

Role of Piperine as an Effective Bioenhancer in Drug Absorption

Mhaske DB*, Sreedharan S and Mahadik KR

Department of Pharmaceutical Chemistry, Bharati Vidyapeeth (Deemed to be) University, Pune, Maharashtra, India

Abstract

Bioenhancers can be defined as chemical entities, which when mixed with drugs promote and augment their bioavailability without showing any synergistic effect with the drug. The factors like toxicity, cost, poor bioavailability and long term administration of drugs give rise to the need of bioenhancers which help overcome most of these problems. Piper species produce a pungent alkaloid named Piperine or 1-peperoyl piperidine. Piperine increases permeability at the site of absorption by modulating lipid environment and membrane dynamics. Piperine has a molecular structure that is suitable for enzyme inhibition. It augments the bioavailability of several drugs like carbamazepine, curcumin, ciprofloxacin, ampicillin, metronidazole, oxytetracycline and many others by inhibiting various metabolizing enzymes. Thus piperine, being an efficacious inhibitor of drug metabolism is a powerful enhancer of absorption. The following review explores the mechanism, metabolism inhibition, influence of structural changes on activity, and drugs bioenhanced by piperine. It provides an insight on the application of piperine as an effective bioenhancer and the superiority of a bioenhanced drug formulation over the one without a bioenhancer. This concept which is found to be beneficial, has its roots in Ayurveda-the traditional Indian system of medicine and has been applied to various drugs. It presents a fine instance of the advantage of amalgamating a traditional system with contemporary medicine.

Keywords: Bioenhancer; Piperine; Molecular structure; Metabolism inhibition

Introduction

Bioenhancers can be defined as chemical entities, which when mixed with drugs promote and augment their bioavailability without showing any synergistic effect with the drug [1]. Piperine was discovered in 1819 by Hans Christian Orsted, who isolated it from the fruits of *Piper nigrum*, the source plant of both the black and white pepper grains. The plants belonging to species like *Piper nigrum* and *Piper longum* of the Piperaceae family produce piperine which is an alkaloid with a pungent taste [2].

Piperine or 1-peperoyl piperidine is a solid having the molecular formula $C_{17}H_{19}O_3N$, melting point $128^{\circ}C$ and is optically inactive, sparingly soluble in water with cis-trans isomerism [3]. It shows high lipophilicity, is weakly basic, and exhibits non-saturable passive absorption kinetics [4]. In 1979, Indian scientists at the Regional Research Laboratory (Indian Institute of Integrative Medicine) in Jammu discovered piperine as the first bioenhancer in the world and also coined the term bioavailability enhancer. In November 2009, the formulation named Risorine that contains 200 mg of rifampicin, 300 mg of isoniazid and 10 mg of piperine was launched by Cadila Pharma in India. The bioavailability of rifampicin was increased by about 60% with the use of piperine. Thus, due to the addition of bioenhancer piperine the dose of rifampicin is reduced from 450 to 200 mg [5]. Piperine when used in combination with various drugs reduces dose, side effects and increases bioavailability [6,7].

Mechanism of Action of Piperine as a Bioenhancer

Some mechanisms which have been proposed for the bioenhancing effect of piperine are as follows-

Increased gastrointestinal absorption

This is brought about by

a. **By enhancing solubility:** Bile acid aids in the formation of micelle, required for the absorption of lipids and lipid soluble drugs. Piperine enhances the secretion of bile acids and also causes inhibition of bile acid metabolism thereby increasing the formation of micelle. This enhances solubility and absorption [8].

b. **Increased blood supply:** In a study by Annamalai et al. [9] it has been proposed that trikatu enhances gastrointestinal blood flow which causes increased absorption of drugs from the digestive tract.

c. **Increased permeability due to epithelial cell modification:** Piperine by interacting with intestinal epithelial cells, stimulates gamma-glutamyl transpeptidase activity and causes an increase in amino acid uptake by epithelial cells [10].

d. It has also been proposed that piperine increases brush border membrane fluidity and increases microvilli length [11].

Efflux of drugs from site of action is reduced

A study done by Bharadwaj et al. [12] shows that piperine increases the stay of a drug at the active site by inhibiting human p-glycoprotein, which is a major efflux pump.

Inhibition of solubilizer attachment

When substances are chemically linked to a highly water soluble substance, their entry in the cells is prevented. This is termed as solubilizer attachment. The substances bound to glucuronic acid, which is an important solubilizer are excreted either into the urine or small intestine. It has been reported that piperine inhibits glucuronic acid thus facilitating increased entry of substances into the cell [13].

Reduced metabolism

a. It has been found that piperine is capable of inhibiting many different cytochrome P-450 isoforms along with UDP-

*Corresponding author: Dr. Deepali Bansode Mhaske, Department of Pharmaceutical Chemistry, Bharati Vidyapeeth (Deemed to be) University, Pune, Maharashtra, India, Tel: +91-9970002387; E-mail: deepali_mhaske@rediffmail.com

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glucuronyltransferase and hepatic arylhydrocarbon hydroxylase. It inhibits glucuronidation, a metabolic step by inhibiting the enzyme UDP-glucose dehydrogenase [14,15].

b. It has also been proposed that piperine is a selective inhibitor of cytochrome P450 enzyme isoforms like CYP1A1, CYP1A2, CYP2C8, CYP2D6, and CYP3A4 [16].

c. Piperine has also been found to inhibit various mixed function oxygenases [17].

Metabolism Inhibition and Structure Activity Relationship

Piperine inhibited CYP450, cytochrome and NADPH cytochrome C reductase [18] and major metabolizing enzyme CYP3A4, which is responsible for the first pass metabolism of drugs [12]. It inhibits drug metabolism in a non-specific way and does not show much bias between different CYP450 forms [19]. It is found to inhibit rat CYP4502B1 which converts aflatoxin B1 to cytotoxic and genotoxic metabolite. Thus piperine increases the bioavailability of parent aflatoxin B1 and produces chemoprotective effect against procarcinogens activated by CYP4502B1 [20].

The enzyme inhibition caused by piperine can be attributed to its structure. The structure comprises of three parts namely the methylenedioxyphenyl (MDP) ring, side chain and the piperidine moiety that are together essential for maximal inhibition of both aryl hydrocarbon hydroxylase (AHH) and 7-methoxycoumarin-O-demethylase (MOCD) activity. The modification of any one moiety in the piperine molecule may not only alter the status of inhibition but also could elicit differential inhibition of the two types of monooxygenase activities. Flexibility can be induced in the molecule by saturating piperine side chain which may aid the interaction of protein domain with the inactivator. The conjugated double bonds can be saturated to tetrahydro derivatives of MDP ring resulting in greater flexibility of the side chain. It is believed that this chain perhaps acts as a handle to orient MDP group to the active site of the CYP450. This is anchored in a strongly hydrophobic environment whose interaction with piperine can be determined by altering its functional groups. This would help to determine the specificity and extent of inhibition.

It appears that the presence of the side chain with saturated double bonds linked through amide linkage impart specificity for inhibiting different forms of CYP450's. The structure of piperine as given in (Figure 1) is ideally suited to affect the microsomal oxidation of large number of compounds. The sensitivity in inhibition of the CYP450 activities can be discriminated due to the presence of piperidine function and MDP ring [21]. In a study by Pfund LY, it has been revealed that piperine is trimorphic. The two novel polymorphs of piperine show increased solubility as compared to the commercial polymorph, thus enhancing its efficacy as a bioenhancer. The π - π interactions are present in the newly discovered forms whereas lacking in the commercial form despite the presence of extended conjugation [22].

Updates on Use of Piperine as a Bioenhancer

Literature survey revealed the following articles listed in (Table 1), which provided information on the use of piperine as a bioenhancer.

Case Studies

In a study by Atal S et al. the bioenhancing effect of piperine along with metformin on lowering the blood glucose level was evaluated in

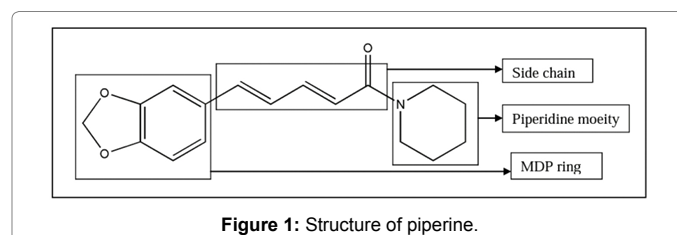


Figure 1: Structure of piperine.

S.No.	Article Title	Journal name and year of publication
1.	Enhancement of oral bioavailability and immune response of Ginsenoside Rh2 by co-administration with piperine.	Chinese Journal of Natural Medicines, 2018 [23].
2.	Piperine-mediated drug interactions and formulation strategy for piperine: recent advances and future perspectives.	Expert opinion on drug metabolism and toxicity, 2018 [24].
3.	Piperine in combination with quercetin halt 6-OHDA induced neurodegeneration in experimental rats: Biochemical and neurochemical evidences.	Neuroscience Research, 2018 [25].
4.	Investigation of Need of Natural Bioenhancer for a Metabolism Susceptible Drug-Raloxifene, in a Designed Self-Emulsifying Drug Delivery System.	AAPS PharmSciTech, 2017 [26].
5.	Role of Risorine in the Treatment of Drug-Susceptible Pulmonary Tuberculosis: A Pilot Study.	J Assoc Physicians India. 2016, [27].
6.	Bio-enhancing Effect of Piperine with Metformin on Lowering Blood Glucose Level in Alloxan Induced Diabetic Mice.	Pharmacognosy Research, 2016 [28].
7.	Piperine containing floating microspheres: an approach for drug targeting to the upper gastrointestinal tract.	Drug delivery and translational research, 2016 [29].
8.	Antioxidant and hepatoprotective effects of mixed micellar lipid formulation of phyllanthin and piperine in carbon tetrachloride-induced liver injury in rodents.	Food and function, 2015 [30].
9.	Effect of piperine on the bioavailability and pharmacokinetics of emodin in rats.	J Pharm Biomed Analysis, 2015 [31].
10.	The Bioenhancer Piperine is at Least Trimorphic.	Crystal growth and design, 2015 [23].

Table 1: List of review articles and research papers describing the use of piperine as a bioenhancer.

alloxan induced diabetic mice. The results showed that piperine (10 mg/kg) in combination with metformin (sub-therapeutic dose of 125 mg/kg) produced significantly higher lowering of blood glucose when compared to control group. It was also reported that the combination produced more lowering of blood glucose as compared to metformin (250 mg/kg) [28].

In another study by Sethiya NK et al. it was reported that piperine significantly influenced the bioavailability of Phyllanthin which is a sparingly water-soluble hepatoprotective lignin. Phyllanthin was combined with piperine and was formulated as a mixed micellar lipid formulation in the study and investigated to enhance hepatoprotective effects on oral administration and resolve the issue of low bioavailability [30].

Piperine and Bioenhanced Drugs

The bioavailability and bioefficacy of many drugs has been effectively potentiated by piperine as given in (Table 2). Piperine has the ability to inhibit several enzyme mediated pathways and biotransformation reactions.

Summary and Conclusion

Bioenhancers embody a fruitful and productive concept which results in enhancement of bioavailability along with reduced dose

S.No.	Drugs	Experimental model
1.	Vasicine	Rats [32]
2.	Pyrazinamide	<i>In vitro</i> [33]
3.	Phenytoin, propranolol, theophylline	Humans [34,7]
4.	Curcumin	<i>In vivo</i> [35]
5.	Nimesulide	Mice [36]
6.	Indomethacin	Rabbits [37]
7.	Oxyphenylbutazone	Rats [38]
8.	Phenytoin	Human volunteers [39,40]
9.	Rifampicin	Human [41]
10.	EGCG [(-)-epigallocatechin-3-gallate]	Mice [42]
11.	Oxytetracycline	White Leghorn hens [43]
12.	Ciprofloxacin	Rabbits [44]
13.	Fexofenadine	Rats [45]
14.	Nevirapine	Human [46]
15.	Pefloxacin	Gaddi goats [47]
16.	Carbamazepine	<i>In vitro</i> [6]
17.	Metronidazole	Rabbits [48]
18.	Ampicillin trihydrate	Human [49]
19.	Resveratrol	Mice [50]
20.	Gatifloxacin	Layer birds [51]
21.	Atenolol	Rats [52]
22.	Ibuprofen	<i>In vitro</i> [53]
23.	Losartan potassium	Rats [54]

Table 2: Drugs that show increased bioavailability when combined with piperine.

and other adverse effects. Various research articles and reviews opine that piperine which inhibits human P-glycoprotein and CYP3A4 is an effective bioenhancer. A wide variety of drugs can be bioenhanced by using piperine.

This review implies that, formulations containing a bioenhancer like piperine are much more effective and suitable as compared to the ones without it. Risorine is one of the best example which utilizes the concept of bioenhancer to help reduce drug dose and side effects along with increased bioavailability. The concept of action of piperine as a bioenhancer should be explored further, as it is quite obvious from literature that piperine has a prospective future as one of the most effective and widely applicable bioenhancer.

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