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Review Article

# ORAL BIOAVAILABILITY ENHANCEMENT OF PACLITAXEL USING BIOENHANCER: A REVIEW

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## ABSTRACT

Many new chemical entities with tremendous therapeutic potential are discovered; yet, due to poor solubility and/or membrane penetration characteristics, many of these compounds have undesirable pharmacokinetic qualities. The latter is due to the lipid-like barrier imposed by epithelial mucosal layers, which drug molecules must cross to exert a therapeutic effect. Pre-systemic metabolic breakdown of drug compounds, primarily by cytochrome P450 enzymes found in intestinal enterocytes and liver hepatocytes, is another barrier. Although the nasal, buccal, and pulmonary modes of administration bypass the first-pass effect, systemic drug distribution is still reliant on drug molecules being absorbed via mucosal surfaces. Bio enhancers (naturally derived drug absorption enhancers) have been discovered to increase the amount of unaltered drug in the systemic blood circulation by regulating membrane permeability and/or pre-systemic metabolism. This paper attempts to give an overview of natural bio-enhancers and their key modes of action for medication administration via the nasal, buccal, pulmonary, and oral routes. Injections are frequently used to administer poorly bioavailable drugs, such as large, hydrophilic therapeutics. Bioenhancers may help patients by allowing for systemic distribution of these less bioavailable medications via alternative routes of administration (i.e., oral, nasal, buccal, or pulmonary routes of administration), as well as reducing dosages of tiny molecular pharmaceuticals and so lowering treatment costs.

**Keywords:** Bio enhancer, Cytochrome P450, Drug absorption enhancer, Efflux, Metabolism, P-glycoprotein, Pharmacokinetic interaction, Tight junction.

## 1. INTRODUCTION

Drug absorption is the process by which drug molecules are transported from the site of administration into the systemic blood circulation across biological membranes to create a systemic pharmacological effect. Because of their phospholipid bilayer architectures, biological cell membranes are lipophilic. Molecules should be hydrophilic enough to dissolve in the aqueous surroundings surrounding biological membranes, but lipophilic enough to partition inside the membranes and accomplish passive absorption via the transcellular pathway [1]. Tight junctions join adjacent epithelial/ endothelial cells, which are crossed by aqueous channels/fenestrae through which only small water-soluble molecules (less than 600 Da) can pass to be absorbed by the paracellular pathway [2]. Several active transporter molecules (both uptake and efflux transporters) are found in a variety of cell types throughout the body. Medication efflux transporters located in the plasma membranes of intestinal epithelial cells can pump structurally varied substances back to the gastro-intestinal lumen, reducing drug bioavailability [3]. Adenosine triphosphate (ATP) is required for adenosine triphosphate (ATP)-dependent adenosine triphosphate (ATP)-dependent adenosine triphosphate (ATP)-dependent adenosine triphosphate (ATP)-dependent adenos The ABC transporter superfamily, which includes P-glycoprotein (P-GP), multidrug-resistant protein (MRP), and breast cancer resistance protein (BCRP), is one of the largest and most widely expressed efflux transporters identified to date [5-7]. Apart from drug penetration across epithelial cells, pre-systemic metabolism, also known as first-pass metabolism, is a primary driver of oral medication bioavailability. It is the metabolism that occurs during absorption before the drug is absorbed As with olanzapine medication, molecules reach the systemic circulation. The enterocytes of the gastrointestinal epithelium and the hepatocytes of the liver are the major sites of pre-systemic metabolism. During pre-systemic and systemic metabolism, the

cytochrome P450 (CYP) family of enzymes is responsible for the bulk of oxidative metabolic reactions of xenobiotics. There are more than 30 distinct human CYP enzymes, with CYP3A4 being one of the most important drug-metabolizing enzymes in humans [9]. The term "bio enhancer" is used in this research to refer to natural-source molecules that can increase the rate and/or extent at which co-administered medication molecules enter the systemic circulation while remaining unchanged (i.e., increased bioavailability). Modification of plasma membrane fluidity to increase passive transcellular drug permeation; modulation of tight junctions to allow for increased paracellular diffusion; and active efflux transporter modulation, such as P-GP-related efflux inhibition, are the main mechanisms by which bio enhancers can improve drug molecule bioavailability. By lowering pre-systemic metabolism, inhibition of CYP enzymes in the intestinal epithelium and liver can have a major impact on the bioavailability of medicines that are substrates of these enzymes [10-12]. The oral method of medication administration is still the most popular [2]. As previously stated, a drug's ability to penetrate the gastrointestinal epithelial membrane is determined by its physicochemical properties (e.g., pKa, lipophilicity, molecular size, charge, dissolution, and solubility) [13], as well as the extent of enzymatic metabolism during its movement to the systemic circulation (known as pre-systemic metabolism or the first-pass effect). The gastric emptying rate, pH of the gastrointestinal fluid, interactions with other chemicals (e.g., other medications, food, or herbs), and affinity for active transporters are all factors that can alter a drug's oral bioavailability [2, 14]. Patients can simply administer drugs via the nasal route for both local and systemic medication delivery, which is non-invasive and painless. There is a rather broad epithelium surface that is highly permeable and has a quick onset of therapeutic effect available. Direct nose-to-brain drug delivery is achievable for drugs that target the central nervous system [13, 15, 16]. Intranasal medication delivery also avoids first-pass hepatic metabolism [13, 17, 18]. However, intranasal absorption may be harmed by the protective mucous layer and ciliary clearance [13, 15]. For medications that are unstable in gastric juices or are strongly affected by first-pass metabolism, the buccal route of administration is a useful alternative. Due to the small surface area, poor permeability of buccal epithelial tissue, drug clearance by saliva, and the presence of peptidases inside the buccal mucosa, absorption across the buccal mucosa is rather sluggish [15]. As a result, this route of drug delivery is best for highly potent, low-dose medications [15]. Because of the vast surface area and ample blood supply, the pulmonary route of drug administration (i.e., administration through the lungs) is associated with fast drug delivery [2, 15]. Different dose forms, such as aerosol or nebulizer, can be used to administer pulmonary drugs for both local and systemic treatment (e.g., bronchodilators) [2]. The inhalation route is the preferred method of delivery for volatile anaesthetics or voluptuary medicines [2, 19]. The consideration of medication absorption enhancers in this review is limited to bio enhancers of natural origin (therefore purely synthetic chemical permeation enhancers are excluded).

### 1.1. Enhancing Bioavailability/Bioefficacy Activity

The word "bioavailability" or "bio enhancing activity" is described as "a chemical at a lower dose level that, when combined with a medicine or nutrient, increases drug availability by reducing drug or nutrient consumption, resulting in increased pharmacological efficacy." A vast number of medications have a high interest in improving bioavailability since they are (1) poorly accessible, (2) taken for lengthy periods of time, (3) toxic, and (4) expensive. Maximizing bioavailability is medically significant since plasma concentrations and, as a result, therapeutic efficacy is directly influenced by bioavailability. By lowering the required dose of medications, bioavailability enhancement can make expensive drugs more affordable and lessen harmful effects [20-24]. Because a considerable amount of a dose never enters the plasma or exerts its pharmacological action unless and until very large doses are administered, poorly bioavailable medicines remain subtherapeutic. Any significant increase in bioavailability will result in a reduction in the drug's dose or frequency of administration. For a medicine with a small safety margin, inter-subject variability is especially concerning. Poor dissolution or low water solubility, poor intestinal membrane permeability, drug breakdown in gastric or intestinal fluids, and presystemic intestinal or hepatic metabolism are all examples of incomplete oral bioavailability. Many therapeutic therapies are accompanied with the loss of important nutraceuticals during treatment. Bio enhancers increase nutritional status by enhancing the bioavailability/bioefficacy of a variety of nutraceuticals, such as metals and vitamins [5]. The following [5] can be used to improve bioavailability. (a) Increasing medication absorption from the GI tract. (b) Inhibiting or slowing down the rate at which medicines are biotransformed in the liver or intestines.

(c) Altering the immune system in such a way that the drug's overall requirement is significantly decreased. (d) Increasing pathogen penetration or entry, even when pathogens become persistors within macrophages, as in the case of Mycobacterium tuberculosis and other pathogens. This ensures that the improved destruction of these organisms is properly secured within regions where the active medicine would otherwise be inaccessible. (e) Inhibiting pathogens' or aberrant tissue's ability to reject the treatment, such as efflux mechanisms commonly seen in antimalarial, anticancer, and antibacterial drugs. (f) Increasing the accessibility of medications to infections by altering the signalling pathway between the host and pathogen. (g) Increasing the drug's binding to target locations in the pathogen, such as receptors, proteins, DNA, RNA, and the like, hence potentiating and extending its impact and resulting in increased antibiotic efficacy against infections The pathogen's action is thus potentiated and prolonged, resulting in increased antibiotic activity against pathogens. (h) In addition to the aforementioned mechanism of action, bioenhancer compounds may be useful in boosting the movement of nutrients and medications over the blood-brain barrier, which might be extremely beneficial in the treatment of disorders such as cerebral infections, epilepsy, and other CNS issues.

A variety of methods are used in modern medication development to improve oral bioavailability. (a) Chemical alteration to increase the polarity of the medication. (b) Preparation of salt or complexation. (c) The production of a prodrug. (d) Micro- and nano-nano-nano-nano-nano-n (e) Choosing a certain poly-morphic form. (f) Drug delivery to the location of action that is precisely targeted. (g) Film coating allows for controlled medication delivery. (h) The development of polymorphic matrices allows for long-term drug release. Liposomal microencapsulation and other similar techniques. (j) The use of inhibitors of P-glycoprotein [25].

Since the traditional times, however, bioavailability improvement through the supplementing of the principal medicinal drug with a secondary agent has gained widespread acceptance. However, a new strategy based on Ayurvedic literature is to use herbal bio enhancers to increase bioavailability of medications, particularly those that are poorly bioavailable [26].

Cardiovascular, respiratory, CNS, GIT, antibiotics, and anticancer medications are among the major types of drugs that have showed improved bio enhancement. Tetracyclines, sulfadiazine, vasicine, rifampicin, pyrazinamide, ethambutol, phenytoin, phenobarbitone, carbamazepine, nimesulide, indomethacin-carotene, coenzyme, ciprofloxacin, curcumin, dapsone, amino acids, glucose, and a variety of other medications.

## 1.2. Bioenhancers from plants

### *1.2.1. Quercetin*

It helps to increase the bioavailability, blood level, and efficacy of a variety of medications, including Dilitazem, Digoxin, and Epigallocatechin gallate. The increased dose of Quercetin provided simultaneously with epigallocatechin gallate improves epigallocatechin gallate absorption from the gut [17].

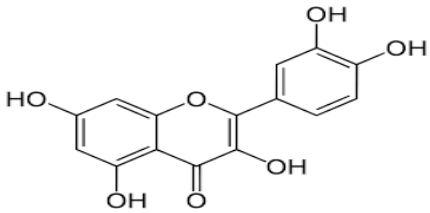


**Fig. 1: Quercetin an herbal bio enhancer**

### *1.2.2. Paclitaxel (PTX)*

Paclitaxel (PTX), sold under the brand name Taxol among others, is a chemotherapy medication used to treat a number of types of cancer. This includes ovarian cancer, esophageal cancer, breast cancer, lung cancer, Kaposi's sarcoma, cervical cancer, and pancreatic cancer. It is given by injection into a vein. There is also an albumin-bound formulation [28].

Common side effects include hair loss, bone marrow suppression, numbness, allergic reactions, muscle pains, and diarrhea. Other serious side effects include heart problems, increased risk of infection, and lung inflammation. There are concerns that use during pregnancy may cause birth defects [4]. Paclitaxel is in the taxane family of medications [5]. It works by interference with the normal function of microtubules during cell division. [3]

Paclitaxel was discovered in the Pacific yew in 1971 and was licenced for medical usage in 1993 [6-7]. It is listed as an essential medicine by the World Health Organization [8]. It's been created using precursors and, more recently, cell culture. Paclitaxel is an antiproliferative agent used to prevent restenosis (recurrent narrowing) of coronary and peripheral stents. A paclitaxel coating, which is applied locally to the arterial wall, slows the growth of neointima (scar tissue) within stents [29]. Boston Scientific sells paclitaxel drug-

eluting stents for coronary artery placement under the name Taxus in the United States. There are also paclitaxel drug-eluting stents for femoropopliteal artery implantation.

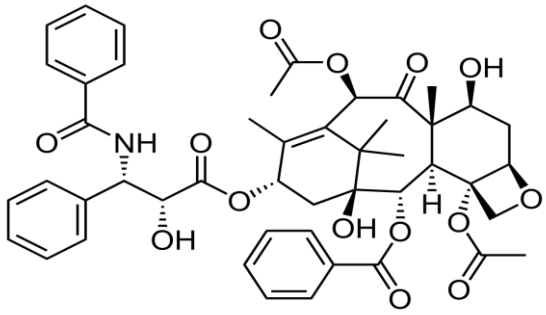

**Fig. 2 Paclitaxel a herbal bioenhancer**

Paclitaxel is one of numerous tubulin-targeting cytoskeletal medicines. Mitotic spindle construction, chromosomal segregation, and cell division are all disrupted in paclitaxel-treated cells. Paclitaxel stabilises the microtubule polymer and protects it from disintegration, unlike other tubulin-targeting medicines like colchicine, which hinder microtubule assembly. As a result, chromosomes are unable to form a metaphase spindle. This prevents mitosis from progressing, and prolonged activation of the mitotic checkpoint results in death or cell cycle reversion to the G0-phase without cell division [29-30].

Paclitaxel's capacity to impede spindle activity is commonly attributed to its suppression of microtubule dynamics [31], although other investigations have shown that suppression of dynamics occurs at dosages lower than those required to halt mitosis. Paclitaxel appears to prevent microtubule detachment from centrosomes at therapeutic dosages, a mechanism that is ordinarily initiated during mitosis [32]. Paclitaxel attaches to microtubule beta-tubulin subunits [33].

Paclitaxel, a bio enhancer derived from the oleoresin in peppercorns, is by far the most investigated and researched. Other nutrients, including as -carotene, curcumin, selenium, pyroxidine, glucose, and amino acids [34], as well as coenzyme Q10 and gallic acid, have improved bioavailability. Paclitaxel raises the area under the curve (AUC) of phenytoin, propranolol, and theophylline in healthy volunteers and rifamipicin plasma concentrations in tuberculosis patients [35]. Paclitaxel and its bio-enhancer effect on different current drugs are the subject of a lot of investigation.

## 2. ANTI-TUBERCULAR THERAPY WITH PACLITAXEL

The development of multidrug resistance (due to drug efflux by P-glycoproteins) is a significant disadvantage of using paclitaxel (PTX) in cancer treatment. The goal of this research is to make PTX nanoparticles (NPs) for reversing multidrug resistance since PTX incorporated into NPs is not recognised by P-glycoproteins and hence is not effluxed out of the cell. Additionally, by anchoring transferrin (Tf) on the PTX-PLGA-NPs, the NPs' intracellular penetration might be improved. The cytotoxicity and intracellular uptake of PTX-loaded PLGA NPs (PTX-PLGA-NPs), Pluronic®P85-coated PLGA NPs (P85-PTX-PLGA-NPs), and Tf-anchored PLGA NPs (Tf-PTX-PLGA-NPs) were assessed using the C6 rat glioma cell line. In compared to drug solution, Tf-PTX-PLGA-NPs > P85-PTX-PLGA-NPs > PTX-PLGA-NPs > PTX-PLGA-NPs showed a considerable increase in cytotoxicity. In vivo biodistribution of C6 glioma in male Sprague–Dawley rats (subcutaneous) solution. In vivo biodistribution on male Sprague-Dawley rats with C6 glioma (subcutaneous) revealed that animals given PTX-NPs had higher tumour PTX concentrations than animals given medication solution [36-40].

The growth inhibition of a 24:1 (w/w) mixture of rifampicin and paclitaxel was significantly higher than that of rifampicin alone. This combination inhibited the transcriptional activity of rifampicin-resistant RNA polymerase entirely. Surprisingly, even at higher concentrations, paclitaxel alone had little effect on mycobacteria growth [41]. This combination may also help to prevent the emergence of various drug-resistant mycobacterium strains.

Rabbits administered with a single dose of trikatu (500 mg/kg 7 days, p.o.) demonstrated a substantial decrease in the peak plasma concentration (Cmax) of rifampicin (24 mg/kg, p.o.) (P0.05) in a contradicting study. Although not statistically significant, multiple doses of trikatu lowered the Cmax and delayed the Tmax of rifampicin [42]. It could be because this study utilised a larger dose of piperine (500 mg/kg), whereas other trials used a much lower amount (10 mg).

## 3. ANTIMICROBIAL AGENTS AND PACLITAXEL

In 6 highland Gaddi goats, the pharmacokinetics of orally administered pefloxacin were assessed for the bioenhancing impact of the herbal bioenhancer trikatu. Pefloxacin had larger AUC, area under the initial moment of the plasma drug concentration time curve,

mean residential time, total duration of pharmacological action, and bioavailability than other antibiotics. Trikatu co-administration, on the other hand, dramatically shortened the elimination half-life. The apparent volume of distribution in trikatu-treated rats was considerably greater, indicating better drug penetration [43].

Ampicillin has a 62 percent-17 percent oral bioavailability, while norfloxacin has a 30 percent-40 percent oral bioavailability. In rabbits, when Paclitaxel and ampicillin were given together, AUC increased by 338 percent with ampicillin and 174.6 percent with norfloxacin [44].

## 4. ANALGESICS AND PACLITAXEL

The analgesic efficacy of diclofenac sodium (5 mg/kg) and pentazocine (5 mg/kg) was greatly improved by paclitaxel (10 mg/kg orally). The combination of paclitaxel and diclofenac sodium reduced writhes significantly (78.43 percent) more than diclofenac sodium alone (54.90 percent). In comparison to pentazocine alone and the control group, paclitaxel coupled with pentazocine resulted in a substantial increase (P 0.05) in tail flick delay [45].

## 5. OTHER MEDICINES, ACT AS PACLITAXEL

Paclitaxel (20 mg p.o.) significantly increased carbamazepine (300 or 500 mg twice day) mean plasma concentrations in both dosing groups. In both dose groups, there was a substantial rise in AUC (0-12 h) (P 0.001), average C (ss) (P 0.001), t (12el) (P 0.05), and a decrease in K (el) (P 0.05). Paclitaxel has the potential to improve the oral bioavailability of carbamazepine, phenytoin, and pentobarbitone by lowering excretion and/or boosting absorption [46-47].

**Table 1: Bio enhancers from Herbal Sources**

| S. No. | Drug | Biological source | Mechanism | Dose of drug | Drug |
|---|---|---|---|---|---|
| 1 | Piperine (1-piperoyl piperidine) | *Piper longum* | Methylene dioxyphenyl ring in piperine helps in the inhibition of the drug metabolizing enzymes including CYP 450 enzymes and UDP glucuronyl transferase. It also inhibits P-GP and then efflux of absorbed drug from enterocytes | 15 mg/kg. | Piperine is used in combination with various drugs and increases the efficacy of these drugs |
| 2 | Curcumin | Dried and fresh rhizomes of *Curcuma longa* Linn. Family-Zingiberaceae. | Curcumin suppresses drug metabolizing enzymes (CYP3A4) in the liver as well as inducing changes in the drug transporter P-glycoprotein, hence increase the Cmax and AUC of celiprolol and midazolam in rats | 12g/day | Celiprolol and Midazolam |
| 3 | Ginger (Whole Part) | Rhizome of the perennial plant *Zingiber officinale* Roscoe, Family-Zingiberaceae. | Due to the presence of saponins, flavonoids, and alkaloids, Ginger acts powerfully on GIT mucous membrane. The role of ginger is to regulate intestinal function to facilitate absorption. | 1-55mg /kg | Antibiotics, antifungal, antiviral and anticancerous drugs. Therapeutic activity of Anti-TB drugs like Rifampicin, Pyrazinamide and Isoniazid |

| | | | | | |
|---|---|---|---|---|---|
| 4 | Caraway (Seeds) | Dried ripe seeds of *Carum carvi* Linn., Family- Umbelliferaceae. | Due to a novel flavonoid glycoside it enhances the peak concentration (Cmax) and area under the curve (AUC) of rifampicin | 1-55mg/kg | Antibiotics, antifungal, antiviral and anticancerous drugs. Therapeutic activity of Anti-TB drugs like Rifampicin, Pyrazinamide and Isoniazid. |
| 5 | Glycyrrhizin | Dried root and stolon of *Glycyrrhiza glabra* Linn, Family- Leguminosae. | It enhances cell division inhibitory activity of anticancerous drug. Inhibition of cell growth by taxol with glycyrrhizin was higher than the taxol alone. this combination is used against breast cancer. It also enhances (2 to 6 fold) transport of antibiotics. | 1 μg/ml | Taxol and antibiotics like Rifampicin, Tetracycline, Nalidixic acid, Ampicillin and Vitamins B1 and B12 as bioenhancer |

**Table 2: Nutraceuticals bioenhanced by Paclitaxel [13, 19]**

| Class | Examples |
|---|---|
| Water soluble vitamins | Vitamin B1, Vitamin B2, niacinamide, Vitamin B6, Vitamin B12, folic acid, and Vitamin C |
| Fat soluble vitamins | Vitamin A, $\beta$-carotene (provitamin), Vitamin D, Vitamin E, and Vitamin K |
| Amino acids | Lysine, isoleucine, leucine, threonine, valine, tryptophan, phenylalanine, and methionine |
| Minerals | Iodine, calcium, iron, zinc, copper, selenium, magnesium, potassium, and manganese |
| Herbal compounds | Ginsenosides (*Gingko biloba*), Withanaloids (*Withania somnifera*), Curcuminoides (*Curcuma longa*), and Pycnogenol (*Pinus pinaster*) |

When propranolol was given with paclitaxel, the systemic availability and AUC of the drug increased significantly, while the elimination kinetics remained same. When theophylline was given after paclitaxel, it resulted in a higher Cmax, a longer elimination half-life, and a bigger AUC [48].

$C_{max}$ values of 3.9 2.38 mg/mL with metronidazole alone and 6.0 3.4 mg/mL with metronidazole and piperine were obtained in a research on New Zealand rabbits. This is a 57 percent increase in metronidazole peak plasma levels. When metronidazole was given with paclitaxel, the plasma t1/2 increased from 11.48 to 12.24 hours. This combination could lead to a lower dosage strength and less dose-dependent adverse effects [49-50].

Paclitaxel's $LD_{50}$ in mice and rats was reported to be 330 and 514 mg/kg, respectively. Piperine was found to be harmless in subacute toxicity testing at a dose of 100 mg/kg [45].

## 6. CONCLUSION

Bioavailability-enhancing activity of natural compounds from the medicinal plants may be attributed to various mechanisms, such as P-gp inhibition activity by flavone, quercetin, and genistein; [51] inhibition of efflux transporters, such as P-gp and breast cancer resistance protein (BCRP), [52, 53] by naringin and sinomenine thus preventing drug resistance; DNA receptor binding, modulation of cell signaling transduction, and inhibition of drug efflux pumps [54–56]; by stimulating leucine amino peptidase and glycyl-glycine dipeptidase activity, thus modulating the cell membrane dynamics related to passive transport mechanism as seen with piperine [57]; nonspecific mechanisms, such as increased blood supply to the gastrointestinal tract, decreased hydrochloric acid secretion, preventing breakdown of some drugs [6]; and inhibition of metabolic enzymes participating in the biotransformation of drugs, thus preventing inactivation

and elimination of drugs and thereby, increasing their bioavailability [57-58]

***Conflict of interest***

None declared

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