POTENTIAL OF PIPERINE AS A BIOAVAILABILITY ENHANCER

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Abstract

Oral absorption of drug is very important issue especially when the drug is poorly bioavailable, given for long periods and expensive. 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 bioenhancerBioenhancers or bioavailability enhancers are mostly the plant-based molecules which promote the biological activity or bioavailability or the uptake of drugs in combination therapy. This review article concludes the bioavailability enhancing property of piperine.

Keywords: Bioenhancers, Piperine, Oral absorption, Alkaloid.

Introduction

The concept of 'bioavailability enhancers' is derived from the traditional age-old system of Ayurveda (science of life). In Ayurveda, black pepper, long pepper and ginger are collectively known as "*Trikatu*". In sanskrit "*Trikatu*" means three acrids.

The action of bioenhancers was first documented by Bose (1929) who described the action of long pepper to *Adhatoda vasika* leaves increased the antiasthamatic properties of *Adhatoda vasika* leaves.

Plant based medicines are used by a majority of the world's population. Our Ayurvedic texts have a mention of thousands of herbal drugs for various diseases including the rare ones. Almost 25% of modern pharmacopoeias too contain drugs of plant origin [1]. Many synthetic and herbal drugs suffer from the problem of low bioavailability. Bioavailability is the rate and extent to which a substance enters systemic circulation and becomes available at the required site of action [2]. Maximum bioavailability is attained by drugs administered via intravenous route, whereas drugs administered orally are poorly bioavailable as they readily undergo first pass metabolism and incomplete absorption. Such unutilized drug in the body may lead to adverse effects and also drug resistance. Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs/molecules enhance their bioavailability. Many natural compounds from medicinal plants have capacity to augment the bioavailability when co-administered with another drug. Thus bioenhancers are chemical

entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit synergistic effect with the drug [3.4].

Bioenhancers should have novel properties such as:

- Nontoxic to humans or animals,
- Should be effective at a very low concentration in a combination,
- Should be easy to formulate, and
- Most importantly, enhance uptake/absorption and activity of the drug molecules [5].

Following the use of bioenhancers, the dose of the drug is reduced and risk of drug resistance is minimized. It also reduces the dose-dependent toxicity of the drug, especially of anticancer drugs.

History as Bioenhancer

The term bioavailability enhancer or bioenhancer was first coined by Indian scientists C.K. Atal, the Director of the Regional Research laboratory, Jammu, who discovered and scientifically validated Piperine as the world's first bioavailability enhancer in 1979. Bioenhancers are molecules, which do not possess drug activity of their own at the dose used but promote and augment the biological activity or bioavailability or the uptake of drugs in combination therapy. [6] C.K. Atal, the Director of the institute scrutinized a list of ancient Indian Ayurvedic formulations used in the treatment of a wide range of diseases. He found that one of the groups of herbals which has been documented very frequently as essential part of about 70% of Ayurvedic prescriptions, is `Trikatu`, that comprises three acrids viz. long pepper, black pepper and dry ginger in equal proportions. He observed that a majority of Ayurvedic formulations contained either Trikatu or else one of the ingredients of Trikatu, namely Piper longum (210 formulations out of 370 reviewed) used in a large variety of diseases. In subsequent experiments using various drugs and extracts with trikatu and its ingredients they found that mainly piperine enhances the bioavailability of most of the drugs used in experiments and the role of ginger is to regulate intestinal function to facilitate absorption. [7,8,9]

Mechanism of Action of Piperine as a Bioenhancer

Some mechanisms which have been proposed for the bioenhancing effect of piperine are as followsIncreased gastrointestinal absorption This is brought about by

- 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 [10].
- Increased blood supply: In a study by Annamalai et al. [11] it has been proposed that trikatu enhances gastrointestinal blood flow which causes increased absorption of drugs from the digestive tract.
- 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 [12].
- It has also been proposed that piperine increases brush border membrane fluidity and increases microvilli length [13].

Pharmacognosy of Black pepper

Piper nigrum (Black pepper) plant is a flowering woody perennial climbing vine that belongs to Piperaceae family. Pepper plants easily grow in the shade on supporting trees, trellises or poles up to maximum height of 13 feets or 4 meters and roots may come out from leaf nodes if vine touch to the ground. The plants have heart shape alternate leaves with typically large size of 5-10 cm in length and 3-6 cm across, with 5 to 7 prominent palmate veins. The flowers are small, monoecious with separate male and female flowers but may be polygamous which contain both male and female flowers. The small flowers are borne on pendulous spikes at the leaf nodes that are nearly as long as the leaves. The length of spikes goes up to 7-15 cm. The black pepper's fruits are small (3 to 4 mm in diameter) called a drupe and the dried unripe fruits of *Piper nigrum* are known as a peppercorn. The fully

mature fruits are dark red in color and approximately 5 mm in diameter. A fruit contains a single seed. The plants bear fruits from 4th or 5th year, and continue to bear fruits up to seven years. A single stem contains 20-30 spikes of fruits. The collected spikes are sun dried to separate the peppercorns from the spikes. The fresh harvested unripe green fruits may freeze-dry to make green pepper. The fresh harvested unripe green fruits may sun-dried to make black pepper. The red skin of the ripen fruits is removed and the stony seeds are sun-dried to make white pepper.

Fig 1:Plant of Black pepper

Fig 2:Black pepper

Isolation and Extraction of Piperine From Piper Species

Piperine was discovered by Hans Christian orsted in 1819. It is known as one of the main components of pepper. [14]Piperine is responsible for the pungency of black pepper and long pepper, along with chavicine (an isomer of piperine). [15] It can be isolated from the fruits of P. nigrum or P. longum. The powdered fruits of the plant are extracted with dichloromethane at room temperature with stirring for 12 hours. The extract is filtered, concentrated in vacuum, and then the residue is purified on an alumina column. Pure piperine can also be obtained by crystallization from ethanol, which may be required for food and/or medicinal usages. Piperine is obtained directly from the crude residue in lesser amounts by extraction in alcohol, filtration and successive crystallization. Piperine can be synthesized from the interaction of piperyl chloride (formed from piperic acid and phosphorus pentachloride) and piperidine. [16]

Properties of Piperine

Piperineis the alkaloid responsible for the pungency of **black pepper** and long pepper, along with chavicine (an isomer of piperine). It has also been used in some forms of traditional medicine and as an insecticide. Piperine forms monoclinic needles, is slightly soluble in water and more so in alcohol, ether or chloroform. the solution in alcohol has a pepper-like taste. It yields salts only with strong acids. The platinichloride $B_4 \cdot H_2PtCl_6$ forms orange-red needles. ("B" denotes one mole of the alkaloid base in this and the following formulae.) Iodine in potassium iodide added to an alcoholic solution of the base in presence of a little hydrochloric acid gives a characteristic periodide, $B_2 \cdot HI \cdot I_2$, crystallising in steel-blue needles, M.P. 145°C. Anderson [17] first hydrolysed piperine by alkalis into a base and an acid, which were later named [18] piperidine and piperic acid respectively. The alkaloid was synthesised [19] by the action of piperoyl chloride on piperidine.

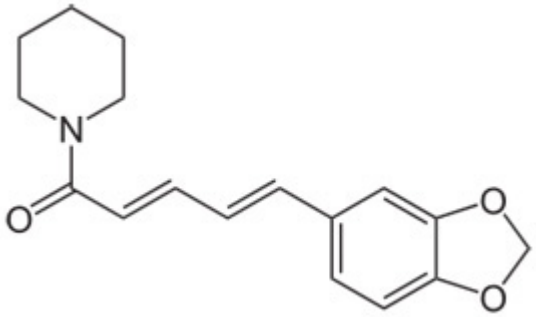

Fig.3: Structure of piperine

Bioavailability Enhancement by Piperine

- Pattanaik S, et al., (2009) evaluated the effect of piperine (20 mg p.o.) on the pharmacokinetics of carbamazepine (300 or 500 mg bid) in epilepsy patients. The comparison of pharmacokinetic parameters from blood samples at regular interval, after the administration of carbamazepine and carbamazepine along with piperine showed that piperine significantly increased the mean plasma concentrations of carbamazepine in both dose groups. There was a significant increase in AUC, average C(ss) and a decrease in K(el) in both the dose groups. Cmax and tmax were increased significantly following piperine administration in the 500 mg dose group. They concluded that piperine could significantly enhance the oral bioavailability of carbamazepine, possibly by decreasing the elimination and/or by increasing its absorption.[20]
- Jin MJ, et al., (2010), investigated the enhanced oral exposure of fexofenadine (10 mg/kg) in rats in the presence and

absence of piperine (10 or 20 mg/kg, given orally). Results of study indicated that combination of piperine increases the oral exposure (AUC) of fexofenadine by 180% to 190% and bioavailability approximately by 2-folds. They concluded that this effect of piperine likely due to the inhibition of P-glycoprotein-mediated cellular efflux during the intestinal absorption.[21]

- Janakiraman K, et al., (2011) aimed to include Piperine (bioenhancer) as a formulation additive in oral formulations of Ampicillin Trihydrate. Physical mixture of Ampicillin Trihydrate and Piperine (1:1) was tested for their compatibility and stability study. The above studies proved that Piperine can be used as a formulation additive for bioenhancing effect in oral formulations of Ampicillin Trihydrate.[22]
- Shoba G, et al., (1998) studied the effect of piperine on the bioavailability of curcumin in rats and healthy human volunteers at a dose 20 mg/kg and 20 mg and 2 g/kg to rats and 2 g respectively. Concomitant administration of piperine increases the tmax while elimination half-life and clearance significantly decreased and the bioavailability was increased by 154%. On the other hand, in humans the increase in bioavailability was 2000%. The study shows that piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects. [23]

Bioenhancing Dose of Piperine

The effective bioenhancing dose of piperine for drugs varies but lots of studies indicate that a dose of approximately 10% (wt/wt) of the active drug or a daily dose of at least 15-20 mg/day could be regarded as an appropriate bioenhancing dose for most drugs. This bioenhancing dose of piperine corresponds to form several thousands to up to 40,000 times less than the LD50 dose of piperine, as established in various experiments on rodents.

Advantages of Using Piperine as Bioenhancer

- There are various advantages of using bioenhancer in combination therapy. These are follows Efficacy of drug is increase due to increase in bioavailability.
- Combination of bioenhancer with drug reduces the dosage and dangers of drug resistance can be minimized.
- Adverse drug reaction/side effect and toxicity of drug will be minimized because of reduced dosage. This is especially true of anticancer drugs like Taxol.
- There are ecological benefits too eg.Toxol used to treat ovarian cancer or breast cancer is derived from bark of Pacific yew tree, one of the slowest growing trees in the world. At present to treat one patient, six trees, 25-100 years old need to be felled with bioenhancers fewer trees will be destroyed.
- They can reduce inter-individual variability as well as intra-individual variability as they increase the bioavailability of drug.

Need for bioavailability enhancement

Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane and to be absorbed systematically following oral or topical administration.

Several plant extracts and phytoconstituents, despite having excellent bioactivity *in vitro* 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. It is often found that, when individual constituents are isolated from the plant extract there is loss of specific bio-activity. Sometimes some constituents of the multi-constituent plant extract are destroyed in gastric environment when taken orally. They reduce the dose, shorten the treatment period and thus reduce drug resistance problems. Due to dose economy, they make treatment cost-effective, minimize drug toxicity and adverse reactions.

Biovailabilities affected by Piperine

It is not yet possible to predict on theoretical grounds the effects piperine will have on any chosen dietary substance or drug. However, some categories of substances have been directly tested and found to have increased bioavailability when consumed with piperine.

barbiturates	isoniazid	selenium (from selenomethionine)
beta-carotene	nalorphine	sulfadiazene
coenzyme Q10 (CoQ10)	phenytoin	theophylline
curcumin (extract from turmeric)	propranolol	vitamin B-6 (pyridoxine)
dapsone	pyrazinamide	glucose (absorption increased)
ethambutol	rifampicin	amino acids (absorption increased)

Table 1. Substances for which piperine has been directly shown to increase bioavailability.

Summary and Conclusion

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

Bioenhancers constitute an innovative concept, the discovery of which was based on a traditional system of Indian medicine (as mentioned by Charaka, Sushruta and other apothecaries in traditional system of medicine). The concept would be useful in decreasing in drug cost, toxicity, and other adverse effects, and thus may ultimately have a positive influence on the national economy (as desired by WHO) of our/one's country. It satisfies all necessary criteria to be considered as an ideal drug. It is safe, effective, economical, easily procured, non-addictive, and has a widely-based effect on several classes of drug. New drug development technologies are concerned about the economics of drug development. Drug discovery process has been highly aided by Ayurveda through reverse pharmacology with new means of identifying active compounds and reduction of drug development cost. The researchers are now aimed at methods of reduction of drug dosage and thus drug treatment cost making treatment available to a wider section of the society including the financially challenged. Hence, it has been proved that novel drug delivery system of herbal as well as of chemical origin has been used to increase the bioavailability of the compounds or their respective constituents (in case of herbal extracts) which has been mentioned in following reported studies related to curcuminoids, silymarin, flavonoids, terpenoids *etc*.

Future Aspects of Piperine

In the present review, an attempt has been made to congregate the erudition of versatile molecule, PIPERINE. Although it has medicinal applications from time immemorial ,but todays need is to develop modern drugs with effective extensive investigation for its bioactivity, mechanism of action, pharmacotherapeutics, and toxicity and after proper standardization and clinical trials. Reviewed interest among the researchers all around the world in the structural modification and synthesis of novel analogues of the privileged molecule piperine is attributed to the wide array of biological activities it possesses. It appears to top in the list of bioenhancers as it has been used as bioenhancer for Allopathic, Ayurvedic and Unani drugs. Several therapeutically as well as industrially useful preparations have been marketed which generates encouragement among the scientists in exploring this medicinal important moiety. As it is very well evident from the literature that piperine has got tremendous potential, thus the appropriate modification in the molecule and synthesis of its analogues to attenuate the toxicity with better economic investment and with good therapeutic utilization presents greater benefit particularly in various treatments and therapies.

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