

## Clove (*Syzygium aromaticum*): Nature's Tiny Powerhouse

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**ABSTRACT:** Medicinal plants have gained significant attention because of their health-promoting properties, affordability, accessibility, and few side effects. Among different herbs that have been studied for the preparation of several traditional remedies since antiquity, clove (*Syzygium aromaticum*) has taken centre stage. Clove is a valuable and unusual spice from all over the globe. Clove is a substantial source of phenolic substances found in plants, including flavonoids, hydroxyl benzoic acids, hydroxyl cinnamic acids, and hydroxyl phenylpropenes. Eugenol is the principal bioactive ingredient found in clove. In addition, clove contains the phenolic acids ferulic, caffeic, elagic, and salicylic. Up to 18% of the essential oils found in cloves are found in the flower buds. The clove essential oil has been found to have a broad-spectrum pathogen-inhibitory effect. The -OH groups at the ortho and meta locations in the chemical structure of clove oil interact with the cytoplasmic membranes of microorganisms. Anti-oxidants included in clove oil, including eugenol, caryophyllene, eugenyl acetate, and humulene, help to protect cells from the harm caused by free radical oxidation. Clove oil has antiviral action against the HSV 1 and 2 and is also used to reduce the inflammation of the pharynx. It also has analgesic, antinociceptive, and anticancer properties. Clove has been used for a variety of therapeutic purposes, including antioxidant activity, antifungal, antiviral, antibacterial, anti-inflammatory activity, antithrombotic activity, antipyretic and analgesic, anticonvulsant effect, antimycotic activity, insecticidal, antimutagenic effect, and antiulcerogenic activity.

**Keywords:** Medicinal plants, Anti-inflammatory, Anticancer, Antinociceptive

### INTRODUCTION

Cloves may be regarded as the finest antioxidants currently available. The word "clove" actually relates to the symbol of honor. It is a valuable and unusual spice from all over the globe. It consists of an unopened flower bud belonging to the same Myrtaceae family as guavas. The fragrant dried flower buds known as cloves (*Syzygium aromaticum*, *Eugenia caryophyllata*, or *Eugenia aromaticum*) are used frequently in biryani, pickles, salads, and garam masala (Milind and Deepa, 2011). The FDA has approved the topical anaesthetic clove oil for use in dentistry and human medicine. It is a distilled substance made from the eugenol acetate, kariofilen-5 and eugenol, and comes from the clove tree *Eugenia aromatica*. Researchers gave common rainbow trout and carp the anesthetic, pharmaceutical preparation containing 10% eugenol, named as FA-100. Effectiveness was demonstrated for concentration ranges between 25 mg/L-100 mg/L. They also applied clove oil to rainbow trout and *Siganus lineatus*, at dosages ranging from 33 to 120 mg/L (Taylor and Roberts, 1999). With between 1200 and 1800 flowering plant species, *Syzygium* is the largest genus in the Mirtaceae family. It is widespread in tropical regions of Africa, Asia, Madagascar, the Pacific, and Oceanic regions (Cock and Cheesman, 2018). The evergreen clove tree grows to a height of between 8 and 12 meters (25 to 40 feet). It has simple,

opposing leaves that are small and have glands on them. Typically, seeds are sown in shaded areas, and these seeds grow into trees. A tree may yield up to 34 kg (75 pounds) of dried buds every year once flowering starts around the fifth year. In the winter, the length of a clove can vary and again in the late summer, the buds are hand-picked before being sun-dried (Britannica, 2019). Significant amounts of volatile oil, which is mostly found in the plant's aerial sections and is used to flavor meals and medicines, are present in cloves. Variables such as plant nutritional status, growing conditions, genetics, unique chemo types, geographic origins, and other factors are thought to be the cause of the fluctuating volatile oil production and composition (Al-Maskri et al., 2011).

For clove development, loamy, well-drained soils with lots of organic matter are essential. This species cannot survive in still water and the ideal temperature range is between 20 and 30 °C, and it's necessary to maintain a temperature over 10 °C. The areas with 150-300 cm of annual rainfall are prime for growth (Milind and Deepa, 2011). Only a few of the many phenolic substances that are present in clove include flavonoids, hydroxybenzoic acids, hydroxycinnamic acids, and hydroxyphenyl propenes. The concentration of eugenol is 650.00 mg/100 g in the weight of the plant, which is the primary bioactive component of clove. Among phenolic acids,

gallic acid is more prevalent (783.50 mg in 100 g of weight) (Shan et al., 2005).

### CHEMICAL COMPOUNDS

Clove is a substantial source of phenolic substances found in plants, including flavonoids, hydroxyl benzoic acids, hydroxyl cinnamic acids, and hydroxyl phenylpropenes. Eugenol, the principal bioactive ingredient in clove, ranges in concentration from 650.00 mg/100 g in weight of the plant (Neveu et al., 2010). Other Gallic acid derivatives, such as hydrolysable tannins (2 375.8 mg per 100 g), are present in high concentrations (Shan et al., 2005). In addition, clove contains the phenolic acids ferulic, caffeic, elagic, and salicylic. Lesser levels of flavonoids such as quercetin, kaempferol, and their glycosylated derivatives are available in clove. Up to 18% of the essential oils found in cloves are found in the flower buds. Eugenol makes up about 89 percent of clove essential oil, with eugenol acetate and cariofileno making up the remaining 5 to 15 percent. Another important component of clove oil, -humulen, can be found in concentrations such as 2.1 percent (Jirovetz et al., 2006).

### EXTRACTION OF CLOVE OIL

Hydro distillation by plants is a common technique for removing bioactive agents, particularly clove oils. It can be carried out on fresh plants before dehydrated. In hydro distillation, the three physicochemical processes are hydrolysis, hydro diffusion, and heat-induced breakdown (Azmir et al., 2013). Some volatile components may evaporate at a high extraction temperature. This drawback limits its usefulness for extracting thermo-labile chemicals. Three distinct flavors of hydro distillation are available (Vankar, 2004). Steam, water, and water-steam distillation are the three types of distillation. Plant material is initially packed into a still compartment for the hydrodistillation process.

Water is then added in the proper quantity, and the process is finished by heating the water to a boil. As an alternative, steam is used to pump plant material directly. The primary influencing variables that cause the release of the bioactive chemicals from plant tissue are hot water and steam. The vaporized mixture of water and oil is cooled indirectly with water. Oil and bioactive chemicals automatically separate from the water in a separator when the condensed liquid leaves the condenser (Silva et al., 2005). Steam distillation has been selected as another method to isolate clove oil. The steam distillation took 3, 4, 5, and 6 hours to complete. Time started to be measured as soon as the first drop of distillate was emitted. The recovered distillate was then extracted with the aid of a separatory funnel and n-hexane as the solvent. Clove oil was created by evaporating the n-hexane (Ratri et al., 2020).

### BIOLOGICAL ACTIVITIES

The clove oil has been demonstrated to have a variety of health benefits, with eugenol being the important one. The other chemicals, however, have also had a number of health advantages.

### Antimicrobial Effects

The clove essential oil has been found to have a broad-spectrum pathogen-inhibitory effect. The basic chemical structure of clove oil has -OH groups at the ortho and meta locations. These groups have been connected to the antibacterial mechanism of action. These can interact with the cytoplasmic membranes of microorganisms (Rajkowska et al., 2016). The gram-positive bacteria *S. aureus*, *Streptococcus*, and *L. monocytogenes*, as well as the fungi *Aspergillus*, *Penicillium bacterium*, *Candida albicans*, and yeast, may all be eliminated using clove oil. Some examples of gram-negative bacteria are *Escherichia coli*, *Salmonella*, *K. pneumoniae*, *E. carotovora*, *Agrobacterium*, and *P. falciparum*. Clove essential oil had a more profound inhibitory effect on Gram-positive bacteria than on Gram-negative bacteria. This behaviour is hypothesized to be brought on by the gram-positive bacteria's diffusible mucopeptide layer, which makes them susceptible to antimicrobial medications. Lipopolysaccharide layers present in the outer cell membrane of Gram-negative bacteria can significantly slow down the passage of lipophilic antibiotic compounds across the membrane (Shahbazi, 2019).

### Antioxidant Activities

Antioxidants, including eugenol, caryophyllene, eugenyl acetate, and humulene, found in clove oil, help protect cells from the harm caused by free radical oxidation. These molecules have been linked to a variety of diseases, including Parkinson's, Alzheimer's, and cancer. Clove essential oil has a preventive effect against the biochemical changes and histological abnormalities caused by ROS in the kidney, liver, and brain. Increases in lipid markers, blood electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>), creatinine levels, blood urea, liver, hepatic enzymes, and liver and kidney weight were among the major ROS modifications that were blocked, as well as an increase in serum creatinine and an increase in serum creatinine levels. Additionally, levels of albumin and total protein dropped (Bakour et al., 2018).

### Insecticide Role

Diseases caused by insects continue to be a problem for public health. Some species are dangerous urban pests that spread a variety of dangerous illnesses that can trigger allergic reactions in both young and old people, resulting in asthma. Most commonly used pesticides have significant dangers and harm the ecosystem over time. In addition, the development of pesticide resistance has been documented. To manage agricultural and urban pests, various studies have focused on the development of natural insecticides that use EO as a base. (Neupane et al., 2020). However, because they are so volatile, essential oils must be used frequently during the day because they do not stay in the body for very long.

### Antiviral Effects

The Clove oil has demonstrated antiviral action against the herpes simplex type 1, type 2, and influenza virus (Ebola) (Dai et al., 2013). Derivatives of eugenol may lessen the activity of the West Nile virus, according to recent research by de Oliveira et al. They can therefore serve as potential antiviral

drugs against flaviviruses, including the dengue, yellow fever, and Zika viruses. Eugenol has been researched as HIV-1 virus's inhibitor of the early stages of infection because of its capacity to reduce viral replication. Eugenol may also encourage lymphocyte development; it's possible that this property provides its anti-HIV-1 activity (Behbahani et al., 2013).

### Antinociceptive Effects

NSAIDs are most frequently used to relieve nociceptive pain associated with inflammation. The anti-inflammatory and antinociceptive properties of eugenol are connected to its ability to inhibit high-voltage Ca<sup>2+</sup> currents in primary afferent neurons, which lower COX-2 and vanilloid transient receptor potential (TRPV). This antinociceptive response involves cholinergic, 2-adrenergic, but not serotonergic receptors; it also involves opioid receptors. Eugenol's antinociceptive effects are likely related to the regulation of GABA receptors, as eugenol injection reduces GABA receptor currents in trigeminal ganglion neurons and inhibits GABA 122, which is expressed in these neurons. Clove buds, which contribute to the anti-inflammatory qualities of clove, contain flavonoids such as kaempferol and rhamnetin. Eugenol has demonstrated anti-inflammatory activity in experimental animal models by decreasing the size of pleural exudates without altering overall blood leukocyte count (at doses of 200 and 400 mg/kg). The generation of proinflammatory interleukins, activation of beta cells' kappa light chain nuclear factor, and extracellular-signal-regulated kinase (ERK)/MAPK cycles are all thought to be under the control of eugenol. According to another study, eugenol and whole clove aqueous extract injections decreased lipopolysaccharide-induced lung inflammation by lowering tumour necrosis factor alpha TNF and NF-B signalling (Nassan et al., 2015).

### Anti-inflammatory potential and lesion healing

Inflammation and oxidative stress are closely connected to a wide range of pathophysiological diseases, including hypertension, diabetes, cardiovascular disorders, and neurodegenerative disorders. Clove oil and eugenol both have anti-inflammatory effects. Diclofenac gel decreases inflammation by 20 to 60 percent after three hours, and similar outcomes were observed in rats given clove oil to treat wounds; these animals showed a greater than 95% contraction within the first 15 days. As a result, it is possible to prevent both the chronic and acute negative effects of synthetic antibiotics, especially if they are used regularly. Clove oil can be used topically to decrease the thickness of the epidermis and the quantity of inflammatory cells that express COX-2 without altering COX-1. The COX-2 expression and the creation of inflammatory mediators are decreased by eugenol's anti-inflammatory effects. It has been proven that eugenol targets cytokines in inflamed dermal cells rather than altering the levels of IL-8 in human skin keratinocytes. These data imply clove oil has anti-inflammatory and lesion-healing properties (Han and Parker, 2017).

### Clove as an Herbal Remedy for Respiratory Ailments

Cloves are employed in traditional medicine as respiratory remedies; in particular, the spice is one of the components in tropical Asian drinks that cause people to cough. Inhaling the scent of hot clove tea is another popular technique of utilizing cloves to treat respiratory disorders like coughs, colds, asthma, bronchitis, and sinusitis (Bhowmik, Kumar et al. 2012). Furthermore, chewing cloves is a traditional treatment for inflammation of the pharynx and irritation of the throat in Asia. It is said that clove is useful in the case of shortness of breath and treatment of persistent coughs when used with honey (Vicidomini et al., 2021).

### Analgesic Effects

Aromatherapy and clove oil have long been used to treat conditions like headaches, joint pain, toothaches, and mouth antiseptics. Eugenol and clove oil are both reliable, affordable analgesics. Additionally, eugenol's analgesic activity in several pain models has been thoroughly demonstrated. According to Khalilzadeh *et al.* (Khalilzadeh et al., 2016), the opioidergic and cholinergic systems play a role in the analgesic impact of clove oil. Additionally, eugenol's inhibitory impact on sodium and calcium-gated channels and activation of TRPV1 can be used to control the analgesic and local anaesthetic effects of the compound. The analgesic properties of eugenol and clove oil are quite comparable to those of lidocaine. The analgesic effectiveness of clove oil in fish was demonstrated by Correia *et al.* There was a reported analgesic effect in rats when clove oil was applied at concentrations between 40 and 80 L. The use of clove oil can reduce the impact of unpleasant stimuli for moral reasons, ensure the safety of animals, and prevent stress and its detrimental effects (Correia et al., 2017).

### Anesthetic Role

When used at reduced concentrations (50–500 l/L), clove oil is recognized as an anesthetic in vertebrates and invertebrates without causing any negative side effects. Faster anesthetic induction, quicker reflex recovery, and reduced mortality rates are all exhibited by clove oil without compromising the sensitivity to external stimuli (Ghanawi et al., 2019). Recent investigations have demonstrated that lidocaine-induced corneal sensitivity in rats can be decreased by topically applying clove oil and eugenol. Clove oil, eugenol, and lidocaine used topically lessen corneal sensitivity. However, the dose and length of exposure vary among compounds to achieve maximum anesthesia and duration. Inducing anesthesia in ringed cichlids, Nile tilapia, angelfish, and cardinal tetra with high efficiency, clove oil impairs swimming ability, causes balance problems, and reduces sensitivity to outside stimuli until total immobilization. The amount of time it takes to reach full anesthesia is reduced by dose concentration. Additionally, the dose and duration of clove oil exposure have no negative effects on returning to normal after anesthesia (da Silva et al., 2021).

For red claw crayfish and other crustaceans, such as grass shrimp and *Nepherops norvegicus*, clove oil works as an

efficient anesthetic. Due to the relationship between crayfish size and oxygen requirement, induction and recovery durations get longer as size increases. The effectiveness of anaesthesia is inversely related to size, and the rate of consumption of oxygen, the distance between the grill surface and the body, and the rate of infusion of the clove oil are used to track the intake and excretion of the clove oil. Due to its superior anaesthetic efficacy, clove oil is advised for invasive and unpleasant treatments (Correia et al., 2017). Many fish species can be given clove oil to make them unconscious. Long-term exposures, however, can result in sub-acute morbidity and mortality. Hekimoglu and Ergun calculated the optimal dose to anaesthetize the angelfish. This research will assist in handling and moving one of the most demanding aquarium fish species. Clove oil can be used to inhibit the germination of potato tubers by altering lipid peroxidation, catalase enzyme activity, peroxidase, glutathione transferase, superoxide dismutase, polyphenol oxidase, and other related enzymes (Afify et al., 2012).

### Anticancer Properties

The eugenol, humulene, and caryophyllene components of clove oil have been used to treat cancer because of their cytotoxic and anticancer effects. Some reports claim that essential oils help to minimize chemotherapeutic side effects include nausea, vomiting, weight loss, and appetite reduction. Since the production of ROS specifically activates signalling pathways that promote the development of cancer through regulating angiogenesis, metastasis, and cell proliferation, the main mechanisms by which it inhibits cancer growth are its anti-inflammatory and antioxidant properties. The usefulness of clove oil in treating many cancers, such as those of the colon, lung, breast, pancreas, leukaemia, cervix, and prostate, has been studied. The clove oil exhibits anticancer properties as a result of the aforementioned mechanisms: activation of detoxifying enzymes, DNA oxidation brought on by oxidative stress, cytotoxicity, and decreased viability, and cytotoxicity (Dahham et al., 2015; Ramadan et al., 2015).

### Termite Repellent Effect

Clove essential oil may be used to suppress the Japanese termite *Reticulitermes Speratus* Kolbe. In a similar way, at a concentration of 5%, clove essential oil was proved to have 100% repellent activity against the chigger *Leptotrombidium Imphalu*, suggesting a possible less costly and less risky substitute to synthetic repellents that are occasionally linked with negative side effects (Eamsobhana et al., 2009). With a protection period of (80.33-10.56) and (60.00-10.00), respectively, a formulation containing clove oil (10%) proved effective against the bite of *Aedes Aegypti* (L.) and Harrion and *Anopheles dirus Peyton*. Oil from soybeans served as the control. Recent investigations compared the structure and anti-*Aedesa egypti* larval activity of synthetic eugenol derivatives to the main constituents of clove oil. Larvicidal measures are one of the best ways to combat dengue because there is no vaccine or medication for treatment. The fascinating actions of eugenol suggest that it might be a feasible alternative to current pesticides (Barbosa et al., 2012). The fastest-acting chemical was eugenol, which also worked well with eugenol acetate and beta-caryophyllene to repel red imported fire ants, *Solenopsis*

*invicta* (Hymenoptera: Formicidae). *Paper wasps*, particularly *Polistes dominulus* and *Vespula pensylvanica*, which are harmful social wasps, can be spatially repelled by clove oil (Zhang et al., 2013).

### Clove in the Fight against COVID-19

Clove's promise in the fight against COVID-19 disease is highlighted by its historical therapeutic use in the treatment of respiratory diseases, its activity against various viruses, along with its anti-inflammatory, immunostimulatory, and antithrombotic qualities. In the battle against COVID-19, clove has a long history of medicinal usage for respiratory conditions, is active against a variety of viruses, and has immunostimulatory, anti-inflammatory, and antithrombotic capabilities. These are appealing characteristics that highlight its potential against COVID-19. In addition to *Eucalyptus globulus*, *Zingiber officinale*, *Cymbopogon citratus*, and other affordable and widely accessible herbs, clove is the therapeutic plant presently used to prevent the SARS-CoV-2 sickness (Kanyinda, 2020). More specifically, Kanyinda (2020) proposed that cloves are used as a medicinal herb in a COVID-19 preventative and treatment strategy. He noted that the medication had demonstrated an effect when it was used in the first stages of the illness. The method recommended was making a decoction, which calls for steeping cloves in water with other plant ingredients for 15 minutes. The patients then breathe in the five minutes' worth of released volatile active compounds. The same process also involved drinking a mixture made of cloves and other plants.

It is important that a study has been done to pinpoint the many herbal and spice-based home medicines that the people of India and Morocco, two nations with minimal pandemic effects, employed to treat COVID-19. It's interesting to note that over 93% of the Indians surveyed thought spices were effective at treating COVID-19 and other viral illnesses as well as boosting immunity. Cloves are described as one of the most often used spices and herbs during the current COVID-19 epidemic in the areas under inquiry, along with numerous other plants such as cinnamon, black pepper, ginger, garlic, basil, and neem. Additionally, Moroccan herbalists from Sale prefecture utilize cloves to cure and prevent COVID-19 (Chaachouay et al., 2021). From a molecular perspective, one of these compounds, kaempferol, was demonstrated in silico to bind the substrate binding pocket of the primary protease of SARS-CoV-2 with high affinity and interact with the active site residues like Cys145 and His41 through hydrophobic interactions and hydrogen bonding, indicating that naturally occurring substances like clove flavonoids can impart inhibition effects. Computational studies have suggested phytochemicals extracted from cloves as effective anti-COVID-19 drugs (Vicidomini et al., 2021).

### TOXICITY AND PHARMACOKINETICS

Clove oil is usually regarded as a safe chemical when used in doses less than 1500 mg per kg. According to the WHO, the appropriate daily dose of clove for people is 2.5 mg/kg of weight. Two aquarium species of fish, *Poecilia Reticulata* and *Danio Rerio*, were utilized to test the toxicity of clove oil. At 96 hours, the moderately fatal doses (LD<sub>50</sub>) were 18.2 and 5.52

mg/mL in *Poecilia Reticulate* and *Danio Rerio*, respectively. Eugenol is easily absorbed when taken orally and immediately reaches the circulation and plasma. Its half-life (mean) is 14.0 hours and 18.3 hours. Theoretically, cumulative effects from repeated exposure can reduce neuropathic pain.

## CONCLUSION

Clove has been used for a variety of therapeutic purposes, including antioxidant activity, antifungal, antiviral, antibacterial, anti-inflammatory activity, antithrombotic activity, antipyretic and analgesic, anticonvulsant effect, antimycotic activity, insecticidal, antimutagenic effect, and antiulcerogenic activity. Many different health problems are treated with clove oil, including stress and blood problems as well as toothaches, indigestion, cough, asthma, and headaches. Clove is used to treat a variety of ailments, including gastrointestinal problems, such as nausea, dizziness, vomiting, diarrhea, and gas, as well as headaches, cold and flu, impotence, intestinal worms, and other conditions. There is a lot of potential for researchers to employ clove to build powerful mixtures.

## REFERENCES

- Afify AEM, M El-Beltagi, HS Aly et al., 2012. Antioxidant enzyme activities and lipid peroxidation as biomarkers for potato tuber stored by two essential oils from Caraway and Clove and their main component carvone and eugenol. *Asian Pacific Journal of Tropical Biomedicine* 2:772-80.
- Al-Maskri AY, MA Hanif, MY Al-Maskari et al., 2011. Essential oil from *Ocimum basilicum* (Omani Basil): a desert crop. *Natural product communications* 6:1934578X1100601020.
- Azmir J, ISM Zaidul, MM Rahman et al., 2013. Techniques for extraction of bioactive compounds from plant materials: A review. *Journal of Food Engineering* 117:426-36.
- Bakour M, N Soulo, N Hammas et al., 2018. The antioxidant content and protective effect of argan oil and *Syzygium aromaticum* essential oil in hydrogen peroxide-induced biochemical and histological changes. *International Journal of Molecular Sciences* 19:610.
- Barbosa JD, VB Silva, PB Alves et al., 2012. Structure-activity relationships of eugenol derivatives against *Aedes aegypti* (Diptera: Culicidae) larvae. *Pest Management Science* 68:1478-83.
- Behbahani M, H Mohabatkar and M Soltani, 2013. Anti-HIV-1 activities of aerial parts of *Ocimum basilicum* and its parasite *Cuscuta campestris*. *J. Antivir. Antiretrovir* 5:57-61.
- Britannica E, 2019. The Editors of Encyclopaedia Britannica. de la Enciclopedia Británica.
- Chaachouay N, A Douira and L Zidane 2021. COVID-19, prevention and treatment with herbal medicine in the herbal markets of Salé Prefecture, North-Western Morocco. *European journal of integrative medicine* 42:101285.
- Correia A, A Pedrazzani, R Mendonça et al., 2017. Basil, tea tree and clove essential oils as analgesics and anaesthetics in *Amphiprion clarkii* (Bennett, 1830). *Brazilian Journal of Biology* 78:436-42.
- da Silva DR, AL Arvigo, PC Giaquinto et al., 2021. Effects of clove oil on behavioral reactivity and motivation in Nile tilapia. *Aquaculture* 532:736045.
- Dahham SS, YM Tabana, MA Iqbal et al., 2015. The anticancer, antioxidant and antimicrobial properties of the sesquiterpene  $\beta$ -caryophyllene from the essential oil of *Aquilaria crassna*. *Molecules* 20:11808-29.
- Dai JP, XF Zhao, J Zeng et al., 2013. Drug screening for autophagy inhibitors based on the dissociation of Beclin1-Bcl2 complex using BiFC technique and mechanism of eugenol on anti-influenza A virus activity. *PLoS one* 8:61026.
- Eamsobhana P, A Yoolek, W Kongkaew et al., 2009. Laboratory evaluation of aromatic essential oils from thirteen plant species as candidate repellents against *Leptotrombidium chiggers* (Acari: Trombiculidae), the vector of scrub typhus. *Experimental and Applied Acarology* 47:257-62.
- Ghanawi J, G Saoud, C Zakher et al., 2019. Clove oil as an anaesthetic for Australian redclaw crayfish *Cherax quadricarinatus*. *Aquaculture Research* 50:3628-32.
- Han X and TL Parker, 2017. Anti-inflammatory activity of clove (*Eugenia caryophyllata*) essential oil in human dermal fibroblasts. *Pharmaceutical biology* 55:1619-22.
- Jirovetz L, G Buchbauer, I Stoilova et al., 2006. Chemical composition and antioxidant properties of clove leaf essential oil. *Journal of agricultural and food chemistry* 54: 6303-07.
- Kanyinda JNM, 2020. Coronavirus (COVID-19): a protocol for prevention and treatment (Covalyse®). *European Journal of Medical and Health Sciences*, 2:340.
- Khalilzadeh E, R Hazrati and GV Saiah, 2016. Effects of topical and systemic administration of *Eugenia caryophyllata* buds essential oil on corneal anesthesia and analgesia. *Research in Pharmaceutical Sciences* 11:293.
- Milind P and K Deepa, 2011. Clove: a champion spice. *Int J Res Ayurveda Pharm* 2:47-54.
- Nassan M, E Mohamed, S Abdelhafez et al., 2015. Effect of clove and cinnamon extracts on experimental model of acute hematogenous pyelonephritis in albino rats: Immunopathological and antimicrobial study. *International journal of immunopathology and pharmacology* 28:60-68.
- Neupane AC, S Sapakuka, P Tao et al., 2020. Repellency and contact toxicity of clove bud oil and its constituents against German cockroaches, *Blattella germanica* (Dictyoptera: Blattellidae), under laboratory conditions. *International Journal of Pest Management* 66:289-97.
- Neveu V, J Perez-Jiménez, F Vos et al., 2010. Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database*, 2010:024.
- Rajkowska K, A Nowak, A Kunicka-Styczyńska et al., 2016. Biological effects of various chemically characterized essential oils: Investigation of the mode of action against *Candida albicans* and HeLa cells. *RSC advances* 6:97199-207.
- Ramadan M, M Ali, K Ghanem et al., 2015. Essential oils from Egyptian aromatic plants as antioxidant and novel anticancer agents in human cancer cell lines. *Grasas y Aceites* 66:080.
- Ratri PJ, M Ayurini, K Khumaini et al., 2020. Clove oil extraction by steam distillation and utilization of clove buds waste as potential candidate for eco-friendly packaging. *Jurnal Bahan Alam Terbarukan* 9:47-54.
- Shahbazi Y, 2019. Antioxidant, antibacterial, and antifungal properties of nanoemulsion of clove essential oil. *Nanomedicine Research Journal* 4:204-08.
- Shan B, YZ Cai, M Sun et al., 2005. Antioxidant capacity of 26 spice extracts and characterization of their phenolic constituents. *Journal of agricultural and food chemistry* 53:7749-59.
- Silva L, D Nelson, M Drummond et al., 2005. Comparison of hydrodistillation methods for the deodorization of turmeric. *Food Research International* 38:1087-96.
- Taylor PW and SD Roberts, 1999. Clove oil: an alternative anaesthetic for aquaculture. *North American Journal of Aquaculture* 61:150-55.
- Vankar PS, 2004. Essential oils and fragrances from natural sources. *Resonance* 9:30-41.
- Vicidomini C, V Roviello and GN Roviello, 2021. Molecular basis of the therapeutic potential of clove (*Syzygium aromaticum* L.) and clues to its anti-COVID-19 utility. *Molecules* 26:1880.
- Zhang QH, RG Schneidmiller and DR Hoover, 2013. Essential oils and their compositions as spatial repellents for pestiferous social wasps. *Pest Management Science* 69:542-52.