

# Ethnomedicinal and Pharmacological Significance of *Syzygium aromaticum* (Clove): A Review

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## Abstract

**Background:** *Syzygium aromaticum* Linn. (clove) is a dried flower bud from the Myrtaceae family, native to Indonesia's Maluku islands. Clove essential oil is recognized for its diverse biological activities, including antiseptic, analgesic, antibacterial, antiviral, antifungal, and anticancer properties. Its high concentration of bioactive compounds, particularly eugenol, caryophyllene, and eugenol acetate, contributes significantly to these effects, making clove a subject of increasing scientific interest. **Methods:** This review compiles and analyzes updated information on the ethnomedicinal uses, phytochemistry, and pharmacological activities of clove and its primary constituent, eugenol. A systematic literature review was conducted, focusing on peer-reviewed studies that detail the extraction methods, chemical composition, and bioactivity assays of clove essential oil. **Results:** Clove essential oil contains approximately 16-18% of essential oils, with eugenol constituting 59-88% of its composition. The oil exhibits notable antioxidant, antimicrobial, anti-inflammatory, analgesic, antipyretic, anticancer, antidiabetic, and antiviral properties. Clove has shown efficacy against various pathogens, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and

*Helicobacter pylori*. Furthermore, eugenol demonstrated significant cytotoxic effects against various cancer cell lines and showed promise in managing metabolic disorders and enhancing immune responses. **Conclusion:** Clove and eugenol possess extensive therapeutic potential, warranting further investigation to unlock their applications in modern medicine. Despite their benefits, attention to their toxicity and safety profiles is essential for ensuring appropriate usage in therapeutic contexts. This review highlights the need for continued research to validate traditional uses and explore novel applications of clove and its bioactive components.

**Keywords:** Clove (*Syzygium aromaticum*), Phytochemistry, Antioxidant properties, Antimicrobial activity, Therapeutic applications

## Introduction

*Syzygium aromaticum* Linn., (Synonyms: *Eugenia caryophyllata*, Clove, Karanfil) is a dried flower bud from the Myrtaceae family and it is native to Indonesia's Maluku islands but has also been found in many countries like India, Indonesia, Malaysia, Pakistan, etc. (Cortés-Rojas et al., 2014). Clove essential oil is known for its potential antiseptic, dental analgesic, antibacterial, antiviral, anticarcinogenic, and antifungal properties (Chaieb et al., 2007). However, due to its significant antibacterial and antioxidant properties, clove has earned a lot of attention among other spices (Shan et al., 2005). The presence of many chemical ingredients in high concentrations with antioxidant activity is ascribed to clove's efficient involvement in the inhibition of several degenerative diseases (Hu et al., 2002).

Clove buds contain large quantities of essential oils (about 16 to 18%) in which eugenol, caryophyllene, and eugenol acetate were found as main constituents and are supposed to be responsible for its bioactivities (Rosarior et al., 2021; Haro- González, et al.,

**Significance** | This review highlights the diverse medicinal properties of clove, supporting its potential in treating various health conditions.

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2021). Besides essential oils, Clove buds also contain other phytochemicals such as saponins, flavonoids, phenolic acids, alkaloids, tannins, steroids, resins, and glycosides (Hemalatha et al., 2016; Cortés-Rojas et al., 2014; Mostafa et al., 2023). Clove has many bioactivities such as such as antioxidant, antimicrobial, analgesic, antiseptic, antifungal, anticancer, antispasmodic, anti-inflammatory, antiviral, and anti-SARS-CoV-2 (El-Saber Batiha et al., 2020; Somrani et al., 2022; Selka et al., 2021; Oliveira et al., 2020; Biernasiuk et al., 2022; Kalembe, & Kunicka, 2003; Manivannan et al., 2022; Han, & Parker, 2017). The aim present review is to compile updated information on Clove's ethnomedicinal uses, phytochemicals, and pharmacological activities so that the therapeutic and pharmaceutical benefits of clove and eugenol could be utilized.

### Ethnomedicinal Uses of Clove

Clove buds are a well-known spice, and they have culinary applications due to their strong aroma and pungency (Sarker and Islam, 2022). Clove essential oil is ethnomedicinally used to relieve dental pain and to treat tooth infections and receding gums (Mittal et al., 2014). Clove is used as a carminative, stimulant, stomachic, and aromatic in traditional Indian and Chinese systems (Batiha et al., 2019). Traditionally, cloves have been used for centuries to treat vomiting, flatulence, nausea, liver, carminative, and bowel disorders, and as a nerve stimulant (Sarker and Islam, 2022). In tropical Asia, cloves have been reported to treat infectious diseases such as cholera, malaria, and tuberculosis (Ayoola et al., 2008). In the United States, cloves have been used to inhibit food-derived infections such as viruses, worms, candida, and various bacteria and protozoan (Bhowmik et al., 2012). Furthermore, its use in numerous industrial applications has been reported, and it is widely employed in perfumes, soaps, and as a washing vehicle in histology work (Sarrami et al., 2002). Furthermore, eugenol has been widely used in dentistry because it can penetrate the pulp tissue of the teeth and enter the bloodstream (Martínez-Herrera et al., 2016; Miyazawa et al., 2001).

### Phytochemistry of Clove and Eugenol

Clove essential oil is a colorless or pale-yellow colored liquid, and it has a distinct clove flavor and taste. Differences in clove essential oil content and composition mainly depend on several factors such as pretreatment, varieties, agroecological conditions, and extraction process (Hastuti et al., 2017). Clove buds chiefly contain flavonoids, phenolic acids, resins, tannins, and terpenoids. The essential oil (terpene and terpenoids) is the main chemical class of clove buds that constitute about 18 % of the total secondary metabolites of clove. The chief constituents in clove essential oil include eugenol, eugenol acetate, and  $\beta$ -caryophyllene (Chaieb et al., 2007; Jirovetz L., et

al 2006; Gülçin 2011; Sulaiman et al., 2020). Moreover, clove contains flavonoids namely quercetin and kaempferol, and phenolic acids like ferulic, caffeic, ellagic, and salicylic acids; gallic acid as hydrolyzable tannin (Cortés-Rojas et al., 2014).

Eugenol ( $C_{10}H_{12}O_2$ ) is a monoterpene compound categorized into the phenylpropanoid class and it is the chief active chemical compound of clove essential oil (Taleuzzaman et al., 2021). Many researchers reported that the eugenol content varies from 59 to 88% in clove essential oil (Ahamad et al., 2022; Hatami et al., 2019). **Table 1** and **Figure 1** summarize the major chemical compounds found in the essential oil of Clove analyzed by GC-MS method by different authors.

### Bioactivities and Therapeutic Implications of Clove and Eugenol

#### Antioxidant Activity

Antioxidants are beneficial in the management and treatment of various chronic human disorders like metabolic syndrome, cancer, liver disorders, neurodegenerative disorders, etc. (Golbidi et al., 2011; Athreya and Xavier, 2017; Matteo and Esposito, 2003). Antioxidant compounds such as clove extracts and essential oils are effective in memory problems caused by oxidative stress (Mehta et al., 2010). Halder et al., (2011), demonstrated that pretreatment with clove essential oil lowered oxidative stress as measured by glutathione and malondialdehyde levels in the brain of mice. The authors concluded that clove essential oil's ability to recover memory and learning deficits caused by short and long-term scopolamine administration is due to its ability to reduce oxidative stress. Many other authors reported the antioxidant activity of clove essential oil (Gülçin et al., 2012; Radünz et al., 2019; Nassar et al., 2007).

Eugenol and its isomer isoeugenol, the main bioactive compound of clove essential oil has shown significant antioxidant activity in many *in-vitro* studies (Ito et al., 2005; Ogata et al., 2000). The health benefits of clove essential oil and its bioactive compound, eugenol are presented in Figure 2.

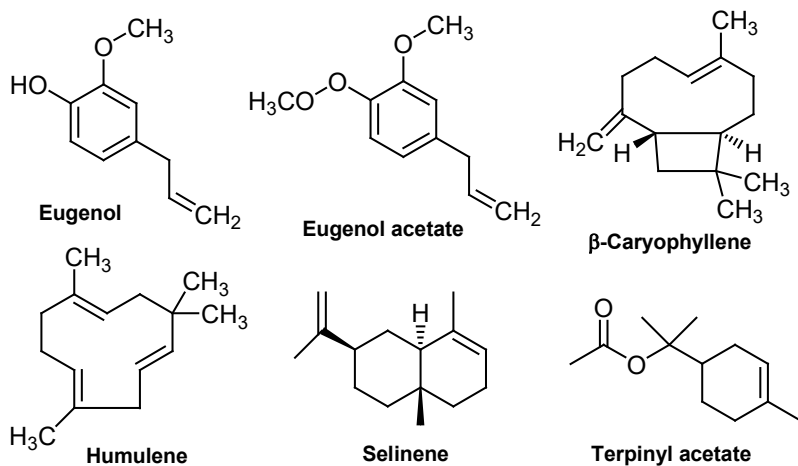
#### Antimicrobial Activity

Clove essential oil, alone or in combination with rosemary oil, was found to have antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus epidermidis*, *S. aureus*, *Proteus vulgaris*, *Escherichia coli*, and methicillin-resistant *S. epidermidis* and *S. aureus* (Palombo and Semple., 2002). Clove essential oil's antibacterial properties are linked to eugenol, which consists of about (85% to 92%) of the total clove oil concentration (Aboubakr et al., 2016).

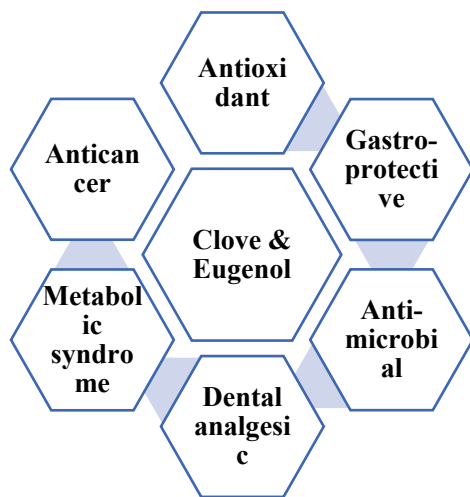
The major components of clove that are responsible for its fungicidal properties against onychomycosis-isolated fungi, *Trichophyton mentagrophytes*, and *Candida albicans* are carvacrol and eugenol (Velluti et al., 2004). Interestingly, by reducing the

**Table 1.** Variation of major chemical constituents in the essential oil of *S. aromaticum*

S. No.	Compounds	Chaieb et al., 2007	Ahamad et al., 2023	Hatami et al., 2019	Kennouche et al., 2015	González-Rivera et al., 2016	Ahamad et al., 2022
1.	Eugenol	88.58	59.87	87.3	65.36	66.9	59.16
2.	$\beta$ -Caryophyllene	1.38	23.58	1.36	24.62	24.8	7.68
3.	Eugenol acetate	5.62	trace	10.4	5.71	2.7	3.35
4.	Selinene	-	4.67	-	-	-	9.34
5.	Terpinyl acetate	-	4.12	-	-	-	-
6.	Humulene	0.27	3.74	0.19	Trace	3.1	2.16



**Figure 1.** The major chemical compounds in the essential oil of Clove



**Figure 2.** Bioactivities and therapeutic uses of clove and eugenol

inoculum size of fungi, a mixture of a concentrated sugar solution and clove oleoresin has a fungicidal effect (Núñez et al., 2001). Batiha et al, (2019) documented the antiparasitic effect of clove methanolic extracts on the proliferation of piroplasm parasites.

Eugenol in combination with  $\alpha$ -pinene and  $\beta$ -pinene significantly inhibits the growth of a gram-positive *Endocarditis* (Leite et al., 2007). In another study, eugenol and cinnamaldehyde synergistically inhibit gastric pathogen *Helicobacter pylori* (Ali et al., 2005)

#### **Anti-inflammatory Activity**

Clove has anti-inflammatory and immunomodulatory activities *via* suppressing the lipopolysaccharide (LPS) action as well as the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway. The active ingredient, eugenol, is responsible for clove's anti-inflammatory properties (Han and Parker 2017). Clove essential oil is beneficial in inflammatory disorders such as arthritis and rheumatism (Bhowmik et al., 2012). At dosages of 0.05 and 0.20 ml/kg, clove essential oil has shown anti-inflammatory properties in animal models. Clove essential oil's anti-inflammatory activity matches with that of standard anti-inflammatory medications like etodolac and indomethacin, which are given at 0.025 and 0.1, and 0.05 and 0.2 ml/kg dosages, respectively (Öztürk A and Özbek., 2005). Clove buds contain anti-inflammatory compounds such as caryophyllene, kaempferol, and rhamnetin (Martin et al., 1993).

Eugenol (at 200 and 400 mg/kg doses) was proven to lower the volume of pleural exudates in experimental animal models without affecting the overall count of blood leukocytes, indicating that this molecule has anti-inflammatory properties (Daniel et al., 2009). Many other researchers reported the anti-inflammatory properties of eugenol in *in-vitro* and *in-vivo* models (Leem et al., 2011; Grespan et al., 2012).

#### **Analgesic and Antipyretic Activities**

Clove and eugenol have been shown to have analgesic properties against toothache and joint pain by activating chloride and calcium channels in ganglion cells (Shields et al., 2004). Eugenol in several animal and *in-vitro* models shows its analgesic effect (Daniel et al., 2009; Park et al., 2011). Eugenol has been found to exert antipyretic activity when given intravenously and intragastrically (Feng J, Lipton, 1987).

#### **Anticancer Activity**

Clove essential oil and eugenol have been shown to have anticancer properties in leukemia, lung, breast, and colorectal cancer cells (Kouidhi B et al., 2010; Kumar et al., 2014; Nejad et al., 2017; Zari et al., 2021; Padhy et al., 2022).

Eugenol, the bioactive compound of clove, has shown its potential in several anticancer studies (Navarová, 2009; Jaganathan et al., 2011; Yoo et al., 2005; Ghosh et al., 2005). Ho et al., (2006) studied the cytotoxic effect of eugenol against human osteoblastic cells. The study finding suggests that eugenol decreases the activity of

dehydrogenase enzymes in a dose-dependent manner. In another study, eugenol shows a cytotoxic effect on the expression of molecular markers related to osteogenic differentiation of human dental pulp cells (Anpo et al., 2011). In addition to the above study, eugenol shows an apoptotic effect in human breast cancer cell lines (Vidhya and Devaraj, 2011).

#### **Antidiabetic Activity**

Clove contains insulin-stimulating constituents in clove extracts may be responsible for their anti-diabetic properties. *In vivo* experiments revealed that blood sugar has been enhanced in clove extracts-treated mice (Kuroda et al., 2012). Eugenol ameliorates insulin resistance, oxidative stress, and inflammation in high-fat diet/streptozotocin-induced diabetic rats (Al-Trad et al., 2019). The antidiabetic effect of eugenol was also established by several researchers (Srinivasan et al., 2014; Carvalho et al., 2021; Topal, 2019; Singh et al., 2016).

#### **Antiviral/ Covid-19 Activity**

Herbal remedies are a significant source of novel pharmacological compounds to suppress and control viral infections (Astani A., et al 2011). Eugenol, a compound found in Clove extract, has been shown to have antiviral activity against several herpes virus strains and the hepatitis C virus by blocking the viral DNA polymerase enzyme during viral DNA synthesis (Cortés-Rojas et al., 2014). In a study, clove aqueous extract in combination with acyclovir has antiviral efficacy against herpes simplex virus type 1 (HSV-1) and influenza A virus (Minami et al., 2003). Tragoolpua and Jatisatienr, (2007) investigated the antiviral activity of whole clove by testing an ethanol extract produced from the plant flower buds for anti-herpes simplex virus (HSV) activities. Clove extract suppressed HSV in a plaque reduction assay. The clove extract, interestingly, has a direct inactivating effect on the particles of the normal HSV strains. Another study using methanol extracts of clove found that the extract had high *in vitro* activity in inhibiting the HCV protease, with a 90% protease inhibition at 100 g/ml. Clove, along with *Eucalyptus globulus*, *Cymbopogon citratus*, *Zingiber officinale*, and other plants with the benefit of being affordable and widely available over the world, is one of the medicinal plants now used to prevent and control the SARS-CoV-2-associated disease (Hussein et al., 2000).

More in detail, a protocol for the prevention and treatment of COVID-19 by utilizing cloves as a medicinal plant, was described by Kanyinda, who reported the effect of the treatment if it was carried out in the early stages of the disease (Kanyinda., 2020). Surveys have been undertaken in India and Morocco, both with low pandemic impact (Samaddar et al., 2020), to identify the numerous home remedies used by populations during COVID-19, which include a wide variety of spices and herbs. Interestingly, more than 93 % of the Indians believed that spices could aid in the treatment of COVID-19 and other viral diseases, as well as increase immunity.

Cloves, along with other plants including cinnamon, ginger, black pepper, garlic, neem, and basil, are identified as the most utilized spices and herbs during the present COVID-19 pandemic in the areas under investigation (Singh et al., 2021).

### Miscellaneous bioactivities of Clove and Eugenol

According to traditional medicine, Clove can stimulate the human immune system and improve illness resistance. Clove essential oil was found to have immunostimulatory properties that were linked to improved cell and humor-mediated immune response pathways (Carrasco et al., 2009). Clove essential oil increased the total white blood cell count and the delayed-type hypersensitivity response in animal models in experimental research (Bhowmik et al., 2012).

The antiobesity activity of clove extracts has been demonstrated *in vitro* and *in vivo* investigations by lowering serum triglycerides and cholesterol levels (Przygodzka et al., 2016).

Clove essential oils have been shown to improve blood circulation and raise body temperature (Cortés-Rojas et al., 2014). Clove has been shown in several studies to reduce the risk of arterial sclerosis, cardiovascular disease, and other diseases linked to oxidative stress. Eugenol also has reversible, dose-related vasodilator and negative inotropic effects in heart muscle, as well as smooth muscle relaxant and hypotensive properties (Pulikottil and Nath., 2015). Clove is utilized as a tonic for the cardiovascular system and is said to enhance blood circulation to both the brain and the heart (Bahramsoltani et al., 2020).

Clove chewing is a common treatment for sore throats and pharyngeal irritation in Asia. Chewing cloves after they have been heated is said to help with severe coughing (Bhowmik et al., 2012). Clove essential oil is used to treat respiratory problems such as colds, bronchitis, cough, asthma, and other upper-respiratory problems (Mittal M., et al 2014). It aids in the treatment of persistent coughs when mixed with honey and is particularly beneficial in the treatment of shortness of breath (Bahramsoltani et al., 2020).

Eugenol has been demonstrated to protect against CCl<sub>4</sub>-induced hepatotoxicity (El-Hadary and Ramadan Hassanien 2016). Other phytochemicals derived from clove extracts, such as sanguinarine and benzo phenanthridine alkaloids, have been shown to protect against liver damage (Ali et al., 2014). In hyperlipidemic rats, clove intake could restore ALT, urea, AST, and lipid levels in the kidneys, serum, and liver (Shyamala et al., 2003).

Clove essential oil inhibits platelet aggregation generated by platelet-activating factors, arachidonic acid, and collagen, with the first two systems having higher action than the latter. Clove oil at 50-100 mg/kg doses provided complete protection against platelet-activating factor and good (70%) protection against arachidonic acid-induced shock owing to pulmonary platelet thrombosis which was carried out in rabbits *in vivo* (Mittal M et al., 2014).

Clove is known for its carminative, gastroprotective, and stomachic properties (Milind and Deepa, 2011). Clove essential oil and eugenol were discovered to contain several biologically active chemicals with significant gastro-protective properties, which were discovered because of their high flavonoid content (Santin et al., 2011; Okasha et al., 2008; Morsy et al., 2008).

### Toxicity of Clove Essential Oil and Eugenol

The American Food and Drug Administration (FDA) has determined that clove buds, clove oil, and other clove compounds are safe to use as a food supplement (Vijayasteltar et al., 2016), while a daily maximum dose of cloves for humans at 2.5 mg/kg body weight determined by the WHO (World Health Organization) has established (Ogunwande et al., 2005). However, there has recently been a lot of conversation about its toxicity (Vijayasteltar et al., 2016). Clove essential oil and eugenol have cytotoxic effects *in vitro* against human fibroblasts and endothelial cells (Prashar A., et al 2006), and the oral toxicity of clove essential oils include intravascular coagulopathy, generalized seizures, and hepatotoxicity if ingested in undiluted (Janes et al 2005).

### Conclusion

Clove is a traditional medicine, and it is also used as a spice in food preparations due to its aromatic flavor and pungency. Clove buds are rich in essential oil, and it has potent antiseptic and analgesic effects. Clove is traditionally utilized for the prevention and treatment of several human ailments. Eugenol, the chief constituent of clove essential oil, has potent antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and anticancer properties. This review explores the ethnomedicinal uses, phytochemicals, bioactivities, and therapeutic applications of clove and eugenol.

### Author contributions

J. A. conceptualized, wrote, edited, and proofread the manuscript.

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### Competing financial interests

The authors have no conflict of interest.

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