Review Article

Bioenhancers: A Comprehensive Review

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Received: 18-11-2019; **Revised:** 26-12-2019; **Accepted:** 03-01-2020.

ABSTRACT

The substances which increases the bioavailability and bio efficacy of active substances when they are combined with a active ingredient, without showing any activity of their own at the dose used, are Bioenchancers. Herbal bioenhancers are of herbal origin and the concept of herbal bioenhancer is originated from Ayurveda. They reduce the dose, shorten the treatment period and thus reduce drug-resistance problems. They increases the bioavailability of various classes of drugs such as anti-hypertensive, anticancer, antiviral, anti-tubercular, antifungal, nutraceuticals and also some ayurvedic formulations. Herbal bioenhancers are derived from both plant and animal origins. The compounds used as a bioenhancer are piperin, naringenin, niaziridin, quercitine, aloe, cuminium cyninum, ghee and cow urine. Now a days herbal bioenhancers is a new approach in modern medicines because of easy bioavailability, safe, free from side effects, minimizes drug toxicity, shorten the duration of treatments and minimize the cost of treatments. In this review various herbal bioenhancer and their mechanism action are discussed.

Keywords: Bioenhancer, Modern medicines, Bioavailability improvement, Bioavailability enhancers.

INTRODUCTION

Bioenhancers can be defined as chemical entities that promote and increase their bioavailability when mixed with drugs without having any synergistic effect with the drug at the dose used.[1]Bioenhencer increases its bioavailability when co-administered with any medication without affecting its pharmacological action.[2]Scientists are now interested in herbal bioenhancer as they are nontoxic and active at very low levels, making it easy to formulate and improve the medication or nutrient's pharmacological function.[3]

Various approaches are taken to improve bioavailability with the help of bioenhancers. Some of the specific strategies are absorption enhancers, prodrugs, permeability enhancers, micronization, formulations of delayed and sustained release dosage forms such as liposomes and emulsions, and inhibitors of P-glycoprotein (P-gp).[4,5]

In Ayurveda ancient medicine scheme, "Trikatu" was used to improve bioavailability. Trikatu is a mixture of black pepper (*Piper nigrum* linn.), long pepper (*Piper longum*) and ginger (*Zingiber officinale*). This can boost mineral and vitamin bioavailability.[6]

If a medication has less bioavailability, possesses long treatment time, is toxic and is costly, it is difficult to produce therapeutic efficacy. In this case, it is necessary to improve bioavailability as bioavailability directly affects concentrations of plasma drugs and subsequently therapeutic effectiveness. Bioavailability increases the cost of drugs and drug toxicity.[7]

Origin of Bioenchancer

Bioenhancers is an ancient word of Ayurveda, which means the growing effect of the drug, as "Yogvahi" in Sanskrit, which in combination indicates an increase in effect.

In 1929, bioenhancer action was documented by Bose where he used long pepper to increase vasaka's antihistaminic ability.

"Bioavailability enhancer" concept was first invented in 1979 by Indian scientists at Indian Institute of Integrative Medicine, Jammu, formerly known as Regional Research Laboratory, Jammu, by discovering and scientifically validating piperine as the first bioavailability enhancer in the world. Later, C.K. Atal, the institute's director, examined a list of ancient Indian Ayurvedic formulations used to treat a wide range of diseases, and observed "Trikatu", which has three ingredients: black pepper, long pepper and ginger to be present in majority of ayurvedic formulations [8,9]

Ideal Properties of Bioenhancers:

The contribution of bioenhancers have been reviewed which states that the ideal bioenhancers are:

i. Should be nontoxic, non-allergenic and non-irritating.

ii. Should not produce own pharmacological effects.

iii. Should be rapid-acting with predictable and reproducible activity.

iv. Should be unidirectional in action.

v. Should be compatible with other active pharmaceutical ingredients.

vi. Should be stable with time and environment.

vii. Should be easily formulated into a various dosage form.

viii. Should be easily available and cost effective.[10]

Benefits of Using Bioenhancers:

i. As it increases bioavailability drug dose can be reduced

ii. Due to reduced dose cost will also reduce

iii. It reduces drug resistance

iv. Also reduces side effects and adverse drug reactions

v. It increases efficacy of drug

vi. In short decreases total treatment cost. [11]

Action Pathways for Herbal Bioenhancers:

Herbal bioenhancers function through several action pathways. Specific bioenhancers of herbs can have the same or specific mechanisms of action. Different action pathways postulated for herbal bioenhancers include

i. Increase blood flow and decrease hydrochloric acid secretion [12]

ii. Suppression of gastric emptying period, gastrointestinal transit and intestinal motility [12,13]

iii. GIT epithelial cell membrane permeability modifications [14,15]

iv. Cholagogic effect [15]

v. Thermogenic and bioenergetic properties [14,16]

vi. Drug metabolizing enzymes inhibition and first-pass metabolism suppression [17-18]

vii. Gamma glutamyl transpeptidase (GGT) enhancement activity enhancing amino acid absorption.[19]

viii. Inhibition of p-gp efflux pump and other efflux pump

ix. Suppressors of CYP-450 enzyme and its isoenzyme.[20]

Classification of Bioenchancers:

i. Plant origin: Niaziridin, *Cuminum cyminum*, *Carum carvi*, Stevia, Lysergol, Glycyrrhizin, Ginger, Allicin, Aloe vera, Simomenine, genistein, 5-methoxy hydnocarpin etc.[21]

ii. Animal origin: Cow urine distillate, honey, ghee.[22]

Mechanism of Action:

i. Inhibition of p-gp efflux pump and other efflux pump: *Carum carvi* (Caraway), Genistein, *Cuminum cyminum*, naringin etc.

ii. Suppressors of CYP-450 enzyme and its isoenzyme: narigin, gallic acid and its esters etc.

iii. Regulators of GIT function to facilitate better absorption: *Aloe vera* (aloe), Niaziridin (drumstick pods), *Zingiber officinale* (ginger) etc.[20]

Some of the Important Bioenhancers:

Herbal bioenhancers:

Piperine:

Piperine (*piperoyl piperidine*) is an active compound in both *Piper longum* (long pepper) and *Piper nigrum* (black pepper) that is responsible for the bioenhancing effect. Piperin is used in the range of 15mg/kg body weight. It will inhibits the ezymes like P glycoprotein(P-gp), CYP3A4 and other drug metabolizing enzymes especially UDP glucuronosyl transferase (UGT) in the gut. Piperine also enhances the blood supply in the enteric vessel due to its local vasodilatory effect.[23] Diclofenac sodium, pentazocin, phenobarbitone, propranolol, theophylline, metronidazole, methotrexate, etoposide, 18-β glycyrrhetic acid, nateglinide, ibuprofen, resveratrol, fexofenadine, carbamazepine, nevirapine, phenytoin, cyclosporine A, nimesulide, vasicine, sparteine, ampicillin, norfloxacin, rifampicin, tetracycline, pyrizinamide, INH, epigallocatechin-3-gallate, sulfadiazine, fexofennadine, curcumin, saquinavir, nelfanavir, lopanavir, amprenavir, ritonavir, ofloxacin, ciprofloxacin, indomethacin, atenolol, oxytetracycline, beta lactums, oxyphenylbutazone, midazolam, linarine, mercaptopurine bioavailability is enhanced by piperin.[24]

Ginger:

Ginger acts intensely on the mucous membrane of GIT. In order to facilitate absorption, the role of ginger is to regulate intestinal function. Ginger is used as a bioenhancer within the range of 10-30 mg/kg body weight.[25] The bioavailability of various antibiotics such as Azithromycin (85%), Erythromycin (105%), Cephalexin (85%), Cefadroxil (65%), Amoxycillin (90%) and Cloxacillin (90%) increased significantly in presence of ginger.[26]

***Allium sativa*:**

Allicin enhances antifungal activity of amphotericin B against pathogens such as *Candida albicans, Aspergillus fumigatus* and *Saccharomyces cerevisiae*. Amphotericin B and Allicin combination showed more antimicrobial action against S. Cerevisiae.[27] Allicin potentiate the Amphotericin B induced vacuole destruction by inhibition ergosterol transport from the plasma membrane to the vacuole membrane in this way it acts as a bioenchacer.[28] The dose

of allicin is 120µM allicin or a non-lethal concentrate on of AmB (0.5 µM)[25]

Curcumin:

Curcumin is obtained from *curcuma longa* it is used in the range of 12g/day.[25] It acts by suppressing drug enzyme metabolization and P-gp efflux pump inhibition.[29,30] It also, suppresses drug metabolizing enzymes such as CYP3A4 in the liver it also suppresses intestinal and hepatic tissue levels of UDP glucuronyl transferase. It also affects the physiological function of the gastrointestinal tract, contributing to increased drug absorption.[31] Examples of drugs include norfloxacin, midazolam, celipropol, docetaxel, midazolam, methotrexate.[29,30]

Niaziridin (*Moringa oleifera*):

Niaziridin, a fresh nitrile glycoside, was isolated from the *Moringa oleifera* pods. It improves the bioavailability of rifampicin, ampicillin, nalidixic acid activity by 1.2-19 folds against gram-positive. It enhances the activity of 5-6 folds against Candida albicans by azole antifungal drugs such as clotrimazole. It also improves vitamin B12 absorption.[32]

Quercetin:

It is derived from citrus fruits, berries, leaves and grains. [33] Its bioenhencer action is caused by inhibition of CYP3A4 enzymes and/or transporters of P-gp efflux pump.[34] Quarcetin bioenchances the drugs such as paclitaxel, ranolazine, valsaratan, clopidogrel, doxorubicin, etoposide, ironotecan, digoxin, polyphenols of green tea, pioglitazone, diltiazem, epigalactocatechin, tamoxyphene, pioglitazone.[35]

Glycyrrhizin:

It is a saponin glycoside obtained from *Glycerhiza glabra* and it is used in the range of 1 µg/ml.[25] It improve the absorption and p-gp efflux pump inhibition. Rifampicin, tetracycline, aconitin, ampicillin, clotrimazole, taxol, vitamin B1, B12 and nalidixic acid are just a few medicines that can be bioenhanced with glycerhizin.[36,37] It also increases the inhibitory action of anticancer drug such as Taxol. It is also reported to improve the transportation of antibiotics such as rifampicin, tetracycline, nalidixic acid, ampicillin across the gut membrane.[38]

Naringinin:

It is a flavonoid glycoside obtained from grapefruit, apples, onions, and tea. It is used in range of 3.3 and 10 mg/kg.[25] It acts by inhibiting CYP3A4, CYP3A1/2 and P-gp efflux pump. The drugs which are enhanced by naringenin are diltiazem, verapamil, clopidogrel, tamoxifen, quinine, nimodipine, felodipine,17-α ethinylestrdiol, paclitaxel, saquinavir, cyclosporine A, nitrendipine, terfenadine, etc.[34,39]

Cuminum cyminum:

Cuminum cyminum obtained from black cumin and the possible mechanism action is stimulate β-adrenoceptors and/or inhibit histamine H1 receptors when aqueous extract is used, it also opens the potassium channels.[25] The doses are ranged from 0.5 to 25mg / kg body weight. *Cuminum cyminum* increases the bioavailability of Erythromycin (105%), Cephalexin (75%), Amoxycillin (111%), Fluconazole (126%), Ketoconazole (156%), Zidovudine (270%) and Fluorouracil (290%).[40]

Indian Aloe (*Aloe vera*):

It is demonstrated that *Aloe vera* gel and whole leaf extract significantly increases the transport of the macromolecular peptide drug, insulin, across the Caco-2 cell monolayers.[41]It enhances the oral absorption of vitamin C and vitamin E.[42]

Genistein:

Genistein isoflavanoid obtained by *Glycin max* and *Pueraria lobata*. They act by inhibiting P-gp and MRP 21 and BCRP 2 efflux functions. Genistein enhances paclitaxel, epigallocatechin-3-gallate action. The dose of range is 3.3 mg/kg or 10 mg/kg.[25]

Sinomenine:

Sinomenine alkaloid obtained from *Sinomenium acutum.* They act by decreasing efflux transport by P-gp. The dose is in the range of 90mg/kg.[25] The drugs like verapamil, quinidine, paeniflorin, digoxin are bio enhanced using sinomentine.[36,37]

Capsaicin:

Bioavailability of theophylline is enhanced using capsaicin which is obtained by capsicum.[43]

Peppermint oil:

Peppermint oil can enhance the bioavailability of cyclosporine. [44]

Gallic acid:

It shows synergistic effect with piperine. And also enhances bioavailability of nifedipine and saquinavir. [45]

Tulasi oil:

Tulasi or *Osmium sanctum*, acts as bioenhancer on naproxen, nimesulide. [46]

Clove Oil:

Bioavailability of carvedilol is increased by clove oil. [47]

Cinnamic acid:

It enhances bioavailability of saquinavir. [45]

Bioenhancers from animal source:

Cow urine:

According to Ayurveda, cow urine is considered the elixir of life. It is the most effective way to treat all kinds of infections, especially the kindney and liver infections. Filtered cow urine, cow urine distillate, distilled cow urine, cow urine fraction are now replaced with pure cow urine. The drug which are bioenchanced are rifampicin,

tetracycline, ampicillin, paclitaxel, zinc, taxol, INH, clotrimazol, cynocobalamin, mercaptopurine. [48-50]

Ghee:

In many ayurvedic formulations such as *Brahmi ghrita*, *Trikutrayadi lauha*, it functions as a bioenhancer. [22]

Honey:

It's also known as madhu. It is a sweet bee food that uses flowers nectar. It is used in crystallized, pasteurized, raw, strained, filtered, ultrasonic, creamed, dried forms in modern practice, and now a days there are also honey decoctions. Used in Trikutrayadi lauha as a bioenhancer.[22]

Recent formulations: [2]

Formulation	Active ingredient	Application	Biological activity	Route of administration
Quercetin Liposome	Quercetin	Reduced dose, enhanced penetration in blood brain barrier	Anti-oxidant Anti-cancer	Intranasal
Liposome encapsulated Silymarin	Silymarin	Improve bioavailability	Hepatoprotective	Buccal
Rutin-alginate chitosan microspheres	Rutin	Targetting into cardiovascular and cerebrovascular system	Cardio-vascular, cerebro- vascular	In-vitro
Zedoaryoil Microspheres	Zedoary	Sustained release and higher bioavailability	Hepato-protective	Oral
Triptolide Nanoparticles	Triptolide	Enhance the penetration of drug through stratum corneum by increased hydration	Anti-inflammatory	Topical
Radix salvia miltiorrhiza nanoparticles	Radix salvia	Improve the bio- availability	Coronary heart diseases, angina pectoris and myocardial infraction	In-vitro
Capsaicin Transferosomes	Capsaicin	Increase skin penetration	Analgesic	Topical
Colchicine Transferosomes	Colchicine	Increase skin penetration	Antigout	In-vitro
Ginseng lipid-based systems	Flavonoids	Increases absorption	Nutra-ceutcal immune modulator	Oral
Green tea lipid-based systems	Ginsenoside	Increases absorption	Nutra-ceutcal, systemic antioxidant and anticancer	Oral

Patent formulations: [25]

Active ingredients	Novel system incorporate
Opioid analgesic and aloe	Nasal spray
Isoflavones	Microencapsulated formulation
Alkaloids of aconitum species	Transdermal delivery system
Oleaginous oil of *Sesamum indicum* and alcoholic extract of *Centella asiatica*	Brain tonic
Glycine max containing 7s globulin protein extract, curcumin, *Zingiber officinalis*	Herbal tablet dosage form
Opioid analgesic (phenanthrene gp)	Transdermal patch
Oleaginous oil of *Sesamum indicum* and alcoholic extract of *Centella asiatica*	Brain tonic

CONCLUSION

Bioavailability, safety and cost are the major problem in the field of medicines. So new developments are emerging nowadays. The use of herbal drugs along with an API is one of the new approaches which was coined by Ayurveda. Herbal drugs are safe, cost effective and also enhances the bioavailability and efficacy by various mechanism of action.

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Source of Support: Nil, **Conflict of Interest:** None.