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Review article

Piperine : A Bioenhancer

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ABSTRACT

Piperine is a major alkaloid of Pepper fruits belonging to family Piperaceae which has a number of medicinal properties. Pepper fruits are one of them which have been established as bioenhancer for some selected drugs. In Ayureveda since centuries it is called as *"Yogvahi"*. Black pepper fruits are the supporting evidence where piperine was one of the ingredients of *"Trikatu"*. Black pepper fruits are used in different food, drink, dessert, perfume as a brandy flavors and preservative of pickles. It is well known as *"King of Spices"*. Piperine enhances the bioavailability of structurally and therapeutically different drugs, either by increasing the absorption or by delaying the metabolism of the drug or by a combination of both processes. It is evident that black pepper fruits have been used as bio-enhancer in allopathic system of medicine. Piperine has been used as bioenhancer for certain antibacterial- antibiotics with promising results. The interaction of piperine with drug-metabolizing enzymes is responsible for oxidation, hydroxylation and glucuronidation. Piperine appears to top in the list of bioenhancers as it has been used as bioenhancer for Allopathic, Ayurvedic and Unani drugs. Piperine enhances Cmax of different drugs significantly.

KEY WORDS: Black Pepper, Bio-enhancer, Trikatu, Piper nigrum, Piperine.

INTRODUCTION

The modern pharmacopoeias also contain almost 25% drugs of plant origin drugs [1-2]. Since ancient time, number of herbs/plants/plant extracts was used frequently for the treatment of different diseases in Ayurvedic, Homoeopathic, Unani, Siddha and Allopathic system of medicines. Some of them were used as enhancement of drug activity. Pepper fruit is one of them which have been established as bioenhancer for some selected drugs. In allopathic system of medicine the concept of bioenhancer appears too late comparatively as Ayureveda since centuries and called it "*Yogvahi*" e.g. use of '*Trikatu'*. Black pepper fruits are the supporting evidence where piperine was one of the ingredients of "*Yogvahi*" [3]. In Ayurvedic system of medicines, black pepper/long pepper/ trikatu was prescribed routinely for a variety of diseases as part of multi-drug formulations [4].

Piperine is a major alkaloid of Pepper fruits belonging to family Piperaceae which has a number of medicinal properties . Black pepper fruits are used in different food, drink, dessert, perfume as a brandy flavors and preservative of pickles. It is well known as "*King of Spices*". Black pepper fruit alone accounts for about 35% of the world's total spice [5].

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. Piperine enhances the bioavailability of structurally and therapeutically different drugs, either by increasing the absorption or by delaying the metabolism of the drug or by a combination of both processes [6-10]. It is evident that black pepper fruits have been used as bio-enhancer for a number of drugs in allopathic system of medicine like oxyphenylbutazone [11,39], phenytoin [12], aflatoxin B_1 [13], beta-carotene [14] propanolol and theophylline[15]. Piperine has been used as bioenhancer for certain antibacterial-antibiotics with promising results e.g. rifampicin[16,17], dapsone[18], curcumin[19], ciprofloxacin[20], cefotoxime sodium, cyclosporine A [21] and metronidazole [22].
Based on the reported interaction of piperine with drug-metabolizing enzymes responsible for oxidation, hydroxylation and glucuronidation [23].

Figure 1: Photograph of Black Pepper Plant in Garden

Bioenhancers

Bioenhancers are considered to enhance the bioavailability of companion drugs either by inhibiting the drug metabolizing enzyme, cytochrome P_{450} [21] or by transepithelial electrical resistance factor (TER) in controlling the permeability of intestinal mucosa [20]. In this process the pore size between the mucosal epithelial cells are increased, which in turn increases the permeability of intestinal muco-

sa resulting in higher rate of absorption. Thus the mechanism of action of piperine is by promoting rapid absorption from gastro-intestinal tract or by protecting the companion drug from being metabolized in its first passage through the liver after being absorbed from gastro-intestinal tract or by a combination of both [24]. These are the usual modes of action of bioenhancers. Piperine do not operate through any hormonal action or uterogenic activity [25] but it affect the central serotonergic system in brain [26, 27].

Various physico-chemical penetration enhancers including ultrasound, chemical enhancers, ionotophoresis and electro-portion have been used for enhancing transdermal drug transport [28]. The magnetic nanoparticle shows the synergistic enhanced effect of the drug uptake of targeted cancer cells. The interaction between the functionalized gold nanoparticles and biologically active molecules on the surface of leukemia cells may contribute the observed enhancement in cellular drug uptake. The serum response during oral Beta-Carotene supplementation is improved through non- specific thermogenic properties of piperine [29].

A number of bioenhancers like glycyrrhizin, niaziridin present in leaves and pods of *Moringa oleifera* [30], *Cuminum cyminum* extract and piperine have been used with different drugs (Nutraceuticals, Anti-infective and Anticancer Agents). The fertilization of eggs with sperm was enhanced by addition of piperine in female hamsters [31]. These bioenhancers on one hand increase the bioavailability of main drugs while on the other hand reduce the amount of specific drugs used, thus minimizing the cost of treatment. Some of the most commonly used bioenhancers in Ayurveda are *cow urine distillate* and *nitrile glycoside* (new bioenhancer) as per DBT-CSIR patent.

Piperine appears to top in the list of bioenhancers as it has been used as bioenhancer both for allopathic drugs like vasicine, spartene, rifampicin, phenytoin, dapsone, ciprofloxacin, phenobarbitone, theophylline, propanolol, oxyphenylbutazone, cefotoxime sodium, cyclosporine A and Ayurvedic drugs like chavanprash, kumayasava, margamadasava, rohitakarista, vasakasav, srikhandasava, vasavaleha, kusmadaka rasayan, chitraka haritaki, aswagandhi leheyam, danti haritaki, dasamula haritaki, draksavahela, bilvadi leha, narikela khanda, mustak arista, mardikadi lehya, vasava lehya, laghu chincadika lehya, satavari guda, suranavalaha, haridravahela, panchasav, vigrophos capsule, medifer syrup, medikof syrup, gastrip syrup, minnitone liquid, decozyme tablet, nasollerin capsule, vikas syrup, vasa syrup, shila forte capsule, nitya syrup, gestrodep tablet, shishu prabha, livdap tablet and syrup, livosyn syrup, digiped syrup, dirstrep capsule, globinol syrup, coughorex liquid, herbokof syrup, asmocline capsule, hepatogard liquid, neoseptin tablet, hepatogard tablet, herboleh tonic, triguni churna, lastup capsule, romati capsule, herbocalm capsule, diabecon tablet, tentex fort tablet, fi-guard liquid, no-obes capsule, levomax capsule, levomax tablet, tonax capsule, tonax syrups, zymex capsule, zymex syrup, satizum liquid, vasaksar liquid, gasex tablet, gariforte tablet, abana tablet, janodine tonic, jrumax tablet, gexol tablet, katcozyme tablet, katcozyme syrup, lipochen syrup, gasorup syrup, restora liquid, herbodil liquid, chokka herbal capsule, laxeen fort tablet, liv fort tablet, vast syrup etc [32].

Unani drugs such as Itrifal Fauladi, Itrifal Kabir, Baslivun Kabir, Barsesha, Tiryaq-I-Samania, Tutiya-I-Kabir, Jawarish Safar-Jali, Qabiz Jawarish Basbasa, Jawarish Jalinus, Jawarish Safar-Jali Qabiz, Jawarish Fila-Fali, Jawarish Kamuni, Jawarish Kamuni Kabir, Jawarish Kamuni Mushli, Jawarish Mastagi Kalan, Hab Asgand, Hab Papeeta, Hab Papeeta, Hab Pachlauna, Hab Tap Balghami, Hab Hiltit, Hab Saqmunia, Hab Shahiqa, Hab Fauladi, Hab Gul Akh, Hab Katha and Hab Maghz Badam also contain pepper as one of the ingredients in these formulations [33].

Piperine: As Bioenhancer

In many of the Ayurvedic prescriptions and formulations recommended for different ailments, *piper* largely included in the formulations. It is still in practice today. Out of 370 drug formulations in about 210 drug formulation contained '*Trikatu*' as one of the ingredients [33]. Certain studies proved that '*Trikatu*' was acting as bioenhancer for the accompanying drugs. Classics referred this action as *Yogvahi.* Black pepper is one of the three ingredients of '*Trikatu'*. The other two ingredients are ginger and long pepper (*Piper longum*).

Nowadays various bio-enhancers are being added to different formulations in Allopathic and Ayurvedic formulations. The active principle of pepper is piperine. Piperine is an alkaloid with the molecular formula C_{17} H_{19} O_3 N which on hydrolysis yields piperic acid and piperidine. Piperine is chemically [1, 5- (1, 3 Benzodioxol-5-yl)-1-oxo, 2, 4-pentadienyl], while the molecular formula of piperidine is $C_{17}H_{19}O_3N$ M. Its pH is 8.6- 8.5 and pKa is 13.2.

Figure 2: Photograph of Black Pepper Fruits

Bose is credited and describe first the importance of the addition of long pepper to vasaka leaves (*Adhatoda vasica*) to increase its antihistaminic properties and showed that addition of long pepper enhances the action of vasaka leaves. After about half a century Atal *et al*. confirmed the concept of bioenhancer put forth by Bose [34]. When compared with known analeptic drug such as Metrazol and Nikethemide, Piperine had more prolong action of reversing respiratory depression induced by either morphine or barbiturate [35].

Atal studied *Piper chaba* and suggested that piperine promotes the rapid absorption of co-drugs by increased absorption from gastro-intestinal tract or by protecting the drug from being metabolized/ oxidized in its first passage through the liver after being absorbed or by a combination of these two mechanisms [36].

Subsequently Atal *et al*. [5] studied the interaction of piperine with the biotransformation reaction of drugs in

hepatic tissue both *in vivo* and *in vitro*. It was shown that piperine inhibit aryl hydrocarbon hydroxylation, ethyl morphine-N-demethylation, 7-ethoxy coumarin-o-de-ethylation and 3-hydroxy benzo pyrene glucorodination in rats. The use of *Piper longum* as powder or piperine crystals with drugs like vasicine and sparteine was found to increase their bioavailability 2.5 to 3.5 times, respectively.

The synergistic effect of piperine and piperic acid was noticed with 1-oxo-tetrahydro carbazole and compound containing methylene-dioy-phenyl ring. Oral administration of piperine in rats strongly inhibits the AHH(Adenosine hydroxy hydroxylase) and UDP(Uridine di-phosphate) glucoronyl transferase activities. Pretreatment with piperine prolongs hexabarbital sleeping and zoxazolamine paralysis in mice. These results demonstrated that piperine is a potent inhibitor of drug metabolism [37].

In vitro and *in vivo* modulation of drug metabolizing enzyme by piperine was investigated in microsomes of rat and guinea pigs [9]. These studies indicated that piperine caused concentration related inhibition of NADPH- dependent cytochrome P-450 oxidase enzymes which play a central role in disposition, steady state balance of drugs and xenobiotics. In addition piperine is a strong inhibitor of UDP-glucoronyl transferase enzyme and impaired down regulation of Cytochrome P-450 1A1 gene expression in the rat heaptoma 5 L cell lines showing that piperine mediated the impairment of benzo (a) pyrene metabolism and consequently protection of toxicity induced by its metabolite in rat hepatoma 5 L cell in culture. It was due to direct interaction of the alkaloid with Cytochrome P-4501A1 enzyme at post – translation level. Benzo (a) pyrene a substrate for Cytochrome P-450 1A1 enzyme is biotransformed actively by these cells [38].

Piperine may also interact with the process of oxidative phosphorylation process like activation/ deactivation of certain metabolic pathways, slowing down the metabolism and biodegradation of drugs. This action of piperine results in higher plasma levels of the drugs, rendering them more available for pharmacological action. Oral administration of piperine in rats strongly inhibits the AHH (Aromatic hydrocarbon hydroxylase) and UDP (Uridine diphosphate) glucuronyl transferase activities.

Recently it was described that NANC (Non-adrenergic non-cholinergic)nerves operate independently and can not be directly controlled at wish. Thus they are independent of adrenergic and cholinergic nervous system. Piperine and capsaicin both increases heart rate / heart beat strength of guinea pig. The metabolism of piperine in the group of human volunteers has been studied. The 5-(3, 4-dihydroxy phenyl) Valeric acid piperidine are the major metabolites of piperine. However in about 15% of the tested person could not be detected [39].

Reen and Singh considered that piperine increases the absorption of drugs from gastro-intestinal tract by causing direct effect on vascular endothelium, smooth muscle and mast cells, resulting in increased vascular permeability and mucosal blood flow. Piperine itself is a weak base, highly lipid soluble which exists in unionized form at intestinal milieu and as an ionized molecule in the stomach. Hot spice like piperine increases permeability of human intestinal epithelial monolayer.

There are two types of hypotheses on the stimulatory effect of gamma-glutamyl trans peptidase activity (GGT). One proposes that piperine increases the affinity of GGT towards the gamma-glutamyl-cysteinyl-glycine transpeptidase (GSH) molecule while the other expresses a possible modifying effect of piperine on the phospholipids of the cellular membrane. This modifying action of piperine may increase membrane fluidity, which affect the binding of this membrane-bound enzyme. In other words, the piperine interacts with and modifies the environment of enzyme, thus the enzyme activity may be increased [40].

The effect of piperine on the metabolic activation and distribution of (3H) AFB1 in rats [14]. Piperine markedly inhibited liver microsome-catalyzed (3H) AFB1 binding to calf thymus DNA *in vitro*, in a dose dependent manner. Rats pretreated with piperine accumulated considerable (3H) AFB1 radioactivity in plasma and in the tissues examined as compared to the controls.

This successful use of piperine to increase bioavailability of certain drugs created interest in the area of nutrient and food absorption since nutritional deficiency due to poor gastro-intestinal absorption is an increasing problem in developing countries as well as in western nations. Recently a bioavailability study showed that a standardized extract of black pepper, increases gastro-intestinal absorption of beta carotene in human [14].

Dapsone, a widely used antileprosy drug is known to produce methaemoglobinaemia as a serious side effect. Based on the reported interaction of piperine with drug metabolizing enzymes, the investigation was undertaken to study the changes in bioavailability of dapsone and possible reduction in methaemoglobinaemia in presence of piperine in rats. Improved bioavailability of the dapsone in the presence of piperine in rats increased up to 62%. Piperine selectively enhanced the bioavailability of structurally and therapeutically different drugs, either by increasing the absorption or by delaying the metabolism of the drug or by a combination of both processes [23].

The absorption of food, nutrients and xenobiotics is carried out by the mucosa of gastro-intestinal tract. The absorption process is particularly intense in small intestine. The movement of a compound is in the lumen helps in its absorption from gastro-intestinal tract and is a part of “biotransformation” process.

Bioenhancer for different drugs

Bioenhancers are substances which when mixed with a drug; enhance the efficacy of the drug without modifying its property. The effective bioenhancing dose of piperine varies with different drugs but on an average 10% concentration of piperine serves the purpose well as bioenhancer [5]. Atal *et al.* in 1981 mentioned that piperine enhanced the antiasthamatic property of vasaka leaves by increasing the bioavailability of vasicine, the active ingredient of vasaka leaves [7]. Increased bioavailability of a number of drugs such as oxyphenbutazone [11], phenytoin [12], aflatoxin B1 [13] theophylline and propranolol [15], rifampicin [16,17], dapsone [18], curcumin [19], ciprofloxacin [20] and phenobaritone [26], were reported time to time when piperine was used with these drugs. In recent past several groups of workers showed that the bioavailability enhancing property of pepper was due to its alkaloid piperine which on hydrolysis with alkali produces piperic acid and piperidine. Piperine content of black pepper is directly proportional to its pungency [41].

Piperine when used with Rifampicin for pharmacokinetics study, Tmax increases (36.61%), and Cmax reduces (18.33%) where as similar experiment of pharmacokinetics study of Rifampicin with piperine shows significant in-

crease in Tmax (4.9%), Cmax (36.15 %), AUC (28.24 %) and $t_{1/2}$ (7.89%) and reduction in drug elimination rate, volume of distribution as well as half life when piperine was co-administered with Rifampicin. Bioenhancing property of piperine with pentobarbitone, increased bioavailability of pentobarbitone by supporting their AUC (68.40%) and Cmax (70.32%), reduction in half life (10.80%) and clearance of drug which supported the minimum toxicity in comparison of taking drug alone. An increase in the absorption brought by piperine can be explained on the basis of its effect on gastric and intestinal mucosal cells. Trans-epithelial electrical resistance (TER) is responsible factor in controlling the permeability of intestinal epithelia. Piperine was observed to decrease the TER and thus increase the pore size between the cells and in turn the permeability of the intestinal milieu resulting in higher rate and extent of absorption of different drugs.

CONCLUSION

Piperine is a major alkaloid of Pepper fruits belonging to family Piperaceae which has a number of medicinal properties. Pepper fruits are one of them which have been established as bioenhancer for some selected drugs. Piperine has been used as bioenhancer for certain antibacterial- antibiotics with promising results. The interaction of piperine with drug-metabolizing enzymes is responsible for oxidation, hydroxylation and glucuronidation. Piperine appears to top in the list of bioenhancers as it has been used as bioenhancer for Allopathic, Ayurvedic and Unani drugs. Piperine enhances Cmax of different drugs significantly.

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