JPharmSci
Journal of Pharmaceutical Sciences
Open access peer-reviewed Journal
www.jpsjournal.com [ISSN: 1520-601x]

Natural Bioenhancer: A Remedy for Poorly Soluble Drugs.

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ABSTRACT

Almost 40% allopathic medicines have formed to be poorly water soluble drugs. Certain herbal medicaments also have low water solubility. For better bioavailability in systematic circulation and to achieve high therapeutic index solubility of any type of drug should be increases in aqueous media. Solubility enhancement of poorly water soluble drugs can be increase by salt phenomenon, co-solvency, precipitation, addition of certain solutes, size reduction etc. use of natural bio enhancers increases solubility of certain medicaments to some extends and can achieve maximum absorption od drugs through GIT. Bio enhancers may play a key role to alter the pharmacokinetic of a drug through different mechanisms.Bio enhancers such as *piperine, Ginger, Naringin, Drumstick pods, Glycyrrhizin Quercetin, Curcumin, Cow urine distillate, Stevia Rebaudiana, Genistein, Sinomenine. Gallic acid esters, Cumin/Caraway (Carum carvi), Cuminum, Capsaicin, Resveratrol* has been used in certain formulations to increase the bioavailability of drug and to achieve maximum concentration of analyte in blood with respect to less time. These bioenhaners have been scientifically proved with no incompatibility with drug and no any size effects after treatment. This review article represents phytochemical nature and scientifically proved pharmacological activities of drug for better absorption.

Keywords: Natural Bioenhancer, Bio availability, Resveratrol, Piperine, Solubilizers.

INTRODUCTION

The word "bioavailability" refers to the pace and degree to which any compounds enters the systemic circulation and exhibit the desired activity. There are several pharmacological classes with strong therapeutic action, but because of their limited bioavailability, drug developers have always placed a high priority on how to employ these medications. Factors responsible for poor bioavailability of drugs are the physiochemical properties of the drug and biological barriers[1,2,3]. Poor aqueous solubility, poor intestinal membrane permeability, first pass metabolism, and poor drug stability in the gastrointestinal tract (GIT) are examples of physiochemical barriers, whereas hepatic and intestinal drug metabolising enzymes and efflux drug transporters make up the biological barrier. Poor aqueous solubility, poor intestinal membrane permeability, first pass metabolism, and poor drug stability in the gastrointestinal tract (GIT) are examples of physiochemical barriers, whereas hepatic and intestinal drug metabolising enzymes and efflux drug transporters make up the biological barrier[4,5]. The liver and the gut wall's and other organs' drug metabolising enzymes (DMEs) are the main causes of decreased medication bioavailability[6]. When a medication is taken orally, it goes through a number of processes, including insufficient drug absorption and first-pass metabolism, which eventually results in limited bioavailability. Increased blood levels of the medicine as a result of improved bioavailability boost effectiveness and result in lower dosages[7,8,9]. Too far, a variety of techniques have been used to increase bioavailability, including micronization, disaggregation of micronized molecules, selective or time-release preparations, solubilization of the active ingredient, and selection of polymorphic/crystal forms and nanotechnology. Numerous substances with plant origin have the potential to increase the bioavailability of the primary medication. As a result, bio enhancers are substances that lack traditional pharmacological action but that, when provided along with the primary moiety, significantly increase the

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

drug's activity. Moreover, greater bioavailability improves effectiveness[10,11]. The word "bioenhancer" was originally used by Bose in 1929, who noted that the antiasthmatic effects of vasaka (Adhatoda vasica) leaves increased when they were taken in conjunction with long pepper. The idea or term "bioavailability enhancers" derived from plants may be traced back to our Ayurvedic medical system. The active ingredient like *piperine, Curcumin, Genistein, Sinomenine, Quercetin, Niaziridin, Stevia, Glycyrrhizin, Caraway, Gingerol* and etc. which may increase the bioavailability of certain medications, nutrients, etc.,[12,13,14].

Need for bioenhancers: [15,16]

The main barriers that prohibit molecules from passing through the biological membrane and from being systematically dissolved after delivery by oral or topical route are lipophilicity and size of the molecule. Even if they have great bioactivity in vitro, some plant extracts and phytoconstituents have low lipid solubility, an inappropriate molecular size, or both. As a result, these substances have poor bioavailability and limited absorption. Bioenhancers are phytomolecules that support and enhance the biological action of drugs at lower dosages. The issue of bioavailability affects a number of synthetic and herbal medications. As a substance's pace and extent at which it enters total systemic circulation determines whether or not it is accessible at the requisite site of action, bioavailability is crucial. They are also favoured for groups of medications that are very toxic, costly, need lengthy therapy, and have low efficacy.

Bioenhancers have proven to be particularly successful when combined with many therapeutic types, such as antibiotics, anti-tuberculosis, antiviral, antifungal, and anticancer treatments. Bioenhancers have many modes of action that might primarily alter medication absorption, drug metabolism, or drug targeting.

Bioenhancers should possess innovative qualities like:[17]

- Non-toxic to both people and animals.
- Effective at combinations of extremely low concentrations.
- Simple to formulate
- Most significantly, increasing uptake/absorption and activity of the therapeutic molecules.

Modern medical bioenhancers: [18,19]

According to the research that has been done so far, Ayurvedic tradition may offer new opportunities for improving the bioavailability of allopathic medicines with established pharmacotherapeutic effects. As a result, this phenomenon is used for drugs with low bioavailability. Therefore, the optimism in contemporary science and industrial influence combine to reap the benefits of developing medication propaganda for advancement in human health care. Drugs used in the treatment of TB, such as "Risorine" by candida Pharma (Nov. 2009), comprise rifampicin and isoniazid and contain piperine as a bioenhancer, which has been shown to increase bioavailability.

Bioenhancers in Ayurveda: [20,21,22,23]
In Ayurveda, the word "bioenhancer" is referred to as "Yogvahi". Raw spices and herbs can help through their aroma too, but ayurveda recommends cooking of spices and herbs, because in cooking material is exposed to heat and molecular interaction between medium (oil/ghee) and spices causes interaction of active components it also sanitize unwanted toxic material present in raw spices and herbs. Access to the digestive system and other systems is aided by cooking. The term "yogvahi" refers to all spices and herbs that serve as carriers for nutrients in food. When necessary, they aid in the digestion of protein, carbs, and fat.

Utilising a bioenhancer may have a synergistic impact that strengthens the benefit and minimises negative effects. The intricate functioning of the human body seems to naturally fit in this domain. To shift this entire symphony in a more harmonic direction, it seems sense that complex medicines, or supplements that may influence the whole at once, would be most helpful. Bioenhancers found in plants are piperine, gallic acid, capmul, allicine, curcumin, ginger, quarcetin, genistein, naringin, caraway, black cumin, niaziridin, lysergol, ammoniac microflora, liquorice, stevia, peppermint oil, aloe, ferullic acid. sinnomenium acutum, capsaicin, gingerol, nitrile glycoside, callistemon rigidus.

Piperine:[24,25,26]

Piperine, an alkaloid from Piper nigrum and other species of piper (Piperaceae), has been demonstrated in several research studies to have bioenhancing properties. In a public-private cooperation with Cadila Pharmaceutical Ltd., Ahmedabad, the Indian Institute of Integrative Medicine, Jammu created the formulation known as risorine. It is a combination of rifampicin (200 mg), isoniazid (300 mg), and piperine (10 mg). It is effective in treating TB, where *piperine* increases bioavailability and lowers the dosage of rifampicin from 450 to 200 mg. In a study, it was shown that the antibacterial agent piperine increases the bioavailability of ampicillin. It has been shown that pentazocine (5 mg/kg) and diclofenac sodium (5 mg/kg) considerably increased when given orally in combination with piper nigrum extract (10 mg/kg). In tail flick and writhing procedures, P. nigrum extract by itself did not exhibit any appreciable analgesic efficacy in albino mice. Combining P. nigrum extract with diclofenac sodium led to a considerable reduction in writhes, which was greater (78.43%) than when diclofenac sodium was used alone (54.90 %). The mean plasma concentrations of carbamazepine (300 or 500 mg twice day) in both dosing groups were considerably raised by piperine (20 mg p. o.). Docetaxel (DTX), an anticancer drug, is made more bioavailable with the use of piperine. Additionally, it increases docetaxel's anticancer properties.

Ginger: [27,28]

Ginger consists of the dried rhizomes of the Zingiber officinale Roscoe, belonging to family Zingiberaceae. Ginger has a strong effect on the GIT mucous membrane. Ginger's role is to control intestinal activity to promote absorption. The dosage of ginger used as a bioenhancer ranges from 10 to 30 mg/kg body weight. The bioavailability of several antibiotics, including azithromycin (85%), erythromycin (105%), cephalexin (85%), cefadroxil (65%), amoxycillin (90%) and cloxacillin (90%) significantly increased.

Naringin: [29,30]

The major component in grape fruit is *naringin*, which is classed as a flavonoid glycoside. Grapefruit's bitter flavour is caused by *naringin*. *Naringin* has a number of pharmacological effects, including an antioxidant impact, the capacity to reduce blood cholesterol levels, and an anti-carcinogenic effect. According to reports, *naringin* inhibits gp and CYP3A1/2 in rats, demonstrating its bio-improving properties. The AUC was considerably increased when oral *naringin* was administered at doses of 3.3 and 10 mg/kg 30 minutes before and after intravenous paclitaxel (3 mg/kg), respectively. It was shown to be 40.8% for a *naringin* dose of 3.3 and 49.1% for a *naringin* dose of 10 mg/kg. *Naringin* contains powerful acyl CoA-cholesterol-O-acyltransferase (ACAT) inhibitory action, macrophage-lipid complex accumulation inhibitory activity, and preventative or therapeutic activity on hepatic disorders. ACAT stimulates the esterification of cholesterol in blood. According to earlier research, *naringin* pretreatment with medicines (such as verapamil, diltiazem, paclitaxel, and tamoxifen) that are substrates of P-gp and/or CYP3A proved to be beneficial across the dosage range of 3-30 mg/kg in rats and rabbits.

Drumstick pods: [31,32]

It contains niaziridin, a nitrile glycoside which is a powerful bioenhancer. Moringa oleifera (Family: Moringaceae) known as drumstick, has been reported as potent hypoglycemic, hypolipidemic, nootropic and anti-inflammatory. It regulates GIT functions to facilitate better absorption. It enhances the bioavailability of rifampicin by 38.8 folds at 1.0 g/ml. It also boosts the bioavailability of Clotrimazole by 5-6 times. The active portion of M. oleifera pods tested in vitro against Mycobacterium tuberculosis (H37Ra) showed no antitubercular activity at the dose that increased rifampicin's antitubercular activity. Using the HPLC-PDA technique, Khanuja et al. conducted a pre-clinical investigation to assess the impact of M. oleifera (MoAF) on the pharmacokinetic disposition of rifampicin. They gave Niaziridin, the active component of M. oleifera, at a dose of 0.1 mg/kg body weight, coupled with 20 mg/kg of rifampicin, orally to Swiss albino mice. They noticed the bioavailability pattern depicted in the accompanying figure, demonstrating Niaziridin's efficacy as a bioenhancer for rifampicin.

Glycyrrhizin:[33,34]

Glycyrrhizin is a glycoside obtained from roots and stolon of Liquorice (Glycyrrhizaglabra). It has an expectorant effect to cure bronchitis and can help ease sore throats, allergies, asthma, gastritis, and peptic ulcers. It is used to treat liver illness and aids in drug detoxification via the liver. It is a diuretic and laxative, boosts the adrenal gland, and increases the immune system. Glycyrrhizin is 50 times sweeter than sugar. The main applications are the therapy of intestinal and respiratory passageways, as well as peptic ulcers and other stomach disorders. Glycyrrhizin demonstrates properties such as antihepatotoxic, anti-inflammatory, anti-cancer, and antiviral action. In terms of the weight of the antibacterial components, glycyrrhizin concentrations range from 0.05 to 50%. Glycyrrhizin is present in nutraceutical substances in concentrations ranging from 0.10 to 10% of their weight. From 0.25 to 20% of the weight of the antifungal medicines are made up of glycyrrhizin. Glycyrrhizin concentrations range from 10 to 10,000 times the weight of the anticancer drugs that are used. Taxol's anti-cancerous action was significantly increased by a factor of five in terms of preventing the growth and division of MCF-7 cancer cells. The cancerous cells growth inhibition by Taxol (0.01 g/mL) in presence of glycyrrhizin (1 g/mL) was higher than even the treatment with Taxol (0.05 g/mL) alone.

Quercetin:[35,36]

Quercetin is a naturally occurring polyphenolic substance that is classified as a flavonoid and has antioxidant potential. It is widely distributed in a number of foods, including grains, vegetables (such as broccoli, onions, and citrus fruits), fruits (such as apples, grapes, and citrus fruits), coffee, green tea, and wine. Additionally, it can be found in medicinal plants including Sambucus canadensis, Ginkgo biloba, and Hypericum perforatum. *Piperine* has also been investigated for a range of medicinal properties like elevated drug permeability, anti-inflammatory, anti-allergic, antihypertensive, anti-cancer, cardio-protective, anti-viral and antioxidant potential owned via fighting with free radicals. It is also reportedly consumed as a supplement to increase energy. It has been claimed to increase the bioavailability of many medications, including verapamil, diltiazem, paclitaxel, digoxin, and tamoxifen.

***Curcumin*:**[37,38]

Curcumin is the principal curcuminoid of the popular Indian spice turmeric (Curcuma longa). *Curcumin* suppresses drug metabolizing enzymes (CYP3A4) in the liver as well as inducing changes in the drug transporter P-glycoprotein, hence increasing the Cmax and AUC of celiprolol and midazolam in rats. After a single oral dosage of norfloxacin to rabbits, it was examined how *curcumin* affected the drug's pharmacokinetic disposition. According to the pharmacokinetic data, mice treated with *curcumin* had considerably greater AUC and AUMC.

Cow urine distillate:[39,40]

In order to boost the efficacy of antibiotic, antifungal, and anticancer medications, cow urine distillate is a more effective bioenhancer than cow urine. Cow urine has antitoxic properties against the toxicity of cadmium chloride and can be utilised as a bioenhancer of zinc. Cadmium chloride exposure reduced the reproductive rate of mature male mice to zero percent. However, the animals exposed to cadmium chloride + cow urine distillate + zinc sulfate showed 90% fertility rate with 100% viability and lactation indices. Fertility index was also found to be 88% in group treated with cadmium chloride + cow urine distillate. Thus, these results indicate that cow urine distillate works as an antitoxic against the cadmium chloride toxicity and it can be used as a bioenhancer of zinc. Cow urine distillate increased the activity of rifampicin by about 5–7 times against Escherichia coli and 3–11 times against Gram-positive bacteria. It probably acts by enhancing the transport of antibiotics across the membrane of gastrointestinal tract. The enhancement in transport is approximately 2–7 times.

Stevia Rebaudiana:[41,42]

In South America, stevia rebaudiana, often known as honey leaf, has been used as a sweetener. Stevioside, a glycoside that is 200 times sweeter than sucrose, is the main ingredient in stevia. Steviol, austroinulin, rebaudioside, and dulcoside A are additional ingredients. Selective stevia extracts, fractions, and pure isolates, either alone or in combination with

piperine, increase the bioavailability and bioefficacy of pharmaceuticals, nutraceuticals, and herbal medicines and formulations. The bioenhancing formula contains stevia in varying amounts, ranging from 0.01 to 80%. The dosage of bioenhancer derived from stevia extract is in the range of 0.01–50 mg/kg body weight and piperine is in the range of 0.01–12 mg/kg body weight. The dose of piperine is in the range of 0.01-10 mg/kg body weight, preferably 8 mg/kg body weight, while the dosage of bioenhancer generated from stevia bioactive fraction or pure chemical is in the range of 0.01-40 mg/kg body weight, preferably 30 mg/kg body weight. The bioenhancer dosage from stevia leaves ranges from 0.01 to 250 mg per dose of the medication, nutraceutical, or herbal extract. No matter how much medication is present in the composition, the dosage of a bioenhancer made from stevia fraction or pure substance is between 0.01 and 75 mg, with 1 to 30 mg being preferred. Stevia increased the bioavailability of many different types of medications, including antibiotics, anti-tuberculosis/anti-ileprosy drugs, anthelmintic/respiratory drugs, anti-fungal/antiviral drugs, anticancer drugs, cardiovascular drugs, anti-inflammatory, antiarthritic agents, immune-modulators, antiulcer drugs, and herbal products or drugs.

Genistein:[43]

The isoflavone class of flavonoids includes genistein (5, 7-Dihydroxy-3-(4-hydroxyphenyl) chromen-4-one), which is also known as a phytoestrogen. The intestinal absorption of paclitaxel, a substrate for efflux transporters such P-glycoprotein, BCRP, and MRP2, was significantly enhanced when co-administered with genistein since it was known to be able to block P-glycoprotein, BCRP, and MRP2 efflux function. After oral administration of the anticancer medication paclitaxel at a dosage of 30 mg/kg in rats, genistein (10 mg/kg) resulted in an increase in AUC (54.7% rise) and a decrease in total plasma clearance (35.2% drop).

Sinomenine:[44]

An alkaloid known as Sinomenine (7, 8-didehydro-4-hydroxy3, 7-dimethoxy- 17-methylmorphinan6-one) is obtained from Sinomenium acutum. Thunb has been utilised as a bioenhancer of Paeoniflorin, a bioactive monoterpene glucoside that is commonly utilised to treat arthritic and inflammatory disorders. When given orally, paeoniflorin has a limited absorption rate and a very low bioavailability (3–4%). Rats' paeoniflorin absorption behaviours were drastically changed by co-administration with sinomenine. Sinomenine may reduce the efflux transport of paeoniflorin by P-glycoprotein in the small intestine, which may be the mechanism driving this improvement in paeoniflorin bioavailability.

Gallic acid esters:[45,46]

The drug biotransformation enzyme in the gut can be inhibited by the chemicals octyl gallate, propyl gallate, lauryl gallate, and methyl gallate. As a result, fewer drug molecules will be metabolised by phase I enzymes in the gut and won't be available for phase II conjugation enzymes. Increased levels of untransformed medication will then flow from the gut into the circulation and into other bodily tissues as a result. As a result, higher levels of untransformed medication will flow from the stomach into the circulation and onto other bodily tissues. The bioenhancing dosage of gallic acid esters is at least 1% by weight gallic acid ester relative to the total weight of the formulation, more preferably at least 2%, and even more ideally at least 5%. In the presence of the gallic acid ester. The biotransformation of CYP3A drugs may be inhibited by competitive, non-competitive, uncompetitive, mixed, or irreversible methods. Compounds (or drugs) that can be administered with gallic acid esters includes acetanilides, anilides, aminoquinolines, benzhydryl compounds, benzodiazepines, benzofurans, cannabinoids, cyclic peptides, dibenzazepines, digitalis gylcosides, ergot alkaloids, flavonoids, imidazoles, quinolines, macrolides, naphthalenes, opiates (or morphinans), oxazines, oxazoles, phenylalkylamines, piperidines, polycyclic aromatic hydrocarbons, pyrrolidines, pyrrolidinones, stilbenes, sulfonylureas, sulfones, triazoles, tropanes, and vinca alkaloids etc. Rosuvastatin (RSV) and herbal bioenhancers (such as piperine, gallic acid, and cinnamic acid) may interact pharmacologically, according to research by Sudipta Basu et al. (2012) in healthy male C57 BL/6 mice. RSV (5 mg/kg) was provided orally along with piperine, gallic acid, and cinnamic acid (5 mg/kg), increasing intravenous

exposure (AUClast) by 174.51%, 176.65%, and 181.08%, respectively, compared to the control group when given alone. P.O. co-administration of piperine, gallic acid, and cinnamic acid (5 mg/kg) substantially raised the oral exposure (AUClast) of RSV (25 mg/kg) by 1.35 folds, 1.66 folds, and 1.62 folds, respectively, in comparison to the control (alone) group. The absolute oral bioavailability of rosuvastatin alone increased from 33% to 45, 56, and 54% with rosuvastatin co-administered with per oral doses of piperine, gallic acid, and cinnamic acid, respectively. In C57BL/6 male mice, this resulted in a 15, 19 and 18% increase in rosuvastatin oral availability.

Cumin/Caraway (Carum carvi):[47]

Caraway consists of the dried ripe fruits of Carum carvi Linn., belonging to family Umbelliferae. Cumin seeds have diuretic, fragrant, somewhat stomachic, and carminative effects. The Carum carvi bioactive fraction's effective dosage as a bioenhancer falls between 1 – 55 mg/kg body weight. It has been reported to increase the bioavailability of antibiotics, antifungals, antivirals, and cancer-preventative medications. Additionally, it is discovered that using piperine (3–15 mg/kg body weight) and bioenhancer from Zingiber officinale (10–150 mg/kg body weight) together increases their effectiveness as bioenhancers.

Cuminum:[48,49]

The cuminum cyminum plant, which is a member of the apiaceae family, produces seeds that are widely used as carminatives in Indian traditional medicine. These are dark brown coloured seeds with aromatic flavour (cuminaldehyde, cymene, terpinoids) and used as spice. It helps in the treatment of belching, gastric refreshment, removal of helminthes from gastrointestinal tract. The essential oil from cumin seeds is used in cosmetics and is said to have the ability to boost biological actions. The bioavailability of drugs including Ketoconazole, Erythromycin, Fluorouracil, Amoxycillin, Fluconazole, Cephalexin, and Zidovudine is said to be improved by it.

Capsaicin:[50]

One of the active phytoconstituents present in the plants of the genus Capsicum, or Chilli peppers, is capsaicin (8-methyl-N-vanillyl-6-nonenamide). Capsaicin and its chemical constituents together are called as capsaicinoids; found to be causing irritation and burning sensation when encounters the skin surface. According to reports, it is a component of formulations used topically to treat pain from pains, arthritis, back pain, etc. Also found to reduce peripheral neuropathy, post-herpetic neuralgia, diabetic neuropathy, and cardiovascular diseases. It has been reported to be showing bio-enhancing effect on theophylline and fexofenadine.

Resveratrol:[51]

Resveratrol (3, 5, 4′-trihydroxystilbene) is a nonflavonoid polyphenol that naturally occurs as phytoalexin. It is produced by plant sources such as grapes, apples, blueberries, plums, and peanut. Resveratrol (3,4′,5- trihydroxystilbene) is a nutraceutical that has recently attracted a lot of research attention due to its exciting pharmacological potential. When apigenin and resveratrol were administered together, plasma levels of apigenin increased 2.39 times more than when apigenin was given alone. .Resveratrol inhibites the formation of apigenin glucuronides by inhibiting UGT1A9 enzyme in a non-competitive manner.

CONCLUSION:

A novel idea in drug development centers on natural bio enhancers. Even though the surfactants can be an effective solution but naturally occurring bio enhancers are preferred over these because of safety, biocompatibility, low cost and abundant availability. They will result in lower medication costs, less toxicity and unwanted effects, and more therapeutic or bioefficacy. Research is still being done to create new, potent bio enhancers like resveratrol, *piperine*, *gallic acid* etc., and its derivatives and to enhance solubility of poorly soluble drugs. The purpose of this article was to highlight the importance of naturally occurring bio enhancers and the need for thorough exploration of natural resources as well as processing of existing naturally occurring bio enhancers to develop novel and effective drug delivery systems.

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HOW TO CITE: Ritesh Patil, Pratik Pawar, Akash Rekhate, Ravita Pawara, Yogesh Patil, Shubham Pawar, Natural Bioenhancer: A Remedy for Poorly Soluble Drugs, J. Pharm. Sci., 2026, 2 (4), 2077-2085. https://doi.org/10.5281/zenodo.19799006