Piper cubeba

Scientific Name

***Piper cubeba* L. f.**

Synonyms

Cubeba officinalis Raf.

Family

Piperaceae

Common/English Names

Cubeb, Cubeb Pepper, False Pepper, Java Pepper, Javanese Pepper, Javanese Peppercorn, Tailed Pepper.

Vernacular Names

Arabic: Kabâbah, Hhabb El'arûs;
Armenian: Hendkapeghpegh;
Bangladesh: Kabab Chini;
Belarusian: Iavanski Perac;
Brazil: Pimenta-Cubeba (Portuguese);
Bulgarian: Kubeba;
Chinese: Bi Cheng Qie, Cheng Qie, Bi Cheng Qie;
Czech: Pepřovník Dlouhý, Pepřovník Kubeba;
Danish: Cubeberpeber, Kubeber, Kubeber-Peber;
Dhivehi: Kabbaabu;
Dutch: Cubebe, Cubebepeper, Staartpeper;
Eastonian: Kubeebapipar;
Farsi: Kubabah;
French: Cubèbe, Poivre À Queue, Poivre De Java, Poivrier Cubèbe, Quibebes;
German: Javanischer Pfeffer, Kubebenpfeffer, Kubeben-Pfeffer, Schwanzpfeffer, Stielpfeffer, Stiel-Pfeffer;
Greek: Koubeba;
India: Kabab Chini (Bengali), Tadamari (Gujerati), Cubab-Chinee, Kabab Chini, Sheetal Chini (Hindu), Kaba-Chini (Maithili), Vaalmilagu (Malayalam), Kankol (Marathi), Kabachin, Kabab Chini (Oriya), Chinamilagu, Sinamilagu, Valmilagu (Tamil), Chalavamiriyaalu, Tokamiriyalu (Telugu), Kabab Chini (Urdu);
Indonesia: Kemukus, Temukus (Java), Rinu Katencar, Rinu Caruluk (Sudanese);
Italian: Cubebe;
Hungarian: Jávai Bors, Hosszú Bors, Kubéba Bors;
Italian: Cubebe, Pepe A Coda;
Japanese: Kubeba, Kubebu;
Korean: Chaba Huchu, Jaba Huchu, Kubepu, Kyubebu, Philjunggadongul, Pilchingga;
Lithuanian: Kubebos Pipirai;
Macedonian: Crniot Piper;
Malaysia: Lada Berkor, Kemukus, Kemungkus, Cabai Berekor, Lada Ekor;
Nepal: Ghanda Maric, Kabaab Chiinii, Thulo Pipla;
Norwegian: Kubebapepper;
Pakistan: Dhumkimirch, Kavabchini;

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Polish: Pieprz Kubeba;
Portuguese: Cubeba;
Romanian: Piper De Cubebe;
Russian: Dikij Perets, Kubeba, Yavanskij Perets, Perets Kubebe;
Serbian: Biber Krupan, Biber Krupni;
Slovak: Kubéba, Piepor Kubébový;
Slovenian: Poper Kubeba;
Spanish: Cubeba;
Swedish: Kubebapeppar;
Thai: Prik Hang;
Tibetan: Ka Ko La;
Turkish: Hind Biberi, Hind Biberi Tohomu, Kebabe, Kebebe, Kebabiye Biber, Kebebiye, Kuyruklu Biber;
Vietnamese: Tiêu Thất;
Yiddish: Kebebe.

Origin/Distribution

Piper cubeba is indigenous to Indonesia – Greater Sunda Islands. It is cultivated in Java, Sumatra, Malaysia and Sri Lanka.

Agroecology

It grows in full or partial shade in the moist deciduous tropical forests, edges of mangrove forest and is grown from sea level to 700 m. It is also found along streams, forest tracks and margins.

Edible Plant Parts and Uses

During the Middle Ages, cubeb was one of the most valuable spices in Europe and today its culinary importance has been surpassed by medicinal uses. In powdered form cubeb was used as a seasoning for meat and in sauces. One common medieval recipe was for *sauce sarcenes* which is composed of almond milk and spices including cubeb. In Poland during the fourteenth century, a vinegar referred to as *Ocet Kubebowy* was infused with cubeb, cumin and garlic and used for meat marinades. Cubeb was often candied and eaten whole as an aromatic confectionery. Cubeb is still used to enhance the flavor of savory soups. In Moroccan cuisine, cubeb is relished in savoury dishes and pastries like *markouts* and the renowned spice mixture *Ras el hanout* a popular mixture of herbs and spices that is used across the Middle East and North Africa. *Ras el hanout* is used in *pastilla*, the Moroccan squab/young pigeon, and almond pastry, is sometimes rubbed on meats, and incorporated into couscous or rice. Today, cubeb is used as a spice to impart flavour to food in south and southeast Asia for example in *gulés* (curries) in Indonesia. It is very popular in West African cooking. They are sold whole and should be crushed or ground before use in cooking. Cubebol a patented compound from cubeb oil is traded by a Swiss company as a cooling and refreshing agent and used in various products like chewing gum, drinks, sorbets, gelatine-based confectionaries and even tooth paste. Cubeb is also used to flavour alcoholic and non-alcoholic beverages and drinks. Bombay Sapphire gin is flavored with cubeb and grains of paradise (*Aframomum melegueta).* Pertsovka, a dark-brown, Russian pepper vodka with a fiery taste, is prepared from infusion of cubeb and capsicum peppers.

Botany

A perennial, climbing woody shrub with glabrous, jointed, cylindrical and striate stem somewhat thickened at the nodes and rooting at the nodes. Stem perennial, smooth, climbing, jointed. Leaves alternate, ovate-oblong or lanceolate, acuminate apex, somewhat unequal base, entire, 10–15 cm by 4-cm wide, wavy, leathery, deep green, smooth, prominently nerved below, on short, stout petioles. Flowers unisexual, dioecious, minute, sessile, each with a bract at the base, without calyx or corolla, densely crowded in small, long, cylindrical, stalked, solid spikes coming off opposite the leaves, two stamens to each flower on male plants, and three pistils on the pistillate plant. Fruit globose, yellowish red berry, 0.6–08 cm across, smooth, wrinkled when dried, hard, one seeded (globose) and stalked (Plates 1 and 2).

Plate 1 Dried Cubeb pepper berries

Plate 2 Close-view of dried cubeb pepper berries

Nutritive/Medicinal Properties

Piper cubeba fruit was found to be a good source of the essential elements while toxic elements are found in trace amounts (Fatima et al. 2011). It was found to be a good source of K (2.10%) and iron. The phytochemical profile of *Piper* species was found to be characterized by the presence of typical classes of compounds such as alkaloids, amides, benzoic acids, chromenes, propenylphenols, lignans, neolignans, sesquiterpenes, terpenes, steroids, kawapyrones, piperolides, chalcones, dihydrochalcones, flavones and flavanones (Jensen et al. 1993; Parmar et al. 1997). Numerous studies had been conducted on the composition of the oil from the berries and one from the leaves.

Cubeba Oil

The main components of berry oil from Sri Lanka were found to be cubebol (31%), α-cubebene (5.1%) and αcopaene (8.1%) (Terhune et al. 1974). Shankaracharya et al. (1995) identified 53 components in the commercial berry oil of which sabinene (28%) and cubebol (16%) were the main components. The main components of the berry oil from India were cubebol (23.6%), a-pinene (18.2%), β-elemene (7.3%), β-cubebene (5.6%) and δ-cadinene (4.7%) (Sumathykutty et al. 1999). In a number of *P. cubeba* berry oil samples, Lawrence (1980) identified 71 components with α-cubenene (7–9%), α-copaene (10–14%), β-cubebene (7–11%), δ-cadinene (9–10%) and cubebol (9–10%) as the main components. Cubenol was also found. In a subsequent analysis of a commercial berry oil sample, Lawrence (2001) found sabinene (30%) to be the main component, whereas cubebol was only present at 5.7%. More recently, Singh et al. (2008) reported the main component of the essential berry oil of *Piper cubeba* to be ß-cubebene (18.94%) followed by cubebol (13.32%), sabinene (9.60%), α-copaene (7.41%) and ß-caryophyllene (5.28%) with many other components in minor amount . All the oleoresins showed the presence of 85 components. The major component in all the oleoresins was cubebol (stereoisomer). The percentage of cubebol in the diethyl ether extract was 32.38, in the ethanol extract 25.51, in the petroleum benzene extract 42.89, in the chloroform extract 28.00 and in methanol extract 19.03.

Hydrodistillation of the berries of *Piper cubeba* yielded 11.8% (w/w) and the leaves 0.9% (v/w) oil (Bos et al. 2007). In total 103 components were identified in the berries, representing 59.6% of the oil. In the leaves, 62 components could be identified, corresponding with 77.9% of the oil. Cubeb berry oil and leaf oils had no large qualitative differences in the composition, although the berries contained a considerable amount of constituents in traces (<0.05%) that were not found in the leaves. Sabinene (9.1%), β-elemene (9.4%), β-caryophyllene (3.1%), epicubebol (4.3%), and cubebol (5.6%) were the

main components of the berry oil. trans-Sabinene hydrate (8.2%), β-caryophyllene (5.0%), epi-cubebol (4.2%), γ-cadinene (16.6%) and cubebol (4.8%) were the main components of the leaf oil. The main monoterpenes in the berry oil were α-thujene (2.5%), α-pinene (1.8%), sabinene (9.1%), and limonene (2.3%), were a-pinene (3.2%), sabinene (3.8%), β-pinene (3.8%) and limonene (3.4%) were the principal monoterpenes in the leaf oil. In the oxygenated monoterpene fractions (3.6% and 10.6%, respectively, for the berry and leaf oil), trans-sabinene hydrate was the main component (2.5% and 8.2%, respectively). α-Copaene (3.8%), β-elemene (9.4%), β-caryophyllene (2.5%), were the main sesquiterpenes (23.7%) in the berry oil, where β-caryophyllene (5.0%), and γ-cadinene (16.6%) were the main sesquiterpenes (30.9%) in the leaf oil. Remarkable is the high content of γ-cadinene in the leaf oil, whereas it was present in the berry oil in only small amounts (0.1%). From the oxygenated sesquiterpenes (15.5% and 18.6%, respectively in berries and leaves), epi-cubebol (4.6% and 4.2%) and cubebol (5.6% and 4.8%), were the main components in both oils. Other major components were guaiol (2.9%) in the berry oil; and γ-cadinol (2.7%) and α-cadinol (1.9%) in the leaf oil.

Other Phytochemicals

Alkaloids: The alkaloid, piperine was isolated from *P. cubeba* (Hadom and Jungkunz 1951). Piperine is responsible for the pungency of cubeb pepper.

Lignans: A bisepoxylignan, ashantin was isolated from *P. cubeba* (Haensel and Pelter 1969) and bisasarin (Yang et al. 1982). From the hot petroleum extract of *Piper cubeba* fruits, six lignans were isolated (Prabhu and Mulchandani 1985). Two of these, were characterized as (2R,3R)-2-(3″,4″,5″-trimethoxybenzyl)-3-(3′,4′-methylenedioxybenzyl)-1,4-butanediol [(−)-dihydroclusin] and (3R,4R)-3,4-bis-(3,4,5-trimethoxybenzyl)tetra-hydro-2-furanol [(−)-cubebinin]. (−)Cubebin, (−)-hinokinin, (−)-clusin and (−)-dihydrocubebin were also found. Six more lignans were isolated from the hot petroleum extract of *Piper cubeba* fruits (Badheka et al. 1986). Of these, three compounds were characterized as (2R,3R)-2-(5″-methoxy-3″, 4″-methylenedi oxybenzyl) butrylactone [(−)-cubebinone],(2R,3R)-2-(3″,4″-methylenedi-oxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyro-lactone [(−)-isoyatein] and (2R,3R)-2-(3″,4″, 5″-trimethoxybenzyl)-3-(3′,4′-dimethoxybenzyl) butyrolactone [(−)-di-O-methyl thujaplicatin methyl ether, i.e. (−)-thujaplicatin trimethyl ether]. The other three compounds were identified as (−)-yatein, (−)-cubebininolide and (2R,3R)-2-(3″,4″-methylenedioxybenzyl)-3-(3′,4′-dimethoxybenzyl) butyrolactone. Seven additional compounds were isolated from *Piper cubeba* and characterized as heterotropan, magnosalin, 2,4,5-trimethoxybenzaldehyde, α-O-ethyl cubebin, β-O-ethyl cubebin, 5″-methoxyhinokinin and the monoacetate of dihydrocubebin (Badheka et al. 1987). The following lignans were isolated from *Piper cubeba* :(-)-clusin, (-)-dihydroclusin, (-)-yatein, (-)-hinokinin, and (-)-dihydrocubebin (Usiaetal.2005a),(8R,8′R)-4-hydroxycubebinone and (8R,8′R,9′S)-5-methoxyclusin, ethoxyclusin (15), and (-)-dihydroclusin (17) (Usia et al. 2005b).

Terpene compounds: The following terpene compounds were isolated from *P. cubeba*: (+)-4-carene, 1.4-cineol, 4-Isopropyl-1-methylcyclohex-l-en-ol (Rao et al. 1928). In the *P. cubeba* berry oil of Indian origin, the following terpenes: α-cadinene and α-copaene were identified (Razdan and Bhattacharvya 1954, 1955). Ikeda et al. (1962) examined the monoterpene hydrocarbon fraction of *P. cubeba* oil and reported the following as the main components α-pinene (12.1%), ce-thujene (13.2%), sabinene (47.1%), and β-phellandrene (12.7%), together with eight other monoterpene hydrocarbons. Opdyke (1976) reported the following terpenesfrom *P. cubeba*: 1,8-cineole, α-Cubebene, *p*-cymene, limonene, myrcene, β-ocimene, α-phellandrene, β-phellandrene, α-pinene, β-pinene, sabinene, α-terpinene, γ-terpinene, terpinolene and α-thujene. A sesquiterpene hydrocarbon, bicyclosesquiphellandrene was isolated from *Piper cubeba* oil (Terhune

et al. 1974). The following terpenes were isolated from *P. cubeba*: cubebol, germacrene D and (-)-muurolene (Shankaracharya et al. 1995).Two new sesquiterpenes (5α,8α)-2-oxo-1(10),3,7(11)-guaiatrien-12,8-olide and (1 α,2 β,5 α,8 α, 10 α)-1,10-epoxy-2-hydroxy-3,7(11)-guaiadien-12, 8-olide were isolated from *Piper cubeba* (Usia et al. 2005b).

Miscellaneous compounds: From the petrol extract of *Piper cubeba*, new oxygenated cyclohexanes were isolated and their structures determined, as (+)-(2S,3R,4R,5R)1-benzoyloxy methyl cyclohex-1(6)-ene-2,3,4,5 tetrol-3-benzoate (piperenol A) and (+)-(1S,2S,3S,4R) 1-benzoyloxy methylcyclohex-5-ene-1,2,3,4 tetrol-4-benzoate (piperenol B) besides the known oxygenated cyclohexanes, (+)-crotepoxide and (+)-zeylenol (Taneja et al. 1991). Further investigation of the petrol extract of *Piper cubeba* yielded two new minor oxygenated cyclohexanes, (−)-rel-(2S,3R,4R,5R)-2,3,4,5-tetraacetoxy-1-benzoyloxy methylcyclohex-1(6)-ene-2,3,4, 5-tetrol[(−)-piperenol C] and (+)-(2S,3R,4R,5R)-2,4,5-triacetoxy-1-benzoyloxy methylcyclohex-1(6)-ene-2,3,4,5-tetrol-3-benzoate[(+)-piperenol A-triacetate] (Koul et al. 1996). In addition, two rare neolignans were isolated and identified as (−)-kadsurin A and (−)-piperenone.

Some pharmacological properties reported on *Piper cubeba* include:

Antioxidant Activity

The n-hexane, dichloromethane (DCM) and methanol (MeOH) extracts of the dried berries (fruit) of *Piper cubeba* showed antioxidant activity(2,2-diphenyl-1-picrylhydrazyl (DPPH)) in the qualitative assay, the most prominent antioxidant activity was observed with the MeOH extract in the quantitative assay with a RC_{50} value of 2.71 × 10−1 mg/ml (Chitnis et al. 2007). The antioxidant potency of the DCM extract was about 3 fold less (RC_{50} = 6.50 × 10−1 mg/ml) than that of the MeOH extract. Like all the *Piper* species, *P. cubeba* was found to have glutathione (GSH) content of around 1–2 μM/g tissue and to exhibit catalyse activity (Karthikeyan and Rani 2003). The antioxidant components of *Piper* species were known to constitute a very efficient system in scavenging a wide variety of reactive oxygen species. Antioxidant potential of *Piper* species was further confirmed by their ability to curtail in vitro lipid peroxidation by around 30–50% with concomitant increase in GSH content.

Using the Fenton-like reaction [Fe(II)+H_2O_2], 16 compounds from *Piper cubeba* (CNCs) were found to inhibit 5,5-dimethyl-1-pyrroline-N-oxide, DMPO –OH radical formation ranging from 5% to 57% at 1.25 mmol/L concentration (Aboul-Enein et al. 2011). The examined CNCs also showed a high DPPH (2,2-diphenyl-1-picrylhydrazyl) antiradical activity (ranging from 15% to 99% at 5 mmol/L concentration). Furthermore, the results indicated that seven of the 16 tested compounds may catalyse the conversion of superoxide radicals generated in the potassium superoxide/18-crown-6 ether system, thus showing superoxide dismutase-like activity. The data obtained suggested that radical scavenging properties of CNCs might have potential application in many plant medicines.

High antioxidant (DPPH scavenging) activity was found in *Piper cubeba* ethanol extract 77.61% with IC_{50} value of 10.54 μg/ml compared to *Piper nigrum* 74.61% and IC_{50} value of 14.5 μg. ml (Nahak and Sahu 2011). *P. cubeba* had the highest total phenolic content of 123.1 μg/g compared to *P. nigrum* with 62.3 μg/g. *P. cubeba* was found to contain alkaloid, glycosides, steroid, flavonoid, tannins and antraquinones while *P. nigrum* contained the same plus terpenoid and reducing sugars.

Anticancer Activity

A number of polyhydroxy cyclohexanes had been isolated from *Piper cubeba* and shown to display tumour inhibitory, antileukemic and antibiotic activities (Taneja et al. 1991). An ethanolic extract of *P. cubeba*, designated P9605 exhibited anti-estrogenic, anticancer and antiinflammatory

properties (Yam et al. 2008b). The extract significantly inhibited growth induced by β-estradiol in MCF-7, a human breast cancer cell line. It inhibited aromatase activity, which was responsible for transforming androgens into estrogens. Additionally the extract inhibited the activities of cyclo-oxygenases (COX-1 and COX-2) and 5-lipo-oxygenase (5-LOX), and attenuated the induction of interleukin 6 (IL-6) in differentiated THP-1 cells stimulated by lipopolysaccharide (LPS). The results supported the potential use of P9605 in phytotherapy against benign prostatic hyperplasia (BPH). The scientists also found that the P9605 extract inhibited proliferation in androgen-dependent LNCaP human prostate cancer cells by reducing DNA synthesis and inducing apoptosis (Yam et al. 2008a). P9605 potently inhibited 5 α-reductase II activity, which was responsible for converting testosterone to its active form, dihydrotestosterone (DHT), in the prostate. It also acted as an antagonist at recombinant wild-type androgen receptors (AR). P9605 suppressed cell growth and prostate-specific antigen (PSA) secretion stimulated by physiological concentrations of DHT in LNCaP cells. Further, it down-regulated androgen receptors levels. The findings suggested that P9605 may potentially retard the growth of androgen-dependent prostate cancer via several mechanisms.

Antiinflammatory and Analgesic Activities

Studies also showed the antiinflammatory and analgesic effects of three dibenzylbutyrolactone lignans, (−)-hinokinin (2), (−)-6,6′-dinitrohinokinin (3), and (−)-6,6′-diaminohinokinin (4), obtained by partial synthesis from (−)-cubebin (1), in different animal models (da Silva et al. 2005). It was observed that compounds from (−)-cubebin and (−)-hinokinin inhibited the edema formation in the rat paw edema assay at the same level and that all responses were dose dependent. Also, at the dose of 30 mg/kg, compounds (−)-cubebin, (−)-hinokinin (2), (−)-6,6′-dinitrohinokinin (3), and (−)-6,6′-diaminohinokinin inhibited the edema formation by 53%, 63%, 54%, and 82%, respectively. In the acetic acid-induced writhing test in mice, compounds 2 and 4 produced inhibition levels of 97% and 92%, respectively, while 3 displayed lower effect (75%), which was still higher than 1.

The medicinal plant extract (*Piper cubeba* (fruit), *Physalis angulata* (flower), *Rosa hybrida* (flower) displayed antiinflammatory activities as determined by carrageenan-induced paw edema, arachidonic acid-induced ear edema and formaldehyde-induced arthritis in mice (Choi and Hwang 2003). These plant extracts clearly exhibited inhibitory effects against acute and subacute inflammation by oral administration (200 mg/kg). Also, administration (200 mg/kg, p.o.) of plant extracts for 1 week significantly inhibited type IV allergic reaction in mice as evaluated by using 2,4-dinitrofluorobenzene (DNFB)-induced contact hypersensitivity reaction (type IV) . in a subsequent study the intake of medicinal plant extract (*Piper cubeba* (fruit), *Physalis angulata* (flower), *Rosa hybrida* (flower)) in rats resulted in an increase in antioxidant enzyme activity and HDL-cholesterol, and a decrease in malondialdehyde, which may reduce the risk of inflammatory and heart disease (Choi and Hwang 2005). After 3 weeks, the superoxide dismutase (SOD) activity of the *Piper cubeba* group and the catalase activity of the *Piper cubeba* and *Rosa hybrida* groups were significantly increased compared with the control group, while the SOD and catalase activities of the *Physalis angulata* group were not significantly changed, thiobarbituric acid reactive substance (TBARS), a marker of lipid peroxidation, was significantly lower in all experimental groups compeered with the control group. No significant changes occurred in the triglyceride (TG, total- and LDL-cholesterol) of all groups, but the HDL-cholesterol of the *Physalis angulata* group was significantly increased. This study showed that the intake of medicinal plants in rats resulted in an increase in antioxidant enzyme activity and HDL-cholesterol, and a decrease in malondialdehyde, which may reduce the risk of inflammatory and heart disease.

Antimicrobial Activity

A crude ethanol extract from *Piper cubeba* seeds, (−)-cubebin and its semi-synthetic derivatives were found to be active against oral pathogens (Silva et al. 2007). The crude ethanol extract was more active against *Streptococcus salivarius* (MIC value of 80 μg/ml). (−)-Cubebin displayed MIC values ranging from 0.20 mm for *Streptococcus mitis* to 0.35 mm for *Enterococcus faecalis*. The natural product (−)-cubebin and its semi-synthetic derivative (−)-hinokinin displayed bacteriostatic activity at all evaluated concentrations, as well as fungicidal activity against *Candida albicans* at 0.28 mm. The O-benzyl cubebin derivative showed fungistatic and fungicidal effects against *C. albicans* at 0.28 and .35 mm, respectively. Also, the other dibenzylbutyrolactone derivatives [(−)-6, 6′-dinitrohinokinin and (−)-O-(N,N-dimethylaminoethyl)-cubebin] displayed bacteriostatic and fungistatic effects at the evaluated concentrations. Moreover, the semi-synthetic derivative (−)-6, 6′-dinitrohinokinin was the most active compound against all the evaluated microorganisms. Another earlier study showed that the essential oil of *P. cubeba* exhibited maximum activity against *Streptococcus faecalis, Bacillus pumilus* and *Pseudomonas solanacearum* (Kar and Jain 1971). The combinations of *Litsea chinensis*, *P. cubeba* and *Colubrina asiatica* displayed the maximum inhibitory response indicating synergistic or potentiating effect.

The essential oil and oleoresins of *Piper cubeba* exhibited moderate to strong antimicrobial and antioxidant activities (Singh et al. 2007, 2008). The radical scavenging capacity of both essential oil and oleoresin on 2, 2′-diphenyl-1-picrylhydrazyl (DPPH) radical were (71.2%) and (69.77%) respectively at 25 μL/ml. It was relatively lower in comparison with synthetic antioxidants (BHA – 96.41%; BHT – 95.91%). The results obtained from reducing power, chelating effect and hydroxyl radical scavenging effect also supported the antioxidant of essential oil and oleoresin. The essential oil and oleoresin showed 100% mycelial zone inhibition against *Penicillium viridicatum* at 3,000 and 2,000 ppm respectively in the poison food method. The essential oil revealed 100% clear zone inhibition against *Aspergillus flavus* at all tested concentrations. None of the extracts namely n-hexane, dichloromethane and methanol extracts of the dried berries (fruit) of *Piper cubeba* showed any antibacterial property against *Bacillus subtilis, Escherichia coli*, and ampicillin resistant *Escherichia coli* (Chitnis et al. 2007). While both the n-hexane and the dichloromethane extracts inhibited the growth of *Bacillus cereus, Pseudomonas aeruginosa* and *Staphylococcus aureus*, the methanol extract was active only against *B. cereus* and *P. aeruginosa*. The most potent antibacterial activity was displayed by the n-hexane extract against *B. cereus* with an MIC value of 1.56 mg/ml. All antibacterial activities of the extracts were found to be bacteriostatic rather than bactericidal.

Antiviral Activity

A water extract of *Piper cubeba*, was reported to be active (≥90% inhibition at 100 μg/ml) in inhibitory effects on hepatitis C virus (HCV) protease (Hussein et al. 2000).

Trypanocidal Activity

Five (−)-cubebin derivative compounds from *P. cubeba* namely, (−)-O-acetyl cubebin (3), (−)-O-benzyl cubebin (4), (−)-O-(N, N-dimethylaminoethyl)-cubebin (5), (−)-hinokinin (6) and (−)-6, 6′-dinitrohinokinin (7), exhibited trypanocidal activity against free amastigote forms of *Trypanosoma cruzi*, the asogic agent of Chagas' disease (de Souza et al. 2005). It was observed that 6 was the most active compound (IC_{50} = 0.7 μM), and that 4 and 5 displayed moderate activity against the parasite, giving IC_{50} values of 5.7 and 4.7 μM, respectively. In contrast, it was observed that compound 3 was inactive and that 7 displayed low activity with IC50 values of ≅1.5 × 104 and 95.3 μM, respectively. (−)-Hinokinin, a dibenzylbutyrolactone lignan,

obtained by partial synthesis from (−)-cubebin isolated from the dry seeds of *Piper cubeba*, exhibited significant trypanocidal activity both in vitro and in vivo. Further studies showed that (−)-hinokinin not only has no genotoxic effect, but is also effective in reducing the chromosome damage induced by the chemotherapeutic agent doxorubicin (DXR). (−)-Hinokinin exerted a significant antioxidant effect on parasite mitochondria in the protocol used, which might be one possible mechanism by which this compound may exert a protective effect on the chromosome damage induced by the free radicals generated by DXR.

Antileishmanial Activity

Piper cubeba and *Piper retrofractum* was found to possess antileishmanial activity (Bodiwala et al. 2007). The n-hexane, ethyl acetate, methanol, and acetone extracts of *Piper cubeba* and *P. retrofractum* exhibited significant in vitro activity at 100 μg/ml against promastigotes of *Leishmania donovani*. Two lignans, cubebin and hinokinin, were isolated from the hexane extract of *P. cubeba*; and one bis-epoxy lignan, (−)-sesamin, and two amides, pellitorine and piplartine, were isolated from the hexane and methanol extracts of *P. retrofractum*. Cubebin and piplartine showed significant antileishmanial activity in vitro at 100 μM and were further tested in vivo in a hamster model of visceral leishmaniasis. Piplartine showed activity at 30 mg/kg dose.

Antiparasitic Activity

Magalhães et al. (2011) suggested that *Piper cubeba* essential oil was efficacious against cercariae, schistosomula, and adult worms of the *Schistosoma mansoni*. At concentrations of 100 and 200 μg/ml, it caused a total absence of mobility after 120 hours. At concentrations from 12.5 to 50 μg/ml, it caused a reduction in the viability of cercariae and schistosomula when compared with the negative control groups. At concentrations ranging from 50 to 200 μg/ml, separation of all the coupled adult worms was observed after 24 hours of incubation, resulting in a reduction in egg production. The main chemical constituents of the essential oil were identified as sabinene (19.99%), eucalyptol (11.87%), 4-terpineol (6.36%), β-pinene (5.81%), camphor (5.61%), and δ-3-carene (5.34%). The essential oil exerted significant cytotoxicity at the concentration of 200 μg/ml after 24 hours treatment.

Antiulcer Activity

The methanolic extract of the fruits of *Piper cubeb*a (400 mg/kg) showed maximum inhibition of gastric acid, free acid and total acid to 23.61%, 66.94% and 56.71% respectively using model of gastric in rats which were induced by pyloric ligation (Parvez et al. 2010). The ulcer index in the *Piper cubeba* treated animals was found to be significantly less in all the models compared to control and standard drug, treated cases. The antiulcer activity of *Piper cubeba* was, however, less than that of Omeprazole. The results suggested that *Piper cubeba* possessed significant antiulcer property which could be due to cytoprotective action of the drug or strengthening of gastric mucosa with the enhancement of mucosal defence.

Cytochrome P450 Inhibition Activity

Five methylenedioxyphenyl lignans namely (-)-clusin (1), (-)-dihydroclusin (2), (-)-yatein (3), (-)-hinokinin (4), and (-)-dihydrocubebin (5), isolated from *Piper cubeba* were found to be potent and selective inhibitors against cytochrome P450 3A4 (CYP3A4) (Usia et al. 2005a). All lignans (**1–5**) inhibited CYP3A4 in a time-, concentration-, and NADPH-dependent manners and thus appeared to be the mechanism-based inhibitors of CYP3A4. Among them, (−)-clusin (1) and (−)-dihydroclusin (2) were found to be the most potent CYP3A4 inactivator. The scientists also tested two new lignans, (8R,8′R)-4-hydroxycubebinone (1) and (8R,8′R,9′S)-5-methoxyclusin (2), and two new sesquiterpenes,

(5 α,8 α)-2-oxo-1(10),3,7(11)-guaiatrien-12,8-olide (3) and (1 α,2 β,5 α,8 α, 10 α)-1,10-epoxy-2-hydroxy-3,7(11)-guaiadien-12,8-olide (4), along with 16 known compounds (5-20) for their inhibitory activity on the metabolism mediated by CYP3A4 or CYP2D6 using [N-methyl-(14)C] erythromycin or [O-methyl-(14)C] dextromethorphan as a substrate, respectively (Usia et al. 2005b). The compounds (8R,8′R,9′S)-5-methoxyclusin (2), (−)-clusin (10), (−)-yatein (13), ethoxyclusin (15), and (−)-dihydroclusin (17), having one methylenedioxyphenyl moiety in their structures, showed very potent and selective inhibitory activity against CYP3A4 with IC_{50} values (0.44–1.0 μM) identical to that of the positive control, ketoconazole (IC_{50}, 0.72 μM).

Genotoxic Activity

Studies by Junqueira et al. (2007) showed that *Piper cubeba* seed extract was genotoxic in-vivo when administered orally to mice and rats. At 1.5 g/kg, the highest dose tested, the extract induced a statistically significant increase in both the mean number of micronucleated polychromatic erythrocytes and the level of DNA damage in the rodent cell types analysed.

Molluscicidal Activity

The dried berries powder of *P. cubeba*, dried fruit powder of *P. longum* and *Tribulus terrestris* singly as well as in binary and tertiary combination exhibited molluscicidal activity against the snail *Indoplanorbis exustus* in a time and concentration-dependent (Pandey and Singh 2009).

Traditional Medicinal Uses

Cubeb pepper is a popular medicinal plant which has been extensively used in Europe since the Middle Ages, as well as in many other countries, including Arabia, India, Indonesia, Malaysia and Morocco in traditional medicine.

Cubeb berry is considered a carminative, diuretic, expectorant, stimulant, stomachic, antiasthmatic, irritant, sedative, anti-dysenteric and antiseptic. It acts particularly on mucous tissues, and arrests excessive discharges, especially from the urethra. Cubeb berry also has a local stimulating effect on the mucous membranes of the urinary and respiratory tracts. It exercises an influence over the urinary apparatus, rendering the urine of deeper colour. It has been employed in the treatment of gonorrhoea, gleet, leucorrhoea, chronic bladder diseases, acute prostatitis bronchial affections, dysentery and in spermatorrhea**.** In England, various preparations of cubeb including *oleum cubebae* (oil of cubeb), tinctures, fluid extracts, oleo-resin compounds, and vapors, were employed for throat complaints. Cubeb was commonly included in lozenges designed to alleviate bronchitis, exploiting the antiseptic and expectoral properties of the drug. The most important therapeutic application of cubeb, however, was in treating gonorrhea. Cubeb berry has been shown to be effective in easing the symptoms of chronic bronchitis. In India, a cubeb paste is used as a mouthwash, and dried cubebs is used internally for oral and dental diseases, loss of voice, halitosis, fevers, and cough. It is also used for digestive ailments and is effective in treating dysentery. The herb has often been associated with the reproductive system and has been used to treat cystitis, leucorrhea, urethritis, and prostate infections. In India, Unani physicians use a paste of cubeb berries externally of the male and female genitals to intensify sexual pleasure during coitus. Indian physicians and Arab physician during the middle ages employ cubeb berries as a main ingredient in an aphrodisiac remedy for infertility. In Malaysia, cubeb was used in many medicinal mixtures administered as tonics, indigestion mixtures and pick-me-ups after childbirth and for rheumatism. It is also prescribed for external application. In Indonesia, cubeb berries have also been used for the treatment of abdominal pain, asthma, diarrhoea, dysentery, gonorrhoea, enteritis and syphilis. In China, cubeb is used in traditional medicine for its warming properties. In Tibet cubeb is one of the six fin herbs in *bzang po* drug.

Other Uses

Cubeb is also used for its fragrance in soaps and perfumes, and can also be found as a flavouring in tooth paste and tobacco (cubeb cigarettes) besides food. In 2000, Shiseido cosmetics company in Japan, patented a line of anti-aging products containing formulas made from several herbs, including cubeb. Cubeb berries are used in love-drawing magic spells by practitioners of hoodoo, an African-American form of folk magic.

Comments

Taken in excessive doses, cubeb berry can cause nausea, vomiting, burning pain, griping and purging.

Selected References

Aboul-Enein HY, Kładna A, Kruk I (2011) Radical scavenging ability of some compounds isolated from *Piper cubeba* towards free radicals. Luminescence 26(3):202–207

Backer CA, van den Bakhuizen Brink RC Jr (1963) Flora of Java, vol 1. Wolter-Noordhoff, Groningen, 647pp

Badheka LP, Prabhu BT, Mulchandani NB (1986) Dibenzylbutyrolactone lignans from *Piper cubeba*. Phytochemistry 25(2):487–489

Badheka LP, Prabhu BT, Mulchandani NB (1987) Lignans of *Piper cubeba*. Phytochemistry 26(7):2033–2036

Bodiwala HS, Singh G, Ranvir Singh R, Dey CS, Sharma SS, Bhutani KK, Pal I (2007) Antileishmanial amides and lignans from *Piper cubeba* and *Piper retrofractum*. J Nat Med 61(4):418–421

Bos R, Woerdenbag HJ, Kayser O, Quax WJ, Ruslan K, Elfami (2007) Essential oil constituents of *Piper cubeba* L. fils. from Indonesia. J Essent Oil Res 19(1):14–17

Burkill IH (1966) A dictionary of the economic products of the Malay Peninsula. Revised reprint. 2 volumes. Ministry of Agriculture and Co-operatives, Kuala Lumpur, Malaysia. Vol. 1 (A–H) pp 1–1240, Vol. 2 (I–Z) pp 1241–2444

Chitnis R, Abichandani M, Nigam P, Nahar L, Sarker SD (2007) Actividad antibacteriana y antioxidante de los extractos de *Piper cubeba* (Piperaceae) Antioxidant and antibacterial activity of the extracts of *Piper cubeba* (Piperaceae). Ars Pharm 48(4):343–350

Choi EM, Hwang JK (2003) Investigations of anti-inflammatory and antinociceptive activities of *Piper cubeba, Physalis angulata and Rosa hybrida*. J Ethnopharmacol 89(1):171–175

Choi EM, Hwang JK (2005) Effect of some medicinal plants on plasma antioxidant system and lipid levels in rats. Phytother Res 19(5):382–386

da Silva R, de Souza GHB, da Silva AA, de Souza VA, Pereira AC, de Royo VA, E Silva MLA, Donate PM, de Matos Araújo ALS, Carvalho JCT, Bastos JK (2005) Synthesis and biological activity evaluation of lignan lactones derived from (−)-cubebin. Bioorg Med Chem Lett 15(4):1033–1037

de Souza VA, da Silva R, Pereira AC, de Royo VA, Saraiva J, Montanheiro M, de Souza GHB, da Silva Filho AA, Grando MD, Donate PM, Bastos JK, Albuquerque S, E Silva MLA (2005) Trypanocidal activity of (−)-cubebin derivatives against free amastigote forms of *Trypanosoma cruzi*. Bioorg Med Chem Lett 15(2):303–307

Fatima I, Waheed S, Zaidi JH (2011) Essential and toxic elements in three Pakistan's medicinal fruits (*Punica granatum, Ziziphus jujuba* and *Piper cubeba*) analysed by INAA. Int J Food Sci Nutr doi:10.3109/09637486.2011.627842

Hadom H, Jungkunz R (1951) Pepper and cubeb. Pharm Acta Helvetia 26:25

Haensel R, Pelter A (1969) Relative und absolute konfiguration von yangambin und aschantin. Arch Pharm 302:940–942

Hussein G, Miyashiro H, Nakamura N, Hattori M, Kakiuchi N, Kunitada Shimotohno K (2000) Inhibitory effects of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. Phytother Res 14(7):510–516

Ikeda RM, Stanley WL, Vannier SH, Spitier EM (1962) The monoterpene hydrocarbon composition of some essential oils. J Food Sci 27:455–458

Jensen S, Hansen J, Boll PM (1993) Lignans and neolignans from Piperaceae (Review). Phytochemistry 33:523–530

Junqueira APF, Perazzo FF, Souza GHB, Maistro EL (2007) Clastogenicity of *Piper cubeba* (Piperaceae) seed extract in an in vivo mammalian cell system. Genet Mol Biol 30(3):656–663

Kar A, Jain SR (1971) Antibacterial evaluation of some indigenous medicinal volatile oils. Plant Foods Hum Nutr 20(3):231–237

Karthikeyan J, Rani P (2003) Enzymatic and non-enzymatic antioxidants in selected *Piper* species. Indian J Exp Biol 41(2):135–140

Koul JL, Koul SK, Taneja SC, Dhar KL (1996) Oxygenated cyclohexanes from *Piper cubeb*. Phytochemistry 41(4):1097–1099

Lawrence BM (1980) Progress in essential oils. Perfum Flavor 5(5):27–32

Lawrence BM (2001) Progress in essential oils. Perfum Flavor 26(4):78–81

Magalhães LG, de Souza JM, Wakabayashi KA, da S Laurentiz R, Vinhólis AH, Rezende KC, Simaro GV, Bastos JK, Rodrigues V, Esperandim VR, Ferreira DS, Crotti AE, Cunha WR, E Silva ML (2011) In vitro efficacy of the essential oil of *Piper cubeba* L. (Piperaceae) against *Schistosoma mansoni*. Parasitol Res doi: 10.1007/s00436-011-2695-7

Medola JF, Cintra VP, Pesqueira E, Silva EP, de Andrade RV, da Silva R, Saraiva J, Albuquerque S, Bastos JK, E Silva MLA, Tavares DC (2007) (-)-Hinokinin causes antigenotoxicity but not genotoxicity in peripheral blood of Wistar rats. Food Chem Toxicol 45(4):638–642

Nahak G, Sahu RK (2011) Phytochemical evaluation and antioxidant activity of *Piper cubeba* and *Piper nigrum*. J Appl Pharm Sci 1(8):153–157

Opdyke DLJ (1976) Monographs on fragrance raw materials. Food Cosmet Toxicol 14(Suppl):729

Pandey JK, Singh DK (2009) Molluscicidal activity of *Piper cubeba* Linn., *Piper longum* Linn. and *Tribulus terrestris* Linn. and their combinations against snail *Indoplanorbis exustus* Desh. Indian J Exp Biol 47(8):643–648

Parmar VS, Jain SC, Bisht KS, Jain R, Taneja P, Jha A, Tyagi OD, Prasad AK, Wengel J, Olsen CE, Boll PM (1997) Phytochemistry of the genus *Piper*. Phytochemistry 46:597–673

Parvez M, Gayasuddin M, Basheer M, Janakiraman K (2010) Screening of *Piper cubeba* (Linn) fruits for anti-ulcer activity. Int J PharmTech Res 2(2):1128–1132

Prabhu BR, Mulchandani NB (1985) Lignans from *Piper cubeba*. Phytochemistry 24(2):329–331

Rao BS, Shintre VP, Simonsen JL (1928) Constituents of some Indian essential oils. XXIII. Essential oil from the fruits of *Piper cubeba* Linn. J Soc Chem Ind 47:92T

Razdan RK, Bhattacharvya SC (1954) Sesquiterpenes from *Piper cubeba* Linn. Part I. Perfum Essent Oil Rec 45:181–183

Razdan RK, Bhattacharvya SC (1955) Sesquiterpenes from *Piper cubeba* Linn. Part II. Perfum Essent Oil Rec 46:8–13

Sastroamidjojo S (1997) Obat Asli. Dian Rakyat, Jakarta, 149pp

Shankaracharya NB, Rao LJ, Nagalakshmi S, Puranaik J (1995) Studies on the chemical composition of cubeb (*Piper cubeba* Linn.). PAFAZ J 17(1):33–38

Silva ML, Coímbra HS, Pereira AC, Almeida VA, Lima TC, Costa ES, Vinhólis AH, Royo VA, Silva R, Filho AA, Cunha WR, Furtado NA, Martins CH, Carvalho TC, Bastos JK (2007) Evaluation of *Piper cubeba* extract, (-)-cubebin and its semi-synthetic derivatives against oral pathogens. Phytother Res 21(5): 420–422

Singh G, Kiran S, Marimuthu P, de Lampasona MP, de Heluani CS, Catalán CAN (2008) Chemistry, biocidal and antioxidant activities of essential oil and oleoresins from *Piper cubeba* (seed). Int J Essent Oil Ther 2(2):50–59

Singh G, Marimuthu P, de Heluani CS, Catalan CAN (2007) Chemical constituents, antioxidative and antimicrobial activities of essential oil and oleoresin of tailed pepper (*Piper cubeba* L). Int J Food Eng 3(6):Article 11

Sumathykutty MA, Rao JM, Padmakumart KP, Narayanan CS (1999) Essential oil constituents of some *Piper* species. Flavor Fragr J 14:279–282

Taneja SC, Koul SK, Pushpangadan P, Dhar KL, Daniewski WM, Schilf W (1991) Oxygenated cyclohexanes from *Piper* species. Phytochemistry 30(3): 871–874

Terhune SJ, Hogg JW, Lawrence BM (1974) Bicyclosesquiphellandrene and 1-epibicyclosesquiphellandrene: two new dienes based on the cadalene skeleton. Phytochemistry 13:1183–1185

Usia T, Watabe T, Kadota S, Tezuka Y (2005a) Metabolite-cytochrome P450 complex formation by methylenedioxyphenyl lignans of *Piper cubeba*: mechanism-based inhibition. Life Sci 76(20):2381–2391

Usia T, Watabe T, Kadota S, Tezuka Y (2005b) Potent CYP3A4 inhibitory constituents of *Piper cubeba*. J Nat Prod 68(1):64–68

Utami D, Jansen PCM (1999) *Piper* L. In: de Guzman CC, Siemonsma JS (eds) Plant resources of South-East Asia no 13 spices. Backhuys Publishers, Leiden, pp 183–188

Yam J, Kreuter M, Drewe J (2008a) *Piper cubeba* targets multiple aspects of the androgen-signalling pathway. A potential phytotherapy against prostate cancer growth? Planta Med 74(1):33–38

Yam J, Schaab A, Kreuter M, Drewe J (2008b) *Piper cubeba* demonstrates anti-estrogenic and anti-inflammatory properties. Planta Med 74(2):142–146

Yuan Y, Wang C, Zhou X (1982) Isolation of bisasarin from *Piper cubeba*. Zhongcaoyao 13:378, 392