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REVIEW

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Bioenhancers from mother nature: an overview

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Abstract

Background The concept of bioenhancer comes from Ayurveda. Many ways have been documented in the literature to boost the bioavailability of poorly bioavailable medications, and one of the most recent techniques is the use of bioavailability enhancers.

Main body of the abstract Herbal bioenhancers are a choice of bioenhancer in modern medicine because of their easy absorption, safety, and lack of side effects. They also reduce drug toxicity, decrease treatment times, and lower treatment costs. Increasing drug bioavailability after oral administration is medically relevant since bioavailability has a direct impact on plasma drug concentrations and therapeutic bioefficacy. When medicine is coupled with a suitable bioenhancer, the bioavailability of the drug is increased. The drug and bioenhancers have no synergistic effect. They reduce the dosage, cost, toxicity, and other side effects, as well as the amount of time it takes to act.

Short conclusion The objective of these survey is that to investigate the thought of the bioavailability to get a superior therapeutic response within the right portion with natural pharmaceuticals containing product, as well as the classification of bioenhancers, mechanism of action, commercial formulation, and future prospects.

Keywords Bioenhancer, Modern medicines, Bioefficacy, Synergistic effect, Herbal drugs

Background

Today, there is a medical need and interest in improving the bioavailability of poorly bioavailable, costly, and dangerous medications that are administered for lengthy periods of time. Poorly bioavailable medications continue to be sub-therapeutic since a significant portion of dosage does not ever achieve a plasma drug concentration as well as exerts its pharmacological activity until and unless exceptionally high dosages are given, which can produce substantial adverse effects. A multitude of variables can contribute to poor oral bioavailability, including poor dissolution and poor solubility in water, intestinal barrier permeability, drug degradation in gastrointestinal as well as intestinal fluid, including systemic intestinal as well as hepatic metabolism [1].

As a result, drug compounds that do not have the same therapeutic action but improve bioavailability when coupled with other medications or molecules are needed. When taken with another medicine, several natural substances of plant origin can improve bioavailability. As a result, bioenhancers are chemical compounds that boost the bioavailability of low bioavailable medications when combined with bioenhancers, but do not have a synergistic impact with the drug [2].

Main text

Rational of bioavailability enhancement

"Biopotentiation or bioenhancement refers to the phenomena of enhancing the overall occurrence of any chemical substance in the biological fluid and systemic circulation, as well as secondary chemicals responsible for the increase in plasma drug concentration of the major component" [3].

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Bioenhancers are utilised in a variety of methods to promote bioavailability. Absorption boosters, prodrugs, permeability boosters, micronisation, and formulations of prolonged and sustained release pharmaceutical formulations such as liposomes and emulsions, as well as P-glycoprotein inhibitors are all examples of specific strategies (P-GP) [4].

Bioenhancers with ideal properties [5, 6]

Bioenhancers have the following properties

- It should be nontoxic in nature.
- It should be simple to formulate.
- At a very low concentration, it should show its effect when combined with the drug.
- It should increase the absorption and activity of the drug.
- Compliance is simple.
- Because of the low cost, acceptance is simple.
- Easily accessible.
- It must be non-irritating and allergy-free.
- It should be stable in its surroundings and quick to react.

Advantages of bioenhancer

- When a bioenhancer is used in combination with a drug, the drug's dosage is decreased, and the possibility of drug resistance is minimised.
- Adverse drug responses or side effects, as well as drug toxicity, will be decreased as a result of the lower dose.
- This is particularly true with anticancer medications such as Taxol.
- Due to an improvement in bioavailability, the drug's efficacy has increased.
- As drug bioavailability is increased, they can lower both inter-individual and intra-individual variability [7].

Disadvantages of bioenhancer

Despite the success of bioenhancers in drug delivery, there are still some challenges for new bioenhancers in development, such as

- Increasing the features of drug formulations such as blood circulation, functional surface area, drug dissolution protection, passing biological barriers, with site-specific targeting.
- Researching and developing bioenhancer for large-scale manufacturing is a challenge. Laboratory or pilot technologies must always be scaled up for ultimate commercialisation. Scaling-up problems include low nanoparticle concentrations, aggregation, and the chemical process; it is easier to modify nanoparticles in the laboratory.
- Regulations regulating the physiochemical and pharmacokinetic features of newer bioenhancers are required [8].

What exactly are bioenhancers?

"Bioavailability is the rate and amount to which an active pharmacological ingredient enters into systemic circulation and then becomes accessible at the necessary site of action." When compared to oral delivery, intravenous medicines have the highest bioavailability since oral administration delivers a lower percentage due to partial drug absorption [9].

Definition

Bioenhancers are compounds that, when combined with pharmacological substances, stimulate and enhance drug bioavailability without having a synergistic activity with the drug.

Bioavailability enhancers are chemicals that, on their own, do not have the same effect as a traditional medicament. But when combined, they enhance drug macromolecular activity in a number of ways, including boosting drug bioavailability all across membranes, enhancing the drug molecule using conformational interactions, serving as drugs molecule receptors, and enhancing drug sensitivity in target cells. "A 'bioenhancer' is a chemical that increases the bioavailability and effectiveness of a medication it is combined with without having its own pharmacological action at the dose used" [10].

There are various benefits of using natural bioenhancer and are given in Fig. 1 [7]

History of bioenhancer

The term "bioavailability enhancer" was created by C.K. Atal, the Chairman of the Regional Research Laboratory at Jammu, when Piperine was discovered and scientifically demonstrated to be the first bioavailability booster in the history of the world in 1979. Bioenhancers are substances that, when taken orally, do not have any pharmacological effects on their own but rather increase biological activity or the uptake of the active ingredient and increase bioavailability during combination therapy [11].

The word "bioavailability enhancer" is derived from Trikatu, an Ayurvedic combination containing black pepper, long pepper, and ginger, is where the name

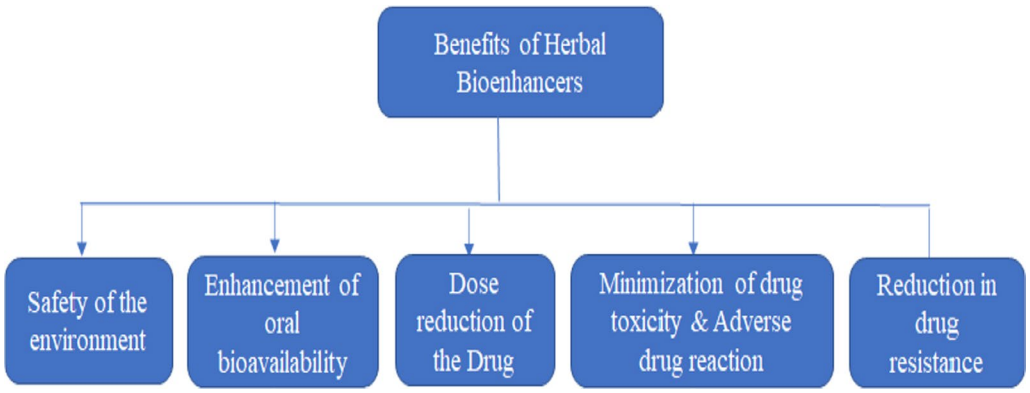

Fig. 1 Benefits of herbal bioenhancers

"bioavailability enhancer" originates. Sanskrit word trikatu translates to "three acrids." In 1929, Bose discovered the bioavailability enhancer activity. Trikatu is a Sanskrit word that means "three acrids." Bose initially found the bioavailability enhancer action in 1929, when he detailed the effect of long pepper on Adhatodavasaka leaves, which improved Vasaka activity [12, 13].

Bioenhancers is an ancient Ayurvedic term that refers to the drug's increasing effect, as well as the Sanskrit term "Yogvahi," which means "to rise in effect" [14].

Classification of bioenhancers

Based on their properties, bioenhancers are divided into two groups. Bioenhancers can be classified into the following types:

Bioenhancers based on origin

Based on their origin, bioenhancers are classified into the following classes [15, 16]

I. *Bioenhancers derived from plant sources* These bioenhancers are made up of different plant parts. Secondary metabolites from a variety of medicinal and aromatic plants are thought to be a rich source of bioenhancers (Table 1).
II. *Bioenhancers derived from other than plant sources* Bioenhancers originating from non-herbal sources are number two. Non-herbal and synthetic chemical compounds can be used to obtain and synthesis these bioenhancers.
III. Bioenhancers from plant sources
IV. Bioenhancer from other than plant sources

Capmul *Source* Glycerolysis of specified fats and oils, as well as esterification of glycerin with specific fatty acids, is used to make capmul (mono-, di-, and triglyceride).

Mechanism of action Capmul functions as a very effective transporter and solubiliser of active chemicals due to its lipophilic nature. Due to its mono-diglyceride medium-chain esters, which are used to dissolve troublesome compounds like sterols, it also has bacteriostatic properties. [27]

Drugs Ceftriaxone 70 (Capmul's lipophilic nature contributes in improving Ceftriaxone 70's solubility.)

Distillate of cow urine Cow urine distillate is more effective as a bioenhancer as compared to cow urine. Its Rasayana helps to modulate the immune system and acts as a bioenhancer [28].

Bioenhancers based on mechanism of action [10]

Inhibitors of P-gp efflux pumps	Example: Cuminumcyminum (Black cumin), Carumcarvi (caraway), Genistein, Sinomenine, Naringin, Quercetin
Suppressors of CYP-450 enzyme and its isozymes	Example: Naringin, gallic acid, and its ester, quercetin
Regulators of GIT function to facilitate better absorption	Example: Niaziridin (drumstick pods), Zingiber Officinale (ginger), Aloe vera (Aloe), and glycyrrhizin (licorice)

Mechanism of action of bioenhancers

Herbal bioenhancers work through a variety of processes. Different bioenhancers may have the same or different mechanisms of action. Nutritional bioenhancers work on the gastrointestinal tract to improve absorption. Antimicrobial bioenhancers primarily influence drug metabolism. [6, 29]

The following are the main mechanisms by which different bioenhancers increase the bioavailability of the medicinal component [30]:

Table 1 Herbs, their origin, dosage as bioenhancements, and mechanism

Sr. no.	Bioenhancer	Biological origin	Class	Dosage as bioenhancements	Drug with bioenhancers	Mechanism	Ref.
1	Piperine Part used-Seeds	Piper longum and Piper nigrum Family- Piperaceae	Amid alkaloid	15 mg/kg	Nevirapine, Rifampicin, Propranolol, Nimesulide, Ciprofloxacin	Piperine's methylenedioxyphenyl ring helps to inhibit drug-metabolising enzymes such as CYP 450 and UDP glucuronyl transferase. P-gp is also inhibited, causing drug efflux from enterocytes	[17]
2	Curcumin Part used-Rhizomes	Curcuma longa Linn Family-Zingiberaceae	curcuminoids	12 g/day	Celiprolol, Midazolam	Curcumin suppresses drug-metabolising enzymes (CYP3A4) in the liver, causing changes in the drug transporter P-glycoprotein, which raises the Cmax and AUC of celiprolol and midazolam in rats	[18–20]
3	Quercetin	This flavonoid may be found in a variety of fruits (apples, citrus fruits such red grapes, raspberries, and cranberries), green leafy vegetables, and black and green tea.	flavonoid	–	Diltiazem, Digoxin, Epigallocatechin gallate	It inhibits the p-glycoprotein efflux pump and the metabolising enzyme CYP 3A4 in the intestinal mucosa and restrains the metabolising enzyme CYP3A4	[21]
4	Ginger Part used-Whole Part	Zingiber officinale Roscoe, Zingiberaceae family	Saponins, flavonoids, alkaloids	10–30 mg/kg	Antibiotics like Azithromycin, Erythromycin, Cephalexin, Cefadroxil, Amoxycillin, and Cloxacillin	The saponins, flavonoids, and alkaloids in ginger have a powerful effect on the GIT mucosal membrane. Ginger aids absorption by modulating gastrointestinal function	[22]
5	Indian aloe Part used-Leaves	Aloe barbadensis Mill.,	Liliopsida	Vitamin C and E	Indian aloe (Leaves)	Aloe, when combined with vitamins, slows down and prolongs absorption	[23]
6	Caraway Part used-Seeds	Carum carvi Linn., Family- Apiaceae	Novel flavonoid	1–55 (mg/kg)	Antibiotics, antifungal, antiviral, and anticancer medications, Anti-TB medications including Rifampicin, Pyrazinamide, and Isoniazid have therapeutic efficacy	Because of new flavonoids, rifampicin's peak concentration (Cmax) and area under the curve (AUC) are increased.	[24, 25]
7	Capsaicin Part used- Fruit	Capsicum annum Linn., Family- Solanaceae	capsaicinoid	–	Theophylline	Capsicum enhances the AUC of the medicines by increasing their absorption	[26]

- By enhancing the GIT tract's blood supply, orally administered drugs are better absorbed.
- Active transporters at diverse places, like glycoprotein (p-GP), the efflux pumps that pumps drugs out of the body and prevents them from reaching its target site, can be modified. Bioenhancer works in these situations by blocking the pop-up from opening.
- Inhibiting drug metabolism enzymes such as CYP3A4, CYP1A1, CYP1B2, and CYP2E1 in the liver, stomach, lungs, and other sites. This will also help with the first-pass action of drugs.
- Reducing passive tubular reabsorption and preventing glomerular filtration as well as active tubular secretion by inhibiting renal clearance. Inhibiting the UDP glucuronosyl transferase enzyme, that conjugates and inactivates the drug, may occasionally obstruct biliary passage.
- Some of the other mechanisms of action of bioenhancers are shown in Figs. 2 and 3.

Marketed formulation

Significant information has been published in a number of national and international journals by the Regional Research Laboratory, Jammu (RRL), and patent applications were filed in India, USA, as well as the Europe. Ant tubercular formulations were created following the proposed step-by-step medication development methodology. The Drug Control General of India (DCGI) granted a licence for antitubercular formulations to be commercialised in India following the conclusion of Phase IIIb clinical studies.

November of 2009, the Medication Control General of India (DCGI) approved CandilaPharma's commercial version of antitubercular drug Risorine, It contains 10 mg of piperine, 300 mg of isoniazid, and 200 mg of rifampicin. When Rifamicin was combined with Piperine, its bioavailability increased by 60%. As a result, Piperine reduced the rifampicin dose from 450 to 200 mg, lowering the drug's cost, dosage, and toxicity [31].

Some of the recent formulations of natural bioenhancers are given in below table (Table 2—Liposomal formulation, Table 3—Nanoparticle Formulation, Table 4—Transferosome Formulation, Table 5—Microspheres Formulation).

Future prospectus

In today's world, the concept of bioenhancers has proven to be quite revolutionary. The dose of bioenhancers is lowered, and the risk of drug resistance is reduced. Due to the lower dosage, the toxicity of the drugs is lower; this is especially true for cancer drugs such as Taxol.

There are also environmental benefits. The bark of the Pacific yew, one of the largest and slowest growing plants in the world, is used to produce Taxol, a drug used to treat prostate and ovarian cancer. Currently, six trees between 25 and 100 years old would have to be cut down to cure one patient. As a result of bioenhancers, fewer people will die.

Conclusion

The cost of therapy in poor countries like India is a major challenge for modern medicine. Systematic and imaginative techniques are needed to reduce these costs. Researchers are currently investigating strategies

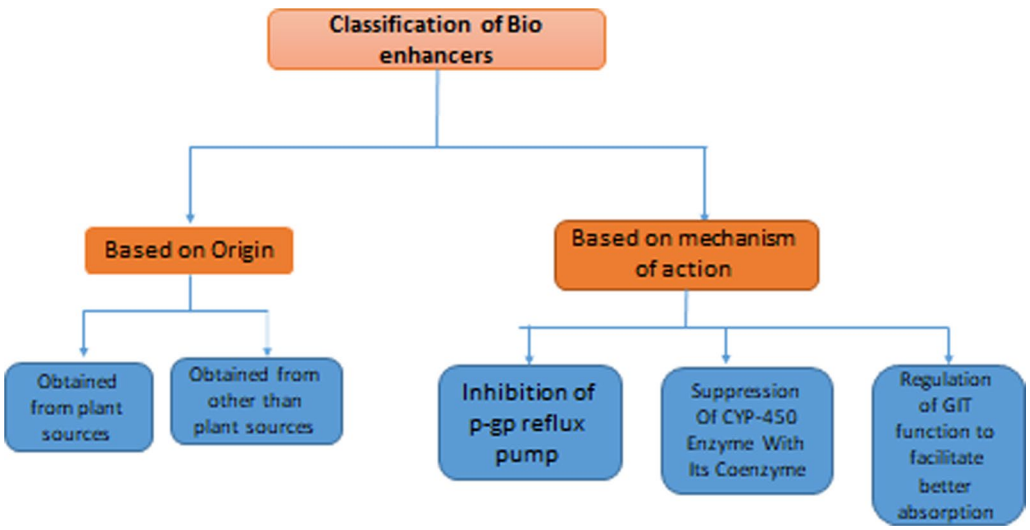

Fig. 2 Classification of bioenhancers

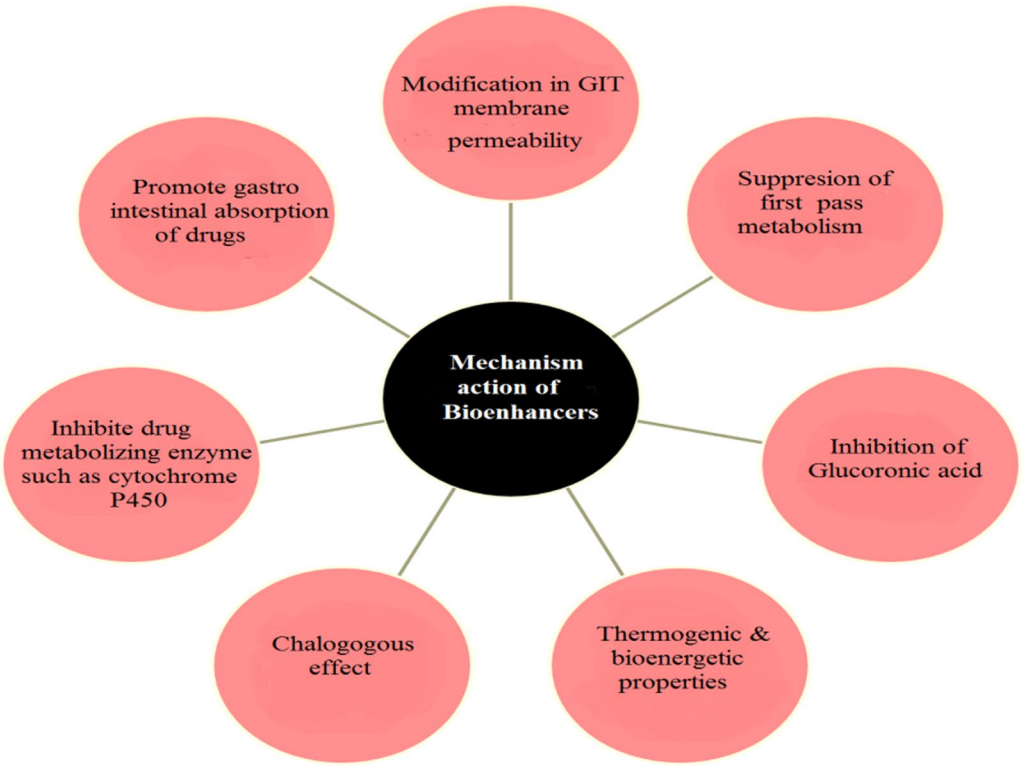

Fig. 3 Mechanism of different natural bioenhancers [28]

Table 2 Liposomal formulation containing natural bioenhancer

Liposomal formulation	Bioenhancer	Application	Preparation method	% of entrapment efficacy	Biological activity	Mode of administration	Ref.
Liposome of quercetin-epigallocatechin gallate	Quercetin	Lowered dose, increased penetration through blood–brain barrier	Reverse Evaporation method	60	Anti-oxidant Anti-cancer	Intranasal	[32]
Liposome of curcumin-piperine	Piperine	High trap efficiency with long circulation	Ethanol injection Technique	88.27	Anti-inflammatory, anti-virus, and anti-tumour	In vitro	[33]
Liposome of artemisia arborescence	Artemisia Arborescenc (Artemisia itself acts as a bioenhancer)	Essential oils may be directed to specific cells	Sonication and the film process	60–74	Antiherpetive	In vitro	[34]
Liposome of garlic-amphotericin	Garlic	Lead to increased efficiency	hydration of thin films	79.7	Anti-fungal	Topical	[35]
Liposome of encapsulated silymarin	Silymarin (Silymarin itself acts as a bioenhancer)	Enhance bioavailability	Technique of reverse evaporation	69.22	Hepatoprotective	Buccal	[36]

to reduce drug doses, and thus treatment costs, so that therapy becomes relatively accessible to a wide range of patients, including the poor.

Enhancement technology is based on the existing medical system, but it is a rapidly evolving sector. New methods of drug discovery are advancing rapidly, but the economics of drug development are a concern. Researchers are currently working on a way to reduce drug doses, and thus the cost of treatment, and make therapy accessible to broad populations, including financial support for the country. The bioenhancing

Table 3 Nanoparticle formulation containing natural bioenhancer

Nanoparticle formulation	Bioenhancer	Application	Preparation method	% of entrapment efficiency	Biological activity	Mode of administration	Ref
Nanocapsules of artemisinin	Artemisinin	Long-term medication release	Layer-by-layer technique	90–93	Anticancer	In vitro	[37]
Nisoldipine-piperine nanoparticles	Piperine	Improve bioavailability	Precipitation method	89.77	Calcium channel blocker	Oral	[38]
Isradipine-rutin nanoparticles	Rutin	Enhanced systemic bioavailability	Homogenszation by the ultra-sonication method	97.85	Hypertension	Oral	[39]
Amphotericin B-piperine nanoparticles	Piperine	Enhanced bioavailability	Solvent evaporation method	48	Antileishmanial activity	Oral	[40]
Paclitaxel-piperine, quercetin nanoparticles	Piperine, Quercetin	In comparison with free paclitaxel, it has greater solubility and bioavailability	Solvent evaporation method	56.12 for Piperine 58.97 Quercetin	Anticancer	Oral	[41]

Table 4 Transferosome formulation containing natural bioenhancer

Transferosome Formulation	Bioenhancer	Application	Preparation Method	% of entrapment efficiency	Biological activity	Mode of administration	Ref
Colchicine-Cyclodextrin Transferosome	Colchicine	Increase skin penetration	Thin-film hydration method	93.8	Acute gout	In vitro	[42]
Capsaicin- mitoxantrone hydrochloride Transferosome	Capsaicin	Increase skin penetration	Conventional Thin film hydration method	60.34	Antiarthritic	Topical	[43]

Table 5 Microspheres formulation containing natural bioenhancer

Microspheres formulation	Bioenhancer	Application	Preparation method	% of entrapment efficiency	Biological activity	Mode of administration	Ref.
Isoniazid-piperine microspheres	Piperine	Sustained Release formulation	Double emulsification method & complex coacervation method	263 nm	Tuberculosis	In vitro	[44]
Acyclovir- piperine microspheres	Piperine	To boost oral bioavailability, place the medicine in the upper gastrointestinal area	Emulsification solvent evaporation method	400–525	Active against HSV-1 and HSV-2 herpes simplex viruses	Oral	[45]
Famotidine-quercetin microspheres	Quercetin	Alternative for treating peptic ulcer	Ionotropic gelation method	906 µm	Peptic ulcer	Oral	[46]

phenomenon is useful in a variety of situations and provides relief to society because of its side effects.

Abbreviations

GIT	Gastrointestinal tract
AUC	Area under the curve
Cmax	Peak concentration
UDP	Uranyl di-phosphate
P-GP	P-glycoprotein
RRL	Regional Research Laboratory
DCGI	Drug Control General of India

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Declarations

Consent for publication

The undersigned, give my consent for the publication of identifiable details, within the text ("Material") to be published in the above Journal and Article.

Competing interests

The authors declare that they have no competing interests.

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