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Sarina Chettri
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India

Chandrika Sharma
Assistant Professor, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India

Rajat Das
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India

Prodipto Roy
Department of Pharmacognosy, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India

Corresponding Author:
Chandrika Sharma
Assistant Professor, Himalayan Pharmacy Institute, Majhitar, East Sikkim, India

An examination of natural bio-enhancers and how they are used in contemporary medicine

Sarina Chettri, Chandrika Sharma, Rajat Das and Prodipto Roy

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Abstract
A Bioenhancer is an agent without exhibiting any usual pharmacological activity of its own at the dose employed, it is capable of increasing the bioavailability and bio efficacy of a specific medicine with which it is coupled. They are a radically new idea in modern medicine. They are quite effective when combined with several drug classes such as antibiotics, antituberculosis, and antiviral drugs. They enhance the oral absorption of vitamins, minerals, herbal extracts, amino acids, and other nutrients. They act through several mechanisms which may affect mainly the absorption process and drug metabolism. They can be classified based on their natural origin and a different mechanism of action elicited by them when combined with a drug to achieve maximum bioavailability. They play a major role in modern medicine. Most bio-enhancers are natural in origin with herbal nature so they have an unlimited source which adds more benefits as it does not require large finances to extract, prepare or produce the bioenhancer. Different kinds of bioenhancer include Piperine, Allicin, Niaziridin, Glycyrrhizin, *Aloe vera*, Ginger, capsaicin, Naringin, and curcumin.

Keywords: Bioenhancer, oral absorption, Bioavailability, Ginger, Piperine, Naringin

Introduction
Bioenhancer is an agent which is capable of enhancing the bioavailability and bio efficacy of a particular drug with which it is being combined, without any pharmacological activity of its own at the dose used. Reducing drug dosage, drug expense, the occurrence of drug resistance, and the possibility of negative drug reactions/side effects are all advantages of using a bioenhancer [1]. Moreover, increased bioavailability improves efficacy. The need for raw materials for the production of drugs is reduced is one of the secondary positive consequences. For example, this is especially advantageous and evident in anti-cancer drugs like Taxol which is used to treat breast cancer [2]. Drugs like The Yew tree are the slowest growing trees in the world, and to obtain taxol for one patient, six trees of 25–100 years are to be chopped. Adding a bioenhancer to Taxol means that fewer trees are chopped. The use of bioenhancer results in ecological, benefits. The first bio enhancer piperine was discovered in 1979, ushering in a new class of medications as well as a brand-new idea. Increased medication bioavailability is a new field that was made possible by this ground-breaking discovery. The best bioenhancer is still piperine [3].

History of Bioenhancer
Bioenhancers is a ancient word which is derived from Ayurveda, meaning the increased amount of effect of drugs, as "Yogvahi" in Sanskrit, which in combination indicates an increase in effect. In 1929, the action of bioenhancer was documented by Bose where long pepper was used to increase the antihistaminic ability of vasaka [4]. the director of the institute C.K. analyzed formulations of ancient Indian Ayurveda and designed the theory that the efficacy of the formulation was enhanced by Trikatu. Ginger, Long pepper, and Black pepper (*Piper nigrum*) were the three ingredients (*Zingiber officinale*). Based on this theory, a key ingredient in Trikatu, "*Piper longum*," was found to boost the bioavailability of various medications, confirming that piperine, a bioenhancer, is present in Trikatu [5].

Drug Absorption Barriers
For the medication to go from the gut lumen into the systemic circulation and exercise its biological effects, it must pass through the intestinal mucosa's epithelial barrier.

There are numerous anatomical and biological barriers for the oral medication delivery system to enter the epithelial membrane [6]. There are many structures in the intestinal epithelium that acts as the barriers to the transfer of the drugs from the gastrointestinal track to the systemic circulation. The membranes around cells are lipid bilayers containing proteins such as receptors and carrier molecules. Drugs crossess the lipid membrane by the passive diffusion or carrier mediated transport which involves the spending of energy. Aqueous channels exist within the proteins which allows the passage of tiny water-soluble molecules like ethanol. It is challenging for medication molecules which is larger than 0.4 nm to pass via these aqueous channels [7].

Ideal Characteristics of the Bioenhancers

The optimal bio-enhancers, according to an assessment of bioenhancers' contributions, are

1. It should not be irritating, allergic, or poisonous.
2. It shouldn't have any pharmacological effects of its own
3. Must have predictable, repeatable behavior that is quick-acting.
4. Action should be one-way only.
5. Must be suitable for use with other active medicinal components.
6. Ought to be environment- and time-stable.
7. It must be simple to formulate in different dosage forms.
8. It ought to be affordable and easily accessible [8].

Classification

Bioenhancer can be classified which is based on.

1. Their origin
2. Mechanism of action
3. Based on origin

Plant origin	Animal origin
Piperine, Allicin, Niaziridin, Glycyrrhizin, *Aloe vera*, Ginger, capsaicin, Naringin, and curcumin	Cow urine distillate

Based on the mechanism of action

- Naringin, *Carum carvi* (caraway), *Cuminum cyminum*, Genistein, etc. all inhibit the p-gp efflux pump.
- Naringin, gallic acid, and its esters are CYP-450 enzymes and isoenzyme suppressors.
- GIT regulators, such as *Aloe vera* (aloe), Niaziridin (Drumstick pods), *Zingiber officinale* (Ginger), etc., work to improve absorption [8].

Bioenhancers from Herbal Sources Resveratrol

Resveratrol (3, 4′, 5- trihydroxystilbene), A nutraceutical that has recently attracted a lot of research attention because of its exciting pharmacological potential. It is a phytoalexin that can be found in a variety of plants, such as berries, red wine, grapes, and peanuts [7]. As a natural compound, resveratrol's use as a nutraceutical and as a therapeutic agent for many diseases has been widely researched in preclinical studies. Its use is especially of interest to cancer patients because of the high risks associated with traditional treatments, including surgery and chemotherapy [9].

Naringin

Naringin (4, 5, 7-trihydroxyflavanone-7-rhamnoglucoside) is a significant flavonoid glycoside that can be found in grapefruit, apples, onions, and tea. It has a variety of pharmacological actions, including blood lipid reduction, antioxidant activity, antiulcer, antiallergic, and anticancer properties [10]. It shows inhibition of P -gp and CYP3A in rats [11]. The Area Under Curve (AUC) of paclitaxel is increased significantly in the presence of naringin (49.1% for naringin at 10 mg/kg) [12].

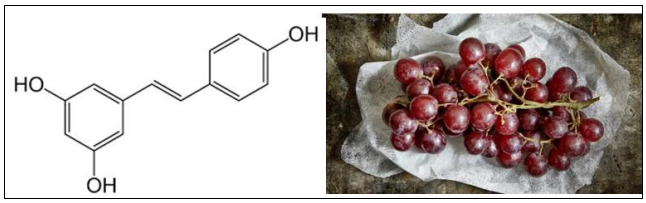

Fig 1: Structure of Resveratrol

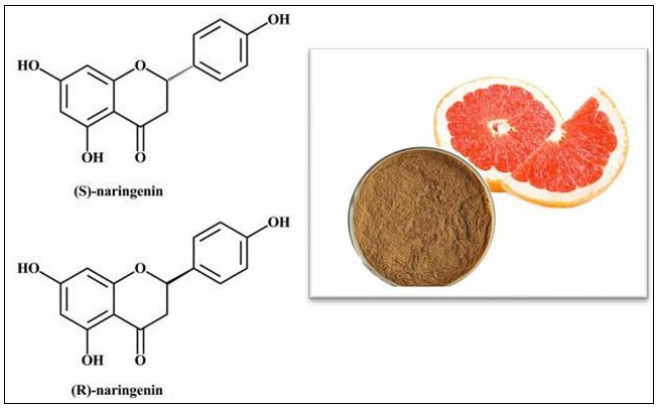

Fig 2: Structure of Naringin

Piper nigrum

The family Piperaceae's main alkaloid, piperine, provides a variety of therapeutic benefits which is found in pepper fruits. One of the foods that has been proven to be a bioenhancer for some specific medications is pepper fruits. With encouraging results, piperine has been employed as a bioenhancer for some antibacterial medicines. Oxidation, hydroxylation, and glucuronidation are caused by the interaction of piperine with enzymes that metabolise drugs. Given that it has been utilised as a bioenhancer for Allopathic, Ayurveda, and Unani medicines, piperine looks to be at the top of the list of bioenhancers. Several medicines' Cmax is dramatically increased by piperine [13].

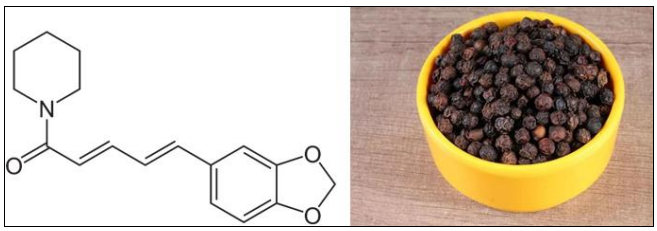

Fig 3: Structure of Piperine

Zingiber officinale

Ginger (*Z. officinale*) is a rhizome that has powerful active ingredients called gingerols. The volatile oil components in ginger are mostly responsible for its odour[6]. Gingerol is the pungent component of ginger. Gingerols have analgesic, sedative, antipyretic, and antibacterial activities in experimental animals and are known to enhance gastrointestinal tract motility. The primary pungent

component of ginger is gingerol. Future alternatives to costly and harmful medicinal medicines are looking promising thanks to the chemopreventive properties of -gingerol. Ginger demonstrates properties such as anti- ulcer, anti-thrombotic, anti-microbial, anti-fungal, anti-inflammatory, antidiabetic, anti-emetic, anthelmintic, analgesic and antipyretic, antioxidant and antiapoptotic, anticancer properties. Ginger has a strong effect on the GIT mucous membrane [14].

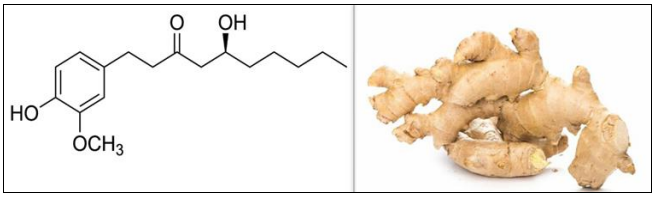

Fig 4: Structure of Gingerol

***Aloe vera* (*Aloe barbadensis* miller)**

It is commonly known as Indian Aloe which contains Aloein and Emodin they are responsible for the improvement of the absorption of both vitamin C and E [15]. Aloe improves the bioavailability of Vitamin C and E in humans by slowing down absorption and extending vitamin retention in plasma. Because of its potential nutritional and therapeutic significance as a herbal bioenhancer, *Aloe vera* is very promising [16].

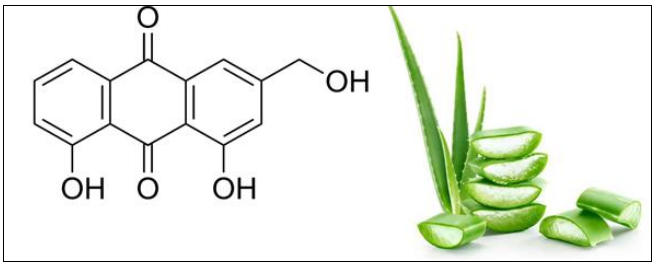

Fig 5: Structure of Aloe emodin

Quercetin

Quercetin is a flavonoid found in Citrus fruits. It is reported that Quercetin increases the bioavailability, blood levels, and efficacy of a number of drugs such as diltiazem,35 digoxin36, and epigallocatechin gallate. 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 1814ng.h/ml, when co-administered with quercetin [17].

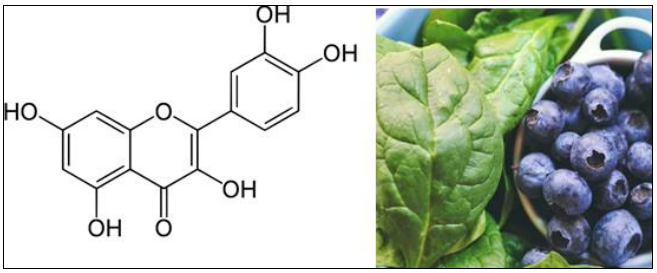

Fig 6: Structure of Quercetin

Distillate of cow urine

Cow urine distillate is effective as a bioenhancer as compared to cow urine. Its Rasayana helps to maintain the immune system and acts as a bioenhancer [18]. An effective amount of bioactive fraction from cow urine distillate is the only bioavailability facilitator obtained from animal sources and is a pharmaceutically acceptable bioenhancer. It has antitoxic activity against cadmium chloride toxicity and it can be used as a bioenhancer of zinc [9].

Curcumin (*Curcuma longa* L)

The main curcuminoid in turmeric, *Curcuma longa L*. of the *Zingiberaceae* family, is called curcumin. It increases the C max and AUC of celiprolol and midazolam in rats by inhibiting the drug metabolising enzyme CYP3A4 in the liver and causing alterations in the drug transporter P-glycoprotein. Similar to piperine, curcumin has a bioenhancing property. It reduces the UDP- glucuronyl transferase in the tissues of the liver and intestine. Moreover, it alters the physiological activity in the gastrointestinal system, which increases drug absorption [19].

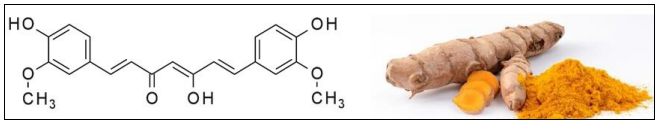

Fig 7: Structure of circumin

Bioenhancers that have just recently been developed

Resveratrol

Plants create the stilbenoid resveratrol (3, 5, 4′-trihydroxy-trans-stilbene) in reaction to harm or an attack by pathogens like bacteria or fungi. The skin of grapes, blueberries, raspberries, and mulberries contain it. When apigenin (a natural anti-inflammatory agent) and resveratrol were administered together, plasma levels of apigenin increased 2.39 times more than when apigenin was administered alone. According to this finding, resveratrol enables apigenin to avoid the hepatic metabolism [20].

Friedelin

A biologically active isolation of Quercus Stenophylla Blume, Orostachys japonica A.Berger, and Azima tetracantha Lam. (Salvadoraceae) is known as Friedelin (Fagaceae). Following oral treatment of apigenin (50 mg/kg body weight) and friedelin (50 mg/kg body weight) to rats, apigenin's bioavailability was improved. Friedelin reduced the P-ATPase glycoprotein's enzyme activity, showing that P-glycoprotein inhibition may be the cause of apigenin's increased bioavailability [21].

Lutein

A xanthophyll called lutein is distributed in green leafy foods including spinach, kale, and yellow carrots. Lutein has anti-atherogenic, anticarcinogenic, and eye protection properties [22].

Bioenhancing activity through different routes of administration

The drug's polarity can be increased through chemical modification, prodrug synthesis, film coating, targeted distribution, encapsulation in an appropriate delivery system, micro- or nanosizing, among other methods. When supplied via various methods, the medication and the bioenhancer mechanisms are outlined.

Route of Administration	Bio-enhancer	Biological Source	Mechanism of Action	Study Design Model	Research compound	References
Buccal	*Aloe vera*	Plant	Intercellular modulation	*In vitro*	Didanosine: Antiviral reverse transcriptase inhibitor	[23]
Buccal	Menthol	Plant	No mechanism specified	Ex vivo	Dideoxycytidine: Nucleoside analog reverse transcriptase inhibitor	[24]
Nasal	Chitosan (Biopolymer)	Chemically modified chitosan	Tight junction modulation	*In vivo* (sheep)	SCT: Endogenous polypeptide hormone	[25]
Nasal	TMC (Cationic polymers)	Chemically modified chitosan	Increased muco adhesion; tight junction modulation	*In vivo* (rat)	Mannitol:Sugar alcohol	[26]
Oral	(-)- Epicatechin (Flavonoid)	Plant (woody plants)	Metabolism (glucuronidation) inhibition	Ex vivo (rat small intestine)	Alpha-naphthol: Organic fluorescent compound	[27]
Oral	Curcumin	Plant	Metabolism (CYP3A4) inhibition	*In vivo*	Midazolam: Benzodiazepine	[28]
Oral	Resveratrol (Polyphenolic phytoalexin)	Plant (berries, grape skins, red wine)	Efflux transporter(P-gp, MRP-2) inhibition; reduced elimination; renal uptake transporter	*In vitro*	Methotrexate: Immunosuppressant	[29]
Pulmonary	Aprotinin, bestatin (Protease inhibitors)	Animal	Metabolism inhibition	*In vivo* (rat)	RhG-CSF: Granulocyte- colony stimulating factor	[30]

Hurdles with bioenhancers

Bio enhancers in drug delivery is a success but various new bio-enhancer which has been discovered recently comes with many challenges. Challenges which include changing of physicochemical characteristics oh the nano particles in order to improve properties like long circulation in the blood, increased functional surface area and site specific targeting.

Conclusion

A Bioenhancer is a substance, when given to a medication, increases its bioavailability and bio efficacy while having no independent pharmacological effects at the dosage used. Bioenhancers ought to be inert, Non-toxic, Compatible with pharmaceutically active chemicals, affordable, stable, simple to synthesise into a variety of forms, and widely accessible. There are various herbal medications that are utilised as bio enhancers and can boost the effectiveness of active medications when used together. This review gives light on various aspects of bioenhancers.

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