MEDICINAL, THERAPEUTIC AND PHARMACOLOGICAL EFFECTS OF *SYZYGIUM AROMATICUM* (LAUNG)

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Summary

The common spice *Syzygium aromaticum* (laung) are used as a food item as well as a medicine all over the world. In the beginning of the 20th century spices were used in treatment of several diseases. These treatments were largely based on the traditional experience passed from generation to generation. Pharmacodynamics of the chemicals present in spices has confirmed the use as medicine. Researches in various fields are now directing their study towards investigating the effects of spices on the human health. Extracts and chemical constituents of spices have been investigated from their possible effects on anti-microbial activity, cancer prevention, cardiovascular risk factors, platelet aggregation inhibitory activity, and anti-diabetic, anti-oxidant and as pesticides. The present review highlights the some important pharmacological uses of *Syzygium aromaticum* in traditional and modern practices.

Keywords- Pharmacology, *Syzygium aromaticum* (laung),

Introduction

The objective of the present review is to highlight the pharmacological and therapeutic use of *Syzygium aromaticum* spices in modern medicine and its use as pesticide against certain pest. *Syzygium aromaticum* Linn. is commonly known as laung (family Myrtaceae). The commercially used clove is the air dried unopened flower-bud obtained from the handsome, medium sized, evergreen, straight-trunked tree that grows in Kerala and Tamilnadu, to a height of 7-12 meters. Clove is the second most important spice of the world, as judged from the world trade, being next only to black pepper. According to an ITC survey the total world, the USA and India are the largest importers of cloves.

The term 'clove' is derived from the French word 'clov' and the English word 'clout' both meaning 'nail' from the likeness of the flower-bud of the clove tree to a broad-headed nail. The leaves, unripe fruit and broken clove including the stalk are all aromatic and yield as essential oil. Good quality clove should be brownish black in colour with full and plump crown, somewhat rough to touch, without wrinkles and should not contain more than 12% moisture and 2-3% foreign matter [1, 2].

Chemical Composition

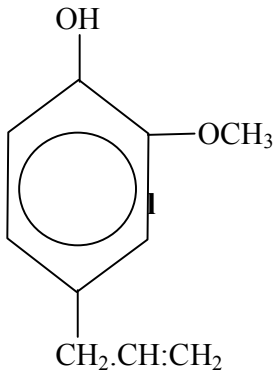
The composition of a clove varies some what according to the agro-climatic conditions under which it is grown, processed and stored. A typical analysis reveals the flowering-moisture: 5.4%; protein: 6.3%; volatile oil: 13.2%; non-volatile ether (fat): 15.5%; crude fibre: 11.1%; carbohydrate: 57.7%; mineral matter: 5.0%; ash insoluble in HCl: 0.24%; calcium: 0.7%; phosphorus: 0.11%; iron: 0.01%; sodium: 0.25%; potassium: 1.2%; vitamins (mg/100g): Vit B_1: 0.11; Vit B_2: 0.04; niacin:1.55; Vit C:80.9 and Vit A: 175 I. U. calorific value (food energy): 430 calories/100g [1, 2].

Steam distillate of the dried clove bud contains free eugenol, eugenol acetate and caryophyllene. Although these substances amount to some 99% of the oil, they are not responsible for the characteristic fresh and almost fruity note of pure clove bud oil, which is due to trace of other compounds, the most important one being methyl-n-amyl ketone [1, 2]. Aroma extract obtained from extract from dried clove buds *Syzygium aromaticum* was obtained by using steam-distillation under mild conditions (55^0 C and 95 mm Hg). A gas chromatography and mass spectrometry study has identified twenty two compounds in the extracts of clove bud. The major aroma constituents of clove buds were eugenol (24.371 mg/g) and eugenyl acetate (2.354 mg/g) [3].

One of the main components of clove oil obtained from the dried flower-buds of *Syzygium aromaticum* is [beta]-caryophyllene, it has local anesthetic activity [4]. Viuda-Martos et al [5] identified five compounds in clove essential oil, which represent 98.5% of the total. The predominant compounds were eugenol (85%), β-caryophyllene (10.54%), α-humulene (3.12%), δ-candidene (0.29%) and caryophyllene oxide (0.20%). Raina et al, [6] found 16 compounds, the main components being eugenol (94%) and β-caryophyllene (2.9%), while Viuda-Martos et al, [5] reported that eugenol (58.62%) eugenyl acetate (19.58%), β-caryophyllene (19.87%) and α-humulene (1.60%) were the major constituents. Viuda-Martos et al. [5] reported that eugenol and eugenyl acetate were the major constituents of clove essential oils made from buds. The yield and quality of the essential oil depends on the part of the plant used, the predominant compounds in essential oil from clove stems being eugenol (83-92%), β-caryophyllene (4-12%), eugenyl acetate (0.5-5%), while the predominant compounds in the essential oil obtained from leaves are eugenol (80-92%), β-caryophyllene (4-17%) and eugenyl acetate (0.2-4%). The predominant compounds in the essential oil of clove buds are eugenol (75-87%), β-caryophyllene (2-7%) and eugenyl acetate (8-15%) [5].

The essential oil of clove is a colorless or light yellowish extract obtained from dried flower buds by steam distillation. Through GC/MS analysis of clove essential oil 36 components were identified [7]. The highest concentration was of eugenol (88.58%), eugenyl acetate (5.62%) and β-cariophyllene (1.38). However, the differences in oil composition are correlated with different regions or countries were the plant is cultivated

[8]. Eugenol is the main volatile compound extracted oil from clove bud (*Syzygium aromaticum*).



Biological Properties

Spices have been traditionally used since ancient times, for the preservation of food products as they have been reported to have antiseptic and disinfectant properties [9]. *S. aromaticum* has been shown to be a potent chemopreventive agent, used by the traditional Ayurvedic healers of India since ancient times to treat respiratory and digestive ailments [10, 11].

Eugenol is the main volatile compound extracted from clove bud, (*S. aromaticum*) and used in traditional medicine, as a bactericide, fungicides and anesthetic [12]. However, eugenol is widely used and well known for its medicinal properties. In traditional uses of clove oil it was used in the dental care, as an antiseptic and analgesic [13]. Eugenol is effective against a large number of other bacteria [14, 15]. Earlier it have been reported that eugenol can be used as antifungal [16], antiallergic [17], anticarcinogenic [18], antioxidant [19], antimutagenic [20] and as pesticidal agent against several pests [21]. The essential oil of *S. aromaticum* shows a huge potential to substitute commercial antibiotics as antimicrobial agents for aquaculture use [3].

Antimicrobial activity

The volatile oils of clove of *S. aromaticum* were assessed for antibacterial activity against 25 different genera of bacteria [22], which include animal and plant pathogens, food poisoning and spoilage bacteria. A crude MeOH extract of *S. aromaticum* (clove) exhibited preferential growth inhibitory activity against Gram-negative anaerobic periodontal oral pathogens, including *Porphyromonas gingivalis* and *Prevetolla intermedia* [23]. Ponce et al. [24] has reported that the essential oil of *Syzygium aromaticum* presented the largest antimicrobial activity. The minimum bactericidal concentration (MBC) were in the range of 0.093-1.5 ml/100 ml. *Syzygium aromaticum* (clove) caused a total inhibition of the fungal development on maize kernels [25]. The methanol extracts of clove (*Syzygium aromaticum*) showed remarkable induction of differentiation of M1 cells into macrophage-like cell [26]. *S. aromaticum* caused a total inhibition of fungal development on maize kernels [25]. Chaieb et al., [7] has been

reported antimicrobial, antifungal properties, the essential oil of *S. aromaticum* shows anti-inflammatory, cytotoxic and anesthetic activities.

Antiviral activity

Syzygium aromaticum contains anti-herpes simplex virus therapeutic activity. It inhibited replication of cytomegalovirus (CMV) and murine CMV (MCMV) in *in vitro*. These anti-CMV activities were examined in an MCMV infection model using immunosupressed mice [27]. Traditional herbal medicines have been safely used for the treatment of various human diseases in ancient China. *S. aromaticum* showed a stronger anti-HSV-1 activity in combination with acyclovir than the other herbal extracts *in vitro* [28]. Several studies have shown that clove has antiviral properties which can be exploited in the treatment of cervical cancer [11, 29].

Antifungal activity

Pinto et al., [30] have reported that the antifungal activity of clove oil from *Syzygium aromaticum* against *Candida*, *Aspergillus* and dermatophyte species. Kunasakdakul and Suwitchayanon [31] have investigated the inhibitory effect of *S. aromaticum* extract against crucifer pathogen. Minimum inhibitory concentrations (MIC) of clove extract 1900 ppm and 2300ppm was effective against *Alternaria brassicicola* and *Fusarium oxyporum*. Several studies [32, 33] have demonstrated that eugenol is potent antifungal component of *S. aromaticum*. Pinto et al., [30] has reported the antifungal activity of the clove (*S. aromaticum*) oil (eugenol) against *Candida*, *Aspergillus*, and dermatophyte species. Ahmad et al., [34] reported that clove oil possess strong antifungal activity against opportunistic fungal pathogens such as *Candida albicans*, *Cryptococcus neoformas* and *Aspergillus famigatus*. The essential oil of clove [35] inhibited the growth of *Rizopus* species at concentration above (600µg ml) and *Penicillum* species above (800µg ml).

Antibacterial activity

The clove oil is active against oral bacteria associated with dental caries and periodontal disease [23] and effective against a large number of other bacteria [14, 15, 36]. Cuman et al., [37] have observed the anti-inflammatory and antinociceptive activities of eugenol essential oil in experimental animal models. Eugenol at doses of 50, 75 and 100 mg/kg had a significant antinociceptive effect in the test of acetic-acid-induced abdominal writhing, compared to the control animal. Betoni et al., [38] have reported that the clove inhibitory effect of clove extract against *Staphylococcus aureus* bacteria. Antibacterial compound of clove oil is effective against food borne Gram positive bacteria (*Staphyococcus aureus*, *Bacillus cereus*, *Enterococcus faecalis* and *Listeria monocytogenes*) and Gram-negative bacteria (*Escherichia coli*, *Yersinia enterocolitica*, *Salmonella choleraesuis* and *Pseudomonas aeruginosa*) [39].

Antiplatelet activity

Srivastava [40] have isolated and identified two anti-platelet components, eugenol and acetyleugenol which inhibit platelet aggregation induced by arachidonate, adrenaline and collagen. In arachidonate-induced aggregation eugenol was on at par with indomethacin.

Eugenol and acetyleugenol when used in combination were more effective in inhibitory platelet aggregation induced by arachidonate adrenaline and collagen [40].

Enzyme activity

Kreydiyyeh et al., [41] has reported the effect of a water extract of some spices on the *in vitro* activity of the rat jejnal Na^+-K^+-ATPase activity. The extracts of clove have the most potent inhibitory effect on the intestinal ATPase as compared to extracts of other spices such as *Nutmeg, Cinnamon, Cumin, Coriander, Turmeric* and *Caraway*. Clove extract also inhibited the *in vitro* Na^+-K^+-ATPase activity in a crude kidney homogenate and the activity of an isolated dog kidney Na^+-K^+-ATPase [41]. The IC_{50} values of eugenol, aqueous clove extract and ethanolic clove extract all fell within the same range and were not significantly different from each other, suggesting that eugenol is the major inhibitory component in both alcoholic and aqueous extracts.

Immune system activity

Syzygium aromaticum flower-bud inhibited local immunoglobulin E (IgE)-mediated passive cutaneous anaphylactic reaction (IC_{50} = 17.78 mg/kg, i.v.; IC_{50} = 19.81 mg/kg, p.o.). When *Syzygium aromaticum* were pre-treated at concentrations ranging from 25 to 100 mg/kg, the serum histamine levels reduced significantly in a dose- dependent manner. Moreover, *Syzygium aromaticum* flower-bud caused dose-dependent inhibition of histamine release from rat peritoneal mast cells (RPMC) by compound 48/80 or anti-dinitrophenyl IgE. When *Syzygium aromaticum* flower-bud were added, the level of camp in RPMC transiently and significantly increased about 47- fold at 10 S compared with that of basal cells. Kim et al., [42] have observed that *Syzygium aromaticum* flower-bud inhibits immediate hypersensitivity by inhibition of histamine release from mast cells. Hot water extracts of *Syzygium aromaticum* have anti-herpes simplex virus (HSV) activity [43]. Eugenol (3 – methoxy - 4 – hydroxy – propenylbenzene) or sodium eugenol acetate (4 – O – acetic acid sodium – 3 methoxy – 1- propenylbenzene) (0.25, 0.5. 1 mM) caused concentration–dependent inhibition of arachidonic acid (AA)., collagen – epinephrine and ADP – induced platelet aggregation [44]. Eugenol or sodium eugenol acetate (0.25, 0.5, 1 mM) caused concentration – dependent inhibition of AA – induced thromboxane B2 and prostaglandin E2 formation [44].

Anticancerous activity

Clove, the sun-dried unopened flower bud from the plant *Syzygium aromaticum* is commonly used spice and for flavor [11]. The chemopreventive potential of aqueous infusion of clove during benzo [a] pyrene (BP)-induced lung carcinogenesis in strain mice [11]. Kim et al., [45] has reported that eugenol inhibited the proliferation of HT-29 cells and the mRNA expression of COX-2, but not COX-1. Eugenol might be a plausible lead condidate for further developing the COX-2 inhibitor as an anti-inflammatory or cancer chemopreventive agent [46]. Zheng et al., [18] has reported that clove, is well known in food preparation, as an anticarcinogenic agent. The cytotoxicity of clove oil and its major components has been investigated [47]. Gemcitabine used for chemotherapy in cancer treatment was highly cytotoxic to both cancer and normal cells, while clove extract (0.7-8 mg ml^{-1}) was comparatively more cytotoxic towards cancer cells [48]

Antioxidant activity

The antioxidant activity of clove bud extract and its major aroma components, eugenol and eugenyl acetate, were comparable to that of the natural antioxidant, [alpha]-tocopherol (vitamin-E) [49]. According to Shyamala et al., [50] hypolipidemic effect of *S. aromaticum* is due to its ability to combat oxidative stress by quenching free radicals generated in the body as a result of high fat diet. They suggested that use of moderate quantity of cloves in diet as an antioxidant is offering protection against hyperlipidemia. Odukoya et al., [51] has reported that antioxidant activity of *S. aromaticum* flower clove is higher (68.65%) than natural antioxidant to copherol (65.21%). Presences of 216.38 mg/100g phenolics provide a source of dietary anti-oxidants in addition to imparting flavor to the food. However, many aromatic plants and spices especially clove buds and their essential oil has been known to support various biological activities such as antimicrobial and antioxidant properties [52]. The ethanol extract of the clove buds showed remarkable scavenging activity (93%), as compared with synthetic antioxidants [53]. Scott et al., [54] has observed that *S. aromaticum* possesses both anti-inflammatory and antioxidant properties.

Pesticidal Properties

Insecticidal activity

The methanol (polar) and hexane (non polar) extracts of *S. aromaticum* were tested against *Tribolium castaneum* and *Sitophilus zeamais* adults via topical application. No contact toxicity of polar extracts was observed for either insect species. However, 100g/100 ml [(w/v)] non-polar extracts caused 90% mortality in *S. zeamis* but had no effect on *T. castaneum*. Both polar and non-polar clove extracts were applied to milled rice which was then exposed to the two species of beetles separately in treated medium tests. The polar system had no effect on the mortality of both species of insects. However, with the non-polar extracts, mortalities of 13% and 44% in *Tribolium castanaeum* were obtained after 7 days and 21 days exposure period, respectively [55].

The toxic and development retarding effect of methanol and ether extracts of *S. aromaticum* were observed against *Culex pipiens* mosquito larvae [56]. Extracts of *S. aromaticum* were less toxic to larvae; however their influence on development was remarkable, causing completely inhibition of adult emergence at 200 and 600 ppm concentrations of the methanol and ether extracts, respectively [56]. Eugenol reduced the growth rate food consumption and food utilization in adults and larvae of *Tribolium castaneum* at concentrations of 35 and 99 mg/g food, respectively [57].

Nematicidal activity

The conventional chemical nematicides used in agriculture production may be deterious to the environment and to non-target organisms. Consequently, alternatives such as biorationals are being investigated for use against plant-parasitic nematodes. One group of plant-derived components, the essential oils, has demonstrated activity against multiple nematode taxa and is traditional use to flok medicines as anthelmintic agents [58, 59, 60, 61, 62, 63]. Clove oil is also active against plant-parasitic nematodes [64, 65, 66, 67]. Application of clove oil as a nematicide would enhance the use of this compound for management for soilborne plant pathogens by increasing the spectrum of target plant

parasites. Presently Meyer et al., [68] have reported lecithin/detergent formulation of clove bud oil for activity against the root-knot nematode *Meloidogyne incognita* (Kofoid and white) chitwood. Microwell test demonstrated that these formulations were very effective against the second stage juvenile population and reduce egg hatch by 50%.

Molluscicidal activity

Syzygium aromaticum clove bud powder and its active components eugenol are potential source of molluscicides against snails *Lymnaea acuminata* [69]. These snails are the intermediate host of liver fluke *Fasciola hepatica* and *F. gigantica*, which causes fascioliasis in the northern part of India [70, 71]. LC_{50} (96h) of eugenol (1.41 mg/l) against *L. acuminata* are lower than the LC_{50} (96h) values of synthetic molluscicides-carbaryl (4.40 mg/l), phorate (15.0 mg/l), formothion (8.56 mg/l) (Singh and Agarwal, 1983) and aldicarb (11.50 mg/l) [71]. 96h LC_{50} of flower-bud powder of *Syzygium aromaticum* (51.98 mg/l) against *L. acuminata* lower than the crude powder of common spices, *Allium sativum* bulb (271.06 mg/l), *Zingiber officinale* rhizome (273.80 mg/l), *Trachyspermum ammi* (97.59 mg/l), *Allium cepa* bulb (253.27 mg/l), *Cinnamomum tamala leaf* (830.90 mg/l), *Ferula asafoetida* dried latex powder (82.71 mg/l) [69, 72, 73, 74]. Kumar et al., [75] has observed that *in vivo* treatment of snail with sublethal concentration (20% and 60% of 24h and 96h LC_{50}) of eugenol caused significant ($P<0.05$) inhibition in AChE (acetylcholinesterase) and ALP (alkaline phosphatase) activity in the nervous tissue of *L. acuminata*. According to their inhibition of these enzymes by eugenol in the nervous tissue of *L. acuminata* is the major cause of the molluscicidal activity of *S. aromaticum.*

Clinical effect

It was reported that the buds of *S. aromaticum* (clove) were used in folk medicine as diuretic, odontalgic, stomachic, tonicardiac, aromatic condiment properties and condiment with carminative and stimulant activity [76]. In general medicine, clove is used as an agent against flatulence, stomach distension and gastro-intestinal spasm [77]. However, the clove oil is useful for treating rheumatoid arthritis and it has analgesic, antiseptic and anti-spasmodic properties. About 4gram of clove is boiled in 3l of water until half the water has evaporated. This water, taken in draughts, will show down severe symptoms of cholera [78]. However, chewing clove with a crystal of common salt relieves the irritation in the throat and stop cough in the pharyngitis. Clove is also an effective medicine for coughs caused by congested throat. The clove oil has been used for long time by dentists, for treating minor oral wounds, as an analgesic in painful and infective diseases of the oral cavity and pharynx as well as for general hygiene [77].

Conclusion

It is clear from above literature that common spices *S. aromaticum* has broad spectrum pharmacological effects against various microorganism as well as in treatment of different health problems in human beings. Chemicals present in *S. aromaticum* have significant effect against cancer, cardiovascular rich factors, and as antidibetic/anti-oxidant. Moreover, *S. aromaticum* have some pesticidal activity against harmful pest. More researches are still needed to explore its use in treatment of various human healths as well as its significant role in control of harmful pests.

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