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Review Article

PIPERINE: A VALUABLE ALKALOID FROM PIPER SPECIES

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ABSTRACT

The present scientific peer review describes on novel natural cyclobutane-containing alkaloid piperine isolated from Piper species. The characterization of this alkaloid showed that it imparts pungency and medicinal value to Piper species. It has been confirmed that piperine acts as an efficient bioavailability enhancer for different nutrients and trace elements and exhibits potential anti-microbial, anti-oxidant, anti-inflammatory, anti-cancer, anti-depressant, anti-apoptotic, anti-pyretic and analgesic activities. In this review, origin, structure and biological properties; extraction, quantification and applications of piperine were presented. Immense study of this type of valuable natural compounds will provide substantial knowledge to scientific world to develop right technologies for its ample production, to meet its demand in food and pharmaceutical industries.

Keywords: Piperine, Alkaloid, *Piper nigrum, Piper longum*, Medicinal value

INTRODUCTION

Plant derived drugs secured importance in recent years because of their unrefuted efficacy as phytomedicines. The active compounds or principles present in these natural products serve either as templates or as intermediates for synthetic drugs. Piperine ($C_{17}H_{19}NO_3$) is an alkaloid found in the fruits and roots of *Piper nigrum* and *Piper longum* species of Piperaceae family (Figure1). This alkaloid is responsible for the pungency of black pepper (*P.nigrum*) and long pepper (*P.longum*), along with chavicine (an isomer of piperine). This alkaloid was first isolated from the fruits of *P.nigrum*, the source plant of both the black and white pepper grains [1]. Fluckiger and Hanbury found that species of "long pepper" *P.longum* and *P.officinarum* also contain this alkaloid [2]. In addition to the above species, this compound is also present in West African pepper species [3]. The pungency of piperine is caused by the activation of the heat and acidity sensing Transient receptor potential vanilloid (TRPV) ion channel TRPV1 on nociceptors (pain sensing nerve cells) [4].

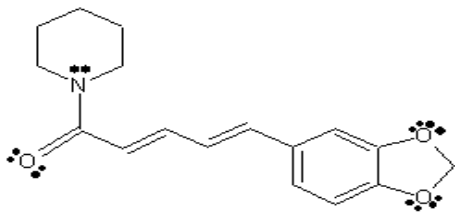

Fig. 1: Chemical structure of piperine.

Piperine forms white prisms, which melt at 128A°-219A°. It is almost insoluble or slightly soluble in water (40mg/L at 18°C), but readily soluble in alcohol (1g/15ml) and ether (1g/1.7ml). It is a very weak base; forms salts only with mineral acids and these are dissociated by water. Piperine was first hydrolyzed by using alkalis [5] into a base and an acid, which were later named as piperidine and piperic acid respectively [6]. This alkaloid was synthesized by the action of piperoyl chloride on piperidine [7]. The genus Piper has more than 1000 species, but the most well-known species are *P.nigrum*, *P.longum* and *P.betel* [8]. Out of these, *P.nigrum* is famous as the spices king due to its pungent quality. *P.nigrum* is a flowering wine (Figure 2) mostly cultivated for its fruit. Its fruits are used to produce black, white and green peppers (Figure 3) which are valued due to the presence of an alkaloid piperine along with its isomers.

Fig. 2: *Piper nigrum* plant (Indian black pepper) with immature pepper corns.

Fig. 3: Black and white peppercorns from *Piper nigrum.*

Black pepper is ground from dried whole unripe fruit, where as white pepper is ground from dried ripe fruit that has had the outer layer removed. People use black and white pepper for stomach upset, bronchitis, malaria, cholera and cancer. Because of these

properties *P.nigrum* is medicinally important [9] and is used to cure digestive and respiratory disorders [10-12]. *P.longum* (long pepper) is also a flowering climber (Figure 4) cultivated for its fruit and root. This plant is source of drugs pippali and pippalimulam which are prepared from dried ripe fruits (Figure 5) and roots of *P.longum* are well known medicines for respiratory tract diseases like asthma, bronchitis and cough. The West African black pepper (*P.guineese*) is important as flavourant and its different parts are used as internal medicine for curing bronchitis, gastric ulcer, rheumatism and viral diseases [13].

Fig. 4: Indian long pepper plant with immature corns.

Fig. 5: Mature dried corns of long pepper

Govindrajan [14] reported that pungent quality of *P.nigrum* and *P.longum* is due to piperine content and other compounds role in imparting pungent nature is very negligible. It is interesting to note that these two species are important components in Ayurveda medicine, which is the ancient Indian medical system for different problems. Nearly 60% of all traditional Ayurveda medicine contains some special blend of ingredients, which include *P.nigrum* in the blend. In addition, *P.longum* is being used in 324 Ayurveda formulations and it is one of the ingredients of Trikatuchurna which is used for bronchitis and asthma. Fruits and roots of *P.nigrum* and *P.longum* contain a number of constituents including volatile oil, alkaloids, isobutyl amides, lignans and esters etc. Out of these, piperine is the primary constituent and reported to be significant in imparting medicinal value for these spices.

Conservation and propagation of Piper species

Seed propagation in spices is cumbersome, uncertain and yields only a few heterogeneous species due to their short viability and high sterility in post fertilization stages [15]. *P.nigrum* is conventionally propagated through cuttings with 2-6 nodes for nursery and field plantations. Because of this, *P.nigrum* germplasm conservation in a seed bank is not pragmatic due to heterozygous nature induced through cuttings [16]. In *P.longum* also conventional propagation is beset with different problems like poor seed viability, low percentage of germination, scanty delayed rooting of vegetative cuttings. Therefore, there is a need for alternative propagation methods [17]. The traditional methods of crop improvement are not suitable to address the problem. So to circumvent the above crises, modern methods of plant propagation and gene transfer are very much useful. Major weakness responsible for low productivity of Piper species is non-availability of healthy planting material and crop losses due to abiotic and biotic stresses [18]. In addition to this, other factors influencing the yield of these species are endogenous microbial contamination and very slow growth rate of cultures. Establishment of contamination free plants from greenhouse grown plants was very difficult due to endogenous microbial contamination as reported in *Piper methysticum* [19].

Procedures for extraction of piperine

Since piperine has many applications in food and pharma industries, it should be extracted in a pure form which is free from residual solvents to enable its direct use in medicinal formulations and food products. On an industrial scale, pepper is comminuted into flakes or ground into coarse powder and then extracted repeatedly with an organic solvent such as acetone, ethanol or chlorinated hydrocarbons [20]. This longer duration of repeated solvent extraction of raw pepper particles results in the extraction of other components such as gums, polysaccharides and non-flavour substances. This type of solvent extraction process usually gives complex crude products, which have to be purified further by multistep techniques such as chromatogramphy or crystallization. High-pressure steam treatment can also be used to extract piperine by an osmotic shock; however, this technique is relatively slow and consumes a large amount of steam [21]. Raman and Gaiker[22]. extracted piperine efficiently by hydrotropic extraction and showed that it has tremendous potential for cell permeabilization and selective extraction of bioactive compounds on a commercial scale. Hamrapurkar et al. [32] reported that supercritical fluid extraction has more extraction efficiency and reduced extraction time than soxhlet extraction method. The % w/w yield of piperine in supercritical fluid extract was 8.76 for *P.nigrum* and 4.96 for *P.longum* in 0.5 hr time period, whereas in the case of Soxhlet extract, the % w/w yield for *P.nigrum* was 8.13 and for *P.longum* was 4.32 in 8.0 hr time period. The yield of piperine was found to be higher in *P.nigrum* compared to *P.longum.*

Quantification of piperine

For estimation and quantification of piperine following methods were used i.e UV spectrophotometry [23], TLC-UV densitometry [24], HPTLC [25-26] and HPLC [27-28]. Mukherjee [29] showed that, the piperine content in fruits of *P.nigrum* and *P.longum* was 3-6% and 0.6-1.6% by HPLC technique. Santosh et al.[30] reported that content of piperine in fruit and root of *P.longum* was 0.879% and 0.31% and in fruit of *P.nigrum* was 4.5% by RP-HPLC analysis. Hu et al. [31] showed that the total yield of piperine in the root of *P.nigrum* was 0.79% by RP-HPLC technique: separately, 0.99% in the thin root (0.5 cm in diam.) and 0.14% in the thick root (3 cm in diam.); 0.44% in the cortex and 0.29% in the stele of a root in diam. of 2 cm were determined. The average content of piperine in three batches of pepper roots was in the range of 6.67～6.77mg·g-1. Hamrapurkar et al. [32] reported that this alkaloid can be quantified with excellent accuracy with in short time period through HPTLC method. The accuracy values obtained were in the range of 97.25% to 98.57% in *P.nigrum* and 96.50% to 97.50% in *P.longum.*

Patents on piperine

The natural extract from black pepper is marketed under the trademark BioPerine® and has unique distinction of having four patents for the efficacy of this unique ingredient. The patents held on BioPerine are 5,5536,506, 5,744,161, 5,972,382 and 6,054,585. They relate to increase the bioavailability of nutritional compounds and making high purity piperine for nutritional use. Various studies have proven the effectiveness of BioPerine and some showed that absorption levels were increased up to 60%. Duessel et al. [33] reported that it will maintain a healthy colon and gives protection against colon cancer. Wattanathorn et al.[34] showed that it has anti-depression like activity and cognitive enhancing properties. Kumar et al.[35] showed that it may contain antibacterial and anti-allergic properties.

Applications of piperine

Piperine has diverse biological and therapeutic activities. It can dramatically increase the absorption of selenium, vitamin B and β-carotene as well as other nutrients [36]. It can stimulate pancreatic and intestinal digestive enzymes and also increases biliary bile acid secretion when orally administrated [37]. It prevents and minimizes diarrhoea produced by various oil and also reduces the intestinal fluid accumo-latin in mouse intestine [38]. In addition to its involvement in increasing the absorption of other nutrients in the body, piperine has other novel applications like helping to fight against colon cancer. It has anti-inflammatory, thermogenic, growth stimulatory, anti-thyroid and chemo preventive activities [39]. This also displays antipyretic, analgesic, insecticidal, immuno-modulatory, antitumor, anti-depressant and anti-apoptotic activities [40-44].

It is involved in inhibition of hepatic drug metabolism [45], enhancing pentobarbitone induced hypnosis[46], bioavailability of oxyphenyl butazone [47], hepatoprotective activity [48], inhibition of lipid peroxidation during experimental inflammation [49], antifertility [50] and radio protective effects [51]. It has also been shown to have analgesic, anti-convulsant, anti-arthritic, anti-ulcer, antioxidant activities and cytoprotective effects [52-57]. In a recent study, Wattanathorn et al. [34] demonstrated that piperine also affects mood and cognitive disorder. Kapoor et al. [58] recently demonstrated that the protective effect of piperine is most likely due to its antioxidant activity. It provides protection against seizures in epilepsy and gained increased attention as a bioavailability enhancer in the formulations of several drugs [59-60]. Because of its protective effect against radiation, it can also be administered to cancer patients before radiotherapy [61]. It has been found to inhibit human CYP3A4, P-glycoprotein and enzymes important for metabolism and transport of xenobiotics and metabolites [62].

Earlier animal studies reported that, piperine can inhibit other enzymes important for drug metabolism [63-64] and in this way by inhibiting drug metabolism it may increase the bioavailability of various compounds and alter the effectiveness of some medications [63]. Notably, piperine enhanced bioavailability of curcumin by 2000% in humans [65]. Chemo preventive efficacy of curcumin and piperine has been shown during 7,12-dimethylbenz[a] anthracene-induced hamster buccal pouch carcinogenesis [66]. Recently, it was reported that piperine can enhance the pharmacokinetic parameters of resveratrol by inhibiting its glucuronidation, thereby slowing its elimination [67]. Some researchers discovered that piperine can stimulate pigmentation in the skin, together with the exposure to UVB light [68]. Toxicity and symptoms of high intake of piperine was not noticed. Piperine may be required in more quantity during times of stress.

Conclusion and future directions

This review collectively presents source, extraction, significance along with applications of piperine in different food and pharmaceutical industries. Piperine is an alkaloid present in the fruits and roots of *P.nigrum* and *P.longum* species of Piperaceae family, which contributes pungent quality to them. The two species are valued for the presence of this important alkaloid and are used medicinally to cure digestive and respiratory disorders. Piperine can be extracted by using an organic solvent like acetone or ethanol and quantified with excellent accuracy through HPTLC method. It has various applications in food and pharmaceutical industries. It is used as a bioavailability enhancer to increase the availability of selenium, vitamin B, β-carotene and other nutritional compounds. In addition, it possesses anti-inflammatory, thermogenic, growth stimulatory, anti-thyroid activities and also acts as a chemo preventive agent. This also displays antipyretic, analgesic, insecticidal, immune-modulatory, antitumor, anti-depressant, anti-apoptotic, anticonvulsant, anti-arthritic, anti-ulcer, antioxidant and cytoprotective effects. Recently it has been shown that, this also affects mood and cognitive disorder and acts as a bioavailability enhancer in the formulations of several drugs. Multiple activities exhibited by this alkaloid can be attributed to prepare large number of medical formulations in pharmaceutical industries. This review can provide tremendous knowledge to conduct research related to this valuable natural product.

CONFLICTS OF INTEREST

The authors do not have any conflict of interest to declare.

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ABBREVIATIONS

HPLC High performance liquid chromatography

RP-HPLC Reverse phase high performance liquid chromatography

HPTLC High performance thin layer chromatography

TLC-UV Thin layer chromatographic- Ultraviolet

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