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Review of Piperine as a Bio-enhancer

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ABSTRACT

Piperine (1-peperoyl piperidine), a pungent alkaloid, is found in various Pipper species. Piperine produces antioxidant, antiplatelet, anti-inflammatory, antihypertensive, hepatoprotective, antithyroid, antitumor, antiasthmatic activities and also a fertility enhancer. Piperine enhances absorption from gastrointestinal tract by various mechanisms and reduces gut metabolism of drugs. 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. Thus piperine is an absorption enhancer and a potent inhibitor of drug metabolism.

Key words: Piperine, Metabolism inhibitor, Absorption enhancer, Bio-enhancer, bioavailability

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INTRODUCTION

Piperine (1-peperoyl piperidine), a pungent alkaloid, is found in *Pipper nigrum, Pipper longum, Pipper retrofractum, Pipper crussi* and *Pipper geniculatum* [1]. Piperine is solid having molecular formula $C_{17}H_{19}O_3N$, melting point 128°C and it is optically inactive, sparingly soluble in water with cis-trans isomerism. It has been used as a flavoring additive in brandy and as an insecticide for houseflies [2]. It is a weak base, highly lipophilic and exhibits non-saturable passive absorption kinetics with short absorption clearance and high apparent permeability co-efficient. Long pepper (Piper longum) is widely used in the Indian System of Medicine (Ayurvedic System) along with black piper and ginger to enhance the therapeutic efficacy of the concurrently administered drugs [3]. Piperine is found to be a bioavailable agent [4] produced antidepressant effect on mice [5] and antidepressant and cognitive enhancing effect on wistar male rats [6]. Piperine protected cisplatin-induced apoptosis through the induction of heme oxygenase-1 expression [7]. Piperine also produces Antioxidant [8], Anti-platelet [9], Anti-inflammatory [10], Antihypertensive [11], Hepatoprotective [12], Antithyroid [8], Antitumor [13], Antiasthmatic [14] activities and found to be Fertility Enhancer [15]. 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 [16]. 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. Bioavailability means the fraction of an orally administered dose that reaches the systemic circulation as intact drug, taking into account both absorption and local metabolic degradation [17]. Piperine enhanced oral bioavailability of various drugs and nutrients, which provides basis for piperine to be a bio-enhancer

Piperine as Absorption Enhancer

In vivo piperine increased fluidity of intestinal brush border membrane (BBM), at 5, 10, 20 mg/kg body weight within 5-15 min of administration and also supported by in vitro studies. Piperine increased micro villi length in time dependent manner up to 2 h after in vivo treatment, which increases the absorptive surface of small intestine. Piperine induced increase in ribosome in free cytoplasm and on endoplasmic reticulum, which promotes mRNA translation and synthesis of extracellular and cytosolic proteins. Piperine induces synthesis of proteins associated with cytoskeletal function, resulting in increased absorptive surface of small intestine and thus assisting permeation through the epithelial barrier. Piperine could modulate membrane dynamics

and permeation characteristics by interacting with lipids and hydrophobic proteins. This may decrease the tendency of membrane lipids to act as steric constraints [18]. A polar piperine molecule absorbed very fast across the intestinal barrier and form a polar complex with drug and solutes [2]. Piperine altered membrane dynamics and permeation characteristics of stratum corneum by lipid extraction and interaction with keratin, resulted in increased permeation across human epidermal membrane. Piperine enhanced transdermal permeation/absorption of Aceclofenac by same mechanism [19]. Piperine was found to inhibit gastric emptying (GE) of solid/liquid in rats and gastrointestinal transit (GT) in mice in a dose and time dependent manner [20]. In vitro piperine significantly stimulated γ-glutamyl transpeptidase (γ-GT), enhanced the uptake of radiolablled L-lucine, L-isolucine and L valine and increased lipid peroxidation in freshly isolated epithelial cells of rat jejunum. Piperine may interact with lipid environment to increase permeability of intestinal cells [21].

Metabolism Inhibition

Piperine inhibited CYP450, cytochrome bs and NADPH cytochrome C reductase [22]. and major metabolizing enzyme CYP3A4, which is responsible for the first pass metabolism of drugs [23]. It is a non-specific inhibitor of drug metabolism which shows little discrimination between different CYP P450 forms [24] and found to inhibit rat CYP4502B1 which convert aflatoxin B1 to cytotoxic and genotoxic metabolite. Thus piperine increase bioavailability of parent aflatoxin B1 and produce chemoprotective effect against procarcinogens activated by CYP4502B1 [25]. Structure of piperine is suitable for enzyme inhibition. Three components of piperine methylenedioxyphenyl (MDP) ring, side chain and the piperidine moiety (Figure 1) together, are essential for maximal inhibition of both the constitutive and inducible arylhydrocarbon hydroxylase (AHH) and 7-methoxycoumarin-O-demethylase (MOCD) activities and 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. Saturation of the side chain of piperine induces flexibility in the molecule which may facilitate interaction of the inactivator with protein domain and may thereby enhance constraints for orientation of the CYP substrates to the active site. Saturation of the conjugated double bonds to tetrahydro-derivatives of MDP ring appear to result in higher flexibility of the side chain which perhaps acts as a handle to orient MDP group to the active site of the CYP450 anchored in a strong hydrophobic environment. Thus, altering the functional groups in piperine would determine its interaction with the hydrophobic environment of the active site and hence it's potential 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 appeared to impart specificity for inhibiting different forms of CYP450s. The structure of piperine is ideally suited to affect the microsomal oxidation of large number of compounds. Presence of piperidine function at the terminal end of conjugated double bond in the side chain and MDP ring offered differential sensitivity in inhibiting the CYP450 activities. Modifications of piperine molecule may provide a useful approach in the development of selective CYP inhibitors [26].

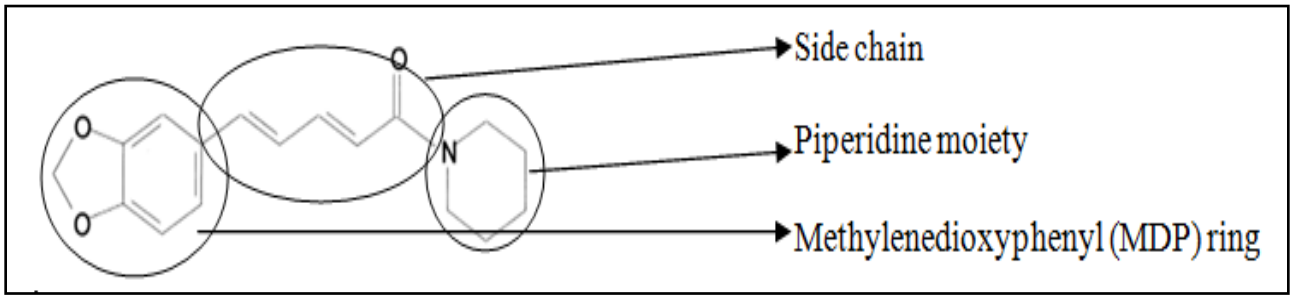

Figure 1: Structure of Piperine

Piperine is a potent inhibitor of UDP-glucose dehydrogenase (UDP-GDH) activity, inhibition is proposed due to conjugated double bond of molecule and inhibition is strong on intestinal glucuronidation than in rat liver. Piperine inhibits the enzyme in a non-competitive and reversible manner by interacting with other than active site of enzyme [27]. Piperine inhibited glucuronidation, gastrointestinal transit and production of EGCG 3-glucuronide [28]. It also inhibited arylhydrocarbon hydroxylation, ethylmorphine N-demethylation, ethoxycoumarine-O-deethylation and 3-hydroxy benzo(a)pyrene glucuronidation in dose dependent manner in rat postmitochondrial supernatant, in vitro. Oral piperine strongly inhibited arylhydrocarbon hydroxylase (AAH) and UDP-glucuronyl transferase activities. Thus piperine is a potent inhibitor of drug metabolism [24]. Piperine inhibited glucuronidation of 3-hydroxy benzo(a)pyrene and reduced UDP-glucuronic acid content in intact epithelial cells of guinea pig small intestine. Piperine caused non-competitive inhibition of hepatic microsomal UDP-glucuronyltransferase and reduced the endogenous UDP-glucuronic acid content [29].

Effect on Chemotherapeutic Agents

A seven days pretreatment of piper longum (15 mg equivalent/kg) enhanced bioavailability of oxytetracyclin, administered orally on 8th day. Animals treated with piperine showed significantly higher AUC, area under the first moment of plasma drug concentration-time curve and mean residential time (MRT). It also reduced elimination rate constant, total clearance and increased total duration of pharmacological action [30]. Oral piperine increased 88.53% of AUC of

metronidazole, which may result in decreased dose requirement of metronidazole [31]. Piperine increased AUC of ampicillin (by 338%, figure 2A) and norfloxacin (by 174.6%, figure 2B).

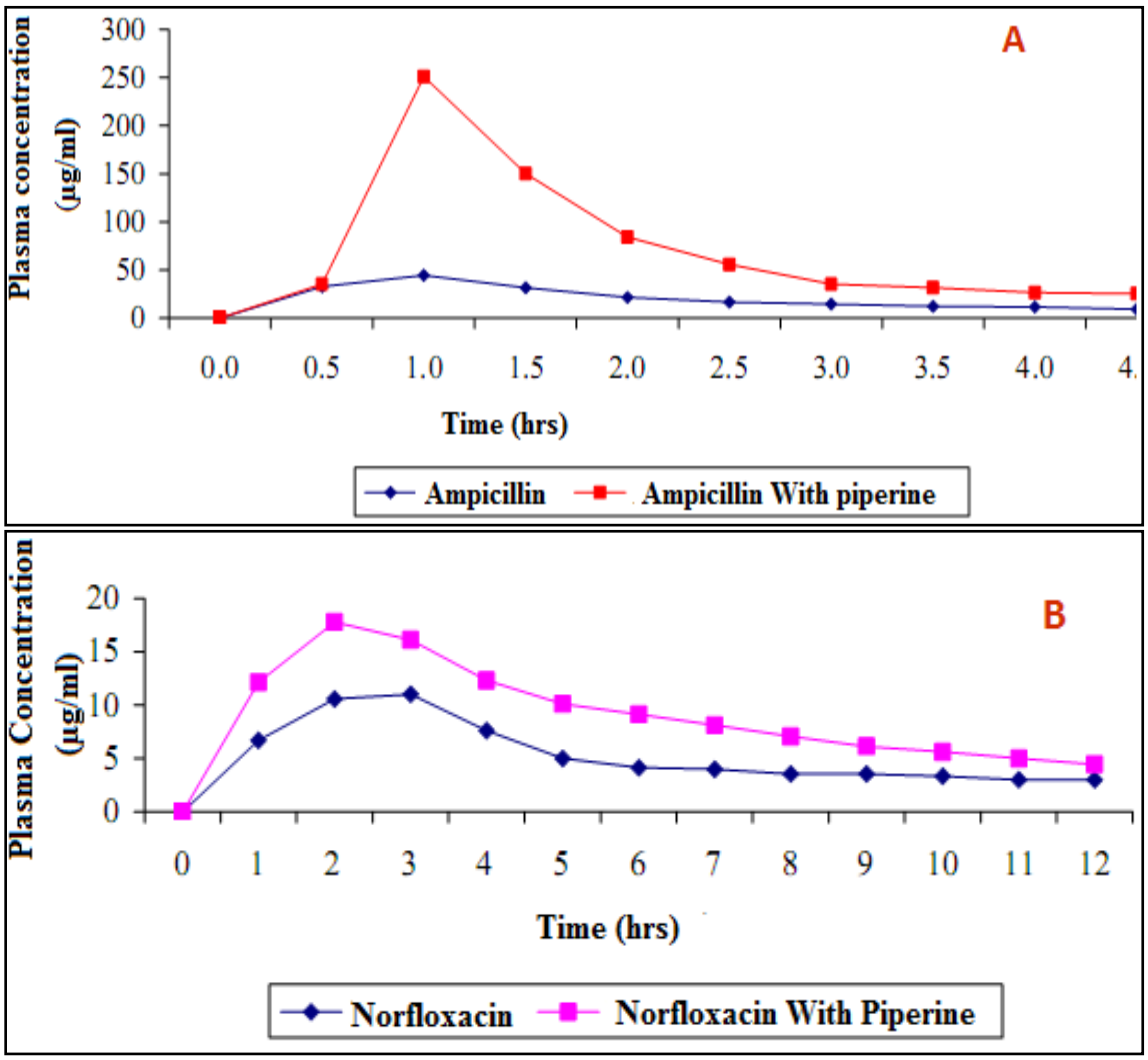

Figure 2: Effect of Piperine on bioavailability of ampicillin (A) and norfloxacin (B)

This effect may allow to reduce the frequency of administration and adverse effects of these antibiotics [32]. Piperine markedly reduced the minimal inhibitory concentration and mutation prevention concentration of ciprofloxacin for *staphylococcus aureus* including methicilen resistant *s. aureus.* The enhanced accumulation and decreased efflux of ethidium bromide in presence of piperine suggests its involvement in inhibition of bacterial efflux pumps [33]. Piperine enhanced bioavailability of betalactum antibiotics, amoxicillin trihydrate and acefotaxime sodium in rats [34]. The bioavailability of gatifloxacin in piperine treated layer birds was 85.74 % which is significantly higher than gatifloxacin alone treated group (74.52 %) and vehicle treated group (72.24%). The significant higher peak plasma levels of gatifloxacin were 2.14 µg/ml in piperine treated group, as compared to 1.81µg/ml in vehicle treated group and 1.74 µg/ml in

gatifloxacin alone group at 2 hours, respectively. Figure 3 shows changes in AUC and plasma concentration of gatifloxacione among various treatments. The values of AUC in piperine treated layer birds was 17.54 µg.h/ml which is significantly higher than gatifloxacin alone treated group (15.25 µg h/ml) and vehicle treated group (14.73 µg h/ml)[35].

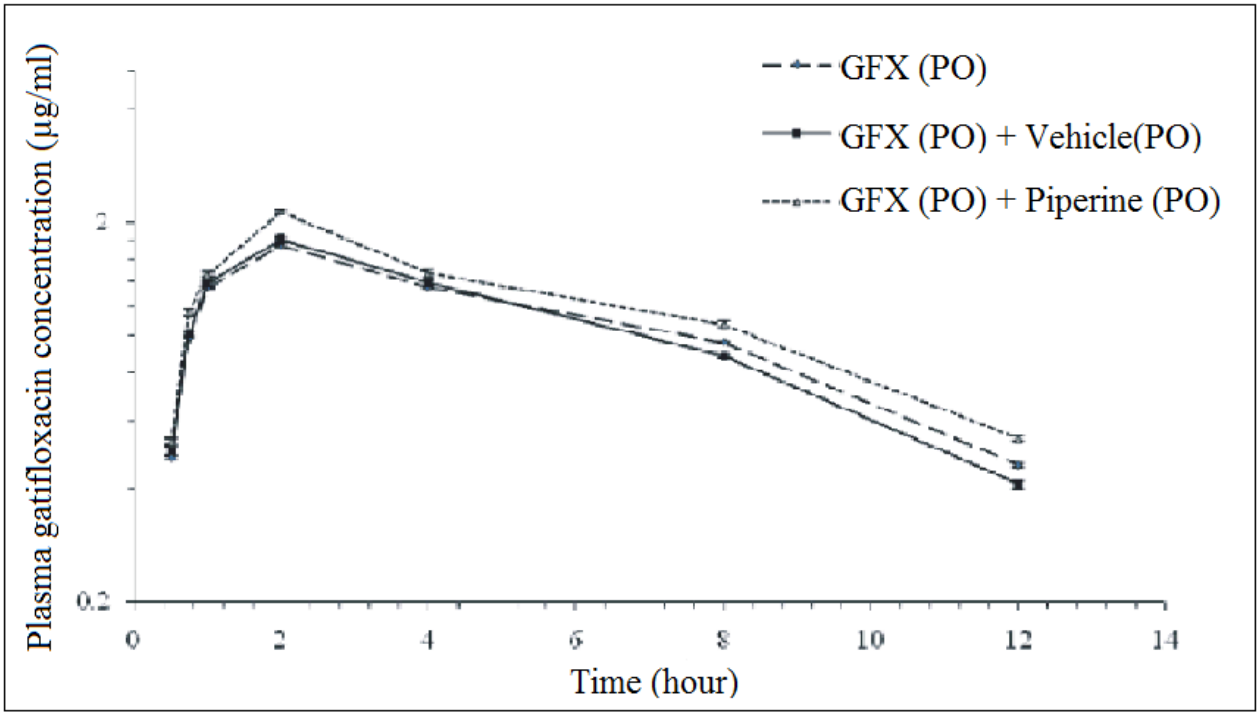

Figure 3: Semi logarithmic plot of plasma concentrations of gatifloxacin in gatifloxacin alone, vehicle control and piperine treated birds after oral administration (10 mg/kg).

GFX – Gatifloxacine, PO – per oral

Effect on P-Glycoprotein

Piperine inhibited P-glycoprotein (P-gp) mediated efflux transport of [3H]-digoxin across Caco-2 cell monolayer. Oral piperine (112 mg/kg body weight) increased intestinal P-glycoprotein, reduced liver P-glycoprotein and kidney P-glycoprotein in rats. Piperine showed to modulate cellular P-glycoprotein activity at sub-cytotoxic concentration [23, 36].

Effect on other drugs/nutrients' bioavailability:

It was concluded that when piperine (40mg/kg) was simultaneously administered with carbimazole (10 mg) for 10 days significant reduction in plasma lipids and lipoproteins levels occurred, except for high density lipoprotein, which was significantly elevated [8]. Six week treatment of oral curcumin with piperine reversed lipid peroxidation in patients with tropical pancreatitis [37]. Oral piperine in combination with curcumin increased C_{max} and AUC of curcumin[38]. After administration of 20, 40, 100, 200 and 400 mg/kg curcumin was detectable in

brain only at 200 and 400 mg/kg. Co-administration of 2.5 mg/kg piperine i.p. with 100 mg/kg curcumin showed detectable curcumin in brain, indicating that piperine enhanced availability of curcumin in brain tissue. Piperine enhanced antidepressant effect of curcumin by potentiating antimobility, neurotransmitter enhancing (serotonin and dopamine) and monoamine oxidaes inhibitory activities [39]. Piperine enhances the serum concentration, extent of absorption and bioavailability of in both rats and humans without any adverse effect [40]. 21 days treatment of 120 mg of coenzyme Q10 with piperine produced about 30% greater area under the plasma curve than was observed with coenzyme Q10 and placebo [41]. Piperine increased area under the serum beta-carotene curve (AUC) as compared to beta carotene with placebo in a double blind cross over study. Piperine did not alter the level of retinol, produced by metabolic pathway from beta carotene occurring predominantly in gastrointestinal epithelium which is the proposed site of piperine action. During the 14 days course piperine did not altered serum concentration of vitamin C and vitamin E which indicate that improved serum response of one nutrient did not affect the serum responses of other micronutrients. Thermogenic action of piperine on intestinal epithelial cells is proposed to increase the rate of beta carotene (nutrient) absorption. There is a possibility of distinction between piperine's effect on nutrients and drugs, because drugs are supposed to be metabolized during/before absorption. Most of nutrients on the other hand enter general metabolism and are essential chemical building blocks and biochemical co-factors and are not subjected to biotransformation [42]. Piperine markedly increased the mean plasma concentration, AUC, elimination half life and decreased elimination rate constant of carbamazepine [43]. It also potentiated the effect of gallic acid and provides a more pronounced therapeutic potential in reducing beryllium induced hepatorenal dysfunction and oxidative stress consequences [44]. Piperine potentiated the antinociceptive and anti-inflammatory action of nimesulide. Co-administration improves therapeutic index of nimesulide, which is suggestive of lesser frequency of adverse effect than seen with nimesulide alone [45] Co-administration of tiferron and piperine played a beneficial role in reducing beryllium induced systemic toxicity at relatively low doses [46]. Bioavailability of nevirapine was enhanced when administered with piperine to healthy volunteers in a placebo controlled study [47]. Piperine potentiated pentobarbitone sleeping time in dose dependent manner and increased levels of pentobarbitone in blood and brain [48]. Co-administration of piperine also enhanced bioavailability of carbamazepine in epileptic patients [49]. Intrgastric co-administration of 163.8 µmol/kg (-)-Epigallocatechin-3-gallate(EGCG), from green tea and 70.2 µmol/kg piperine to mice, increased the plasma C_{max} and AUC by 1.3 fold compared to mice treated with EGCG alone. Piperine increased plasma

level of total and unconjugated EGCG by 1.1 and 1.4 fold respectively [28]. Piperine increased the C_{max} and degree of exposure of resveratrol through inhibition of glucuronidation and thereby enhance the bioavailability. This may allow to decrease the dose of esveratrol [50]. When vasicine (an alkaloid of adhatoda vasica) given orally with powdered long pepper (250 mg/kg), the bioavailability of vasicine was enhanced by more than 200%. (Figure 4A) Piperine co-administered with sparteine, enhanced the bioavailability by more than 100%. (Figure 4B) [51]. In addition, PA-1[4-ethyl5-(3,4 methylenedioxyphenyl)-2E,4E-pentadianoic acid piperidine], a piperine analogue has shown a concentration dependent inhibition of NADPH-associated O-demethylation, O-deethylation as well as N-demethylation reactions in rat liver microsomes, which could significantly prevent first pass elimination of drug.

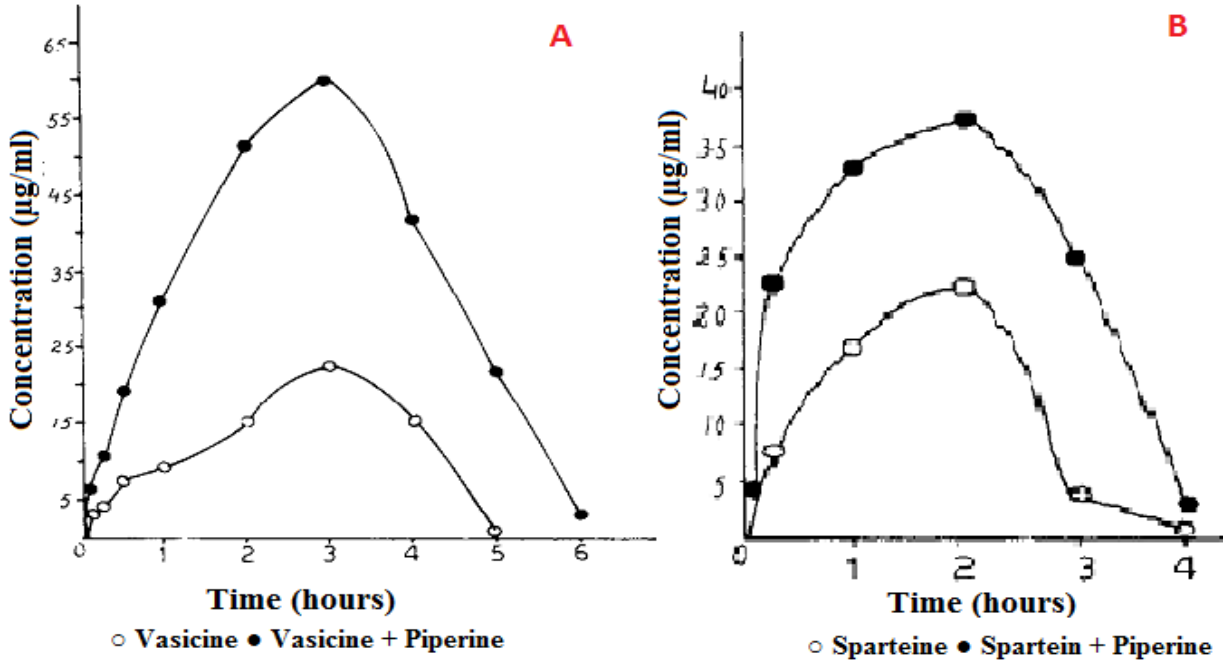

Figure 4: Effect of Piperine on bioavailability of Vasicine (A) and Spartein (B)

PA-1 significantly inhibited P-gp, enhanced C_{max} (by 76%) and AUC (by 96%) of etoposide, a semi synthetic derivative of podophylotoxin, and an anticancer agent [52]. A pretreatment of 20 mg piperine for 7 days significantly changed pharmacokinetic profile of phenytoin and increased bioavailability [49] and piperine enhanced bioavailability of oral phenytoin in mice. Bioavailability of phenytoin is of great importance as it has a narrow therapeutic index. Subsequently, oral pharmacokinetics of phenytoin was carried out in six healthy volunteers in a crossover design where piperine increased Ka (absorption), AUC (0-48), AUC (0-infinity), and delayed elimination of phenytoin. Intravenous phenytoin in the oral piperine-treated rat group showed a significant alteration in the elimination phase indicating its metabolic blockade [53].

CONCLUSION

From this literature one can conclude that piperine is a bioavailability enhancing agent as it enhances bioavailability of various drugs and nutrients. It enhances gastrointestinal as well as local absorption and inhibits various metabolizing enzymes. This provides scientific basis for use of Piper longum to enhance the therapeutic efficacy of the concurrently administered drugs in ayurvedic system and also provides a research tool to enhance bioavailability of suitable Allopathic medicines.

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