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Piper Cubeba: Review onpharmacological activity

Abhay P. Singh
Research Scholar, Department of Pharmacy, Mansarovar Global University, Sehore, Bhopal, Madhya Pradesh, India
Corresponding author email: Abhaypratap1.singh@gmail.com

Amit Agrawal
Department of Pharmacy, Mansarovar Global University, Sehore, Bhopal, Madhya Pradesh, India

Jai Narayan Mishra
Department of Pharmacy, Kailash Institute of Pharmacy & Management, GIDA, Gorakhpur, UP, India

Vishal Gupta
Department of Pharmacy, Mansarovar Global University, Sehore, Bhopal, Madhya Pradesh, India

***Abstract*---**Plants are thought to be the richest source of prospective medication development. Since ancient times, medicinal plants have been utilised to treat a variety of ailments. Bioactive components, such as phytochemicals, are isolated from diverse portions of medicinal plants and used as traditional herbal medicines. These drugs are well-known in the modern medical system since they are made from natural ingredients, are considerably safer, more successful in curing various diseases, and have less adverse effects. Pharmaceuticals commonly use secondary metabolites such as tannine, saponin, flavonoids, alkaloids, and phenolic chemicals. As a result, several plants are used as medicine to treat various ailments. Piper cubeba (Kabab Chini) is a tropical medicinal plant that is found around the world, including Indonesia. Piper cubeba is a possible therapeutic plant with antimicrobial, anti-inflammatory, antibacterial, antioxidant, anti-cancerous, hepatoprotective, nephroprotective, and antileishmanial properties, according to reports. The goal of this literature study is to describe the phytochemicals and pharmacological properties of Piper cubeba, a plant with a wide spectrum of biological activity.

***Keywords*---** phytochemicals, pharmacological, biological activity.

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Introduction

Piper cubeba, often known as cubeb pepper or tailed pepper, is a plant in the Piper genus that is grown for its fruit and essential oil. Because it is primarily grown in Java and Sumatra, it is also known as Java pepper. The fruits are picked before they ripen and dried with care. Commercial cubeb is made out of dried berries that look like black pepper but have stalks attached — hence the name "tailed pepper." The wrinkled dried pericarp ranges in colour from greyish brown to black. The seed is oily, firm, and white. Cubeb has a pleasing and aromatic odour, as well as a pungent, acrid, slightly bitter, and long-lasting flavour. It tastes like allspice or a cross between allspice and black pepper, according to some. [1]

Cubeb arrived in Europe via India, where he traded with Arabs. By way of Old French quibibes, the name cubeb originates from Arabic kabba. [3] Cubeb is referred to by its Arabic name in alchemical texts. Around 1640, the monarch of Portugal banned the sale of cubeb to promote black pepper (*Piper cubeba*), according to John Parkinson's *TheatrumBotanicum.* It had a brief comeback for therapeutic purposes in 19th-century Europe, but has since vanished from the European market. In the West, it's still used as a flavouring agent for gins and cigarettes, while inIndonesia, it's used as a spice for food.

Fig. 1: Piper cubeba

History

Theophrastus cited komakon in the fourth century BC, along with cinnamon and cassia, as an ingredient in aromatic confections. komakon has been linked to cubeb by *Guillaume Budé*and *Claudius Salmasius*, most likely due to the word's closeness to the Javanese name for cubeb, kumukus. This is seen as intriguing evidence of Greek trade with Java prior to Theophrastus' period [2-4]. Because

Javanese producers safeguarded their monopoly on the trade by scorching the berries, the vines were impossible to be cultivated elsewhere [2], it's doubtful that Greeks acquired them from anywhere else.

Cubeb was imported to China from Srivijaya during the Tang Dynasty. The spice was given the name kabab chini in India, which means "Chinese cubeb," potentially because the Chinese were involved in its trade, but more likely because it was a key commodity in the trade with China. This pepper was known in China as vilenga and vidanga, the Sanskrit word for it [5]. It grew on the same tree as black pepper, according to Li Hsun. It was used by Tang physicians to restore hunger, remove "demon vapours," darken hair, and perfume the body. Cubeb was not utilised as a condiment in China, according to the evidence.

The Book of One Thousand and One Nights, written in the 9th century, cites cubeb as a fertility treatment, indicating that it was already utilised for medicinal purposes by Arabs. Around the 10th century, cubeb was introduced to Arabic cuisine [6-7]. Java is described as a producer of cubeb, as well as other precious spices, in Marco Polo's Travels, recorded in the late 13th century. Cubeb was transported into Europe from the Grain Coast in the 14th century by merchants from Rouen and Lippe under the name pepper. The eating habits of a worldly cleric who consumes a weird mixture of egg yolks with cinnamon and cubeb after his baths, perhaps as an aphrodisiac, are described in a 14thcentury morality storey by Franciscan writer Francesc Eiximenis [8-9].

Cubeb was regarded to be unpleasant to demons by both Europeans and Chinese people. Cubeb is a component in an incense to fend off incubus, according to Ludovico Maria Sinistrari, a Catholic priest who wrote about exorcism practises in the late 17th century. Even today, neopagan publications cite his incense mixture, with some claiming that cubeb can be used in love sachets and charms [11-12].

Cubeb's culinary use in Europe declined considerably when its sale was prohibited, and only its medical use persisted until the nineteenth century. Cubeb was commonly exported from Indonesia to Europe and the United States in the early twentieth century. After 1940, the trade had dwindled to an average of 135 t (133 long tonnes; 149 short tonnes) per year, and it had all but vanished [12-14].

Chemistry

Essential oil from dried cubeb berries contains monoterpenes (sabinene 50%, -thujene, and carene) and sesquiterpenes (caryophyllene, copaene, - and -cubebene, -cadinene, germacrene), as well as the oxides 1,4- and 1,8-cineole and the alcohol cubebol. By distilling cubeb with water, about 15% of a volatile oil is obtained. The liquid component, Cubebene, has the formula C15H24 and is available in two forms: - and -. Only the location of the alkene moiety differs, with the double-bond in -cubebene being endocyclic (part of the five-membered ring), whereas in -cubebene it is exocyclic. It's a pale green viscous liquid with a slightly camphoraceous, warm woody odour. [15] This deposits rhombic crystals of camphor of cubeb after rectification with water or on keeping. [16]

In 1839, Eugène Soubeiran and Hyacinthe Capitaine discovered cubebin (C20H20O6) [10], a crystalline compound found in cubeb. It can be made from cubebene or the pulp left over after the oil has been distilled. Along with gum, fatty oils, and magnesium and calcium malates, the medicine also contains around 1% of cubebic acid and about 6% of a resin. The fruit has a dose of 30 to 60 grains, and a tincture with a dose of 4 to 1 dram is available in the British Pharmacopoeia [17-19].

Piper cubeba Chemical Composition Phytochemical studies of P. nigrum indicated that it includes a number of phytochemicals. Piperine was the first pharmacologically active chemical discovered in the Piperaceae family of plants. Many various types of chemicals were isolated, including phenolics, flavonoids, alkaloids, amides and steroids, lignans, neolignans, terpenes, chalcones, and many others. Brachyamide B, Dihydro-pipericide, (2E,4E)-N-Eicosadienoyl-pereridine, N-trans-Feruloyltryamine, N-Formylpiperidine, Guineensine, pentadienoyl as piperidine, Guineensine, pentadienoyl as piperidine, Guineensine, pentadienoyl as piper (2E,4E) - Nisobutyl-decadienamide, isobutyl-eicosadienamide, Tricholein, Trichostachine, isobutyl-eicosatrienamide, Isobutyl-eicosatrienamide, Isobutyl-octadienamide, Piperamide, Piperamine, Piperettine, Pipericide, Piperine, Piperolein B, Sarmentine, Sarmento A 1st Figure Because of the presence of these phytochemicals, several pharmacological actions have been reported. Piperine has four isomers: Piperine, Isopiperine, Chavicine, and Isochavicine, according to reports. Among all of the identified chemicals from *P. cubeba*. The pharmacological actions of piperine, pipene, piperamide, and piperamine have been discovered [20-23].

Pharmacological uses
History in folk medicine

Cubeb was employed, under the name kababa, when producing the water of al butm by Middle Ages Arab herbalists who were usually versed in alchemy. In England, cubeb was first used to treat gonorrhoea, where its antiseptic properties were quite useful. [24] Cubeb berries, according to William Wyatt Squire in 1908, "operate primarily on the genitourinary mucous membrane."

Culinary During the Middle Ages in Europe, cubeb was a valued spice. It was ground and used as a meat spice or in sauces. [25] Cubeb is used in a mediaeval recipe for sauce sarcenes, which is made with almond milk and many spices. [26] Cubeb was commonly candied and eaten whole as an aromatic confectionery [27]. During the 14th century, a vinegar infused with cubeb, cumin, and garlic was used for meat marinades in Poland. Cubeb can be added to savoury soups to enhance their flavour [28].Cubeb arrived in Africa via the Arabs. Cubeb is used in Moroccan cuisine in savoury meals as well as desserts such as markouts, which are small semolina diamonds filled with honey and dates. [6] It also occurs on sometimes in the ingredient list for the well-known spice blend Rasel hanout. Cubeb is commonly used in Indonesian cuisine, particularly in Indonesian gulés (curries) [29].

Cigarettes and alcoholic beverages

Cubeb cigarettes were commonly used to treat asthma, chronic pharyngitis, and hay fever. Edgar Rice Burroughs, who enjoyed smoking cubeb cigarettes, joked that tarzan might not have been if he hadn't smoked so many cubebs. Marshall's Prepared Cubeb Cigarettes were a popular brand, with enough sales to keep the company afloat during WWII.

Cubeb oil was included to the Tobacco Prevention and Control Branch of the North Carolina Department of Health and Human Services' list of additives present in cigarettes in 2000. Cubeb and grains of paradise are among the botanicals used to flavour Bombay Sapphire gin. Although the brand was first introduced in 1987, its creator says that it is based on a 1761 secret formula. Pertsivka is a dark brown Ukrainian pepper-flavored horilka with a smoky flavour made from cubeb and capsicum pepper infusion. [30-31]

Improvement of CCl4-Induced Liver Damage

Liver illnesses continue to be a serious health concern around the world. Furthermore, medicinal plants have grown in popularity as a cure for a variety of ailments, including liver illness. The purpose of this study was to see how effective *Piper cubeba* fruits were at reducing CCl4-induced liver lesions and oxidative damage in a mouse model. Methods. Biochemical markers such as SGOT, SGPT, -GGT, ALP, total bilirubin, LDH, and total protein were used to determine hepatoprotective efficacy. Meanwhile, rat liver antioxidant activities such as LPO, NP-SH, and CAT were evaluated in vivo, as was mRNA expression of cytokines such as TNF, IL-6, and IL-10, as well as stress-related genes iNOS and HO-1. Histopathological findings were also used to determine the amount of liver injury. Results PCEE treatment effectively and dose-dependently reduced drug-induced increases in hepatic enzyme levels in the blood.

Anti-bacterial activity

Karsha and Laxmi [32] investigated the antibacterial activity of black pepper (Piper cubeba Linn.) with particular attention to its mode of action on bacteria and discovered that it inhibited the growth of Gram positive bacteria such as *Staphylococcus aureus, Bacillus cereus,* and*Streptococcus faecalis* very effectively. *Pseudomonas aeruginosa* was the most sensitive Gram negative bacteria, followed by *Salmonella typhi* and *Escherichia coli.* The antibacterial activity appears to be a lack of control over cell membrane permeability, making Gram positive bacteria more sensitive to the extracts [33]. Khan and Siddiqui [34] tested the antibacterial efficacy of aqueous decoctions of *Piper cubeba*L. (black pepper), *Laurus nobilis* L. (bay leaf), *Pimpinella anisum*L. (aniseed), and *Coriandum sativum* L. (coriander) against bacterial isolates from the mouths of 200 volunteers. At a concentration of 10 l/disc, black pepper (aqueous decoction) had the greatest antibacterial action, equivalent to aqueous decoctions of *Laurus nobilis* and *Pimpinella anisum.*Palkumar et al. [35] tested the antibacterial activity of *Piper cubeba* leaf and stem assisted green manufacture of silver nano-particles against agricultural plant infections and found that these silver nano-particles had outstanding antibacterial activity against plant pathogens. Ganesh et al. [25] investigated the photochemical analysis and antibacterial activity of *Piper cubeba* against human pathogenic bacteria, finding that the presence of alkaloids, tannins, flavonoids, cardiac and cardiac glycosides exhibit antibacterial activity against *Staphylococcus aureus, Salmonella typhi, Escherichia coli,* and *Proteus sp.*

Antioxidant activity

Antioxidants can be found in abundance in plants [36]. Antioxidants can either totally stop or postpone the oxidation process [37]. In vitro investigations found that piperine suppressed free radicals and reactive oxygen species, indicating that it may protect against oxidative damage [3]. Many diseases are caused by free radicals [38]. Different free radicals assault membranes, producing lipid oxidation, loss of various enzyme activity, and the possibility of cancer [39]. In vivo, Piper cubeba or piperine was similarly demonstrated to reduce lipid peroxidation [40]. The presence of flavonoids and phenolic compounds in Piper cubeba has been linked to antioxidant action [41]. *Piper cubeba* has been shown to reduce lung carcinogenesis in animal tests by decreasing lipid peroxidation, human lipoxygenase, and halting hydroxyl and superoxide free radicals. In a rat Alzheimer's disease model, the memory-enhancing and antioxidant properties of the methanolic extract of *Piper cubeba* were examined [43]. The extract's memory-enhancing properties were investigated in vivo. The antioxidant activity was assessed in the hippocampus by measuring glutathione peroxidase, catalase, and superoxide dismutase activities, as well as total content of reduced glutathione, malondialdehyde, and protein carbonyl levels [44]. Administration of the methanolic extract of *Piper cubeba* significantly improved memory performance and exhibited antioxidant potential.

Anti-cancer activity

In various experimental models, Piper cubeba has been shown to suppress tumour formation [47]. Piperine has been shown to prevent lung cancer by changing lipid peroxidation and activating antioxidative protection enzymes, according to Ahmad et al. [23]. Piperine contains a variety of pharmacological properties, as well as anti-cancer properties [48]. Piperine has been shown to block the G1/S transition and proliferation of human umbilical vein endothelial cells (HUVECs), as well as migration and in vitro tubule formation and angiogenesis produced by collagen and breast cancer cells in chick embryos [49]. Piperine suppresses some of the pro-inflammatory cytokines produced by tumour cells, so interfering with the signalling pathways between cancer cells and reducing the likelihood of tumour growth, according to Landscron et al. [50]. Piperine has previously been shown to have anticancer properties against a variety of cancer cell types. Piperine's anticancer effectiveness against both androgen independent and dependent cells of prostate cancer was examined as a result [51]. Piperine administration was also reported to cause apoptosis in prostate cancer cells such as PC-3, DU-145, and LNCaP prostate cancer cells by activating caspase-3 and cleaving PARP-1 proteins [29]. Piperine treatment was also reported to impair androgen receptor expression in LNCaP prostate cancer cells, resulting in a substantial reduction in Prostate Specific Antigen levels in LNCaP cells [52]. Piperine therapy reduced the expression of phosphorylated STAT-3 and Nuclear factor-B transcription factors in LNCaP, PC-3, and DU-145 prostate cancer cells [28]. Piperine is non-genotoxic and has been discovered to have anti-mutagenic and anti-tumor properties [3]. Piper cubeba was found to diminish lung cancer by modifying lipid peroxidation and activating an anti-oxidative protection enzyme, according to Dayem et al. [53].

Digestive activity

Many spices have a stimulating effect on the digestive system [54]. According to Srinivasan [2,] black pepper improves digestion by stimulating pancreatic enzymes and reduces food transit time in the gastrointestinal tract. Piperine enhances saliva production and gastric secretions, as well as salivary amylase synthesis and activation, according to Ahmad et al. [23]. Oral administration of piperine or P. nigrum stimulates the liver to release bile acids, which play a vital role in the absorption and digestion of lipids, according to Platel and Srinivasan [55].

Black Pepper's Antidepressant Activity

Ahmad et al. [23] investigated piperine's antidepressant efficacy and probable mechanisms in a corticosterone-induced depression paradigm in mice. After three weeks of corticosterone injections, mice displayed depression-like behaviour. In the forced swim test and tail suspension test, the depression was evidenced by a significant decrease in sucrose utilisation and an increase in immobility time [55]. Furthermore, corticosterone-treated animals had considerably lower levels of brain derived neurotrophic factor protein and mRNA in the hippocampus. After treating mice with piperine, Bai et al. [57] found that corticosterone caused behavioural and physiological alterations.

Insecticidal Properties

According to a phytochemical analysis of black pepper fruit, the berry contains 4% alkaloids [13]. Piperine, piperettine, tricostacine, peepuloidin, piplartin, and trichonine are among the amide olefinic or alkyl isobutylamides compounds identified by Awoyinka et al. [59]. Fruit flies, adzuki bean weevils, cockroaches, and a variety of other insect species have been shown to be poisonous to these chemicals [59]. Upadhyay and Jaiswal [60] investigated the biological activities of *Piper cubeba*oil against*Triboliumcastaneum*and discovered that the oil had a dose response relationship, with larval and adult mortality increasing as the concentration of essential oil increased, while larval survival and adult emergence decreased. *Piper cubeba* extracts, according to Khani et al. [61], provide a unique and valuable source of bio-pesticide material for the control of insect pests. *Piper cubeba* was found to have a harmful effect on several test insects. *Callosobruchus chinensis, Acanthoscelides obtectus, C. cephalonica, and Ephestiacautella*Hubn were found to be the most toxic, followed by *Oryzaephilussurinamensis* (L.), *Sitophilus zeamais*Mosteh, *Rhyzoperthadominica* (Fab.), and *Triboliumcastaneum* Herbst. The presence of significant amounts of the well-known poisonous component piperine is linked to the high toxicity of *Piper cubeba* essential oils against *S. oryzae* adults and *C. cephalonica* 3rd instar larvae. Kraikrathok et al. [62] investigated the bioefficacy of several piperaceae plant extracts against *Plutella xylostella* third instars in the lab, finding that the extracts of *Piper cubeba* plants were dosage dependent and connected to exposure time. The hexane extract of *Piper cubeba* proved active, with an LD50 of 18435 ppm, and research into the mode of action of these extracts as well as their impact on other developmental parameters is ongoing. Extracts from two Piperaceae species were found to be effective by Scot et al. [63]. The colorado potato beetle *Leptinotarsa decemlineata* larvae and adults were studied, and it was discovered that immature larvae and neonates were the most vulnerable. A 0.05 percent extract of *Piper cubeba* reduced larval survival by up to 70% within one week following treatment of potato plants. *Piper cubeba*at 0.5 percent reduced adult *L. decemlineata* feeding as well as combinations of two botanical preparations, garlic and lemon grass oil, in the greenhouse. The residual activity of the Piper cubeba extracts was less than 3 hours in field circumstances. Leaf damage rapidly increased when mature *L. decemlineata* were planted on treated plants exposed to full sunshine for 0, 1.5, and 3 hours, with the major active component, piperine, degrading by 80% after 3 hours. Piper extracts could be utilised as a contact botanical insect control treatment to prevent potato plants from growing *L. decemlineata* larvae at concentrations of less than 0.1 percent, according to the findings.Paula et al. [64] reported that the natural lipophilic amides piperine and piperiline were isolated from *Piper cubeba*, and that they tested the contact toxicity of all synthetic amides, as well as piperine and piperiline, for the economically important Brazilian insects *Asciamonusteorseis*Latr*, Acanthoscelides obtectus*Say*, Brevicorynebrassicae*L*,* and*Protopolybiaexigua* The findings revealed that insects have varying sensitivity to various amides, with mortality rates ranging from 0% to 97.5 percent depending on the chemical and insect type. Samuel et al. [65] investigated the larvicidal effects of black pepper (Piper cubeba L.) and piperine against insecticide resistant and susceptible Anopheles malaria vector mosquitoes, finding that black pepper and piperine mixtures caused high mortality in the Anopheles Gambiae complex strains, with black pepper being significantly more toxic than piperine. According to the findings, black pepper has the potential to be used as a larvicide to control some malaria vector species.

Activity against platelets

Piperine is a valuable component of several piper species, according to Srivastava et al. [66], and it is largely responsible for varied actions. Piperine has anti-platelet action, according to Park et al. [67]. According to Ahmad et al. [23], the harmful impact of piperine on platelet aggression in experimental rabbits was generated by various substances that activate platelets, such as collagen and thrombin.

Antireproductive activity

Srivastava et al. [75] investigated piperine'santireproductive effect in the snail *Lymnaea acuminata*, finding that piperine reduced fertility, hatchability, and survival of the snail *Lymnaea acuminata* in each month from November 2011 to October 2012. Snail hatching period is also lengthened by piperine treatment. After a 96-hour exposure period, sublethal piperine treatment resulted in a substantial (p0.05) reduction in protein, amino acids, DNA, RNA, and AChE in the ovotestis/nervous tissue of treated snails compared to controls. Simultaneously, there was a decrease in acetylcholinesterase (AChE) activity in nerve tissue.

Piperine (*Piper cubeba*), the active ingredient, is an efficient molluscicide against L. acuminata. Piperine inhibits 5-lipoxygenase and COX-1 enzyme activity in vitro, which are responsible for leukotriene and prostaglandin formation. [76]. The freshwater pulmonate snail Lymnaeastagnalis' cerebral neurosecretory caudo dorsal cells (CDCS) regulate egg laying, which involves a pattern of stereotyped behaviour [78]. The CDCS produce and release a variety of peptides, including the ovulation hormone (CDCS). Each peptide is assumed to be in charge of a different component of the egg-laying process [77].

Activity of cosmoperine

Cosmoperine, made from piperine and used in cosmetics, is a natural bio-enhancer that improves the permeability of active chemicals via skin and activates and stimulates the skin's inherent ability to absorb nutrients [85, 86], according to Sabina Corporation [84]. Cosmoperine is a nonirritant that interacts quantitatively and qualitatively with the skin in a variety of ways. It also relieves pain and induces skin reddening due to vascular engorgement, as well as a subtle tingling sensation.

Conclusion

In this review, we have attempted to compile botanical, phytochemical, and toxicological data on *Piper cubeba*, a therapeutic herb used in Indian medicine. A review of the literature revealed the existence of alkaloids, lignans, *volatile* oils, and esters in various portions of this plant. Alkaloids have gotten a lot of interest recently since several of them have demonstrated promise anti-inflammatory, hepatoprotective, stimulant, anti-amoebic, and antibacterial properties. This review will undoubtedly aid academics and practitioners dealing with this plant in understanding its optimal application.

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