

Nutritional Pharmacology Aspects and Potential Clinical Uses of Clove Essential Oil in the Treatment of Coronavirus infection and Possibility Protect from Coronavirus (COVID-19) induced Sudden Death due the Embolism

Abdulrahim Abu Jayyab*

Faculty of Medical and Health Sciences, Emirates College of Technology

Abstract

Nowadays, most of the natural products are processed and developed as potential pharmaconutrient. The majority of antimicrobials of essential oils appear to act either directly on the virus itself on the envelope or during the early stages of virus replication following the internalization of the virus into its host cell. The bioactive components (Pharmaconutrients) of clove essential oil display many pharmacological activities such as antioxidant, antibacterial, antiviral, antifungal, antimutagenic, anti-inflammatory, anti-allergic, and dental caries properties. Besides, their inhibitory effects against multiple viruses including HIV and have also inhibitory effects against certain RNA of the respiratory syncytial virus (RSV), and DNA against enveloped viruses (HSV-1 and Newcastle disease virus). In addition, it has been found that the two phytochemicals, betulinic acid and savinin, which found in the essential oil of cloves have been shown to inhibit post binding entry of severe acute respiratory syndrome (SARS) coronavirus into cells, Cloves act directly upon the virus envelope such as Coronaviruses (COVID-19), which are enveloped viruses. Recently, it has been found that acute pulmonary embolism associated with hypercoagulable state with marked increase levels seen in C-reactive protein, and D-Dimer, which considered the main cause of sudden death. It has been shown that the clove lowers the risks for cardiovascular disease clove oil-induced dilate arteries while reducing systemic blood pressure. Besides, it is a potent platelet inhibitor and prevents the formation of a thrombus or a blood clot, this effect is considered an advantage to using clove essential oil for the treatment of coronavirus induced acute pulmonary embolism associated with hypercoagulable leading to sudden death.

In conclusion, clove essential oil may have Nutritional Therapeutic Potential effects due to its various effects, which includes antimicrobial, anti-fungal, anti-viral, anti-inflammatory, cytotoxic, analgesic, anesthetic activities, very potent as antioxidants, and inhibits post binding entry of severe acute respiratory syndrome (SARS) coronavirus into cells. Besides, anti-platelet activities; prevent the formation of a thrombus or a blood clotting. Therefore, essential oil of cloves may be considered the most candidates to combat the coronavirus and protecting against sudden death seen in some patients infected by Coronavirus (COVID 19), resulting from embolism associated with hypercoagulable formation. Clove Oil should only be diffused in well-ventilated places, and diffusing treatments shouldn't exceed more than 60 minutes each time under clinical observation.

Keywords: Clove Essential Oil, Coronavirus, Embolism, Sudden Death, Platelet Inhibitor, Ventilation

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Since

Prehistoric times, humans have used natural products, such as plants, animals, microorganisms, and marine organisms, in medicines to alleviate and treat diseases [1,2]. The Plants biosynthesize thousands of chemical compounds, which some be used for the treatment of various diseases [3,4]. Herbal medicine is the use of medicinal plants for treatment and prevention of diseases in many of the world cultures: it ranges from traditional and popular medicines of every country to the use of standardized and tritiated herbal extracts [4]. Herbal medicine has become a popular form of healthcare and still plays an important role in the therapeutics of many diseases. [4- 6] The use of herbal medicines and phytonutrients or nutraceuticals continues to expand rapidly across the world with many people now resorting to these products for the treatment of various health challenges in different national health-care

settings [6, 7]. Indeed, these herbal derivatives have shown promising therapeutically potential applications with the efficacy of a good number of herbal products clearly demonstrated. Herbal Medicines are presently in demand and their acceptance is increasing progressively due to the natural products have lesser toxicity and side effects as well as improving the efficacy than their chemical synthetic counterparts [4-8]. The traditional herbal medicines still play an important role in the therapeutics of many diseases in many of the world cultures. It has been postulated that the enormous natural products and traditional medicines have their impressive advantages, such as abundant clinical experiences, and their unique variety of chemical structures and biological activities [6,9], therefore, the herbal are getting significant attention in global health care [6-9]. Clove tree known as *Syzygium aromaticum*, It belongs to the Myrtaceae families. It was found first in the Maluku Islands of provinces of Indonesia in the

eastern country, this aromatic spice is still the prominent product of Indonesia. Today, cultivated in many parts of the world, including India, Pakistan, Madagascar, Sri Lanka, India, Tanzania, Zanzibar and even areas of East Africa [10, 11]. Cloves are best known as an aromatic spice to be used in the preparation of food, in addition, they have been used in traditional medicine. Clove can provide some important phytochemicals, which are commercially used for many medicinal purposes and in the perfume industry and clove are considered one of the spices that can be potentially added as preservatives in many foods, especially in meat processing, to replace chemical preservatives due to their antioxidant and antimicrobial properties [12]. Ancient Indian and Chinese medicines utilized cloves to treat various health conditions including toothaches, infections, indigestion, muscle and joint pain. The popularity of cloves continued to grow with each generation, finding new medicinal applications as a stand-alone or as a spice tonic [13]. Traditional Chinese medicine using cloves for its strong ability to combat the fungi and bacterial infections, also ancient India, Ayurvedic they used cloves to treat different digestive diseases, fever, toothaches, pain and respiratory problems [13]. Cloves contain several antioxidants agents like anthocyanin, quercetin and eugenol. Eugenol. Indeed it has been also shown to act as a natural antioxidant [14]. Antioxidants [15] are compounds that reduce oxidative stress, which can contribute to the development of chronic inflammation. This is where antioxidants play a vital role by seeking out free radicals, neutralizing their harmful effects, and protecting the body tissues and systems [14, 15]. A research study found that eugenol stopped oxidative damage caused by free radicals five times more effective than vitamin E due to its potent antimicrobial and antioxidant activities. The results of the study on the antioxidant activities of 26 various spices have been indicated that cloves to be one of the highest concentrations among other powerful superfoods such as garlic, thyme, rosemary, and oregano. [16]. Cloves are also good sources of antioxidants, and also fight inflammation and protect the organs against cancer [6]. The inhibitions of degenerative diseases are usually due to the presence of various bioactive chemical constituents in high concentrations with antioxidant activities such as flavonoids that are naturally occurring in herbal plants including cloves. These agents are believed to have positive effects on human health and diseases. Studies on flavonoid derivatives have demonstrated a wide range of therapeutic activities such as antibacterial, antiviral, anti-inflammatory, anticancer, and anti-allergic activities [17-19]. Besides, flavonoids have been found to have highly effective scavengers of the most oxidizing molecules, including singlet oxygen, and the different free radicals, [20] which involved in several diseases. Besides, numerous studies showing strong antioxidant properties, for an instant the clove, as well as flavonoids isolated from clove buds, acted as strong free radical scavengers in comparison to commercial anti-oxidants like BHT) [20, 21]. This property is especially true for clove oil [20]. Therefore, these explain the clove oil used for treating asthma [22]. The asthma is due to the inflammation in the airways along with changes in immune. Diet may affect the inflammation, depending on the types of food. Diet-induced inflammation can strongly

affect asthma risk which considered as a trigger induced asthma, in contrast, there is certain food rich in an essential oil that used in the treatment of respiratory tract diseases highlighting their role in bacterial infections and their anti-inflammatory action as anti-asthma agents (here I gave new names for such agents as Phytochemicals), which also present in the clove oil have therapeutic potential for the treatment of inflammatory diseases. [23]. It has been described that inflammation is a complex protective response of the body against harmful agents, such as microorganisms damaged cells or toxic agents [24, 25], clove is also known by anti-inflammatory activity [22, 26], which may be related to the anti-inflammatory action of eugenol [22]. In addition, the clove essential oil has shown to soothe the respiratory tract and also has anti-inflammatory effect. Supplementation with clove oil was found to prevent bacteria from forming colonies in the lungs [27]. Studies demonstrated that the eugenol found in high concentrations in cloves [14], which related to produce decreases the oxidative stress and acts against liver cirrhosis [28]. Indeed, It has been found that the eugenol an excellent agent for the prevention of metastasis-related to oxidative stress and acts against liver cirrhosis [28]. Indeed, It has been found that the eugenol an excellent agent for the prevention of metastasis-related to oxidative stress [29]. The alcoholic extracts of clove were found to possess anti-stress properties [30], which might be related to the antioxidant effects of clove [26]. The clove essential oil is widely used to treat various diseases including human dermal fibroblasts [31] this may be due to its pharmacological action as a powerful anti-inflammatory and antioxidant agents [6,26]. The essential oil of clove is a natural agent that has many potential therapeutically uses in wide areas [32], it is extensively used in aromatherapy to treat headaches; this pharmacological action may be attributed to the eugenol in clove oil, which has anesthetic and analgesic (pain-relieving), this also holds true for clove essential oil is widely available [26, 32,33]. This might explain the use of the clove to relieve the tooth pain, the eugenol the substance is found to have anesthetic and has also antibacterial properties, [32-34]. Moreover, the clove has also shown to fight inflammation of the mouth and throat. A research study has been demonstrated that clove oil has an anti-plaque, anti-gingivitis, and antimicrobial properties and has been suggested to use it in the treatment of the teeth inflammation associated with plaque and gingivitis [35]. Indeed, the antibacterial, research has been demonstrated that the Clove essential oil inhibit Staphylococcus bacteria. [36]. Besides, Carvacrol and eugenol, in clove oil, have an anticandidal and antifungal effect, and suggested to be it used to heal candidiasis caused due to a fungus, *Candida albicans* [37], The anti-fungal properties of cloves have also been recommended in the aromatherapeutic literature for treating acne and improving skin health. [38], This action may relate to of the eugenol in the oil that has antibacterial properties and can stop infection and fight inflammation, thereby effectively treating acne [38]. Eugenol has been widely used in dentistry because it can penetrate the dental pulp tissue and enter the bloodstream [39]. More research has been demonstrated that the cloves essential oil has the potential to replace benzocaine as a topical anesthetic in dental treatments. [40]. Due to its antiseptic

activities, clove oil can be used for preventing infections. [41]. Several studies have been indicated that constituents of clove have anti-oxidant activities and inhibit lipid peroxidation [42]. Besides, more studies indicated that the eugenol is very potent an anti-inflammatory and antioxidant effects [22]. In addition, animal studies have been shown that the eugenol in cloves reduced the pro-inflammatory cytokines; therefore, it could use to treat the inflammation associated with arthritis in humans [44]. The cloves are good sources of antioxidant, anti-inflammatory and properties that have therapeutic potential to fight inflammation and protect the body against cancer [22, 44]. Moreover, it has been reported that the anti-cancer properties of clove might be attributed to eugenol, which also found to reduce the risk of esophageal cancer [45]. In addition, it was shown clove extract prevents tumour growth and induce cancer cell death [46]. More research studies indicated that clove extract was also proven to Inhibits tumour growth and promote cell of breast cancer [47]. Free radicals that contain the element oxygen are the most common type of free radicals produced in living tissue, reactive oxygen species, (ROS) [48, 49]. The damage to cells caused by free radicals, especially the damage to DNA, may play a role in the development of cancer, infection diseases, which affect health conditions [47, 48]. Oxidative stress has been implicated in the etiology of microorganism infections, cardiovascular disease, inflammatory diseases, cancer, and other chronic diseases [50, 51]; as mentioned earlier the clove has been found that constituents of clove impart anti-oxidant activities and inhibit lipid peroxidation [38 42]. In addition Clove has antimicrobial [35, 36, 47], anti-fungal [36, 47, 38,51], anti-viral [47, 51] anti-inflammatory [22,39,43,44, 51], cytotoxic [45, 56, 51], analgesic, and anesthetic [32,34,47, 51] activities. Beside, essential oils of aromatic plants have been reported to have antibacterial, antifungal, antiviral, and cytotoxic properties [52]. In addition, the compound isolated from *S. aromaticum* extract has been shown to have antiviral effects against various herpes virus strains and the hepatitis C virus via its action on the biosynthesis of the viral DNA by inhibiting the viral DNA polymerase enzyme [51, 53]. Studies have been demonstrated that flavonoids in clove essential oil have potent anti-inflammatory properties, which may use to treat all kinds of inflammation in the body [54]. In addition, numerous studies have demonstrated that the Flavonoid compounds which are one of the cloves compositions produced inhibitory effects against multiple viruses including the against HIV [55, 56]. Indeed, numerous studies have demonstrated that the Flavonoid compounds which are one of the cloves compositions produced inhibitory effects against multiple viruses including against HIV [55-58], another study has found that flavone derivatives are inhibitory to the respiratory syncytial virus (RSV) [58-59]. This in agreement with the finding that the naturally occurring flavonoids possess a variable spectrum of antiviral activity against certain RNA (RSV, Pf-3, polio) and DNA (HSV-1) viruses acting to inhibit infectivity and/or replication [60], and this might explain the fact that the clove has been traditionally used in inhibiting food-borne pathogens to treat viruses, worms, candida, and different bacterial and protozoan infections [61]. This finding is harmony with the role of essential oils and their volatile constituents in the treatment of respiratory tract infections (RTIs), showing essential oils as potential

antimicrobials and as anti-inflammatory agents to alleviate symptoms and signs of Respiratory tract diseases (RTDs) including RTIs [23]. Further, the combination *S. aromaticum* aqueous extracts with acyclovir enhancements the antiviral efficacy against herpes simplex virus type 1 (HSV-1), and influenza A virus [62-65]. The viruses can be classified into classes based on structure, enveloped type (e.g.COVID-19) and non-enveloped type (e.g.Norovirus) [66]. Studies have been investigated the antiviral efficacies of plant antimicrobials such as the clove oil on both enveloped and nonenveloped viruses; the results of antiviral effects of oregano oil and clove oil have been greater against enveloped viruses (HSV-1 and Newcastle disease virus) but not against nonenveloped viruses (poliovirus type 1 [PV1] and adenovirus type 3 [67] Several studies have shown that various plant antimicrobials may act directly on enveloped viruses (e.g., HSV-1 and HSV-2), but they do not prevent adsorption of the viruses to host cells [68-71]. Moreover, a study has been found that two phytochemicals, betulinic acid and savinin, which found in the essential oil of cloves [72] has been shown to inhibit post binding entry of severe acute respiratory syndrome (SARS) coronavirus into cells [73], and It has been suggested that that *Syzygium caryophyllatum* oil can be used as a potential source of natural antimicrobial compound possessing strong antioxidant potential [74], as well as a potential anti-breast cancer [73]. Indeed, essential oils have been used for thousands of years, in folk medicine, because of their many different pharmacological properties, including antimicrobial activities [75]. Evidence from TEM imaging has been found that some plant antimicrobials including cloves act directly upon the virus envelope [76, 77]. Numerous studies have been shown that the various compounds in the cloves oil have a strong antibacterial, antiviral, and antifungal properties and can inhibit the growth of molds, yeasts, and bacteria, can kill a number of gram-negative and gram-positive bacteria [17-19, 78]. Indeed, the effects of antibacterial properties of Cloves' extend to all types of bacteria, including the strains which are resistant to antibiotics. These strains included *Staphylococcus aureus* (causes skin acne) and *Pseudomonas aeruginosa* (causes pneumonia). [36,87]. In vitro studies indicated that phenylpropanoids derived from cloves inhibit the mutation within *Salmonella t.* [79], Mutagen is a physical or chemical that changes the genetic material (DNA), eugenol the most derivative of cloves was also demonstrated to protect against DNA damage from free radicals via increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione (GSH), which prevent free radicals from attacking lipids embedded in cell walls [80]. Further studies reported that the isoeugenol and its analogues inhibit NO biosynthesis and iNOS expression in LPS-stimulated RAW cells, may be related to block the phosphorylation of ERK1/2 and p38 kinase, degradation of I- κ B α , and activation of NF- κ B [81]. It has been shown that the clove lower the risks for cardiovascular disease, arterial sclerosis and other disease related to oxidative stress as it is rich in polyphenols derivatives [82-84]. The activity is shown by dose-dependent, reversible vasodilator responses, negative inotropic effects in heart muscle, hypotensive effects and smooth muscle relaxant effects, which are related to the presence of eugenol. [85-87]. Also, a research study has been showed that eugenol in clove oil induced-dilate

arteries while reducing systemic blood pressure. [88], the two chief chemical constituents of clove eugenol and acetyl eugenol have also anti-platelet activities and prevent the formation of a thrombus or a blood clot [89]. Clove has been shown a minor drug interaction with anticoagulant/antiplatelet drugs [90]. Indeed, Thus, It is recommended that the clove should not use along with other blood-thinning medications that means taking clove oil along with other drugs also slow clotting might increase the chances of bleeding such as warfarin [90]. Studies on the effect of overconsumption of cloves may induce side effects, such as the risk of bleeding, decreasing blood sugar levels, and may also induce allergies in some subjects [90-92]. Moreover, the clove oil slow clotting might increase the chances of bleeding is considered an advantage in the treatment of coronavirus, since it has been reported that acute pulmonary emboli associated with novel coronavirus infection [93]. As recent studies described Novel Coronavirus Disease 2019 (COVID-19) is commonly complicated with a hypercoagulable state and increased risk for venous thromboembolism, deep vein thrombosis (D V T) or fatal pulmonary thromboembolism (PTE) [93-100]. Further, COVID-19 has been found in causing a proinflammatory and hypercoagulable state with marked increase levels seen in Lactate Dehydrogenase, Ferritin, C-reactive protein, D-Dimer, and Interleukin levels [93,94]. The clinical studies have also been demonstrated severe coronavirus disease 2019 (COVID-19) that is commonly developed coagulopathy, markedly elevated D-dimer, which associated with poor prognosis of severe COVID-19 [96, 98]. Patients with severe pneumonia induced by SARS-CoV2 had higher platelet count than those induced by non-SARS-CoV2, and only the former with markedly elevated D-dimer may benefit from anticoagulant treatment. [101]. The effect of SARS-CoV2 infection on pulmonary coagulation and fibrinolysis is related to various proinflammatory cytokines, and similar to pneumonia induced by other pathogens [98, 99]. Since, it has been shown that the eugenol in cloves reduced the pro-inflammatory cytokines [39], The pharmacological and clinical studies reported in the present review confirm the therapeutic value of the clove and its oil. It is thought of interest to suggest that the clove oil has an advantage slowing clotting, so, it is highly recommended for treatment of coronavirus complicated with a hypercoagulable state and increased risk for venous thromboembolism, deep vein thrombosis (D V T) or fatal pulmonary thromboembolism (PTE) [93-99]. Thus, the essential oil of cloves could be used to treat the COVID-19 infection and its severe complications associated with such infection. Therefore, It is thought of interest to use clove oils that may protect against coronaviruses (COVID-19). Essential oils can easily reach the upper and lower parts of the respiratory tract via inhalation. Further, due to their antimicrobial and anti-inflammatory potency, they produce an effective treatment in respiratory tract infections (RTIs) [23]. The essential oils of various plants were shown to possess strong antibacterial activity against *Salmonella typhi*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [102]. Clove oil was shown to be the most effective among all the tested essential oils. Clove Oil should only be diffused in well-ventilated places, and diffusing treatments shouldn't exceed more than 60 minutes each time. Clove oil is a powerful substance, so the best is to start with the

smallest dose and observe how the infected patient's body reacts. Then it can slowly increase the amount of the dose and we see how the patient body responds to the treatment. We can use a diffuser to release the essential oil into the air. In reference to the World Health Organization (WHO), the recommended daily dose of cloves is 2.5 mg per 1 kg of body weight [12]. Anything beyond this can cause undesirable effects. Clove oil should only be administered in well-ventilated rooms, and diffusing treatments shouldn't exceed more than 60 minutes each time. Clove oil is a powerful substance, so the best is to start with the smallest dose and observe how the patient's body reacts. Then we can slowly increase the amount of the dose and we see how the patient's body responds. We can use a diffuser to release the essential oil into the air.

In Summary

Clove essential oil may have Nutritional Therapeutic Potential effects due to its various effects, which includes antimicrobial, anti-fungal, anti-viral, anti-inflammatory, cytotoxic, analgesic, anesthetic activities, very potent as antioxidants, and inhibits post binding entry of severe acute respiratory syndrome (SARS) coronavirus into cells. Therefore, essential oil of cloves may be considered the most candidates to combat and control the infection of coronavirus. Besides, slow clotting may also aid in protecting against sudden death seen in some patients infected by Coronavirus (COVID 19), resulting from embolism associated with hypercoagulable formation that indicated by elevated D-Dimer plasma level. Clove Oil should only be diffused in well-ventilated places, and diffusing treatments shouldn't exceed more than 60 minutes each time.

Conclusion:

This case supports my accepted abstract, which suggests that essential oil of cloves is considered the most candidates to combat the coronavirus infection and cure the infected patients. And due to its anti-platelet activities; which prevent the formation of a thrombus or a blood clotting, clove oil protecting against sudden death seen in some patients infected by Coronavirus (COVID 19), due to the acute pulmonary embolism associated with hypercoagulable state and marked increase levels seen in C-reactive protein, and D-Dimer, which considered the main cause of sudden death.

Key learning points and implications for clinical practice:

Clove Oil can be used to treat coronavirus (COVID 19). Essential oil of cloves may be considered the most candidates to combat and protecting against coronavirus (COVID 19) induced sudden death, should only be diffused in well-ventilated places, and diffusing treatments shouldn't exceed more than 60 minutes each time under clinical observation

The Doses should be taken into consideration in the following cases:

1. Diabetics patients should observe the blood sugar and adjust the dose of antidiabetic Drugs.
2. The patients who take anticoagulant/antiplatelet drugs should be monitoring the bleeding time to and adjust the doses of these medications.

3. May induce allergies in some subjects should be observed.
4. The Blood Pressure should be measured may induce hypotension

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***Correspondence to**

Abdulrahim Abu Jayyab

Faculty of Medical and Health Sciences, Emirates
College of Technology, Dhabi, United Arab Emirates

Email: abdulrahim.abujayyab@ect.ac.ae