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## PIPERINE AS A BIOAVAILABILITY ENHANCER: A REVIEW

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### ABSTRACT

Piperine is used in many different ways to influence our lives. The piperine, in the spicy food, stimulates perspiration, which causes a cooling effect of the body. Thus very helpful during hot summer. Piperine (1-peperoyl piperidine), an amide alkaloid, is found in various *Pipper* species and posses antioxidant, antiplatelet, anti-inflammatory, antihypertensive, hepatoprotective, antithyroid, antitumor, antiasthmatic activities. It also believed to be a fertility enhancer. Piperine act as absorption enhancer of many drugs and nutrients from gastrointestinal tract by various mechanisms and a potent inhibitor of drug metabolism by inhibiting various metabolizing enzymes. This review article gives an account of bioavailability enhancing property of piperine.

### KEYWORDS

Piperine and Bio-enhancing activity.

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### INTRODUCTION

Bioenhancers are agents, which by themselves are not therapeutic entities but when combined with an active drug lead to the potentiation of pharmacologic effect of the drug. Such formulations have been found to increase the bioavailability / bioefficacy of a number of drugs<sup>1</sup>. Piperine, chemically, is 1-peperoyl piperidine (Figure No.1) and it is a pungent alkaloid found in *Pipper nigrum*, *Pipper longum*, *Pipper retrofractum*, *Pipper crussi* and *Pipper geniculatum*.

Piperine protects cisplatin-induced apoptosis through the induction of heme oxygenase-1

expression. Piperine also produces Antioxidant, Anti-platelet, Anti-inflammatory, Antihypertensive, Hepatoprotective, Antithyroid, Antitumor, Antiasthmatic activities and found to be Fertility Enhancer<sup>2</sup>.

Bioavailability is affected by gastric emptying time, intestinal transit time, blood flow through GIT, gastrointestinal contents and pre-systemic metabolism through luminal enzymes, gut wall enzymes, bacterial enzymes, and hepatic enzymes. Some drugs show poor oral bioavailability because a drug must not only penetrate the intestinal mucosa, it must also run the gauntlet of enzymes that may inactivate it in gut wall and liver. Piperine modulates membrane dynamics and lipid environment and increases permeability at site of absorption. Molecular structure of piperine is suitable for enzyme inhibition and it inhibits various metabolizing enzymes like cytochrome bs, NADPH cytochrome, CYP3A4, UDP-glucose dehydrogenase (UDP-GDH), aryl hydrocarbon hydroxylase (AAH) and UDP-glucuronyl transferase. Structural modification of piperine provides selective inhibitors of various cytochrome p450 enzymes. Inhibition of these enzymes by piperine results in enhanced bioavailability of drugs and nutrients like oxytetracyclin, metronidazole, ampicillin, norfloxacin, ciprofloxacin, acefotaxime, amoxicillin trihydrate, curcumin, beta-carotene, carbamazepine, gallic acid, nimesulide, tiferron, nevirapine, pentobarbitone, phenytoin, resveratrol, vasicine and sparteine by different mechanisms<sup>3</sup>. The bioenhancing property of piperine was first utilized in the treatment of tuberculosis in human. Piperine which is used in combination with antiretroviral agents for the treatment of HIV-1 infection<sup>4</sup>. And it also showed effect on chemotherapeutic agents. Piperine increases the bioavailability of curcumin, the active principle of *Curcuma longa*<sup>5</sup>.

### History

In the 1920's, Bose, an acknowledged author of "Pharmacographia Indica," reported an enhanced antiasthmatic effect of an Ayurvedic formulation containing *vasaka (Adhatoda vasica)* when administered with long pepper. The term

bioavailability enhancer was first coined by Indian Scientists at the Regional Research laboratory, Jammu who discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979<sup>6</sup>.

### Need for bioavailability enhancers

Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane and to be absorbed systemically following oral or topical administration. Several plant extract and phytoconstituents, having excellent *in vitro* bioactivity, demonstrate less or no *in vivo* actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. And also, when individual constituents are isolated from the plant extract there is loss of specific bio-activity. Bioenhancers reduce the dose, shorten the treatment period and thus reduce drug resistance problems. Due to economy, they make treatment cost effective, minimize drug toxicity and adverse reaction. Secondary beneficial effects include reduced requirement of raw material for drug manufacture<sup>7</sup>.

### Bioenhancers should have the following properties:

- Nontoxic to humans or animals
- Should be effective at a very low concentration in a combination
- Should be easy to formulate
- Enhance uptake/absorption and activity of the drug molecules<sup>8</sup>.

### Mechanism of action of Piperine as a bioenhancer

Different mechanisms for the bioenhancer activity of piperine have been proposed including- DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump. In general, it inhibits drug metabolizing enzymes, stimulates absorption by stimulating gut amino acid transporters, inhibits the cell pump responsible for drug elimination from cells and inhibits intestinal production of glucuronic acid, thus permitting a more active form of drug to enter the body<sup>9</sup>. It may increase the absorption of drug in the GIT, or inhibit

enzymes responsible for drug metabolism, especially in the liver when the drug passes through the liver after absorption from GIT. Oral administration of piperine in rats strongly inhibited the hepatic arylhydrocarbon hydroxylase (AHH) and UDP-glucuronyl transferase activities. Some other mechanisms include- making target receptors more responsive to drugs, acting as receptors for drug molecules, increasing GIT vasculature by vasodilation to increase absorption of drugs, modulation of the cell membrane dynamics to increase transport of drugs across cell membranes<sup>10</sup>.

#### **Thermogenesis**

Piperine, potentially, improve the process of nutrient absorption by enhancing thermogenesis. The theory of food-induced thermogenesis relates to the autonomous nervous system. The autonomous nervous system includes two main receptors in the gastrointestinal tract, the alpha and beta adrenergic receptors. Most of the food or thermogenic induced thermogenesis is facilitated by beta receptors, which include a compound known as cyclic adenosine 3', 5' monophosphate (cAMP). The role of cAMP as a "second messenger" to the hormonal and enzymatic actions in the body is well recognized. The demand for fresh nutrients to sustain the metabolic processes rapidly increases, when thermogenesis occurs. Piperine stimulates the release of catecholamines, thermogenic hormones, whose action is made possible by the presence of cAMP. But, the nature of the thermogenic response mediated by catecholamines is relatively short-lived<sup>11</sup>.

#### **Effect on P-Glycoprotein**

Piperine inhibited P-glycoprotein (P-gp) mediated efflux transport of [3H]-digoxin across Caco-2 (human colon carcinoma cell lines) cell monolayer. Oral piperine increased intestinal P-glycoprotein, reduced liver P-glycoprotein and kidney P-glycoprotein in rats. Piperine modulate cellular P-glycoprotein activity at sub-cytotoxic concentration<sup>3</sup>.

#### **Piperine and Curcumin**

The medicinal properties of curcumin obtained from *Curcuma longa* Linn., cannot be utilized effectively because of its poor bioavailability as a results of

rapid metabolism in the liver and intestinal wall. Figure No.2 shows the enhancement of bioavailability of curcumin by 2,000% upon concomitant administration of piperine, through inhibition of hepatic and intestinal glucuronidation in both animals and humans without adverse effects<sup>13</sup>.

#### **Effect on anti-tubercular drugs**

In patients with pulmonary tuberculosis piperine enhances bioavailability of rifampicin. Piperine is the first and most potent bioenhancer to rifampicin by about 60%. Therefore adding bioenhancer Piperine reduces the dose of rifampicin from 450 to 200 mg. This reduces dosage, cost and toxicity of rifampicin. Rifampicin considered to be a most potent anti-tubercular drug, primarily metabolised in liver microsomal enzyme system. Piperine increases bio-availability of rifampicin by inhibiting Cytochrome P-450 enzymes thus decreasing metabolism of drug. Piperine improves intestinal permeability and inhibits P-glycoprotein and thereby prevents efflux of absorbed drug from enterocytes. It also has potential immunomodulatory activity and has protective efficacy against *Mycobacterium tuberculosis*. Protective immunity against *Mycobacterium tuberculosis* requires the generation of cell-mediated immunity. Secretion of Th-1 cytokines by antigen-specific T cells plays important role in protective granuloma formation and stimulates the antimicrobial activity of infected macrophages. Piperine demonstrated augmentation of Th-1 response. Thus piperine can be synergistically combined with rifampicin to improve its therapeutic efficacy in immune-compromised TB patients. Rifampicin when combined with piperine exhibited a significantly lower mutation frequency. Piperine increases the bioavailability of anti-tubercular drugs like rifampicin, isoniazid, and pyrazinamide. In addition, use of piperine along with anti-tubercular drugs may prevent hepatotoxicity and increase compliance of patients with these drugs. Risorine is a formulation containing rifampicin (200 mg), isoniazid (300 mg), and piperine (10 mg)<sup>15</sup>.

### Effect on other drugs / nutrients' bioavailability

Piperine have a thermogenic action on intestinal epithelial cells is proposed to increase the rate of beta carotene absorption. Piperine markedly increased the mean plasma concentration, AUC, elimination half-life and decreased elimination rate constant of carbamazepine. And it potentiated the effect of gallic acid and also provides a more pronounced therapeutic potential in reducing beryllium induced hepatorenal dysfunction and oxidative stress consequences. Piperine potentiated the antinociceptive and anti-inflammatory action of nimesulide. Co-administration improves therapeutic index of nimesulide with piperine, which is suggestive of decreasing the frequency of adverse effect than seen with nimesulide alone. Co-administration of tiferron and piperine played a beneficial role in reducing beryllium induced systemic toxicity at relatively low doses.

In a placebo controlled study, bioavailability of nevirapine was increased when administered with piperine to healthy volunteers. Piperine potentiated

pentobarbitone sleeping time in a dose dependent manner and it also increase levels of pentobarbitone in blood and brain. Intragastric co-administration of Epigallocatechin-3-gallate (EGCG), from green tea and piperine to mice, increased the plasma Cmax and AUC by 1.3 fold compared to mice treated with EGCG alone. Through inhibition of glucuronidation piperine increased the Cmax and degree of exposure of resveratrol and thereby enhance the bioavailability. This causes decrease the dose of resveratrol. When vasicine (an alkaloid of adhatoda vasica) given orally with powdered long pepper, the bioavailability of vasicine was enhanced by more than 200%. Piperine co-administered with sparteine, enhanced the bioavailability of sparteine by more than 100%. Also PA-1[4-ethyl5-(3,4 methylenedioxyphenyl)-2E,4E-pentadienoic acid piperidine], a piperine analogue has a concentration dependent inhibition of NADPH-associated O-demethylation, O-deethylation as well as N-demethylation reactions in rat liver microsomes, which prevent first pass elimination of drug<sup>2</sup>.

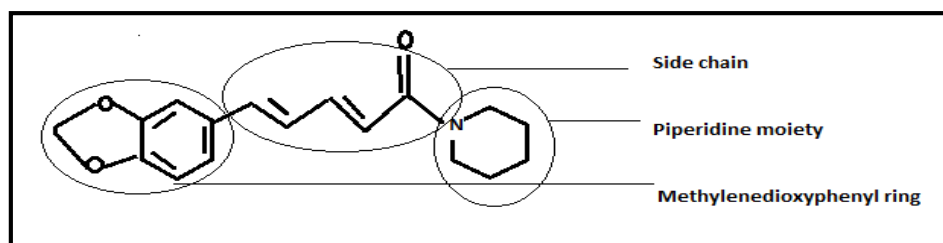


Figure No.1: Structure of Piperine

### CONCLUSION

In conclusion, Piperine is an absorption enhancer of many drugs and nutrients from gastrointestinal tract by various mechanisms and a potent inhibitor of drug metabolism by inhibiting various metabolizing enzymes.

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### CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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