



Review Article

A COMPREHENSIVE REVIEW ON NATURAL BIOENHANCERS

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ABSTRACT

Natural bioenhancers reported to improve bioavailability and bioefficacy in combination therapy. Many studies are increasingly showing interest toward the improvement of bioavailability of a large number of synthetic and herbal drugs by natural bioenhancers. In modern medicine treatment cost and adverse effect are major concern, hence systematic innovative means to reduce treatment cost and adverse effect are needed. Natural compounds such as resveratrol, piperine, glycyrrhizine, quercetin, sinomenine and Cumins demonstrated capability to enhance bioavailability. The objective of this review is to summarize upto date information of natural bioenhancers.

Keywords: Natural Bioenhancers, Bioavailability, Resveratrol, Piperine, Quercetin Cumins.

INTRODUCTION

According to the Code of Federal Regulations, bioavailability is the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.¹ A natural 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. They tend to decrease the dose of active drug required for the optimal endpoint of the treatment strategy.² Oral bioavailability depends on a number of factors, primarily drug permeability, aqueous solubility, dissolution rate, presystemic metabolism, first-pass metabolism and susceptibility to efflux mechanisms. Among these factors low permeability and poor solubility stands as the most frequent causes of low oral bioavailability.³ The bioavailability and bioefficacy of some drugs may be enhanced by food, for example, an acid environment is necessary for the absorption of ketoconazole and absorption of griseofulvin is increased by high fat diet. Fenofibrate, mebendazole, isotretinoin, tamsulosin, carbamazepine and labetalol are some examples of drugs that show better absorption while taken with food.^{4,5} Food, dietary supplements and their components can have impact on the achievement of drug action and on the side effect profiles of various drugs. Upon entry into the stomach, food may alter the rate or the extent of drug absorption through a variety of direct and indirect mechanism. The interactions are not always detrimental to therapy, but in some cases can be used to improve drug absorption or to minimize adverse effects. These interactions have received more interest recently.⁶

Polyphenols such as anthocyanins, coumarins, flavonoids, lignans and tannins present in herbs, vegetables, fruits, flowers, and leaves in many plants, are believed to be beneficial to human health by exerting biological effects such as free radical scavenging.⁷⁻⁹ Most dietary flavonoids present in food exist as *O*-glycosides with glucose, glucorhamnose, galactose, arabinose, or rhamnose.¹⁰ The β -linkage of these glycosides resist hydrolysis caused by acidity in the stomach and the attack by pancreatic enzymes. However, β -endoglucosidases present in small intestine are able to hydrolyse flavonoid glycosides.¹¹ Additionally,

colonic microflora hydrolyses the sugar moiety from the flavonoid aglycone, thus increasing the absorption of flavonoids. During absorption, the flavonoids may interact with metabolising enzymes and transport proteins, and thus affect the uptake of co-administered drugs. Indeed, polyphenols are potent inhibitors or inducers of CYPs, UGTs and transport proteins, if consumed in large amounts.¹²⁻¹⁴ However, only few studies on herbal bioenhancers has been reported.^{2, 15} Hence, the present review aims to compile a comprehensive up-to-date information on the progress made on natural bioenhancers.

MECHANISMS OF ACTION OF NATURAL BIOENHANCERS

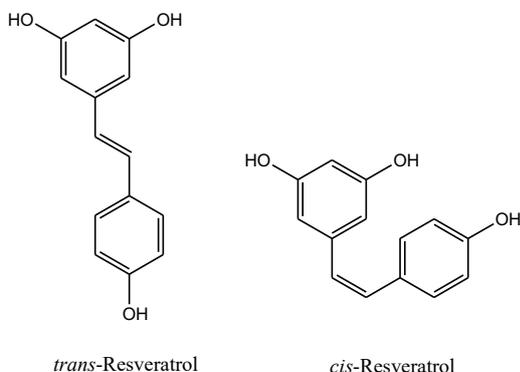
There are several mechanisms of action by which herbal bioenhancers work. Among the various mechanism of action postulated for natural bioenhancers some are P-gp inhibition activity, reduction in acid secretion, increase in gastrointestinal blood supply, inhibition of gastrointestinal transit, gastric emptying, inncrease in intestinal motility, modifications in GIT epithelial cell membrane permeability and inhibition of first pass metabolism and metabolizing enzymess.^{2, 15} Flavone, quercetin and genistein have showed a considerable P-gp inhibition activities. Additionally, naringin and sinomenine were also reported to be inhibitors for efflux transporters such as P-gp and breast cancer resistance protein.^{16, 17} Many natural compounds are effective in improving the intestinal absorption of other drugs and nutrients, example of such agents are: bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers. These surfactants act as bioenhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes.^{18, 19} Trimethylated chitosan increase drug absorption by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions.²⁰

NATURAL PRODUCTS AS BIOENHANCERS

Resveratrol

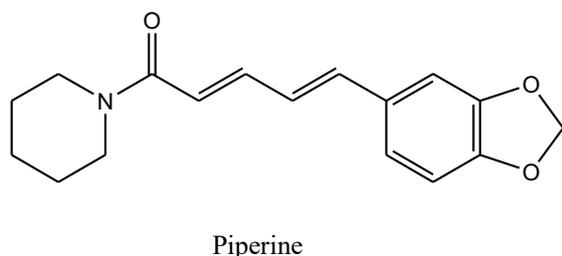
Resveratrol (3,4',5- trihydroxystilbene) is a nutraceutical that has recently attracted a lot of research attention due to its exciting

pharmacological potential. It is a phytoalexin found in many plants including red wine, grapes, peanuts, and berries.³ Co-administration of apigenin and resveratrol led to a 2.39 fold increase in plasma apigenin levels compared to administration of apigenin alone. Resveratrol inhibits the formation of apigenin glucuronides by inhibiting UGT1A9 enzyme in a non-competitive manner.²¹



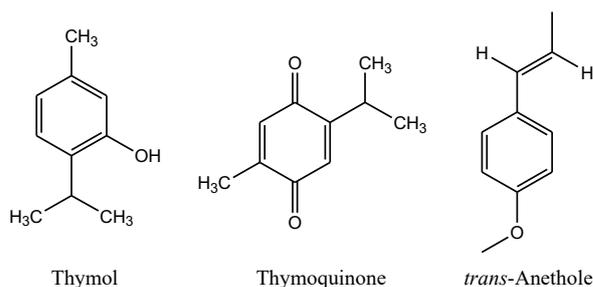
Piperine

Piperine is a major alkaloidal component of *Piper nigrum* Linn. (Piperaceae). Piperine, or mixtures containing piperine, has been shown to increase the bioavailability, blood levels and efficacy of a number of drugs including vasicine, sparteine, sulfadiazine, rifampicin, phenytoin and propranolol.^{22, 23} Piperine act by suppressing P-gp and cytochrome P450 enzymes, which counteract the metabolism of rifampicin *via* these proteins, thus enhancing the oral bioavailability of rifampicin. It also decreases the intestinal production of glucuronic acid, thus allowing more substances to enter the body in active form. It was found to increase the bioavailability of various drugs from 30% to 200%.²⁴



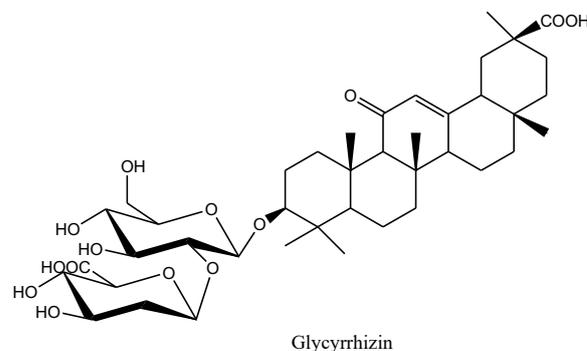
Black Cumin

Nigella sativa (Black cumin) belonging to family Ranunculaceae. It is extensively used in the Indian diasporas as spice, which may interact with co-administered drugs and affect their intestinal availability. In the *in-vitro* study methanolic and hexane extracts of *Nigella* increased the permeation of amoxicillin significantly. In *in-vivo* experiments black *cumin* enhanced amoxicillin bioavailability. C_{max} of amoxicillin increased in rat plasma when administered orally alone and in combination with hexane extract correspondingly from 4138.25 ± 156.93 to 5995.04 ± 196.28 ng/ml while as $AUC_{0 \rightarrow t}$ increased from 8890.40 ± 143.33 to 13483.46 ± 152.45 ng/ml.h.⁷



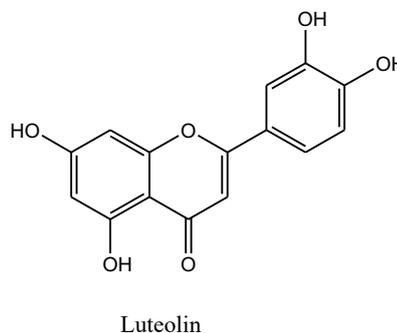
Glycyrrhizin

Glycyrrhizin is a triterpenoid saponin found in *Glycyrrhiza glabra* Linn. (Leguminosae). The absorption-enhancing activity of sodium deoxycholate and dipotassium-glycyrrhizinate was much greater when coadministered with glycyrrhizin. The absorption enhancing activity of glycyrrhizin was increased by presence of other absorption enhancers.²⁵ Glycyrrhizin showed a more potent absorption enhancing activity than caproic acid at the same concentration tested.²⁶



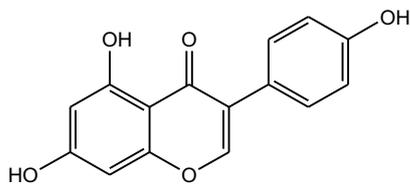
Cumin oil

Cuminum cyminum Linn. (Apiaceae) is an annual herb, its fruits are generally used as spice. Cumin oils and its bioactive compound like luteolin seemed to attribute the bioavailability enhancing activity. Luteolin has been reported to be a potent P-gp inhibitor.²⁷ Bioavailability enhancing activity of *C. cyminum* was revealed toward a number of drugs.²⁸



Genistein

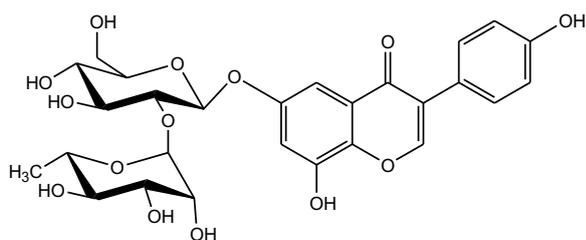
Genistein, well known as a phytoestrogen²⁹ inhibits P-gp, Breast Cancer Resistance Protein (BCRP) and Multidrug Resistance-Associated Protein 2 (MRP2) efflux function. The intestinal absorption of paclitaxel, a substrate for efflux transports such as P-gp, BCRP and MRP2 considerably increased when co-administered with genistein. It has been reported that the inhibition of the efflux transporters by genistein improve systemic exposure of paclitaxel.³⁰



Genistein

Naringin

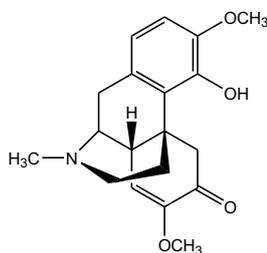
Naringin is the major flavonoid glycoside found in grapefruits, that shows the inhibition of P-gp and CYP3A in rats.³¹ Area under curve (AUC) of paclitaxel is increased significantly in presence of naringin (49.1% for naringin at 10 mg/kg).³²



Naringin

Sinomenine

Sinomenine, an alkaloid extracted from *Sinomenium acutum* (Menispermaceae). Paconiflorin, bioactive monoterpene glucoside has a poor bioavailability (3-4%) when administered orally.³³ Co-administration of paconiflorin with sinomenine, the AUC of paconiflorin significantly increased, thus the oral bioavailability of paconiflorin was enhanced by more than 12 times in rats treated with sinomenine.³⁴

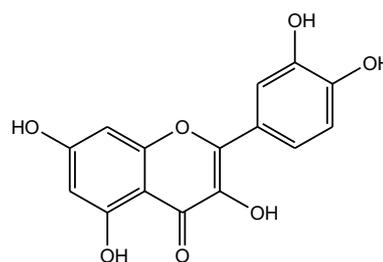


Sinomenine

Quercetin

Quercetin is a flavonoid found in *Citrus* fruits. It is reported that quercetin increase bioavailability, blood levels and efficacy of a number of drugs such as diltiazem,³⁵ digoxin³⁶ and epigallocatechin gallate.³⁷ The absorption of epigallocatechin gallate has been enhanced with red onion supplementation, which is a rich source of quercetin. The AUC of epigallocatechin gallate determined over a period of 6 h increased from 1323 to 1814

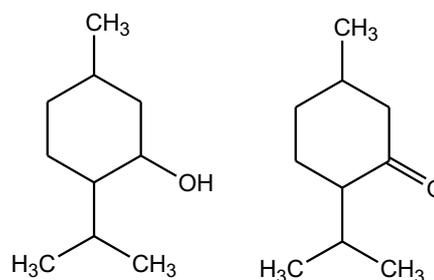
ng.h/ml, when co-administered with quercetin.³⁷



Quercetin

Peppermint oil

Peppermint oil extracted from *Mentha* species contains mainly menthol and menthone. Co-administration of cyclosporine and Peppermint oil, it increased cyclosporine maximum concentration (C_{max}) and area under the concentration versus time curve ($AUC_{0-\infty}$) from 0.60 to 1.6 $\mu\text{g/ml}$ and 8.3 to 24.3 $\mu\text{g.h/ml}$, respectively in *in vivo* experiment.³⁸

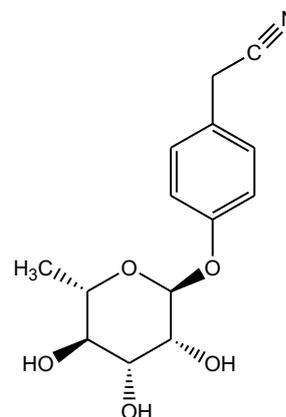


Menthol

Menthone

Nitrile glycosides

Nitrile glycosides and its derivatives such as niazirin and niaziridin is obtained from the leaves, pods, and bark of *Moringa oleifera* (Moringaceae). These glycosides enhanced the absorption of commonly used antibiotics such as rifampicin, tetracycline and ampicillin, vitamins and nutrients^{39, 40}

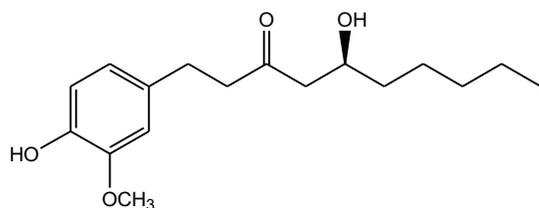


Niazirin

Ginger

Zingiber officinale (Zingiberaceae) is one of the components of *Trikatu* which also possess significant bioavailability enhancement activity.⁴¹ Ginger mainly contains zingiberene,

gingerol and shagol. Gingerols and shagols are responsible for pungency of Ginger. It has a powerful effect on mucous membrane of the gastrointestinal tract. It regulates the intestinal functions to facilitate absorption. Ginger when used in the dose of 10–30 mg/kg body weight acts as bioenhancer. Pharmacological studies shows that it dramatically enhanced the bioavailability of various medicines especially antibiotics such as amoxicillin, azithromycin, erythromycin, cephalexin, cefadroxil, and cloxacillin⁴².



Gingerol

CONCLUSION

Natural bioenhancers leads an innovative concept in the drug discovery. They will lead to reductions in drug cost, toxicity, adverse effects and enhances therapeutic efficacy or bioefficacy. Research aimed at developing novel and powerful bioenhancers such as Resveratrol and Piperine and their derivatives continues.

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