 7-Dihydroxy-3-(4-hydroxyphenyl) chromen-4-one)](image)

Aloe-Vera preparations, i.e. whole leaf extract and inner fillet gel have been informed to improve the absorption of both the vitamin C and E. The absorption is slower and vitamins last longer in the plasma with aloes, thus increasing the bioavailability of Vitamin C and E in human. Aloe Vera may be a promising future nutritional herbal bioenhancer [16].

Nitrite glycoside has also been reported as a bioenhancer for drugs and nutrients. Niaziridin and niazirin, novel bioactive nitrile glycosides are obtained from the leaves, pods and bark of Moringaoleifera. The leaves of Moringa have also been reported to have an immune-enhancing polysaccharide, niaziminin that has a structural requirement to inhibit tumor promoter-induced Epstein–Barr virus activation. It promotes the activity of common antibiotics & also facilitates the absorption of drugs, vitamins, and nutrients through the gastrointestinal membrane, thus increasing their bioavailability [17].

![Structure of niazmicin (Carbmothioic acid)](image)

C. carvi (cumin) has also been well-versed to act as a bioenhancer and modifier of kinetics of antitubercular drugs favorably. Increase in the absorption of antitubercular drugs by C. carvi extract is possibly attributed to the enhancement of mucosal to serosal permeation. Another factor responsible for this action of C. carvi extract could be the modification of permeation characteristics of the intestine [19]. In addition, a possible reason could be its influence on the P-glycoproteins. However there have been encouraging results on the use of this extract in animals [20].

**Conclusion**

As the drug development techniques are concerned about the economics of drug development, scientists are now aiming at finding out the methods of reducing drug dosage and ultimately the treatment cost, making it available to wider sections of the society. The above illustrated review hence can be used to collect ideas about naturally available drugs to decrease their cost, toxicity, and other side effects. Herbal Bioenhancers are safe, effective, economical and easily procurable molecules having a broad-spectrum impact on drugs. Their application may ultimately have a positive influence on the national economy of our country.

**References**


