

Clove

Syzygium aromaticum

Clinical Summary: Traditional usage of Clove has a long history of use as a culinary and household spice in many cultures. The word clove comes from the Latin word “clavus” which means nail – referring to the similarity between the seed and a nail. In cooking, clove is used in sweet and savoury dishes alike. In ancient times, cloves were used as a natural preservative in food, for embalming and as an ingredient in incense and herbal cigarettes. Clove has also been used as a medicinal plant in many cultures including in Ayurveda and Traditional Chinese Medicine as well as western herbal medicine. The main applications were for digestive disorders and pain relief in tooth ache as the oil has an anaesthetic and antiseptic action. The German Commission E has approved the use of clove as a topical antiseptic and anaesthetic.

Constituents: Clove has a range of constituents including volatile oils, tannins, ferulic acid, gallic acid and gums. The chemical components of the essential oil is primarily the phenol, eugenol (approximately 85%), but it also contains methyl salicylate, pinene and vanillin.

Actions: Astringent, anaesthetic, antioxidant, anti-inflammatory, vulnerary, carminative, antibacterial, antifungal.

Indications: Tooth aches & gum disorders; Candida and other fungal infections; Bacterial and viral infections; Digestive disorders, especially ulcers; Anal fissures (topical); Immune modulation; Oxidative stress.

Toxicity: Most cases of toxicity or problems with clove have been reported with the essential oil and not the extract.

Use in pregnancy: While culinary use is safe, medicinal dosages of clove in pregnancy should be avoided.

Contraindications and cautions: Clove should be avoided in those with a known allergy or hypersensitivity.

Drug interactions: Based on its actions, Clove has theoretical potential to inhibit or potentiate some drugs with similar actions and should also be avoided in drugs metabolised by the CYP2E1 pathway.

Description: Clove is native to Indonesia but is now also grown in Madagascar, Zanzibar, West Indies, Sri Lanka and Pakistan.

The clove tree is a small, aromatic evergreen tree that grows 8-12 metres tall and forms a pyramid shape. A member of the Myrtaceae family, the tree has large oblong leaves and smooth and greyish bark. The flowers are numerous and appear as clusters at the end of the each branch. The flower buds start out green and develop from yellow into a bright red, when they are ready for harvest.

The clove buds are harvested and dried when somewhat immature to enhance the oil content and potent fragrance. The distinctive flavour of Clove is due to an aromatic essential oil that makes up approximately 15-20% of the seed.

Traditional usage: Clove has a long history of use as a culinary and household spice in many cultures. The word clove comes from the Latin word “clavus” which means nail – referring to the similarity between the seed and a nail. During the explorations of the fifteenth and sixteenth centuries, Clove was a highly sought-after spice where at one time it was worth its weight in gold. In cooking, clove is used in sweet and savoury dishes alike, but is particularly popular in biscuits and curries. In ancient times, cloves were used as a natural preservative to prevent food spoiling as well as deterring insects. Cloves were used historically for embalming as well as being an ingredient in incense and very popular addition to herbal cigarettes.

Clove has also been used as a medicinal plant in many cultures including Ayurveda and Traditional Chinese Medicine as well as western herbal medicine. The main applications were for digestive disorders – where it is a powerful carminative and stimulant of gastric secretions. It has also been favoured for pain relief in tooth ache as the oil has an anaesthetic and antiseptic action. The German Commission E has approved the use of clove as a topical antiseptic and anaesthetic.

Constituents: Clove has a range of constituents including volatile oils, tannins, ferulic acid, gallic acid and gums. The chemical components of the essential oil is primarily the phenol, eugenol (approximately 85%), but it also contains methyl salicylate, pinene and vanillin.

Pharmacological activities: The research into the whole plant extracts of clove is not as extensive as the research into the essential oil of clove or its chief constituent, eugenol. However, given the large percentage of essential oil in the extract, similar effects may be found with the extract.

Antioxidant & Immune Modulating Actions: Extracts of *Syzygium aromaticum*, clove essential oil, and eugenol displayed strong free radical-scavenging antioxidant activity in a range of studies.^{1, 2, 3, 4, 5} Clove was also shown to inhibit lipid peroxidation⁶ and reduce cardiac and renal damage through antioxidant actions.⁷

Clove extract and essential oil (eugenol) have been found to possess varying immune modulating actions in both cell mediated and humoral immune responses.^{8, 9, 10, 11}

Antibacterial & Antiviral: A trial examined the effects of various toothpaste compositions on the presence of bacteraemia in 100 adult orthodontic patients. Bacteraemia was assessed before and after tooth brushing with or without using any toothpaste. While no bacteraemia was detected in pre-brushing blood samples, post-brushing bacteraemia was detected in some patients using standard toothpaste. No bacteraemia could be detected in the pre and post-brushing cultures of the subjects in the essential oil toothpaste group (contained clove, tea tree and peppermint oils).¹²

Clove demonstrated inhibitory effects against hepatitis C virus (HCV) protease (PR) in vitro¹³ and also herpes simplex virus.¹⁴ Clove was also found to inhibit the replication of human cytomegalovirus (CMV) in vitro.^{15, 16}

Insect Repellant Actions: Essential oil of clove has been used in various trials along with other essential oils as an effective insect repellent.^{17, 18} Undiluted clove oil repelled multiple species of mosquitoes for up to two hours.¹⁹ Eugenol has also demonstrated insecticidal activity against the house dust mites *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*.^{20, 21, 22}

Antifungal effects: Clove has been shown to prevent mycotoxin production by *Aspergillus* species and exhibit activity against other fungal pathogens, including *Cryptococcus neoformans* and *Candidia albicans*.^{23, 24, 25, 26, 27, 28} Another study suggests that clove may have a high inhibitory effect on dermatophytic fungi.²⁹

Eugenol was found to have an antifungal action by altering both the membrane and cell wall of yeast.³⁰ Another study indicated that eugenol exerted an anti-candidal effect by damaging the yeast envelope and interfering with cell growth. The fungicidal activity was similar with the reference drug, nystatin.^{31,32}

Anaesthetic Actions: Clove may exert its anaesthetic action through varying mechanisms. Eugenol was shown to inhibit prostaglandin biosynthesis and thereby depress pain sensory receptors.³³ Eugenol has also been shown to inhibit the formalin-induced nociceptive response an effect that may result from action via the capsaicin receptor.^{34, 35, 36} Other studies have shown that eugenol produces its antinociceptive effects via vanilloid receptors expressed by the sensory nerve endings in the teeth³⁷ or through other effects.³⁸

One randomized trial found that a homemade clove gel is as effective as an oral anesthetic benzocaine 20% gel.³⁹ Another trial compared the occurrence and severity of postoperative pain after gingivectomy with different dressings. Some patients received a standard dressing and others received different dressings that contained eugenol plus local anesthesia. Patients receiving the eugenol dressings reported less pain and less need for analgesics.⁴⁰

Vulnerary Actions: A trial examined the effects of a 1% clove oil cream on healing of chronic anal fissure. Patients received 1% clove oil cream or stool softeners and 5% lignocaine cream for six weeks. Patients were included if they had symptoms (defecatory pain, bleeding, or both) lasting for more than six weeks and clinical examination revealed anal ulcer with fissure of anal sphincter. Primary outcome measures included healing of anal fissures. Healing occurred in 60% of patients in the clove oil group and in 12% of patients in the control group. Patients in the clove oil group showed significant reduction in resting anal pressure compared with patients in control group. Two patients in the study group developed allergic reactions to clove oil (itching and burning).⁴¹

Digestive Activities: *Syzygium aromaticum* reduced ulcer number and area in ethanol and HCl-ethanol models and in an indomethacin model.⁴²

Eugenol has been found to exert a gastroprotective effects against indomethacin-induced ulcer in rats. It was found to reduce gastric mucosal lesions, gastric acid outputs, and pepsin activity associated with a significant increase in mucin concentration⁴³. Clove was also found to relax the tracheal and smooth muscles of the ileum.⁴⁴

Male Reproductive Actions: Clove has been studied in combination with other herbs in a topical cream for the treatment of premature ejaculation with good results. Though it is hard to ascertain the individual usefulness of clove in such studies.⁴⁵

Actions: Astringent, anaesthetic, antioxidant, anti-inflammatory, vulnerary, carminative, antibacterial, antifungal.

Indications: Tooth aches & gum disorders; Candida and other fungal infections; Bacterial and viral infections; Digestive disorders, especially ulcers; Anal fissures (topical); Immune modulation; Oxidative stress.

Toxicity: Most cases of toxicity or problems with clove have been reported with the essential oil and not the extract. Some individuals have been reported with allergic reactions to clove oil and nephrotoxicity and hepatotoxicity have been noted in case reports of accidental ingestion of clove oil.^{46,47,48}

Use in pregnancy: While culinary use is safe, medicinal dosages of clove in pregnancy should be avoided as there is insufficient safety data and some animal studies have shown clove can interfere with implantation or have teratogenic effects.^{49,50}

Contraindications and cautions: Clove should be avoided in those with a known allergy or hypersensitivity.

Drug-interaction: Based on its actions, Clove has theoretical potential to inhibit or potentiate some drugs with similar actions. An animal study found clove could induce cytochrome P450 enzymes, particularly CYP2E1 and potentially decrease levels of drugs metabolized by these enzymes.^{51,52}

References:

- (1) Buyukbalci, A. and El, S. N. Determination of in vitro antidiabetic effects, antioxidant activities and phenol contents of some herbal teas. *Plant Foods Hum.Nutr.* 2008;63(1):27-33.
- (2) Yadav, A. S. and Bhatnagar, D. Free radical scavenging activity, metal chelation and antioxidant power of some of the Indian spices. *Biofactors* 2007;31(3-4):219-227.
- (3) Feng, R., He, W., and Hiroto, O. [Experimental studies on antioxidation of extracts from several plants used as both medicines and foods in vitro]. *Zhong.Yao Cai.* 2000;23(11):690-693.
- (4) Ogata, M., Hoshi, M., Urano, S., and Endo, T. Antioxidant activity of eugenol and related monomeric and dimeric compounds. *Chem.Pharm.Bull (Tokyo)* 2000;48(10):1467-1469.
- (5) Wei, A. and Shibamoto, T. Antioxidant activities of essential oil mixtures toward skin lipid squalene oxidized by UV irradiation. *Cutan.Ocul.Toxicol.* 2007;26(3):227-233.
- (6) Toda, S., Ohnishi, M., Kimura, M., and Toda, T. Inhibitory effects of eugenol and related compounds on lipid peroxidation induced by reactive oxygen. *Planta Med* 1994;60(3):282.
- (7) Bafna, P. A. and Balaraman, R. Antioxidant activity of DHC-1, an herbal formulation, in experimentally-induced cardiac and renal damage. *Phytother.Res.* 2005;19(3):216-221.
- (8) Segura, J. J. and Jimenez-Rubio, A. Effect of eugenol on macrophage adhesion in vitro to plastic surfaces. *Endod. Dent.Traumatol.* 1998;14(2):72-74.
- (9) Fotos, P. G., Woolverton, C. J., Van Dyke, K., and Powell, R. L. Effects of eugenol on polymorphonuclear cell migration and chemiluminescence. *J Dent.Res.* 1987;66(3):774-777.
- (10) Chen, D. C., Lee, Y. Y., Yeh, P. Y., Lin, J. C., Chen, Y. L., and Hung, S. L. Eugenol inhibited the antimicrobial functions of neutrophils. *J Endod.* 2008;34(2):176-180.
- (11) Carrasco, F. R., Schmidt, G., Romero, A. L., Sartoretto, J. L., Caparroz-Assef, S. M., Bersani-Amado, C. A., and Cuman, R. K. Immunomodulatory activity of *Zingiber officinale* Roscoe, *Salvia officinalis* L. and *Syzygium aromaticum* L. essential oils: evidence for humor- and cell-mediated responses. *J Pharm.Pharmacol.* 2009;61(7):961-967.
- (12) Hussein E, Ahu A, and Kadir T. Investigation of bacteremia after toothbrushing in orthodontic patients. *Korean Journal of Orthodontics* 2009;39(3):177-184.
- (13) Hussein, G., Miyashiro, H., Nakamura, N., Hattori, M., Kakiuchi, N., and Shimotohno, K. Inhibitory effects of sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. *Phytother.Res.* 2000;14(7):510-516.
- (14) Kurokawa, M., Nagasaka, K., Hirabayashi, T., Uyama, S., Sato, H., Kageyama, T., Kadota, S., Ohyama, H., Hozumi, T., Namba, T., and . Efficacy of traditional herbal medicines in combination with acyclovir against herpes simplex virus type 1 infection in vitro and in vivo. *Antiviral Res.* 1995;27(1-2):19- 37.
- (15) Shiraki, K., Yukawa, T., Kurokawa, M., and Kageyama, S. [Cytomegalovirus infection and its possible treatment with herbal medicines]. *Nippon Rinsho* 1998;56(1):156-160
- (16) Yukawa, T. A., Kurokawa, M., Sato, H., Yoshida, Y., Kageyama, S., Hasegawa, T., Namba, T., Imakita, M., Hozumi, T., and Shiraki, K. Prophylactic treatment of cytomegalovirus infection with traditional herbs. *Antiviral Res.* 1996;32(2):63-70.

- (17) Trongtokit, Y., Rongsriyam, Y., Komalamisra, N., Krisadaphong, P., and Apiwathnasorn, C. Laboratory and field trial of developing medicinal local Thai plant products against four species of mosquito vectors. *Southeast Asian J Trop. Med Public Health* 2004;35(2):325-333.
- (18) Trongtokit, Y., Rongsriyam, Y., Komalamisra, N., and Apiwathnasorn, C. Comparative repellency of 38 essential oils against mosquito bites. *Phytother Res* 2005;19(4):303-309.
- (19) Barnard, D. R. Repellency of essential oils to mosquitoes (Diptera: Culicidae). *J Med Entomol.* 1999;36(5):625-629.
- (20) Saad, el, Hussien, R., Saher, F., and Ahmed, Z. Acaricidal activities of some essential oils and their monoterpenoidal constituents against house dust mite, *Dermatophagoides pteronyssinus* (Acari: Pyroglyphidae). *J Zhejiang Univ Sci B* 2006;7(12):957-962.
- (21) Fichi, G., Flamini, G., Giovanelli, F., Otranto, D., and Perrucci, S. Efficacy of an essential oil of *Eugenia caryophyllata* against *Psoroptes cuniculi*. *Exp. Parasitol.* 2007;115(2):168-172.
- (22) Kim, E. H., Kim, H. K., and Ahn, Y. J. Acaricidal activity of clove bud oil compounds against *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (Acari: Pyroglyphidae). *J Agric. Food Chem.* 2-12-2003;51(4):885-889.
- (23) Ahmad, N., Alam, M. K., Shehbaz, A., Khan, A., Mannan, A., Hakim, S. R., Bisht, D., and Owais, M. Antimicrobial activity of clove oil and its potential in the treatment of vaginal candidiasis. *J Drug Target* 2005;13(10):555-561.
- (24) Mabrouk, S. S. and El Shayeb, N. M. Inhibition of aflatoxin formation by some spices. *Z. Lebensm. Unters. Forsch.* 1980;171(5):344-347.
- (25) Kamble VA and Patil SD. Spice-Derived Essential Oils: Effective Antifungal and Possible Therapeutic Agents. *Journal of Herbs, Spices, and Medicinal Plants (USA)* 2008;14:129-143.
- (26) Lima I, Oliveira R, Lima E, and et al. Inhibitory effect of some phytochemicals in the growth of yeasts potentially causing opportunistic infections. *Brazilian Journal of Pharmaceutical Sciences (Revista Brasileira de Ciencias Farmaceuticas)* 2005;41:199-203.
- (27) Giordani, R., Regli, P., Kaloustian, J., Mikail, C., Abou, L., and Portugal, H. Antifungal effect of various essential oils against *Candida albicans*. Potentiation of antifungal action of amphotericin B by essential oil from *Thymus vulgaris*. *Phytother. Res.* 2004;18(12):990-995.
- (28) Braga, P. C., Sasso, M. D., Culici, M., and Alfieri, M. Eugenol and thymol, alone or in combination, induce morphological alterations in the envelope of *Candida albicans*. *Fitoterapia* 2007;78(6):396-400.
- (29) el Naghy, M. A., Maghazy, S. N., Fadl-Allah, E. M., and el Gendy, Z. K. Fungistatic action of natural oils and fatty acids on dermatophytic and saprophytic fungi. *Zentralbl. Mikrobiol* 1992;147(3-4):214-220. 3030 Bennis, S., Chami, F., Chami, N., Bouchikhi, T., and Remmal, A. Surface alteration of *Saccharomyces cerevisiae* induced by thymol and eugenol. *Lett. Appl. Microbiol.* 2004;38(6):454-458.
- (31) He, M., Du, M., Fan, M., and Bian, Z. In vitro activity of eugenol against *Candida albicans* biofilms. *Mycopathologia* 2007;163(3):137-143.
- (32) Chami, N., Bennis, S., Chami, F., Aboussekhra, A., and Remmal, A. Study of anticandidal activity of carvacrol and eugenol in vitro and in vivo. *Oral Microbiol. Immunol.* 2005;20(2):106-111.
- (33) Pongprayoon, U., Baeckstrom, P., Jacobsson, U., Lindstrom, M., and Bohlin, L. Compounds inhibiting prostaglandin synthesis isolated from *Ipomoea pes-caprae*. *Planta Med* 1991;57(6):515-518.
- (34) Ohkubo, T. and Shibata, M. The selective capsaicin antagonist capsazepine abolishes the antinociceptive action of eugenol and guaiacol. *J Dent. Res.* 1997;76(4):848-851.
- (35) Lee, M. H., Yeon, K. Y., Park, C. K., Li, H. Y., Fang, Z., Kim, M. S., Choi, S. Y., Lee, S. J., Lee, S., Park, K., Lee, J. H., Kim, J. S., and Oh, S. B. Eugenol inhibits calcium currents in dental afferent neurons. *J Dent. Res.* 2005;84(9):848-851.
- (36) Ohkubo, T. and Kitamura, K. Eugenol activates Ca(2+)-permeable currents in rat dorsal root ganglion cells. *J Dent. Res.* 1997;76(11):1737-1744.
- (37) Yang, B. H., Piao, Z. G., Kim, Y. B., Lee, C. H., Lee, J. K., Park, K., Kim, J. S., and Oh, S. B. Activation of vanilloid receptor 1 (VR1) by eugenol. *J Dent. Res.* 2003;82(10):781-785.
- (38) Daniel A, Sartoretto S, Schmidt G, and et al. Anti-inflammatory and antinociceptive activities of eugenol essential oil in experimental animal models. *evista Brasileira de Farmacognosia (Brazil)* 2009;19:212-217.
- (39) Alqareer, A., Alyahya, A., and Andersson, L. The effect of clove and benzocaine versus placebo as topical anesthetics. *J Dent* 2006;34(10):747-750
- (40) Jorkjend, L. and Skoglund, L. A. Effect of non-eugenol- and eugenol-containing periodontal dressings on the incidence and severity of pain after periodontal soft tissue surgery. *J Clin Periodontol.* 1990;17(6):341-344.
- (41) Elwakeel, H. A., Moneim, H. A., Farid, M., and Gohar, A. A. Clove oil cream: a new effective treatment for chronic anal fissure. *Colorectal Dis.* 2007;9(6):549-552.
- (42) Agbaje, E. O. Gastrointestinal effects of *Syzygium aromaticum* (L) Merr. & Perry (Myrtaceae) in animal models. *Nig. Q. J Hosp. Med* 2008;18(3):137-141.
- (43) Morsy, M. A. and Fouad, A. A. Mechanisms of gastroprotective effect of eugenol in indomethacin-induced ulcer in rats. *Phytother. Res.* 2008;22(10):1361-1366.

- (44) Reiter, M. and Brandt, W. Relaxant effects on tracheal and ileal smooth muscles of the guinea pig. *Arzneimittelforschung*. 1985;35(1A):408-414.
- (45) Choi, H. K., Jung, G. W., Moon, K. H., Xin, Z. C., Choi, Y. D., Lee, W. H., Rha, K. H., Choi, Y. J., and Kim, D. K. Clinical study of SS-cream in patients with lifelong premature ejaculation. *Urology* 2000;55(2):257-261
- (46) Janes, S. E., Price, C. S., and Thomas, D. Essential oil poisoning: N-acetylcysteine for eugenol-induced hepatic failure and analysis of a national database. *Eur.J Pediatr* 2005;164(8):520-522.
- (47) Brown, S. A., Biggerstaff, J., and Savidge, G. F. Disseminated intravascular coagulation and hepatocellular necrosis due to clove oil. *Blood Coagul.Fibrinolysis* 1992;3(5):665-668.
- (48) Lane, B. W., Ellenhorn, M. J., Hulbert, T. V., and McCarron, M. Clove oil ingestion in an infant. *Hum.Exp Toxicol*. 1991;10(4):291-294.
- (49) Hattan D. In Utero Phase Carcinogenicity Testing. *International Journal of Toxicology* (Taylor & Francis) 1998;17(3):337-353
- (50) Domaracky, M., Rehak, P., Juhas, S., and Koppel, J. Effects of selected plant essential oils on the growth and development of mouse preimplantation embryos in vivo. *Physiol Res*. 2007;56(1):97-104.
- (51) Kumari, M. V. Modulatory influences of clove (*Caryophyllus aromaticus*, L) on hepatic detoxification systems and bone marrow genotoxicity in male Swiss albino mice. *Cancer Lett*. 1991;60(1):67-73.
- (52) Gardner, I., Wakazono, H., Bergin, P., de Waziers, I, Beaune, P., Kenna, J. G., and Caldwell, J. Cytochrome P450 mediated bioactivation of methyleugenol to 1'-hydroxymethyleugenol in Fischer 344 rat and human liver microsomes. *Carcinogenesis* 1997;18(9):1775-1783