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Review Article

Biological action of *Piper nigrum* - the king of spices

Arun Kumar Srivastava*, Vinay Kumar Singh

Malacology Laboratory, Department of Zoology, DDU Gorakhpur University, Gorakhpur - 273009 U.P. India

* Corresponding author: Dr. Arun Kumar Srivastava; Phone: +91-9792250710 (Mobile); E-mail: aksgkp5@gmail.com

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ABSTRACT

Piper nigrum - the king of spices is originated in the Western Ghats of India. It has gained a global consideration because of its volume in the spice industry. It contains major pungent alkaloid piperine which is known to possess many interesting pharmacological actions. Medicinally black pepper can be used digestive disorder like large intestine toxins, different gastric problems, diarrohea and indigestion and also can be used against respiratory disorder including cold fever, asthama. Piperine exhibits diverse pharmacological activities like antihypertensive, antiplatelets, antioxidant, antitumor, antipyretic, analgesic, anti-inflammatory, anti-diarrheal, antibacterial, antifungal, anti-reproductive, insecticidal activities. *Piper nigrum* also found to decrease lipid peroxidation *in vivo*. It has reported to possess antioxidant activity that might be due to the presence of flavonoids and phenolic contents.

Keywords: *Piper nigrum*; Alkaloids; Antireproductive; Antioxidant; Flavonoids.

1. INTRODUCTION

Piper nigrum (Black pepper) is one of the most commonly used spices and considered as "The King of Spices" due to its trade in the international market [1, 2]. It is commonly known as Kali Mirch in Urdu and Hindi, Pippali in Sanskrit, Milagu in Tamil and Peppercorn, White pepper, Green pepper, Black pepper, Madagascar pepper in English [3]. Black pepper is used as medicinal agent, a preservative, and in perfumery [4]. The genus Piper has more than 1000 species but the most well known species are *Piper nigrum*, *Piper longum* and *Piper betli* [5]. Black pepper can be used for many different purposes such as human dietaries, as medicine, as preservative, as biocontrol agents [2, 6, 7]. Pepper is used worldwide in different types of sauces and dishes like meat dishes. It contains major pungent alkaloid piperine (1-peperoyl piperidine) which is known to possess many interesting pharmacological actions [8]. Tiwari and Singh [9] reported that this plant and its active components piperine can stimulate the digestive enzymes of pancreas and intestine and also increases billiary bile acid secretion when orally administered. Black pepper is important for its medicinal values [10]. Medicinally black pepper can be used digestive disorder like large intestine toxins, different gastric problems, diarrohea and indigestion and also can be used against respiratory disorder including cold fever, asthama [11-13]. Piperine exhibits diverse pharmacological activities like antihypertensive and anti-platelets [14], antioxidant, antitumor [15], antipyretic, analgesic, anti-inflammatory, anti-diarrheal, antispasmodic, hepato-protective [16], antibacterial, antifungal, anti-thyroids, anti-apoptotic, anti-spermatogenic, insecticidal and larvicidal activities etc. Piperine has been found to enhance the therapeutic efficacy of many drugs, vaccines and

nutrients by increasing oral bioavailability by inhibiting various metabolising enzymes [17]. In recent pasts, different therapeutic potentials of *Piper nigrum,* its extracts, or its important active chemical constituent "piperine" have been published in different international research journals. The current review is aimed to provide an updated literature review on recent research advancement of pharmacognosy, chemistry and pharmacological activities of *Piper nigrum* L. We have compiled a review on therapeutic potential of *Piper nigrum* by collecting updated scientific research information's from internet using Google search engine.

2. TAXONOMICAL CLASSIFICATION OF *PIPER NIGRUM*

Kingdom: Plantae
Class: Equisetopsida
Sub class: Magnoliidae
Super order: Magnolianae
Order: Piperales
Family: Piperaceae
Genus: *Piper*
Species: *nigrum*

3. GEOGRAPHICAL DISTRIBUTION

Black pepper is grown in many tropical regions like Brazil, Indonesia and India [3]. Geographically, it is confined to Western-Ghats of South India [18]. However, some reports of cultivation from Malaysia, Indonesia, Brazil, Sri-Lanka and West Indies are also available [19]. *P. nigrum* had been found in vast altitudinal regions and showed great adaptability to a wide range of environmental conditions which led to inter-species diversity [20]. "Black-pepper" as its generalized name is due to the color of the peppercorn. It is considered as the "king of spices" due to its trade in the international market [1, 2].

4. PHYTOCHEMISTRY

There are many biologically important phytochemicals are extracted from *P. nigrum* plants. They contain alkaloids, amides, propenyphenols, lignans, neolignans, terpenes, steroid, kawapyrones, piperolides, chalcones, dihydrochalcones, brachyamide, dihydropipericide, 3,4-dihydroxy-6 (N-ethyamine), benzamide, (2E, 4E)-N-eicosadienoyl pereridine, N-trans-feruloyltryamine, N-formyl piperidine, guineensine, (2E, 4E)-N-5[(4-Hydroxyphenyle)-pentadienoyl] piperidine, (2E,4E)-N-isobutyldecadienamide), (2E,4E)-N-isobutyl-eicosadienamide, (2E,4E,8Z)-N-isobutyl-eicosatrienamide, (2E,4E)-N-isobutyloctadienamide, piperamide, piperamine, piperettine, pipericide, piperine, piperolein, trichostachine, sarmentine, sarmentosine, tricholein, retrofractamide [21-27] (Figure 1). Pino et al. [27] observed that the major components of the essential oil obtained from the aerial parts of *P. nigrum* were gluulol, α-pinene, β-caryophyllene and α-terpinene. Piperine was the first amide to be isolated from piper species and it is the major active principle of black pepper, is closely related in structure to the known natural carcinogens-safrole, estragole and methylengenol which are also widely distributed in spices and plant oils [5]. Zheng et al. [28] studied that the fruits contain 1.0-2.5% volatile oil, 5-9% alkaloids, of which the major ones are piperine, chavicine, piperidine, and piperetine, and a resin. The terpenes, steroids, lignans, flavones, and alkaloids/alkamides have been identified as the primary constituents of the peppers [29]. Khan et al. [30] reported that most of the pharmacological properties of *P. nigrum* fruits are attributed to a piperidine alkaloid, piperine, which is present in the fruits in amounts of 1.7-7.4%. Piperine has also been shown to enhance the bioavailability of several drugs, for example sulfadiazine, tetracycline, streptomycin [31], rifampicin, pyrazinamide, isoniazid, ethambutol and phenytoin [30]. Vasavirama and Upender [5] concluded that due to its diverse pharmacological properties, piperine is important as a biomarker for standardization of fruit of *P. nigrum* and *P. longum* and of polyherbal formulations containing these raw materials.

5. ANTI-BACTERIAL ACTIVITY

Karsha and Laxmi [32] reported that anti-bacterial activity of black pepper (*Piper nigrum* Linn.) with special reference to its mode of action on bacteria and found that excellent inhibition on the growth of Gram positive bacteria like *Staphylococcus aureus,* followed by *Bacillus cereus* and *Streptococcus faecalis.* Among the Gram

negative bacteria *Pseudomo-nas aeruginosa* was more susceptible followed by *Salmonella typhi* and *Escherichia coli*.

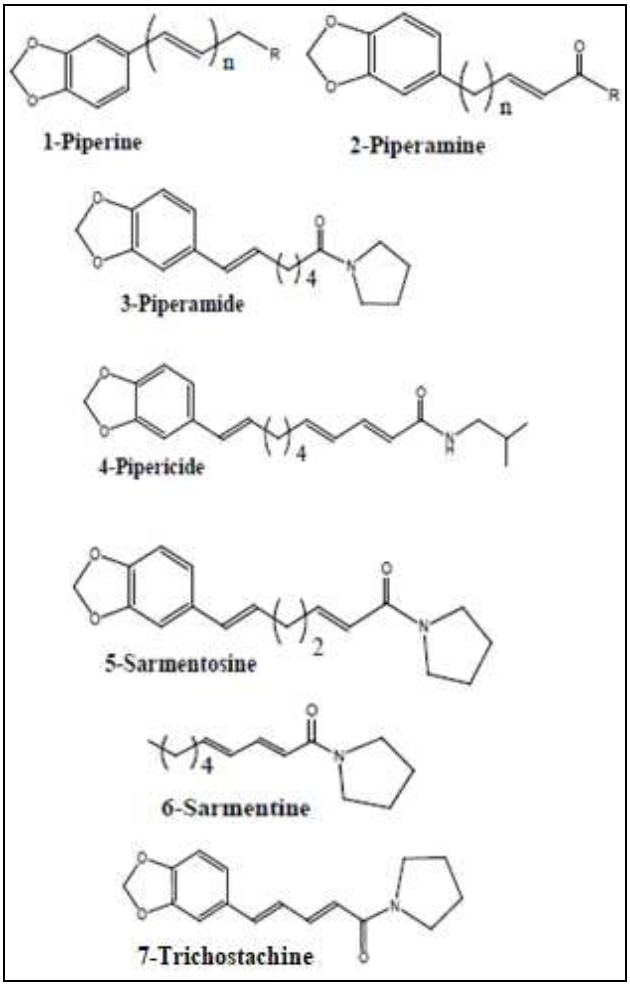

Figure 1. Structure of important chemical constituent of *Piper nigrum.*

Gram positive bacteria are more susceptible to the extracts due to antibacterial action appears to be loss of control over cell membrane permeability [33]. Khan and Siddiqui, [34] evaluated the antibacterial potential of aqueous decoction of *Piper nigrum* L. (black pepper), *Laurus nobilis* L. (bay leaf), *Pimpinella anisum* L. (aniseed), and *Coriandum sativum* L. (coriander) against different bacterial isolates from oral cavity of two hundred individual volunteers. Black pepper (aqueous decoction) showed strongest antibacterial activity comparable to aqueous decoction of *Laurus nobilis* and *Pimpinella anisum* at the concentration of 10 µl/disc. In a recent study, Palkumar et al. [35] experimented on *Piper nigrum* leaf and stem assisted green synthesis of silver nano-particles and evaluated its antibacterial activity against agricultural plant pathogens and observe that these silver nano-particles showed the excellent antibacterial activity against plant pathogens. Ganesh et al. [25] experimented photochemical analysis and antibacterial activity of *Piper nigrum* against human pathogenic bacteria and noted that presence of alkaloids, tannins, flavonoids, cardiac and cardiac glycosides shows antibacterial properties against the *Staphylococcus aureus, Salmonella typhi, Escherichia coli* and *Proteus sp.*

6. ANTIOXIDANT ACTIVITY OF BLACK PEPPER

Plants are important source of antioxidants [36]. Antioxidants completely stop or delay the process of oxidation [37]. Some *in vitro* studies revealed that piperine inhibited free radicals and reactive oxygen species, therefore known to possess protective effects against oxidative damage [3]. Free radicals cause many diseases [38]. Different free radicals attack on membranes causing oxidation of lipids, loss of different enzyme activities and may cause cancer [39]. *Piper nigrum* or piperine also found to decrease lipid peroxidation *in vivo* [40]. *Piper nigrum* reported to possess antioxidant activity that might be due to the presence of flavonoids and phenolic contents [41]. *Piper nigrum* was found to prevent the oxidative stress by inhibiting lipid peroxidation, human lipoxygenase and arresting hydroxyl and superoxide free radicals, decrease lung carcinogenesis in animal studies [42]. The memory enhancing and antioxidant proprieties of the methanolic extract of *Piper nigrum* were investigated in Alzheimer's disease model in rats [43]. The memory-enhancing effects of the extract were studied by means of *in vivo*. While, the antioxidant activity was evaluated by measuring activities of glutathione peroxidase, catalase, superoxide dismutase, and by measuring the total content of reduced glutathione, malondialdehyde, and protein carbonyl levels in the hippocampus [44]. Administration of the methanolic extract of *Piper nigrum* significantly improved memory performance and exhibited antioxidant potential. These studies suggest that methanolic extract of *Piper nigrum*

ameliorates amyloid beta (1-42)-induced spatial memory deterioration by depletion of the oxidative stress in the hippocampus of rats [3]. The anti-oxidant effect of three Piper species viz *P. nigrum, P. guineense* and *P. umbellatum* was evaluated for the protection of renal, cardiac, and hepatic anti oxidant status in atherogenic diet fed hamsters [42]. Piper species significantly inhibited the atherogenic diet induced increased lipid profile and alteration in antioxidant enzymes activities [45]. Ahmad et al. [47] reported that regenerated tissue of *Piper nigrum* like callus, *in vitro* shoots, roots, in vitro plantlets, possesses antioxidants activity which is probably due to the presence of flavonoids and phenolic contents. Piper species significantly inhibited the atherogenic diet induced increased lipid profile and alteration in antioxidant enzymes activities [45].

7. ANTI-CANCER ACTIVITY OF BLACK PEPPER

Piper nigrum had been reported to inhibit tumors formation in different experimental models [47]. Ahmad et al. [23] reported that piperine reduce the lung cancer by altering lipid peroxidation and by antioxidative protection enzymes activation. Piperine has distinct pharmacological activities along with anti-cancer activity [48]. Piperine was reported to inhibit G1/S transition and the proliferation of human umbilical vein endothelial cells (HUVECs), migration of HUVECs and *in vitro* formation of tubule and angiogenesis induced by collagen and breast cancer cell in chick embryos [49]. Landscron et al. [50] reported that piperine inhibits some of the pro-inflammatory cytokines that are produced by tumour cells, there by interfering with the signalling mechanisms between cancer cells, thereby reducing the chances of tumour progression. The anticancer activity of piperine against many cancer cell lines has been reported earlier. Therefore, the mechanisms of anticancer activity of piperine against both androgen independent and dependent cells of prostate cancer were investigated [51]. Piperine treatment was also found to induce apoptosis, by the activation of caspase-3 and by the cleavage of PARP-1 proteins in different prostate cancer cells like PC-3, DU-145 and LNCaP prostate cancer cells [29]. Treatment with piperine also found to disrupt the androgen receptor expression in LNCaP prostate cancer cells and cause significant diminution in the level of Prostate Specific Antigen in LNCaP cells [52]. The expression of phosphorylated STAT-3 and Nuclear factor-κB transcription factors were reduced in LNCaP, PC-3 and DU-145 prostate cancer cells after treatment of with piperine [28]. Piperine is non-genotoxic and found to possess anti-mutagenic and anti-tumor influences [3]. Dayem et al. [53] reported that *Piper nigrum* reduced lung cancer by modulating lipid peroxidation and through the activation anti oxidative protection enzyme.

8. DIGESTIVE ACTIVITY OF BLACK PEPPER

Many spices are known for their digestive stimulant action [54]. Srinivasan, [2] reported that black pepper enhances digestion by stimulation of the pancreatic enzymes and considerably decreases the food transit time of gastrointestinal tract. Ahmad et al. [23] reported that piperine increases the saliva production and gastric secretions, and increases the production and activation of salivary amylase. Platel and Srinivasan, [55] reported that orally administration of piperine or *P. nigrum* stimulate the liver to the secrete bile acids which in turn play key role in the absorption and digestion of fats

9. ANTIDEPRESSANT ACTIVITY OF BLACK PEPPER

Ahmad et al. [23] reported the antidepressant activity of piperine and its possible mechanisms was evaluated in corticosterone-induced model of depression in mice. Depression-like behavior in mice was developed after 3 weeks corticosterone injections. The depression was revealed by the significant reduction in sucrose utilization and augmentation in immobility time in the forced swim test and tail suspension test [55]. Further, the brain-derived neurotrophic factor protein and mRNA levels in the hippocampus were also significantly decreased in corticosterone-treated mice. Bai et al. [57] reported that corticosterone induced the behavioral and biochemical changes after treatment to animals with piperine. These results showed that piperine produces an antidepressant-like effect

in corticosterone-induced model of depression in mice [58].

10. INSECTICIDAL PROPERTIES

The phytochemical screening of black pepper fruit shows that it contains 4% alkaloids in the berry [13]. Awoyinka et al. [59] reported that the amide olefinic or alkyl isobutylamides compounds such as piperine, piperettine, tricostacine, peepuloidin, piplartin and trichonine contribute no small measure. These compounds have been demonstrated to be toxic to fruit flies, adzuki bean weevils, cockroaches and several other insect species [59]. Upadhyay and Jaiswal [60] evaluated the biological activities of *Piper nigrum* oil against *Tribolium castaneum* and found that oil had shown a dose response relationship as the larval and adult mortality increased while the larval survival and adult emergence decreased with increase in the concentration of essential oil. Khani et al. [61] reported that the *P. nigrum* extracts offer a unique and beneficial source of bio-pesticide material for the control of insect pests. The toxic effect of *P. nigrum* was reported against some test insects. *P. nigrum* was shown to be most toxic to *Callosobruchus chinensis*, *Acanthoscelides obtectus*, *C. cephalonica*, *Ephestia cautella* Hubn., followed by *Oryzaephilus surinamensis* (L.), *Sitophilus zeamais* Mosteh, *Rhyzopertha dominica* (Fab.) and *Tribolium castaneum* Herbst. The high toxicity effects of *P. nigrum* essential oils against *S. oryzae* adults and 3rd instar larvae of *C. cephalonica* are attributed to the presence of high concentrations of well-known toxic components piperine. Kraikrathok et al. [62] reported that bio efficacy of some piperaceae plant extracts against *Plutella xylostella* third instars under laboratory conditions and observed that the extracts of *Piper nigrum* plants was dose dependant and correlated to duration of exposure. The hexane extract of *P. nigrum* was active with an LD_{50} of 18435 ppm and mode of action of these extracts and effect on other developmental parameters was in progress. Scot et al. [63] reported the efficacy of extracts from two Piperaceae species. *Piper nigrum* and *P. tuberculatum* were evaluated using larvae and adults of the colorado potato beetle *Leptinotarsa decemlineata* and noted that young larvae and neonates were the most susceptible to 0.05% extract of *P. nigrum* reduced larval survival up to 70% within one week after treatment of potato plants. In the greenhouse, *P. nigrum* at 0.5% was as effective at reducing adult *L. decemlineata* feeding as combinations with 2 separate botanical mixtures, garlic and lemon grass oil. Under field conditions, the residual activity of the *P. nigrum* extracts was less than 3 h. When adult *L. decemlineata* were placed on treated plants exposed to full sunlight for 0, 1.5, and 3 h, leaf damage progressively increased as the main active compound, piperine, was found to degrade by 80% after 3 h. The results suggest that Piper extracts could be used effectively as contact botanical insect control agents to protect potato plants from developing *L. decemlineata* larvae at concentrations less than 0.1%. Paula et al. [64] noted that the natural lipophilic amides piperine and piperiline were isolated from *Piper nigrum* evaluated the contact toxicity of all synthetic amides, and also that of piperine and piperiline, at the dose 10 mg per insect, for the Brazilian economically important insects *Ascia monuste orseis* Latr, *Acanthoscelides obtectus* Say, *Brevicoryne brassicae* L, *Protopolybia exigua* DeSaus and *Cornitermes cumulans* Kollar. The results demontrated that the insects have different sensivities to the various amides, with mortality ranging from 0 to 97.5%, according to the compound and insect species. Samuel et al. [65] reported that the larvicidal effects of black pepper (*Piper nigrum* L.) and piperine against insecticide resistant and susceptible strains of *Anopheles* malaria vector mosquitoes and observed that Black pepper and piperine mixtures caused high mortality in the An. Gambiae complex strains, with black pepper proving significantly more toxic than piperine. It is concluded that black pepper shows potential as a larvicide for the control of certain malaria vector species.

11. ANTIPLATELET ACTIVITY

Srivastava et al. [66] reported that the valuable component of different piper species is piperine which is mostly responsible for various activities. Park et al. [67] reported that piperine possesses anti-platelet activity. Ahmad et al. [23] noted that the toxic effect of piperine on aggression of platelet in experimental rabbit induced by

different factors which activate platelet, by collagen and thrombin.

12. MOLLUSCICIDAL ACTIVITY

Srivastava et al. [66] reported that the effect of sublethal treatment (40% and 80% of 24h LC_{50}) of *Piper nigrum* fruit and *Cinnamomum tamala* leaf/bark and their different organic solvent extract, purified fraction singly and binary combination with synergist PB or MGK-264 (1:5) on level of different biochemical parameters viz. protein, amino acid, nucleic acids and phospholipids and rate of lipid peroxidation in nervous tissue of *L. acuminata.* Treatment of 80% of 24h LC_{50} of piperine caused maximum reduction in protein (12.95% of control), total free amino acid (10.33% of control), DNA (12.70% of control) and RNA (9.17% of control) levels in nervous tissue of *L. acuminata.* Maximum reduction (18.64% of control) in phospholipid levels and elevation of rate of lipid peroxidation (273.17% of control) were observed in the nervous tissue of snails treated with 80% of 24h LC_{50} of piperine. Treatment of 80% of 24h LC_{50} of purified fraction of *Cinnamomum tamala* leaf/bark caused significant reduction in protein (41.98% of control), total free amino acid (30.06% of control), DNA (43.71% of control) and RNA (16.42% of control), phospholipid (40.86% of control) level and increase the rate of lipid peroxidation (272.69% of control) in nervous tissue of *L. acuminata*. Binary combinations (1:5) plant products with PB or MGK-264 caused significant decrease in the different biochemical parameters. It is clear from the results that there is a significant elevation in lipid peroxidation levels with a reduction in phospholipid levels of nervous tissue of *L. acuminata* treated with different preparations of *P. nigrum* and *C. tamala* leaf/bark. Phospholipids are needed for the growth of endoplasmic reticulum or other cellular membranes [68]. It has been reported that all classes of phospholipids decrease markedly following high dose piperine treatment [69]. The enhancement of lipid peroxidation might be due to oxidative degradation of polyunsaturated fatty acids of the biomembrane leading to pathological infestation [70]. Formation of activated oxygen can have extremely detrimental consequence not only for phospholipids but also protein, nucleic acids, polysaccharides and inhibition of vital enzymes [71, 72]. The alkaloid, piperine, found in *P. nigrum* destroys the cytochrom P-450 and inhibits mono-oxygenase activity [73]. Some workers reported the effect of piperine activity in rat. Johri et al. [74] studied that the effect of piperine on the absorptive function of the intestine. *In vitro* experiments showed an increased rate of lipid peroxidation in the freshly isolated epithelial cells of rat jejunum. These results suggested that piperine may interact with the lipid environment to produce effect which leads to increased permeability of the intestinal cells.

13. ANTIREPRODUCTIVE ACTIVITY

Srivastava et al. [75] reported that the anti-reproductive activity of piperine against the snail *Lymnaea acuminata* and observed that piperine caused a significant reduction in the fecundity, hatchability and survival of the snail *Lymnaea acuminata* in each month of the year Nov. 2011 to Oct. 2012. Treatment with the piperine also prolong the hatching time of snails. Sublethal treatment of piperine caused a significant ($p<0.05$) reduction in protein, amino acids, DNA, RNA and AChE in the ovotestis/nervous tissue of treated snails with respect to control after 96h exposure period. Simultaneously, inhibition in acetylcholinesterase (AChE) activity in nervous tissue was also noted. The active component piperine (*Piper nigrum)* is an effective molluscicide against *L. acuminata*. Constituent of piperine *in vitro* inhibit enzyme activity which is responsible for leukotriene and prostaglandin biosynthesis; 5-lipoxygenase and COX-1 [76]. The cerebral neurosecretory caudo dorsal cells (CDCS) of the fresh water pulmonate snail *Lymnaea stagnalis* control egg lying, an event that involves a pattern of stereotyped behavior [78]. The CDCS synthesize and release multiple peptides, among which is the ovulation hormone (CDCS). It is thought that each peptide controls a specific aspect of the processes involved in egg laying [77].

The synthesis of protein in any of a tissue can be affected in two ways by a chemical, (1) it either affects the RNA synthesis at the transcription stage or (II) it somehow affects the uptake of amino acids in the polypeptide chain. Both these possibilities may account for the lower protein content in the

affected tissue. In the first case, the RNA synthesis would be inhibited resulting in reduced RNA as well protein content. In the second case, only the protein content would be affected [66, 78, 79]. Piperine inhibits P-glycoprotein and the major drug metabolizing enzyme CYP3A4 [81]. It seems that cumulative effect of molluscicide piperine on the level of protein, amino acids and nucleic acids in ovotestis of *L. acuminata* directly/or indirectly CDCs, which release ovulation hormone and ultimately affect the reproduction of snails in each month of the year. The AChE activity is one of the biomarker most frequently used in ecotoxicology. The enzyme is responsible for the breakdown of ACh in cholinergic synapses, preventing continuous nerve firing, which is vital for normal cellular neurotransmitter functioning [81]. The AChE inhibition result in accumulation of acetylcholinesterase at the nerve synapses so that the post synaptic membrane is in a state of permanent stimulation producing paralysis, ataxia and general lack of coordination in neuromuscular system and eventual death [82, 83].

14. COSMOPERINE ACTIVITY

Sabina Corporation [84] reported that cosmoperine prepared from piperine used in cosmetics, a natural bio-enhanser which improve the permeability of active compounds through skin. Cosmoperine activate and stimulate the natural power of skin to absorb nutrients [85, 86]. Cosmoperine isolated from piperine are non-irritant, interacts with the skin quantitatively and qualitatively in various means, furthermore, cosmoperine are pain relieving and causes skin reddening due to vascular engorgement as well as a slight skin tingling sensation.

15. CONCLUSION

In the present review we have made an attempt to congregate the botanical, phytochemical, toxicological information on *Piper nigrum* a medicinal herbs used in the Indian system of medicine, Survey of literature revealed that the presence of alkaloids, lignans, volatile oils and esters in different parts of this plants. Research on alkaloids has gained a special attention in recent times as several of them have shown promising activities like anti-inflammatory, hepatoprotective, stimulant effect, anti-amoebic and antibacterial etc. This review definitely helps for the researchers as well as practioners, dealing with this plant, to know its proper usage.

AUTHORS' CONTRIBUTION

Both authors contributed equally for the success of this review article. The final manuscript has been read and approved by both authors.

TRANSPARENCY DECLARATION

The authors declare that there is no conflict of interest regarding the publication of this article.

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