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Piperine: An Effective Bioenhancer for Drug Absorption

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Opinion

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Discovery of new drugs with high therapeutic potential but having poor solubility and poor membrane permeation characteristics leads to use of bioenhancers in drug delivery. In general, bioenhancers have been identified as chemical entities of natural origin that can increase the quantity of unchanged drug that appears in the systemic blood circulation by means of modulating membrane permeation and/or pre-systemic metabolism. Since antiquity, various herbs and spices were used for the treatment of different ailments and drug formulations. In modern pharmacopoeias also, approximately 25 % of drugs have been documented as plant origin drugs [1-3]. Pepper fruit of Piperaceae family is one of them which have been established as bioenhancer for some selected drugs. Piper species have a special and importance place in Ayurvedic literature and formulations. Out of 370 drug formulations, about 210 drug formulation contained 'Trikatu' as one of the ingredients [4]. Black pepper is one of the three ingredients of 'Trikatu'. The other two ingredients are ginger and long pepper (Piper longum). Certain studies proved that 'Trikatu' was acting as bioenhancer for the accompanying drugs. This action is referred as Yogvahi in ancient classic literature. The concept of bioenhancer appears too late in allopathic practice as compared to Ayurveda [5].

Piperine is a major alkaloid obtained from Piper nigrum and Piper longum belonging to family Piperaceae which has a number of pharmacological properties [6-8]. The anti-inflammatory, anti-pyretic, anti-fungal, anti-diarrheal, and anti-cancer effects of piperine have been well documented by several workers [6,9]. Probably, piperine can be considered as one of the world's first bioenhancers as far back as the 7th century. Piperine has molecular formula $C_{17}H_{19}O_3N$. Chemically, it is [1-(5- [1, 3-benzodioxol-5-yl]-1-oxo-2, 4-pentadienyl) piperidine. Its pH is 8.6- 8.5 and pKa is 13.2 (Figure 1).

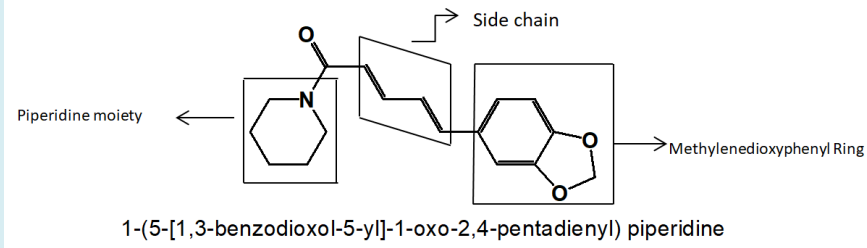

Figure 1: Structure of piperine.

Researchers have documented in detail [10-12] about the bioenhancing effect for a number of drugs in allopathic system of medicine such as oxy-phenylbutazone, phenytoin, aflatoxin B1, beta-carotene, propranolol, and theophylline. Piperine has been used as bioenhancer for certain antibacterial-antibiotics with promising results e.g. rifampicin, dapsone, curcumin, ciprofloxacin, cefotoxime sodium, cyclosporine A, and metronidazole [10]. The effective

dose of piperine recommended for drug compounds varies, but a dose of approximately 10% (w/w) of the active drug could be regarded as an appropriate bioenhancing dose for most of the drugs [13].

Mode of action of any drug mainly depends upon its bioavailability which in turn depends upon the rate at which the unchanged drugs are made available to the body and the extent to which the dose is ultimately absorbed after administration. The mechanism of action of piperine is documented in reports [6,10-12] mainly describes these actions-

1. Promoting rapid absorption of drugs and nutrients from gastro-intestinal tract
   - ✓ Increased blood supply to the gastrointestinal tract
   - ✓ Decreased hydrochloric acid secretion which prevents breakdown of some drugs
   - ✓ Increased emulsifying content of the gut and inhibits lipid peroxidation
2. Inhibiting enzymes participating in biotransformation of drugs
   - ✓ Hepatic and intestinal glucoronidation inhibition
   - ✓ Cytochrome P-gp enzymes and CYP3A4 inhibition
   - ✓ Increased γ-glutamyl transpeptidase activity which increases uptake of amino acids.

Piperine as bioenhancer for drugs	Mechanism of Action
Piperine and Rifampicin	Piperine augments transcription inhibitory activity of rifampicin by several folds against Mycobacterium smegmatis. Combining piperine with rifampicin decreased the dose of rifampicin from 450 to 200 mg.
Piperine and Resveratrol	Effect of piperine on oral bioavailability of resveratrol was studied in mice and the study demonstrated that piperine significantly improves the in-vivo bioavailability of resveratrol
Piperine with Propranolol and Theophylline	The effects of piperine on the bioavailability an pharmacokinetics of propranolol and theophylline were studied. An earlier tmax and a higher Cmax and AUC were observed in the subjects who received piperine and propranolol. It produced a higher Cmax, longer t1/2, and a higher AUC with theophylline.
Piperine and Coenzyme Q10	In a double-blind study, it is postulated that the bioenhancing mechanism of piperine to increase plasma levels of supplemental coenzyme Q10 is nonspecific and possibly based on its description in the literature as a thermonutrient
Piperine and β-Carotene	The effectiveness of piperine was evaluated for its ability to improve serum response of β-carotene during oral supplementation using a double-blind, crossover study design. Study suggested that the serum response during oral β-carotene supplementation is improved through the nonspecific, thermogenic property of piperine
Piperine and Curcumin	Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers was studied. Piperine, a known inhibitor of hepatic and intestinal glucuronidation, enhanced the serum concentration, extent of absorption, and bioavailability of curcumin in both rats and humans with no adverse effects.
Piperine and Aflatoxin B1	Piperine enhances bioavailability of aflatoxin B1 in rat tissues. A 10 mg dose of piperine causes a marked increasein serum gonadotropins and a decrease in intratesticular testosterone concentration, despite normal serum testosterone titres in adult male albino rats.
Piperine and Pentobarbitone	Effect of piperine on pentobarbitone-induced hypnosis in rats was studied. Piperine treatment in rats, treated chronically with phenobarbitone, significantly potentiated pentobarbitone sleeping time, as compared to the controls There was no alteration in barbital sodium sleeping time. It is possible that piperine inhibits liver microsomal enzyme system and thereby potentiates the pentobarbitone sleeping time.
Piperine and Phenytoin	Effect of piperine on pharmacokinetics of phenytoin was studied in healthy volunteers. The results of a crossover study, showed that a single daily dose of piperine for 7 days decreased the $t1/2\alpha$ ($P < 0.05$), prolonged the t1/2 ($P < 0.01$), and produced a higher AUC ($P < 0.05$) in comparison to phenytoin alone.

Table 1: Some examples of bioavailability enhancement of various drugs by piperine.

Structure of piperine mainly comprises of three parts, namely, the methylenedioxyphenyl (MDP) ring, side chain, and the piperidine moiety. The structural organization is well suited for maximal inhibition of both aryl hydrocarbon hydroxylase (AHH) and 7-methoxycoumarin-O-demethylase (MOCD) activity [11]. The enzyme inhibition action caused by piperine can be attributed to its structure. Table 1 describes the bioenhancing effect of piperine with drugs [12].

In recent years, much attention and concern is developed for increasing the bioavailability of poorly bioavailable drugs. The major portion of poorly bioavailable drugs never reaches the plasma or exerts its pharmacological effects unless their large doses are supplied which may lead to serious side effects. The improvement in their bioavailability will reduce the dosage as well as the toxicity of these drugs. Formulations containing bioenhancers open up a new horizon for the pharmaceutical sectors. The bioavailability and bio-efficacy of many drugs have been effectively potentiated by piperine and well supported by reports that provide an area to explore in future emphasizing on the various factors which influence dissolution and absorption of drugs.

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