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Review Article

A Systematic Review of Piperine as a Bioavailability Enhancer

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Abstract

Drug oral absorption is a crucial concern, particularly when the medication is costly, poorly bioavailable, and administered for extended periods of time. Chemical substances known as "bioenhancers" are those that, when combined with pharmaceuticals, increase their bioavailability without having a synergistic impact on the drug itself. Toxicity, expense, poor bioavailability, and long-term medication administration all contribute to the need for bioenhancers, which aid in solving the majority of these issues. Piperine, also known as 1-peperoyl piperidine, is an aromatic alkaloid produced by the Piper species. Piperine alters the lipid milieu and membrane dynamics at the site of absorption to improve permeability. The molecular nature of piperine makes it appropriate for inhibiting enzymes. By blocking several metabolising enzymes, it increases the bioavailability of many medications, including carbamazepine, curcumin, ciprofloxacin, ampicillin, metronidazole, oxytetracycline, and many more. As a result, piperine, a potent inhibitor of medication metabolism, effectively increases absorption. The mechanism, metabolic inhibition, influence of structural alterations on activity, and medications that are bioenhanced by piperine are all explored in the review that follows. It offers insight into the use of piperine as a useful bioenhancer and the advantages of a bioenhanced drug formulation over one without one. Bioavailability enhancers are typically plant-based molecules that support the biological activity, bioavailability, or uptake of drugs in combination therapy. This review article finishes with discussing piperine's capacity to increase bioavailability.

Keywords: Bioenhancers, Piperine, Oral absorption, Alkaloid.

Introduction

The traditional, centuries-old Ayurvedic medical system is where the idea of "bioavailability enhancers" originated (science of life). Black pepper, long pepper, and ginger are collectively referred to as "Trikatu" in Ayurveda. "Trikatu" signifies three acrids in Sanskrit. Bose (1929) was the first to report how long pepper boosted the antiasthmatic qualities of Adhatodavasika leaves, which is how the activity of bioenhancers was originally discovered. The majority of people on earth utilise plant-based medications. Many herbal remedies, especially those for unusual ailments, are mentioned in our Ayurveda texts. Approximately 25% of contemporary pharmacopoeias also include medications with botanical origins1. Low bioavailability is a problem that affects a lot of synthetic and herbal medications. The rate and degree to which a chemical enters systemic circulation and becomes accessible at the needed location of action is known as bioavailability[2]. Drugs given intravenously have the highest bioavailability, whereas those given orally have lower bioavailability due to easy first pass metabolism and insufficient absorption. Such unused medications in the body might have negative consequences as well as increase drug resistance. So, there is a need for compounds that, when mixed with other medications or chemicals, increase their bioavailability but do not themselves have the same therapeutic action. Several naturally occurring substances found in medicinal plants have the ability to increase a drug's bioavailability when supplied alongside it. Bioenhancers, then, are chemical substances that increase the bioavailability of medications when they are combined with them without having a synergistic effect on the drug[3,4]. In addition to being nontoxic to both humans and animals, bioenhancers should also be simple to make, effective at very low concentrations in combinations, and, most importantly, increase the uptake/absorption and activity of the therapeutic molecules[5]. The therapeutic dose is decreased and the danger of drug resistance is reduced after the usage of bioenhancers. Moreover, it lessens the drug's dose-dependent toxicity, particularly for anticancer medications.

History as Bioenhancer

Indian scientist C.K. Atal, the Director of the Regional Research Laboratory in Jammu, first used the phrase "bioavailability enhancer" or "bioenhancer" in 1979 after discovering and scientifically validating piperine as the first bioavailability enhancer in history. Bioenhancers are compounds that, when used in combination therapy, enhance the biological activity, bioavailability, or absorption of pharmaceuticals by promoting pharmacological activity while lacking drug action on their own at the dose used6. The institute's director, C.K. Atal, carefully examined a list of traditional Ayurvedic medicines from ancient India that were once used to cure a variety of illnesses. He discovered that one of the herbal groupings, called "Trikatu," which consists of the acrids long pepper, black pepper, and dry ginger in equal amounts, has been noted frequently as a vital component of roughly 70% of Ayurveda medicines. He noticed that, out of the 370 Ayurveda formulations examined, 210 contained either Trikatu or one of its constituents, Piper longum, which is used to treat a wide range of ailments. The bioavailability of the majority of the

medications employed in subsequent trials utilising different pharmaceuticals and extracts with trikatu and its constituents was found to be enhanced by piperine, while ginger's purpose is to control intestinal function to aid in absorption[7-9].

Mechanism of Action of Piperine as a Bioenhancer

The following are some ways that have been put out for how piperine works to enhance biological function: An increase in gastrointestinal absorption is caused by

- Bile acid assists in the creation of micelles, which are necessary for the absorption of lipids and lipid soluble medicines, thereby increasing solubility. Piperine increases bile acid secretion while also inhibiting bile acid metabolism, which increases micelle formation. This improves absorption and solubility[10].
- Enhanced blood flow: According to a study by Annamalai et al.[11], trikatu improves gastrointestinal blood flow, which increases the absorption of medications from the digestive system.
- Piperine interacts with intestinal epithelial cells to activate gamma-glutamyltranspeptidase activity, which increases amino acid intake by epithelial cells and results in increased permeability[12].
- Moreover, piperine has been suggested to improve brush border membrane fluidity and microvilli length[13].

Pharmacognosy of black pepper

The Piperaceae family includes the blooming, woody, perennial climbing vine known as Piper nigrum (black pepper). Pepper plants can grow easily in the shadow on supporting trees, trellises, or poles, reaching a maximum height of 13 feet (4 metres). If the vine touches the ground, roots may emerge from the leaf nodes. The plants have huge, heart-shaped alternate leaves that are typically 5–10 cm long and 3-6 cm wide, with 5–7 distinct palmate veins. The tiny, monoecious blooms have separate male and female flowers, yet they can also be polygamous, including both male and female flowers. At the leaf nodes, tiny flowers are carried on pendulous spikes that are almost as long as the leaves. Spikes can be up to 7 to 15 cm long. Little (3 to 4 mm in diameter), called drupes, are the dried, immature fruits of Piper nigrum, and peppercorns are those fruits. The fruits are around 5 mm in diameter and dark red when completely grown. A fruit has just one seed. The plants begin to produce fruit in their fourth or fifth year and continue to do so for up to seven years. A single stem has 20–30 fruit spikes on it. To remove the peppercorns from the collected spikes, they are sun dried. Green pepper can be made by freeze-drying the just harvested unripe green fruits. To manufacture black pepper, the freshly picked, unripe green fruits can be sun-dried. To manufacture white pepper, the rocky seeds of mature fruits are sun-dried after the red skin has been removed.

Fig 1: Plant of Black pepper

Fig 2: Black pepper

Isolation and extraction of piperine from piper species

Hans Christianorsted made the discovery of piperine in 1819. It is regarded as one of the key ingredients in pepper 14. Together with chavicine (a piperine isomer), piperine is what gives black pepper and long pepper its pungent flavour 15. It can be separated from P. nigrum or P. longum fruits. Dichloromethane is used to extract the plant's powdered fruits during a 12-hour period while stirring at room temperature. The extract is filtered, vacuum-concentrated, and the remaining material is then cleaned on an alumina column. It is also possible to crystallise pure piperine from ethanol, which may be necessary for food and/or medicinal purposes. Piperine is extracted in smaller amounts straight from the crude residue using alcohol extraction, filtration, and subsequent crystallization. Piperidine[16] interacts with piperyl chloride, which is created from piperic acid and phosphorus pentachloride, to produce piperine.

Properties of piperine

Together with chavicine, piperine is the alkaloid that gives black pepper and long pepper their pungent flavour (an isomer of piperine). Moreover, it has been employed as an insecticide and in some traditional medical procedures. Piperine creates monoclinic needles and is more soluble in alcohol, ether, or chloroform than it is in water. The alcohol-based solution tastes peppery. Only with powerful acids does it produce salts. Needles made of orange-red platinichloride B4•H2PtCl6 are produced. (In this and the formulas that follow, "B" stands for one mole of the alkaloid base.) When iodine in potassium iodide is added to an alcoholic base solution while a little amount of hydrochloric acid is present, the result is a distinctive periodide, B2•HI•I2, which crystallises in steel-blue needles with a melting point of 145°C. Anderson[17]initially used alkalis to hydrolyze piperine into a base and an acid, which were subsequently given the names[18] piperidine and piperic acid. The piperoyl chloride's reaction with piperidine produced the alkaloid[19].

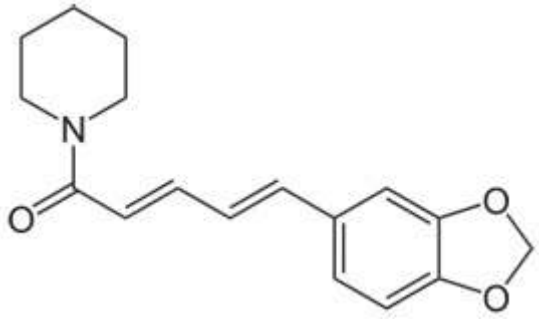

Figure 3: Structure of piperine

Bioavailability enhancement by piperine

- In epilepsy patients, Pattanaik S, et al. (2009) assessed the impact of piperine (20 mg orally) on the pharmacokinetics of carbamazepine (300 or 500 mg dose). Following the administration of carbamazepine and carbamazepine combined with piperine, the analysis of pharmacokinetic parameters from blood samples taken at regular intervals revealed that piperine considerably raised the mean plasma concentrations of carbamazepine in both dose groups. In both dosing groups, there was a statistically significant rise in AUC, average C(ss), and fall in K(el). Following the injection of piperine, the 500 mg dosage group experienced a considerable rise in Cmax and tmax. They came to the conclusion that piperine could greatly improve carbamazepine's oral bioavailability, probably by reducing its excretion and/or boosting its absorption[20].
- Jin MJ, et al. (2010) looked into whether or not piperine (10 or 20 mg/kg, given orally) would increase the oral exposure of fexofenadine (10 mg/kg) in rats. The study's findings showed that adding piperine to fexofenadine increased its oral exposure (AUC) by 18% to 19% and its bioavailability by around twofold. They came to the conclusion that piperine's effects were probably caused by its ability to block P-glycoprotein-mediated cellular efflux during intestinal absorption[21].
- As an addition in oral formulations of ampicillin trihydrate, piperine (a bioenhancer) was the goal of Janakiraman K, et al(2011) .'s study. Ampicillin Trihydrate and Piperine (1:1) were evaluated physically for compatibility and stability. In the oral formulations of ampicillin trihydrate[22], the aforementioned investigations shown that piperine can be employed as a formulation additive for a bioenhancing effect.
- Shoba G. et al. (1998) investigated the impact of piperine at doses of 20 mg/kg for rats and 2 g for healthy human volunteers on the bioavailability of curcumin. While the elimination half-life and clearance considerably decreased and the bioavailability increased by 154% when piperine was administered concurrently, the tmax was enhanced. However, the increase in bioavailability in humans was 2000%. According to the study, piperine increases curcumin's serum levels, degree of absorption, and bioavailability in both rats and people without having any negative effects[23].

Bioenhancing dose of piperine

Many studies suggest that a dose of about 10% (wt/wt) of the active medication or a daily intake of at least 15-20 mg/day might be regarded as a suitable bioenhancing dose for the majority of pharmaceuticals. The effective bioenhancing dose of piperine for drugs varies. This piperine dose for bioaugmentation is 40,000 times smaller than the piperine LD50 dose, which was determined through several mouse trials.

Advantages of using piperine as bioenhancer

- The use of bioenhancer in combination therapy has a number of benefits. These are they the drug's increased bioavailability has increased its efficacy.
- Drug dosage is decreased when a bioenhancer is added, and the risks associated with drug resistance are reduced.
- Because of the lower dosage, drug toxicity and adverse medication reactions/side effects will be reduced. This is particularly accurate for anticancer medications like Taxol.
- There are ecological advantages as well, for instance, Taxol, a drug used to treat breast or ovarian cancer, is made from the bark of the Pacific yew tree, one of the world's slowest-growing species. Now, six trees between 25 and 100 years old must be cut down to cure one patient; however, with the use of bioenhancers, fewer trees will be lost.
- In addition to increasing the drug's bioavailability, they can lower both intra- and inter-individual variability.

Need for bioavailability enhancement

The primary barriers to chemicals passing the cellular membrane and being systemically absorbed after oral or topical administration are lipid solubility and molecular size. Many plant extracts and phytoconstituents exhibit low absorption and bioavailability despite having great bioactivity in vitro because of their poor lipid solubility, incorrect molecular size, or both. It is frequently observed that unique bio-activity is lost when individual elements from the plant extract are isolated. When consumed orally, part of the multi-constituent plant extract's contents may occasionally be eliminated in the stomach environment. They lower the dosage, shorten the course of therapy, and as a result, tackle medication resistance issues. They reduce drug toxicity and side responses and make treatment more affordable thanks to dose economy.

Biovailabilities affected by piperine

The effects of piperine on a particular dietary ingredient or medicine cannot yet be predicted theoretically. Yet, when taken with piperine, some drug classes have been directly studied and proven to have higher bioavailability.

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

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)

Summary and Conclusion

Bioenhancers represent a useful and effective idea that improves bioavailability while reducing dose and associated side effects. Since it is clear from the literature that piperine has a promising future as one of the most potent and commonly used bioenhancers, the concept of action of piperine should be further investigated. An novel idea known as "bioenhancers" was developed based on an ancient Indian medical method (as mentioned by Charaka, Sushruta and other apothecaries in traditional system of medicine). The idea would be helpful in lowering medicine costs, toxicity, and

other negative consequences, and might ultimately have a favourable impact on the national economy of our/country one's (as sought by WHO). It meets all requirements to be regarded as an excellent drug. It has a significant impact on many different drug classes and is non-addictive, inexpensive, easy to obtain, and safe. The economics of drug development are an issue for new drug development technology. With innovative ways to identify active molecules and lower costs associated with medication development, Ayurveda has greatly aided the drug discovery process. Researchers are now focusing on strategies for lowering drug dose and, consequently, drug treatment costs, making treatment accessible to a wider segment of society, including those who are struggling financially. In order to increase the bioavailability of the compounds or their respective constituents (in the case of herbal extracts), it has been demonstrated that novel drug delivery systems of both herbal and chemical origin have been used. These studies include those involving curcuminoids, silymarin, flavonoids, terpenoids, and others.

Future aspects of piperine

An effort has been undertaken in the current review to gather the knowledge on the versatile chemical PIPERINE. Although it has been used medicinally since the dawn of time, the development of new pharmaceuticals is now required. This requires thorough examination of the bioactivity, mechanism of action, pharmacotherapeutics, and toxicity, as well as proper standardisation and clinical trials. The extensive range of biological actions that piperine is capable of is what has sparked global interest among researchers in the structural modification and synthesis of novel analogues. Given that it has been utilised as a bioenhancer for Allopathic, Ayurvedic, and Unani medicines, it looks to be at the top of the list of bioenhancers. Several preparations that are both medically and commercially helpful have been marketed, which encourages scientists to research this crucial component of medicine. Since it is abundantly clear from the literature that piperine has enormous potential, it would be advantageous to modify the molecule appropriately and create its analogues in order to lessen its toxicity with better financial investment and therapeutic utilisation. This would be especially beneficial for a variety of treatments and therapies.

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