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Review Article

Short and spicy evergreen tree: Clove

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ABSTRACT

A clove is the flower bud of a tropical tree called clove tree (Eugenia Caryophyllata = Syzygium aromaticum). Family Myrtaceae, Cloves are used in the cuisine of Asian, African, and the near and Middle East countries, lending flavor to meats, curries, and marinades, as well as fruit such as apples, pears or rhubarb. Cloves may be used to give aromatic and flavor qualities to hot beverages, often combined with other ingredients such as lemon and sugar. Reported anti-carcinogenic activity,cardiovascular,effectively reduced benzo[a] pyrene (BP) induced lung carcinogenes ological activities and better response when compared to the standard drugs

Keywords: Clove; myrtaceae; Eugenol; anti-oxidant; anti-tumour; chemo preventive

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INTRODUCTION

A clove is the flower bud of a tropical tree called clove tree (***Eugenia Caryophyllata* = *Syzygium aromaticum***). The word "*caryophyllata*" is Greek for "walnut leaves" and the name comes from the similarity with the leaves of this tree with the walnut tree. Its immature fruit was called in Spanish "clavo" (= nail) and similar names in other languages by the similarity it has with a nail

Cloves are the aromatic flower buds of a tree in the family Myrtaceae, ***Syzygium aromaticum***. They are native to the Maluku Islands in Indonesia and are commonly used as a spice. Cloves are commercially harvested primarily in Bangladesh, Indonesia, India, Madagascar, Zanzibar, Pakistan, Sri Lanka, and Tanzania. Cloves are available throughout the year.

The clove tree is an evergreen that grows up to 8–12 m tall, with large leaves and sanguine flowers grouped in terminal clusters. The flower buds initially have a pale hue, gradually turn green, then transition to a bright red when ready for harvest. Cloves are harvested at 1.5–2.0 cm long, and consist of a long calyx that terminates in four spreading sepals, and four unopened petals that form a small central ball.

Cloves are used in the cuisine of Asian, African, and the near and Middle East countries, lending flavor to meats, curries, and marinades, as well as fruit such as apples, pears or rhubarb. Cloves may be used to give aromatic and flavor qualities to hot beverages, often combined with other ingredients such as lemon and sugar. They are a common element in spice blends such as pumpkin pie spice and speculoos spices. [1]

A major component of clove taste is imparted by the chemical Eugenol, [2] and the quantity of the spice required is typically small. It pairs well with cinnamon, allspice, vanilla, red wine and basil, as well as onion, citrus peel, star anise,or peppercorns.

Cloves are used in Indian Ayurvedic medicine, Chinese medicine, and western herbalism and dentistry where the essential oil is used as an anodyne (painkiller) for dental emergencies. Cloves are used as a carminative, to increase hydrochloric acid in the stomach and to improve peristalsis. Cloves are also said to be a natural anthelmintic. [3]The essential oil is used in aromatherapy when stimulation and warming are needed, especially for digestive problems. Topical application over the stomach or abdomen is said to warm the digestive tract. Applied to a cavity in a decayed tooth, it also relieves a toothache. [4]

In Chinese medicine, cloves or *Ding Xiang* are considered acrid, warm, and aromatic, entering the kidney, spleen and stomach meridians, and are notable in their ability to warm the middle, direct stomach *qi* downward, to treat hiccup and to fortify the kidney *yang*. [5] Because the herb is so warming, it is contraindicated in any persons with fire symptoms and according to classical sources should not be used for anything except cold from *yang* deficiency. As such, it is used in formulas for impotence or clear vaginal discharge from *yang* deficiency, for morning sickness together with ginseng and patchouli, or for vomiting and diarrhea due to spleen and stomach coldness. [5]

The U.S. Food and Drug Administration (FDA) has reclassified eugenol (one of the chemicals contained in clove oil), downgrading its effectiveness rating. The FDA now believes not enough evidence indicates clove oil or eugenol is effective for toothache pain or a variety of other types of pain. [6]

Studies to determine its effectiveness for fever reduction, as a mosquito repellent, and to prevent premature ejaculation have been inconclusive.[6] It remains unproven whether clove may reduce blood sugar levels.[7]

In addition, clove oil is used in the preparation of some kinds of toothpaste and Clovacaine solution, which is a local anesthetic used in oral ulceration and inflammation. Eugenol (or clove oil generally) is mixed with zinc oxide to form a temporary tooth cavity filling. [8]

Clove oil can be used to anesthetize fish, and prolonged exposure to higher doses (the recommended dose is 400 mg/l) is considered a humane means of euthanasia. [9]

Eugenol composes 72–90% of the essential oil extracted from cloves and is the compound most responsible for clove aroma. [2] Other important essential oil constituents of clove oil include acetyl eugenol, beta-caryophyllene, and vanillin, crategolic acid, tannins such as bicornin, [2,10] gallotannic acid, methyl salicylate (painkiller), the flavonoids eugenin, kaempferol, rhamnetin, and eugenitin, triterpenoids such as oleanolic acid, stigmasterol, and campesterol and several sesquiterpenes.[11]

Eugenol is toxic in relatively small quantities; for example, a dose of 5–10 ml has been reported as a near fatal dose for a two-year-old child. [12]

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Myrtales
Family:	Myrtaceae
Genus:	*Syzygium*
Species:	***S. aromaticum***

PHARMACOLOGICAL ACTIVITIES

Anti-tumor activity: The authors have reported that the clove has the anti-carcinogenic and anti-mutagenic potential.[13] The side effects caused by the chemotherapy can be avoided by replacing Clove essential oil which inhibits delays, blocks, or reverses the initiation of and promotional events associated with carcinogenesis. The anti-carcinogenic activity is shown by Sesquiterpenes which are the chemical constituents of *Syzygium aromaticum.* [14] The cytotoxic action is exhibited by the Volatile oils against the human tumor cell lines PC-3 and Hep G2 50. The apoptosis of human cancer cells can be induced by the derivative of eugenol, dihydro-eugenol. [15] Studies also revealed that the skin cancer induced chemically can be protected by eugenol. [16]

Cardiovascular activity: Clove can lower the risks for cardiovascular disease, arterial sclerosis and other disease related to oxidative stress as it is rich in polyphenols. [17-19] The activity is shown by dose-dependent, reversible vasodilator responses, negative inotropic effects in heart muscle, hypotensive effects and smooth muscle relaxant effects which are produced by the presence of eugenol. [20-22]

Anti-diabetic activity: In hepatocytes and hepatoma cells clove extract reduces the Phosphoenolpyruvate carboxykinase (PEPCK) and Glucose 6- phosphatase (G6Pase) gene expression and thus acts like insulin. Similar to insulin, repression mediated by clove is reversed by PI3K inhibitors and N-acetylcysteine (NAC). Many DNA microarray analysis of gene expression disclosed that clove and insulin regulated the expression of the many genes in similar manner [23].

Chemopreventive activity: Aqueous infusion of Clove effectively reduced benzo[a] pyrene (BP) induced lung carcinogenesis in strain A mice. The incidence of hyperplasia, dysplasia, and carcinoma were effectively reduced and there was a significant reduction in the number of proliferating cells and increased number of apoptotic cells in BP induced lung lesions with the clove infusion. It also down regulates the expression of some growth promoting proteins, viz, COX-2, cMyc, Hras [24]. Aqueous infusion of cloves showed chemopreventive action on 9, 10-dimethyl benz (a) anthracene (DMBA) and croton oil induced skin carcinogenesis in Swiss mice. Oral administration of aqueous infusions of clove at the dose of 100 µl /mouse /day not only delayed the formation of papilloma but also reduced the incidence of papilloma as well as the cumulative number of papillomas per mouse [25].

Antiviral activity: Clove is a potent antiviral agent. Eugenin isolated from clove buds showed antiviral activity against Herpes Simplex virus at a concentration of 10 µg /ml [26].

Anti-fungal activity: The authors reported that inhibitory activity was showed by EO and eugenol against all the tested strains as Candida, Aspergillus, and Dermatophyte clinical and American Type Culture Collection strains. Quantity of ergosterol, a specific fungal cell membrane component was reduced by clove oil and eugenol. Germ tube formation by Candida albicans was completely or almost completely inhibited oil and eugenol concentrations below the MIC values. The present study indicates that clove oil and eugenol have considerable antifungal activity against clinically relevant fungi, including fluconazole-resistant strains, deserving further investigation for clinical application in the treatment of fungal infections. [27]

Anti-microbial activity: Clove oil was found to be more effective than sodium propionate (standard food preservative) against some foodborne microbes and also against Staphylococcus species and Aspergillus niger among the fungi. The germicidal effect was also exhibited when clove oil is dispersed (0.4% v/v) in a concentrated sugar solution against various bacteria such as Aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Clostridium perfringens, E.coli and also Fungi like Candida albicans [28]. It was observed that to kill bacillus tuberculosis 0.05% solution of eugenol was sufficient. Antimicrobial activity was also expressed by clove oil against human pathogenic bacteria which are resistant to antibiotics [29]. Antifungal activity against Candida, Aspergillus and dermatophyte species and also clinically relevant fungi including Fluconazole-resistant strains was exhibited by the clove oil and eugenol which is the main component. [30]

Hepatoprotective activity: The hepatoprotective activity of clove was evaluated on the paracetamol-induced liver injury. The hepatic damage was estimated by the level of increased cytoplasmic enzymes AST, ALT in circulation which exhibits the functional status of the liver in both clinical and experimental settings. Ethanolic extract of Clove

restored the activity of enzymes AST, ALT and ALP in serum towards normal values. [31]

Anti-oxidant activity: Clove and Eugenol possess strong antioxidant activity, which is comparable to the activities of the synthetic antioxidant, BHA (butylated hydroxy anisole) and Pyrogallol [32]. Clove has the highest capacity to give off hydrogen and reduce lipid peroxidation. With respect to the lipid peroxidation, the inhibitory activity of clove oil determined using a linolenic acid emulsion system indicated a higher antioxidant activity than the standard BHT (Butylated hydroxyl toluene). It also showed a significant inhibitory effect against hydroxyl radicals and act as an iron chelator [33]. The metal chelating activity, bleomycin dependent DNA oxidation, diphenyl-p-picrylhydrazyl (DPPH) radical scavenging activity and the ferric reducing antioxidant power (FRAP) of different spices were measured in rat liver homogenate. Cloves showed the highest DPPH radical scavenging activity & highest FRAP values [34]. The antioxidant activity of clove bud extract and its major aroma components, eugenol and eugenol acetate were comparable to that of the natural antioxidant α-tocopherol [35]. Eugenol inhibited 5- lipoxygenase activity and leukotriene C-4 in human PMNL cells[36].

Gastroprotective activity: Syzygium aromaticum, a medicinal plant commonly known as clove, is used to treat a toothache, respiratory disorders, inflammation, and gastrointestinal disorders. From the flower buds of S. aromaticum, it is possible to obtain an essential oil comprised of a mixture of aliphatic and cyclic volatile terpenes and phenylpropanoids, being eugenol as the main component. The aims of this study were: (1) to extract the essential oil of the flower buds of S. aromaticum, (2) to identify and quantify the main component of the essential oil, and (3) to evaluate its antiulcer activity using different animal models. Assays were performed using the following protocols in rats: indomethacin-induced and ethanol/HCl-induced ulcer model. Both essential oils from S. aromaticum and eugenol displayed antiulcer activities in the rat models of indomethacin- and ethanol-induced ulcer. Studies focusing on the possible mechanisms of gastroprotection were also undertaken using the following experiments: evaluation of gastric secretion by the pylorus-ligated model, determination of mucus in gastric content, participation of nitric oxide (NO) and endogenous sulfhydryl in gastric protection. The results show that there was no significant effect on the volume of gastric juice and total acidity. However, the quantification of free gastric mucus showed that the clove oil and eugenol were capable of significantly enhancing mucus production. With regard to the NO and endogenous sulfhydryls, the results demonstrated that the gastroprotection induced by clove oil and eugenol are not related to the activities of the nitric oxide and endogenous sulfhydryls. No sign of toxicity was observed in the acute toxicity study. In conclusion, the results of this study show that essential oil of S. aromaticum, as well as its main component (eugenol), possesses antiulcer activity. The data suggest that the effectiveness of the essential oil and eugenol is based on its ability to stimulate the synthesis of mucus, an important gastroprotective factor. However, further pharmacological and toxicological investigations are required to enable its use for the treatment of gastric ulcer.[37]

Anti-inflammatory activity: Anti-inflammatory action of clove is exhibited by the major chemical constituent present in it. The addition of clove extract to the diet which is rich in anti-inflammatory components like cod liver oil, with its ω-3 fatty acids shows a synergistic effect in animal studies. The other major chemical components which contribute to clove's anti-inflammatory and antioxidant properties are a variety of flavonoids including kaempferol, rhamnetin, and β- caryophyllene. [38]The essential oil of Eugenia caryophyllata has shown the anti-inflammatory effect which is equivalent to etodolac at 0.025 and 0.1 ml/kg and indomethacin at 0.05 and 0.2 ml/kg.

Anti-pyretic effect: The antipyretic effect of clove oil is shown due to the presence of the major chemical constituent, Eugenol, when administered intravenously, intragastrically and centrally to rabbits which are made febrile by interleukin-1. The effect was shown primarily by acting centrally similar to that of common anti-pyretic drugs, such as acetaminophen and was more effective in reducing fever than acetaminophen. [39]

Anti-platelet activity:
The platelet aggregation which is induced by arachidonate, adrenaline, and collagen was inhibited by the two chief chemical constituents of clove which are eugenol and acetyl eugenol. The effect shown by clove was more potent than aspirin and it was at par with indomethacin in the aggregation which was induced by arachidonate.[40]

Anti-stress activity: The biochemical changes induced by the sound stress such as elevated plasma levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, cholesterol and corticosterone and development of cold restraint induced gastric ulcers are reduced by the clove extract. It was also effective in increasing the latency of anoxic stress induced convulsions in mice. [41]

Anaesthetic effect: Clove oil is found to be an alternative to Tricaine or MS-222 the only registered anesthetic for several fish species. Exposure of channel catfish (*Ictalurus punctatus*) to clove oil at the concentration of 100mg/l induced anesthesia within 1min [42]. Clove oil and eugenol were reported to be acceptable anesthetics for rabbitfish (Saiganus lineatus), coral reef fish (*Pomacentrus amboinensis*) and rainbow trout (*Oncorhynchus mykiss*) for use in aquaculture and aquatic research [43]. It was found to be useful as a crab anesthetic. Clove oil proved to be highly effective and easy to use on juvenile (*Valamugil cunnesius and Monodactylus argenteus*) tropical marine fish at the dose of 0.05ml/l. This dose anesthetized the fish in less than a minute.

Aphrodisiac effect: The ethanolic extract of clove(50%) has produced a significant and sustained increase in the sexual activity of normal rats, with the absence of conspicuous gastric ulceration and adverse effects. [44]

Mosquito repellent activity: Clove oil gave the longest duration of 100% repellency (2-4 h) against three species of mosquitoes i.e. Aedes aegypti, Culex quinquefasciatus and Anopheles dirus under laboratory conditions using human subjects. [45]

Larvicidal activity: Malaria and dengue are the cause of a heavy public health burden in the Amazon region. The authors evaluated the larvicidal activity of aqueous and methanolic extracts from clove, *Eugenia caryophyllata* Thunberg (Myrtaceae), and a chemical component which is found in cloves, eugenol, against malaria and dengue mosquito vectors. Bioassays were carried out with these extracts and eugenol on *Anopheles darlingi* Root, 1926 and *Aedes aegypti* Linnaeus, 1762 (Diptera, Culicidae) third instar larvae. The median lethal concentration values obtained with aqueous extract against *A. aegypti* (LC_{50} = 6.4 mg/mL) were higher than those observed against *A. darlingi* (LC_{50} = 99 mg/mL). Eugenol exhibited an LC_{50} value of 3.6 mg/mL against *A. aegypti* larvae. These findings show eugenol´s potential as a larvicide against malaria and dengue vectors. [46]

Anti- giardia activity: The present work evaluates the anti-Giardia activity of Syzygium aromaticum and its major compound eugenol. The effects were evaluated on parasite growth, adherence, viability, and ultrastructure. S. aromaticum essential oil (IC (50)=134 µg/ml) and eugenol (IC(50)=101 µg/ml) inhibited the growth of G. lamblia. The essential oil inhibited trophozoites adherence since the first hour of incubation and was able to kill almost 50% of the population of the parasite in a time-dependent manner. The eugenol inhibited G. lamblia trophozoites adherence since the third hour and not induce cell lysis. The main morphological alterations were modifications on the cell shape, presence of precipitates in the cytoplasm, autophagic vesicles, internalization of flagella and ventral disc, membrane blebs, and intracellular and nuclear clearing. Taken together, our findings lead us to propose that eugenol was responsible for the antigiardial activity of the S. aromaticum essential oil and both have the potential for use as therapeutic agents against giardiasis. [47]

Anti-convulsant activity: In this study, the effect of an essential oil of *Eugenia caryophyllata* (Myrtaceae), an antiepileptic remedy in Iranian folk medicine, against seizures induced by maximal electroshock (MES) or pentylenetetrazole (PTZ) in male mice was studied. The essential oil exhibited anticonvulsant activity against tonic seizures induced by MES. Although it was not effective against clonic convulsions induced by intraperitoneal administration of PTZ, the seizure threshold which was determined by an increase in the dose of intravenously infused PTZ required to induce clonus, was elevated by the essential oil. In addition, at some anticonvulsant doses, the essential oil produced motor impairment on the rotarod. [48]

CONCLUSION

Cloves are used in Indian Ayurvedic medicine, Chinese medicine, and western herbalism and dentistry where the essential oil is used as an anodyne (painkiller) for dental emergencies. Cloves are used as a carminative. Cloves are also said to be a natural anthelmintic. The pharmacological and clinical studies reported in the present review confirm the therapeutic value of Clove shows Anti-tumour activity, Cardiovascular activity Anti-diabetic activity, Chemo- preventive activity, Hepato-protective activity, Anti-oxidant activity because of it is rich in flavonois, and essential oil. In this regard, further studies need to be carried out to explore *Clove* for its potential in preventing and treating diseases. So, the present review gives a direction for future investigators to carry out research on the plant.

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