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A review on biological and therapeutic uses of *Syzygium aromaticum Linn.* (Clove): Based on phyto-chemistry and pharmacological evidences

Ayushi[1], Urooj A Khan[2], Syed Mohammad Danish[3], Mohammad[4], Uzma Parveen[5*]

[1] Department of Pharmaceutics, Delhi Pharmaceutical Science and Research University, New Delhi, India

[2-4] Nanoformulation Research Laboratory, Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India

[5] Department of E.N.T, Hayat Unani Medical College and Research Centre, Lucknow, Uttar Pradesh, India

Abstract
Clove (*Syzygium aromaticum*) is naturally occurring spice used as a drug and a preservative due to its antimicrobial and antioxidant properties. Clove is a native of Indonesia but is also cultivated in many coastal areas at higher altitudes around the world. Health benefits of clove have been proved from centuries in treatment of many ailments and disease. Clove also shows antimicrobial, antiviral, anti-inflammatory, hepatoprotective, anti-stress, antinoceptive, anesthetic activities. Larvicidal activity of clove in dengue is a new application. Commercially, clove has been used for volatile oil extraction in formulating medicinal, food and cosmetic products. Clove oil comprises of many phytoconstituents, eugenol being an important one of the phenolic compounds. In respect to the points mentioned, this report is one of its kind as an attempt has been made to compile knowledgeable data of clove together in this article. Pharmacological activities, botanical description, phytochemistry, toxicity studies and uses of clove have been discussed.

Keywords: anti-microbial; clove; medicinal uses; pharmacological activities; phtyochemistry; *Syzygium aromaticum*; volatile oil

1. Introduction
A spice like clove is used as a natural preservative and as an herbal drug from centuries for its antioxidant and antimicrobial properties [1]. *Syzygium aromaticum* (*S. aromaticum*) commonly called as clove is a native from Maluku islands in east Indonesia belongs to *Myrtaceae* family and consists of about 1200 to 1800 flowering plant species [2, 3]. Clove cultivation is carried out at high altitudes above sea level of about 200 m in coastal regions [4]. It's wide distribution is in the regions of tropical and subtropical lands of Asia (Indonesia, Sri Lanka, India, Tanzania, Malaysia), Madagascar, Africa and all over the pacific and oceanic regions [5]. Clove is cultured in Brazil in its north east region in Bahia state (regions of Valenca, Itubera, Taperoa, Camamu & Nilo) on around 8000 hectares of land [6].

Fig 1: Plant of *Syzygium aromaticum showing branches of tree*

Clove is used for the treatment and cure of many diseases. One of the new applications include it as larvicidal agent to combat one of the serious health problems of tropical countries i.e. dengue [7]. Clove is otherwise used in the treatment of digestion related disorders like loose motions, nausea, flatulence & dyspepsia. It acts as an antibacterial agent by improving body defense system against invading microbes. It is also used in the treatment of Athletes Foot disease, onchomysosis, and respiratory conditions like cough, cold, asthma, bronchitis and sinusitis. Clove has shown to be affective in lung and skin carcinomas and also in diabetes as it controls blood glucose levels. Topical application of clove oil relieves muscular cramps and soothes headache. Sniffing its aroma helps in the reduction of restlessness, relieve mental fog, depression and drowsiness [8].

Fig 2: Different varieties of clove (A) Penang; (B) Zanziber; (C) Ripe fruit of clove plant

Pharmacological actions of clove is classified into various categories based on its activity into antimicrobial [9], anti-inflammatory [9], anti-stress [10], antioxidant [10], antiviral [10], hepatoprotective [11], and antinoceptive activities [12] etc.

1.1 Taxonomical Classification

Taxonomical or scientific classification of clove is given in Table 1 [13, 14].

Synonyms are: *Syzygium aromaticum (L.)* Merrill & Perry, *Caryophyllus aromaticus L.*, *Eugenia aromatic* (*L.*) Baill, *Eugenia caryophyllata* Thunb [14, 15].

Table 1: Taxonomical Classification

Kingdom	Plantae	Subclass	Rosidae
Domain	Eukaryota	Superorder	Myrtanae
Subkingdom	Viridaeplantae	Order	Myrtales
Phylum	Tracheophyta	Suborder	Myrtineae
Subphylum	Euphyllophytina	Family	Myrtaceae
Infraphylum	Radiatopses	Genus	Syzgium
Class	Magnoliopsida	Specific epithet	Aromaticum

1.2 Vernacular Names

Different names are used for clove in various parts of the globe due to linguistic diversity. Clove called by very unique names in India (Table 2A) and internationally (Table 2B) [16].

1.3 Parts Used

Clove consists of a bud and stalk. Both the parts have useful properties if consumed raw or in a processed form. Clove oil is extracted from clove by decoction and percolation methods and it is used as an important raw material in both medicinal and food industry [17].

1.4 Taste

Cloves are being used for over 2000 years by Asians in meals like food, soups, tea and also in herbal medicinal formulations due to its intense flavor and aroma. It has a sharp, pungent and aromatic taste with slightly bitter in nature. When used in cooking, it tastes much like nutmeg. Just like in medicinal preparations, it is also used in meals to give a milder to complementary taste and odour [18].

Table 2: (A) Vernacular names in Indian languages

Languages	Names used
Bengali	Lavanga
Gujarati	Lavang
Hindi	Laung, Laumg, Lavang
Kannada	Lavanga, Daevakusuma, Krambu
Malayalam	Grampu, Karampu, Karayampu
Marathi	Luvang
Oriya	Labanga
Punjabi	Laung
Sanskrit	Bhadrasriya, Devakusuma, Devapuspa, Haricandana, Karampu, Lavanga, Lavangaka, Lavangam, Varala
Tamil	Kirampu, Ilavankam, Kiraambu, Kirambu,Grambu
Telugu	Devakusumamu, Lavangamu, Lavangalu, Kaaravallu
Urdu	Laung, Loung

(B) Vernacular names in International languages

Languages	Names used
Arabic	Kabshqarunfil, Kabshqaranful
Bulgarian	Karamfil
Chinese	Ding xiang
Dutch	Kruindnagel
Danish	Nellike
French	Giroflier
German	Nelke
Greek	Garifalo Georgian
Georgian	Mixaki
Hungarian	Szegfu
Indonesian	Cengke
Italian	Chiodo di garofano
Japanese	Girofla, Choji, Kurobu
Korean	Jeonghyang
Latvian	Krustnaglinas
Nepalese	Lwaang
Swedish	Kryddnejlika, Kryddnejlikor
Spanish	Clavo, Clavo de olor

1.5 Dosage

Clove oil extracted from clove is generally used in herbal preparations and 0.75 ml of clove oil is present in 20ml of clove oil gel for periodontal treatment [19]. It was established by World Health Organization (WHO) that 2.5 mg/kg of clove per day is acceptable in humans [20].

1.6 Method of Uses

Clove and its products have been used as an effective remedy since centuries for relieving pain. It is used in various ways like topical application of clove oil and oral consumption of clove either in raw form or in the form of a formulation. At the site of tooth ache, pressing a clove bud in between the jaws can ease pain. Clove buds can be chewed for bad breath, hyperacidity, pharyngitis, and with salt relieves coughing [21]. A decoction of 5-6 cloves in 30ml water with honey, three times a day can be used as an expectorant. Clove oil can cure stomach aches if consumed with sugar and can even be applied at the site of mouth cavities to relieve pain. Paste of clove can reduce headaches when taken with salt and milk and even acts as an antiemetic especially for pregnant ladies. Clove is also eaten with betel leaves against catarrh. Clove oil also used as insect-repellant if sprayed in water [22].

1.7 Adverse Effects

Adverse effects or side effects caused by consumption of clove can be different if taken orally or applied topically. If taken orally, either in an excess quantity or by a person who is allergic to clove may lead to lactic acidosis (muscle pain and weakness), nausea (vomiting), numbness, dizziness, or a feeling of tiredness [23]. It may also lead to liver problems

associated with stomach pain, clay colored stools, dark urine, and in some cases jaundice. Sore throat, flu symptoms, troubles breathing are all signs of infection [24]. If applied topically may cause itching, rashes with mild skin irritation, swollen or bleeding gums, erection problems and delayed ejaculation are its rare side effects [23].

1.8 Substitutes and Adulterants
Spices like ground cloves, cinnamon, nutmeg, white or black peppers are some of the substitutes that can be used in place of clove due to similar aromatic and medicinal properties [25].

Clove bud should contain 15-21% of clove oil. Any substandard or overripe buds may not contain this much quantity of oil and is mixed with other genuine drugs for its sale which causes adulteration. Different forms of adulterated cloves are, exhausted clove, clove fruits, blown clove etc [26].

1.9 Correctives
Myristica fragrans and *Cinnamomum verum*

2. Botanical Description
2.1 Habitat
Rich loamy soils of tropical areas with humid climate are well good to grow clove trees. Red soils of Kerala midlands have showed successful growth of clove trees. In Tamil Nadu hilly terrains at higher elevations of Western Ghats with well distributed rainfall (150-130cm/year), cooler climate are the best location for clove culture. Moreover, cultivating lands should have well drainage system due to poor withstand of water logging by clove plants [27].

2.2 Macroscopic description
Clove as whole is dark brown in color with an aromatic, spicy and strong odor. Length of a clove is around 12-17mm. It is an actinomorphic, bisexual, epigynous flower. The buds of flower have a spherical head with a hypoxanthium which is sub-cylindrical tapering towards the lower end. Corolla is polypaptalous with four petals that are imbricate and enclosed the stamens to form the head of the bud androecium. Stamens are numerous in number, free and introrsely. Calyx is polysepalous with hard and thick sepals containing oil glands. Gymnasium is binocular, inferior to ovules and stamens with a free placentation axially (Fig. 3A). Style is single and erect. Schizolysigenous oil glands or ducts present all over in one part of flower buds (hypodermis) have volatile oil situation [14].

2.3 Microscopic description
In a transverse section of a clove hypoxanthium epidermis, cortex and columnella are observed below the ovary. Epidermis is a single layer of small cells with a straight wall having very thick cuticle. Ranunculaceous stomata intercepts this epidermal layer. There are 3 distinguished regions in the cortex, loosely arranged aerenchymatous cells account for the inner-region. Bicollateral vascular bundle rings with a few pericyclic fibres which are embedded in thick walled parenchyma in the middle region of cortex. Upto three layers of big ellipsoidal, schizolysigenous oil glands which are embedded in radially elongated parenchymatous cells lie in the peripheral regions of cortex. Columnella forms the central cylinder with thick wall parenchyma and bicollateral bundle rings. Throughout the columnella, many sphaeraphides are seen to a certain limit in cortical middle zone [14] (Fig. 3B).

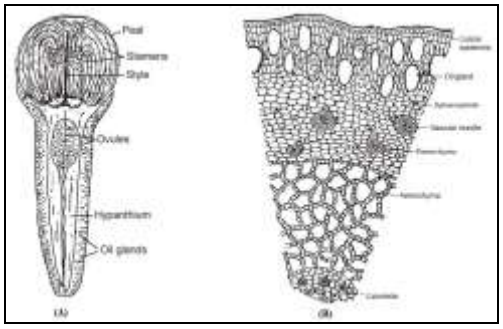

Fig 3: (A) Longitudinal section; (B) Transverse section of clove bud

3. Phytochemistry
Clove is a vital source of many phenolic compounds such as flavonoids, hydroxybenzoic acids, hydroxycinnamic acids, and hydroxyphenyl propenes [28]. One of the main bioactive compounds of clove is eugenol, present in the concentration range of 9381.70 to 14650.00 mg/100gm in fresh plant material [29, 30]. In phenolic acids, gallic acid is comparably found in higher concentrations of 783.50mg/100gm of fresh weight [1]. Some other phenolic acids are freulic, elagic, caffeic and salicylic acids. Kaempferol and quercitin are some flavonoids found in lower concentrations [31]. Further the clove constituents can also be divided into volatile and non-volatile constituents.

3.1 Volatile constituents
Different types of volatile oils can be extracted from different parts of clove including bud oil, leaf oil, clove stem oil and fruit oil [32]. These oils differ on the basis of their origin, quality of raw material, methods of distillation etc. The most important phytoconstituent in all of them is eugenol. Table 3 shows the description of different concentrations of phytoconstituents present in each type of volatile oil [33, 34].

Table 3: Quantities of phytoconstituents present in volatile oils

	Essential oil (%)	Eugenol (%)	Eugenal acetate (%)	Caryophyllene (%)	References
Bud oil	15-20	70-85	15	5-12	Pino JA et. al., 2001
Leaf oil	3-4.8	38.3-95.2	51.2-1.5	6.3-0.2	Gopalakrishnan et. al., 1988
Clove stem oil	6	80.2	-	6.6	Pino JA et. al., 2001
Fruit oil	2	50-55	-	-	Narayanan et. al., 1988

3.2 Non-volatile constituents
Tannins, sterols, triterpenes and flavonoids are some of the few non-volatile constituents isolated from clove[34]. Tannins are present in the concentration of 10-13% same as that of gallotanic acid. Other tannins like eugin, ellagi-tannin, eugenol glucoside gallate, gallolyl and hexahydroxy diphenylesters of 2, 4, 6-trihydroxyacetiphenone-3-glucopyranoside were obtained from clove leaves [35, 36].

Triterpenes are present in 2% concentration. Some derived sterols are stigmasterol and campesterol [37].

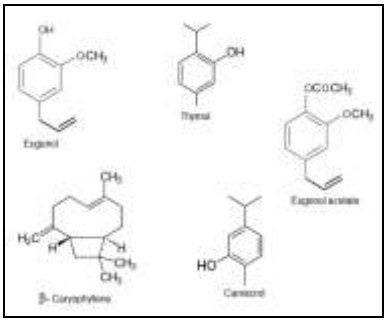

Fig 4: Structures of few important chemical constituents present in clove oil

4. Pharmacological Activities

4.1 Antioxidant activity

Antioxidants are compounds which are essential for the treatment of oxidative stress causing memory deficit [38]. Treatment with clove oil reduces oxidative stress mediated by reduced glutathione levels and helps in reverting memory back. Strong antioxidant activity of clove is comparable to synthetic antioxidants like BHA (Butylated Hydroxyl Anisole) and pyrogallol [39]. Clove oil has an inhibitory activity and reduces lipid peroxidation due to its highest capacity in giving off hydrogen which is determined by linoleic acid emulsion system. It also showed inhibition against hydroxyl radical DPPH (2,2-diphenyl-1-1picrylhydroxy), ferric reducing antioxidant power, oxygen radical absorbance capacity. 2-deoxyguanosine and xanthine oxidase have also been used to determine the antioxidant activity of clove [40].

4.2 Antimicrobial activity

Clove oil has proved to be effective against *Staphylococcus* species of bacteria and *Aspergillus niger* species of fungi. Germicidal activities against S.aureus, pseudomonas aerugunosa, and Klebseilla pneumonia have been shown by dispensing clove oil in (0.4% v/v) concentrated sugar solution [41]. *E. coli* was used to test the antimicrobial activity of clove oil [36]. Determination of antifungal activity of clove oil was done by Rana.et.al reporting a sensibility scale of fungi [*Mucor sp.>Microsporum gypseum> Fusarium monoliforme NCIM 1100> Trichophytum rubrum> Aspergillus sp.> Fusarium oxysporum MTCC 284*] [42].

Solid lipid nanoparticles containing eugenol were formulated using acrylic triglyceride, stearic acid & poloxamer 188 by modified hot homogenization ultrasonication method. These nanoparticles were characterized and evaluated for in-vivo antifungal activity using oral candidiasis model. Therapeutic efficacy of eugenol increased and modification in the drug release behavior was observed after administration of nanoparticles [44].

4.3 Anti-inflammatory activity

Anti-inflammatory agent in clove oil is eugenol. A synergistic effect was observed in animal studies when clove oil extract was added to other anti-inflammatory compounds like cod liver oil. On the other hand flavonoids like rhamnetin, kaempeferol and β-caryophyllene enhanced its anti-inflammatory property [45].

4.4 Antiviral activity

Eugenin isolated from clove was effective against herpes virus at 10µg/ml concentration. Eugenin showed its affect by inhibiting DNA polymerase of virus [46].

Aqueous extracts of *S. aromaticum* (L.) Merr. et Perry and some more plants like *Geum japonicum* Thunb., *Rhusjavanica* L., and *Terminalia chebula* Retzus together showed strong antiherpes simplex virus type 1 (HSV-1) activity when combined with acyclovir. Stronger synergistic activity was observed in the brain than in the skin and was also proved to be non-toxic to mice [47].

4.5 Hepatoprotective activity

Hepatoprotective activity was shown by ethanolic extracts of clove on liver injury induced by paracetamol. Hepatic toxicity is analyzed by the increase concentration of certain cytoplasmic enzymes like AL, AST in blood circulation. Its ethanolic extract controlled and maintained the level of these enzymes thus increasing the functionality of liver [48].

4.6 Antinoceptive activity

Eugenol is the compound responsible for the analgesic activity of clove since 13th century for toothaches, joint pains and as an antispasmodic. It acts by activating calcium and chloride channels in ganglion cells [49]. It also act as a capsaicin agonist to contribute in analgesic effect [50].

4.7 Anti-stress activity

Clove extracts reduce the development of cold restraint induced gastric ulcers and also helps in preventing biochemical changes caused by sound stress like elevated plasma levels of alanine aminotransferase, aspartate aminotransferase, glucose, corticosterone and cholesterol [51].

5. Uses

5.1 Medicinal uses

Clove possesses antibacterial properties and is therefore used in toothpastes, mouthwashes, dental creams, throat sprays. It acts as an anodyne that is soothes pain in dental emergencies [45]. It is used as a carminative by increasing hydrochloric acid in stomach to improve peristalsis. It also promoted faster healing of cuts and bites. Clove oil when inhales helps in the removal of mucous discharge as well as relieves cold, cough, asthmatic issues, stimulates blood flow, benefit diabetic patients in lowering blood glucose level, relieves muscular pains. Sniffing its aroma soothes headaches, dizziness and irritability [21].

5.2 Culinary uses

It is used as an important spice in the cuisines of Greece, India, China and Russia. It is also used in studding tomatoes, sausages, salads, soups and herbal teas. It is also used as a flavoring agent of meat products, candies, cookies, pastries, spiced foods, chocolate drinks, puddings, sandwiches, curries, cakes, pickles etc [21].

6. Formulations Available

Clove is used in the formulations of health supplements like chyawanpras, honey, glucose which helps improve body's immunity and memory, acts as an anti-inflammatory, an energy booster, diuretic to remove excess fluid from your

body. It is using in formulating shampoos that help protect hairs against damages like dandruff, dryness, hair fall, split ends, scalp infections. Also used as an ingredient in formulation of digestives like hajmola to cure gas & indigestion problems and act as carminatives. Skin products are formulated using clove which moisturizes the skin deeply, acts as a pore cleanser, gentle exfoliator, lightens scars, useful in sunburn etc [52].

7. Toxicity Studies & Pharmacokinetics

Clove oil if consumed in the concentration of less than 1500 mg/kg is considered safe. Also, World Health Organization (WHO) has declared that 2.5 mg/kg of clove per day is considered acceptable for consumption. Clove oil toxicity was tested in two aquarium fish species *Poecilia reticulate* and *Daniorerio* [53, 54]. Medium Lethal concentration (LD_{50}) at 96h in *Daniorerio and Poecilia reticulate* was found to be 18.2 ± 5.52 mg/ml and 21.7 ± 0.8 mg/ml respectively.

8. Precautions

In children, clove oil if taken by mouth is likely unsafe. It can cause severe side effects such as seizures, liver damage, and fluid imbalances. There is not enough reliable information about the safety of taking clove in medicinal doses. Avoid its use if you are pregnant or breast-feeding. Eugenol in clove oil seems to slow blood clotting. There is a concern that taking clove oil might cause bleeding in people with bleeding disorder[55]. It might also cause bleeding during or after surgery. Therefore, one should stop using clove at least 2 weeks before a scheduled surgery.

9. Conclusion

The fruit of the plant *Syzygium aromaticum* has been used since centuries in every part of the globe. It has pharmacological benefits like antimicrobial, anti-inflammatory, antinoceptive, hepatoprotective, anti-stress, and anesthetic. Clove has proved to be a good antioxidant as well. The single drop of its oil is many times stronger and effective as compared to other antioxidants like blueberries and wolf berries. Based on all the above information it is found to be a very effective plant with many proved benefits having least adverse effects. The proved biological activities suggest the development of more herbal products containing clove as an ingredient which are useful medicinally for humans as well as for animals.

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