CHAPTER

Health-promoting activities of clove (*Syzygium aromaticum*) extracts

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1. Introduction

Clove (*Syzygium aromaticum* or *Eugenia caryophyllus*) is a tropical plant in the Myrtaceae family with aromatic flower buds (Ryu et al., 2016). It can be classified as a large-leaved evergreen species, with a height between 8 and 12 m tall and crimson flowers grouped in terminal clusters (El-Shouny et al., 2019). The clove flower buds are initially pale hue; however, they transit to a bright red color when ready to be harvested at 1.5–2 cm long (Singh et al., 2018). The *S. aromaticum* dried flower buds are among the most valuable spices with a long history of applications in pharmaceutical, cosmetic, food, and agricultural industries (Cortés-Rojas et al., 2014). Because of these, cloves are now commercially farmed in different places worldwide, although they are known to be native to Maluku Islands in eastern Indonesia (Lambert et al., 2020). The world's top producers of cloves are Indonesia, India, Malaysia, Sri Lanka, West Indies, Madagascar, Tanzania, and Comoros (Idowu et al., 2021).

The ethnobotanical knowledge of clove provides a bird's eye view to understand a wide range of beneficial health-promoting activities, active biological properties, and unique aromatic structures (Cortés-Rojas et al., 2014). For instance, in Indian and Chinese traditional medicine, clove was documented to treat diverse complications like arthritis, digestive disorders, erectile dysfunction, diabetes, coughs and colds, diarrhea, toothaches, vomiting, memory loss, and nausea (Batiha et al., 2020). Over the last few years, numerous research studies have attempted to provide scientific evidence of the biological activities of clove as a potential drug candidate for these ailments (Cortés-Rojas et al., 2014; Ajiboye et al., 2016; Radünz et al., 2019; Batiha et al., 2020). Some of these studies were focused on the effects of clove toward suppression of microbial growth, improvement of neurological problems, and diabetes symptoms (Singletary, 2014). On the other hand, other preclinical studies supported the contribution of clove to counteract inflammation, inhibit oxidative stress, and oppose processes associated with cardiovascular disease (El-Maati et al., 2016; Mittal et al., 2014). Interestingly, various

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constituents of *S. aromaticum* were analyzed to determine the relationship between pharmacological activity and a diverse array of secondary metabolites toward a wide range of beneficial health-promoting activities, active biological properties, and unique aromatic structures (Mittal et al., 2014; Oliveira et al., 2016). This chapter gives insights into the effects of clove extracts on health promotion and their potential applications.

2. Ethnobotanical knowledge and traditional uses

For centuries, clove and clove essential oil were used in Asian traditional medicine to treat multiple illnesses, including microbial diseases (Singletary, 2014). Some of these illnesses include arthritis, asthma, bronchitis, bruises, burns, cholera, colds, colic, coughs, diarrhea, digestive disorders, earaches, gum diseases, headaches, hypertension, impotence, inflammation of the pharynx, intestinal worms, nausea, malaria, rheumatism, scabies, toothache, tuberculosis, ulcers, vomiting, and wounds (Batiha et al., 2020; Singh et al., 2018).

In a culinary setting, *S. aromaticum* was documented as a flavoring addition to food and alcoholic beverages (El-Shouny et al., 2019). This was due to its ability to preserve property that enables it to inhibit food-borne pathogens like bacterial, fungal, viruses, worms, and protozoan contamination (Suliman et al., 2021). Histological data also revealed that clove was used to make perfumes, oral products, soaps, and detergents in various industrial applications (Ajiboye et al., 2016; Lambert et al., 2020; Mansourian et al., 2014). Furthermore, cloves were added to tobacco, known locally as kretek in Indonesia (El-Shouny et al., 2019). Other uses of clove include insect-repellent and growth-promoter agents. In addition, clove buds have been used as an antiepileptic remedy (Avicenna, 1988). They are traditionally used as spices in almost every household in India, with several therapeutic properties, including asthma, dental, digestive, and other respiratory disorders (Shah et al., 2012). Vicidomini et al. (2021) reported on the traditional therapeutic use of clove in respiratory disorders and its biological activity against several viruses, alongside its well-known anti-inflammatory, immunostimulatory, and antithrombotic properties, signifying its potential to fight COVID-19 disease. Two ethnobotanical studies that have been reported recently have shown the potential uses of cloves in the prevention and treatment of the COVID-19 pandemic in India (Singh et al., 2021) and Morocco (Chaachouay et al., 2021) in combination with other medicinal plants such as basil black pepper, cinnamon, garlic, ginger, and neem.

3. Biological activities

Literature has reported the antibacterial, antifungal, antibiotic, anticarcinogenic, antiseptic, anti-inflammatory, antioxidant, antiviral, antithrombotic, and antiparasitic properties of *S. aromaticum* (Ajiboye et al., 2016; Batiha et al., 2020; El-Maati et al., 2016; Lambert et al., 2020; Radünz et al., 2019). Active compounds in clove, like eugenol [2-methoxy-4-(2-propenyl)phenol] and other phenolic compounds, were believed to be the main contributors to its biological actions (Singh et al., 2018). In addition, cloves are well known for their antiemetic activity to relieve nausea and vomiting and their carminative properties (Singh et al., 2021). For this reason, clove has been considered safe for use in food and medicinal applications for a wide range of beneficial health-promoting activities.

3.1 Antioxidant activity

The clove extracts were documented with high antioxidant activity, both in vitro and in vivo (Cortés-Rojas et al., 2014; Radünz et al., 2019; Singletary, 2014). Clove represents one of the potent antioxidants and radical scavenger foods (Dudonné et al., 2009; Shan et al., 2005), with the ability to inhibit lipid peroxidation and malonaldehyde formation and to scavenge superoxide anions, thus assisting in promoting beneficial health activities (El-Maati et al., 2016). Generally, spice plants are known to have higher phenolic contents, and this is not an exception with clove extracts, whereby there is a strong correlation between the phenolic contents and their antioxidant activities (Kumar et al., 2014; Feng et al., 2021). Several studies attributed the antioxidant properties in clove to its secondary metabolites profile, like flavonoids, hydroxybenzoic acids, hydroxycinnamic acids, gallic acids, hydroxyphenyl propenes, flavonol glycosides, volatile phenolic oils (eugenol, acetyl eugenol, isoeugenol), and tannins (Mittal et al., 2014; Embuscado, 2015; Oliveira et al., 2016). These metabolites had effective reductive potential, free radical scavenging, superoxide anion radical scavenging, and metal chelating activities (Gülçin, 2011) whereby clove buds' aqueous and ethanol extracts inhibited 95% of both superoxide and 2,2- diphenyl-1-picrylhydrazyl (DPPH•) radicals activity (Gülçin et al., 2012).

Because of these, the antioxidant activity of clove can promote beneficial health activities by decreasing oxidative stress, reverting memory, and learning deficits caused by scopolamine in the short and long term (Halder et al., 2011; Mehta et al., 2010). Clove extracts were found to possess high antioxidant activity (DPPH• = 1353%), comparable to synthetic antioxidants against DPPH• radicals and the formation of peroxides (Ivanovic et al., 2013). Hemalatha et al. (2016) reported that the methanolic extract of *E. caryophyllus* showed a maximum antioxidant capacity of 93.2%; meanwhile, the antioxidant activity for the acetone extract was 85.4% and 81.4% for the chloroform extract. The ethanol clove leaf extract's effect on the oxidative stress response has been reported recently in *Schizosaccharomyces pombe,* which directly depends on ROS scavenging activity (Fauzya et al., 2019).

3.2 Antibacterial activity

The oldest study on clove antibacterial activity was reported by Bachmann (1916). Clove extracts were reported to be a potent antimicrobial agent of a variety of bacteria associated with foodborne diseases and human infections that include *Bacillus cereus*, *Escherichia coli*, *Helicobacter pylori*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Propionibacterium acnes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus mutans*, *S. pyogenes*, *Shigella* species, *Salmonella enterica serovar typhi*, and *Vibrio cholera* (Ajiboye et al., 2016; Radünz et al., 2019; El-Shouny et al., 2019). Literature provided evidence that clove extracts were bacteriostatic and bactericidal against most of these pathogens (El-Maati et al., 2016). Cai and Wu (1996) reported that the crude methanol extract of *S. aromaticum* exhibited a superior growth-inhibitory activity against Gram-negative oral pathogens, especially accompanying dental caries and periodontal diseases, e.g., *Porphyromonas gingivalis* and *Prevotella intermedia*. The antibacterial activity of *E. caryophyllus* extracts has been reported against several pathogenic bacteria such as *Klebsiella pneumonia*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Vibrio chlorea* (Feres et al., 2005; Hemalatha et al., 2016).

According to Singletary (2014), clove extracts mechanisms of antibacterial action inhibit quorum sensing (QS) and biofilm formation (BF), disrupt cellular membranes, and reduce the expression of virulence-related *exo*-proteins. Based on these, clove is used to preserve food and treat human infections caused by bacteria, therefore improving health-promoting activities in our daily lives. The bud chloroform, hexane, and methanol extracts of *S. aromaticum* have been evaluated for their anti-QS property by estimating the reduction in quorum-controlled violacein pigment in biomarker strains of *Chromobacterium violaceum* CV026, *E. coli* pSB1075, and *Pseudomonas aeruginosa* PA01, suggesting clove buds extracts potential for anti-infective drugs development (Krishnan et al., 2012). Furthermore, the anti-virulence potential of partially purified *S. aromaticum* bud extracts against two clinically isolated *Pseudomonas aeruginosa* (RRLP1 and RRLP2) from patients with catheter-associated urinary tract infection has been reported by Rathinam and Viswanathan (2018). They have used bioactivity-guided partial purification, size exclusion chromatography, and GC-MS analysis to confirm that eugenol is the major bioactive compound with well-known medicinal properties (Nisar et al., 2021). QS is a well-known cell communication, and regulatory system bacteria use to signal their communications to the external environment. It influences antibiotic synthesis, bacterial growth and proliferation, biofilm formation, environmental adaptation, and virulence factor(s) production (Yang et al., 2020).

3.3 Antiviral activity

Crude extracts of clove were documented in vitro effective against human viruses like herpes simplex virus and hepatitis C virus strains (Singletary, 2014; Batiha et al., 2020). According to Cortés-Rojas et al. (2014), *S. aromaticum* attacks viral DNA synthesis by inhibiting the viral DNA polymerase. Therefore, the clove can enhance health-promoting activities by treating viral diseases such as sores around the mouth, lips, genitals, or rectum, hepatitis C, and some cancers such as liver cancer and lymphomas in humans. Furthermore, Batiha et al. (2020) reported a synergistic action between acyclovir and *S. aromaticum* extract with an important impact on the inhibition of viral replication.

Eugeniin was isolated from *S. aromaticum* has been identified as antiherpes simplex virus compound at 5 μg/mL concentration (Kurokawa et al., 1998; Singh et al., 2021), and its inhibitory action on the viral DNA synthesis as a selective inhibitor of the HSV-1 DNA polymerase and another well-known eugenol for its action on viral replication and reducing infection (Kurokawa et al., 1998).

A Feline Calicivirus (FCV) was used as a surrogate for human norovirus to test the aqueous extract of clove to test its antiviral activity. Clove extract scored similar antiviral activity to pure eugenol even though at a lower level (Aboubakr et al., 2016). Mehmood et al. (2020) synthesized silver nanoparticles using the aqueous extract of *S. aromaticum* flower buds, and they reported their novelty and efficacy against Newcastle Viral Disease (NDV) in vitro and embryonated eggs. Vicidomini et al. (2021) reported the anti-COVID-19 molecular basis and the therapeutical potential of *S. aromaticum*. Mputu Kanyinda (2020) reported a protocol that can help in the prevention and treatment of the early stages of COVID-19 disease using cloves, whereby a decoction is prepared via boiling cloves in water with other plant materials (*Eucalyptus globulus, Cymbopogon citratus*, and *Zingiber officinale*) for 15 min. The presented protocol further explained that it could be used either via inhalation of the released active volatile compounds for 5 min or taken as a drinkable decoction.

3.4 Anti-inflammatory activity

S. aromaticum extracts contain a diverse array of phenylpropanoids, like eugenol, which have a variety of pharmacologic activities, including anti-inflammatory action (Barboza et al., 2018). A study by Daniel Apparecido et al. (2009) has demonstrated that eugenol from clove has antioxidant and anti-inflammatory capacities; thus, it was more effective in reducing inflammation.

Literature (Barboza et al., 2018; Daniel Apparecido et al., 2009; Han and Parker, 2017; Sugihartini et al., 2019) reported that this could be achieved either:

a) Modulates the macrophage functions and regulates negatively the inflammation,
b) Decreased the in vitro and in vivo leukocytes migration in response to chemotactic factors by the modulation of rolling and adherence to perivascular tissue,
c) Modulates the bone remodeling,
d) Inhibition of enzymes and oxidative processes, for instance, inhibition of pro-inflammatory cytokines in pre-inflamed human dermal fibroblast cells.

Because of these, a diverse array of secondary metabolites in clove has the potential to boost health-promoting benefits and consequently improve the quality of life. Hypersensitivity was treated with the aqueous extract of *S. aromaticum* flower bud (Kim et al., 1998). In animal model (rate), the aqueous extract inhibited compound 48/80-induced systemic anaphylaxis with an $IC_{50} = 31.2$ mg/kg, i.p., as well as it inhibited the local immunoglobulin E (IgE)-mediated passive cutaneous anaphylactic reaction with an $IC_{50} = 17.7$ mg/kg, i.v. and $IC_{50} = 19.8$ mg/kg, p.o. They emphasized that aqueous clove extract inhibits immediate hypersensitivity by inhibiting histamine release from mast cells in vivo and in vitro (Kim et al., 1998). Lipopolysaccharide (LPS)-induced lung inflammation was relieved through treating with both eugenol and whole clove aqueous extract (WCAE) via reducing tumor necrosis factor-alpha (TNF-α) and inhibiting the signaling of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$_k$B), alongside alveolar damage improvement (Magalhães et al., 2010; Chniguir et al., 2019).

3.5 Antifungal activity

Clove extracts (methanol, ethyl acetate, *n*-hexane, and diethyl ether) had effective inhibitory activity against fungi causing diseases such as vaginal candidiasis from *Candida* species (*C. albicans*, *C. glabrata*, and *C. tropicalis*) and *Trichophyton* species, both in vivo and in vitro (Khan et al., 2009; Singletary, 2014; Gonelimali et al., 2018; Yassin et al., 2020). For example, Yassin et al. (2020) reported that the minimum inhibitory concentration (MIC) of the *S. aromaticum* ethyl acetate extract was 250 μg/disc against *C. tropicalis* and 500 μg/disc against *C. albicans* and *C. glabrata*, while the minimum fungicidal concentration (MFC) was 0.5 mg/disc against *C. tropicalis* and 1 mg/disc against *C. albicans* and *C. glabrata*.

Various mechanisms of antifungal action have been reported, such as arresting the cell cycle, preventing biofilm formation, suppressing virulence factors, and disrupting the architecture of cell envelopes (Cortés-Rojas et al., 2014; Radünz et al., 2019). These actions were likely due to eugenol, the primary antifungal agent in clove (Mittal et al., 2014). In light of this, secondary metabolites in cloves promote health benefits by inhibiting the growth of fungal pathogens that cause human diseases and food poisoning. For example, the *S. aromaticum* and *Elettaria cardamomum* extracts demonstrated a protective effect on black tea by inhibiting the growth of *Xerophilic aflatoxigenic* fungi and advocated adding these extracts as preservation and flavoring agents in marketed black tea (Al-Sohaibani et al., 2011). Furthermore, a recent study on the aqueous extract of clove demonstrated protective effects on an animal model of pyelonephritis (Nassan et al., 2015), which is a recent kidney inflammation in COVID-19 patients that had been reported (Su et al., 2020).

3.6 Anticancer activity

Several studies reported the anticancer activities of clove extracts (Banerjee et al., 2006; Arung et al., 2011; Dwivedi et al., 2011; Kumar et al., 2014; Liu et al., 2014). In a mouse model of benzo[*a*]pyrene (BP)-induced lung cancer, an infusion prepared from clove has been shown to inhibit the incidence of hyperplasia and dysplasia (Banerjee et al., 2006). In addition, the ethanolic and ethyl acetate extracts of *S. aromaticum* were effective in inhibiting BEL-7402 liver cancer cells, HeLa cervical cancer cell line, ovarian cancer (SKOV-3 cell line), pancreatic cancer (PANC-1 cell line) (Liu et al., 2014), esophageal cancer (TE-13 cell line), and prostate cancer (DU-145 cell line) (Dwivedi et al., 2011). Secondary metabolites, like β-caryophyllene and tannin compounds such as eugeniin and tellimagrandin, were identified from cloves to possess anticancer actions (Arung et al., 2011). Aisha et al. (2012) investigated the anti-breast cancer effect of *S. aromaticum* extracts (bark, leaves, and stem) on the MCF-7 and MDA-MB-231 and prepared betulinic acid fraction by crystallization from clove leaves. They further reported that the stem extract induced apoptosis in MCF-7 cells by activating caspase 3/7 (Aisha et al., 2012).

Liu et al. (2014) reported the anticancer activity of ethyl acetate extract of cloves against colon cancer (HT-29) cells xenograft model with significant cell growth inhibition. The reported mechanism includes arresting the cell cycle, inducing apoptosis, increasing proteins expression, and decreasing cell cycle-regulated proteins. However, the same extract has shown a toxic effect against the non-tumorigenic colon 841 cells (Liu et al., 2014).

Vijayasteltar et al. (2016) have confirmed the safety of clove bud extracts in Wistar rats, whereby they reported the absence of toxicological changes in behavioral observations, body weights, organ weights, ophthalmic examinations, feed consumption, hematology, urinalysis, and clinical biochemistry parameters compared to the untreated group of animals confirming the safe use of clove bud extracts as dietary supplements. Fadipe et al. (2016) tested an isolated oleanoleic acid and its derivative, 3-*O*-Acetyl-Oleanolic acid (OAA), from the flower buds of *S. aromaticum* against both human embryonic kidney (HEK293) and hepatocellular carcinoma cell lines (HepG2) using the MTT assay with both compounds, exhibited LC_{50} of ˃300 μg/mL suggesting that these compounds may not be toxic at low to moderate concentrations and their potential to be used in the treatment of tuberculosis and malaria. In a preliminary in vitro screening against the human ovarian cancer cells (A2780) using MTT assays, Ryu et al. (2016) reported that the ethanol extract (70%) of the flower buds of *S. aromaticum* displayed a significant inhibitory activity with an IC_{50} value of 22.6 μM. Kubatka et al. (2017) reported the antineoplastic effects of clove buds in the model of breast carcinoma and have shown that the ethanol extract was able to decrease the MCF-7 cell survival through dose- and time-dependent mechanism via the induction of S phase cell cycle arrest and apoptosis (Liu et al., 2014). Other cell lines of MCF-7 and MDA-MB-231 were used to evaluate the anticancer activities of clove extracts (ethanol, oil, and water) and exhibited cytotoxic effects toward MCF-7 cells. However, only water and oil extracts were toxic toward MDA-MB-231 cells, whereby this effect was attributed to the induction of cancer cell death via apoptosis (Dwivedi et al., 2011). Oyedeji et al. (2014) reported two semisynthetic compounds, 3-acetoleanolic hydrazide and 3-acetoxyoleanolic hydrazine, derived from ethyl acetate fraction of *S. aromaticum* and have shown cytotoxic activity against MCF-7 cells. Ali et al. (2019) reported an in vitro inhibition of cell migration and cellular apoptosis caused by four chloroform extract fractions of *S. aromaticum* using human A549 and H1299 lung cancer cell lines. They reported inhibition of wound closure/cell migration of A549 and H1299 and apoptosis induction of H1299.

The anticancer activities of clove extracts were reviewed by Chua et al. (2019). The World Health Organization (WHO) stated 2.5 mg/kg body weight as the acceptable daily amount of clove in humans (Idowu et al., 2021). Yassin et al. (2020) tested the toxicity of different clove extracts (diethyl ether, ethyl acetate, methanol, and *n*-hexane) against the HUH7 cell line using the 3-(4,5-dimethylthiazol)-2,5-diphenyl tetrazolium bromide (MTT) assay. They reported that diethyl ether clove extracts showed the lowest toxic effect against the HUH7 cell line (IC_{50} = 62.4 μg/mL), while higher toxicity was obtained with the methanol extract (IC_{50} = 24.1 μg/mL); meanwhile, the *n*-hexane (IC_{50} = 42.1 μg/mL) and ethyl acetate (IC_{50} = 33.6 μg/mL) extracts of clove exhibited moderate toxicity (Yassin et al., 2020). In conclusion, the water extract of *S. aromaticum* at lower doses may be safe; meanwhile, ethanol extract and essential oil, even at minimal concentrations, possess toxicity (Chua et al., 2019).

3.7 Antimycobacterial and antiplasmodial activities

Fadipe et al. (2016) isolated oleanoleic acid from the flower buds of *Syzygium aromaticum*. Then, they synthesized 3-*O*-acetyl-oleanolic acid from oleanoleic acid and reported the antiplasmodial and antimycobacterial activities of both (oleanoleic acid and its derivative) against *Plasmodium falciparum* (Chloroquine Sensitive Strain) NF54 and *Mycobacterium tuberculosis* H37Rv, respectively, with IC_{50} of 4.3 μg/mL against *P. falciparum* and IC_{50} of 0.042 μg/mL against *M. tuberculosis* for OA (Fadipe et al., 2016).

3.8 Antidiabetic activity

Recently, the antidiabetic potential of *Syzygium* sp. has been reviewed and reported by Zulcafli et al. (2020). The polyphenol-rich extract of *S. aromaticum* in a dose-dependent manner showed better inhibition of α-glucosidase than α-amylase. It exhibited potential antioxidant activities and inhibition of Fe(2+)-induced lipid peroxidation in rat pancreas in vitro (Adefegha and Oboh, 2012). The EtOH extract clove flower buds were reported to have a significant suppression effect on increased blood glucose levels in type 2 diabetic KK-A(y) mice (Kuroda et al., 2012). Two main compounds of dehydrodieugenol and dehydrodieugenol B have shown potential peroxisome proliferator-activated receptor (PPAR)-γ ligand-binding activities in a GAL4-PPAR-γ chimera assay; meanwhile, the major compound in the EtOH extract, oleanolic acid, reported a moderate activity (Kuroda et al., 2012). Oleanolic acid and maslinic acid from the *S. aromaticum* extract were reported to improve glucose homeostasis and suppress postprandial hyperglycemia in diabetic rats through the inhibition of carbohydrate hydrolysis, glucose transporters reduction, and glycogen synthesis in the gastrointestinal tract (Khathi et al., 2013a,b). Another study by Sompong et al. (2016) reported beneficial effects (antihyperglycemic and antihyperlipidemic) of *S. aromaticum* extracts and its triterpene constituents and their ability to reduce the formation of cholesterol micelles in vitro. The aqueous extracts of clove and other culinary/medicinal plants have shown an insulin-like biological activity in vitro model (Broadhurst et al., 2000). Shukri et al. (2010) reported on the effects of *E. aromaticum* on some target organs of Streptozotocin (STZ or N-ethylnitrosocar-bamoyl-D-glucosamine)-induced oxidative stress in diabetic rats and confirmed that cloves could protect the heart, liver, and lens of diabetic rats. *S. aromaticum* extract was reported to regulate energy metabolism in C2C12 myocytes and has been shown to perform comparable insulin effect through significant reduction in blood glucose levels in animal models (Tu et al., 2014).

The in vitro and in vivo effects of the crude extracts and chemical components of cloves that attributed to their antidiabetic, lipid-lowering, and anti-obesity activities has been reported by Habtemariam (2019). Ladurner et al. (2017) reported that the flower buds extracts of *S. aromaticum* activated the bile acid receptor, Takeda G protein-coupled receptor 5(TGR5) at 100 mg/mL with a stronger effect than the positive control lithocholic acid (LCA) at 10 mM. In hepatocytes and hepatoma cells, *S. aromaticum* extracts act like insulin through their ability to reduce phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase) gene expression (Prasad et al., 2005). Clove extracts can perform a comparable effect to insulin by significantly reducing blood glucose levels in animal models (C2C12 myocytes) and demonstrating that it could significantly increase glucose consumption (Tu et al., 2014). Clove extracts increase the phosphorylation of AMP-activated protein kinase (AMPK), as well as its substrate, acetyl-CoA carboxylase (ACC) as well as transcriptionally regulates sirtuin 1 (SIRT1) and PPARγ coactivator 1α (PGC1α) genes that are involved in metabolism. Furthermore, clove extracts in a dose-dependent can increase muscle glycolysis and mitochondrial function (Tu et al., 2014).

3.9 Anticonvulsant activity

Pharmacological studies demonstrated the anticonvulsant and anti-stress properties of eugenol (Dallmeier and Carlini, 1981). Kamkar Asl et al. (2013) reported the analgesic effects of aqueous and ethanol extracts of clove buds in mice whereby, the administration of three doses (50, 100, and 200 mg/kg) of the ethanol extract increased the maximal percent effect (MPE) in the animal groups and suggested a similar opioid system in the analgesic effect for clove extracts. Traditionally, clove was served as an analgesic agent for treating dental pain (Diaz and Sembrano, 1985).

3.10 Hepatoprotective activity

An in vivo study revealed the significant role of eugenol in protecting male rats during exposure to aflatoxins-induced hepato, nephrotoxicity, and oxidative stress (Abdel-Wahhab and Aly, 2005). In an animal model study using the liver in a hypercholesterolemia rabbit, the methanol extract of clove leaves has been reported to stabilize enzymes that are essential for oxidative stress response (Cu-SOD and Zn-SOD); at the same time, it reduces the malondialdehyde (MDA) which is known as one of the final products of polyunsaturated fatty acids peroxidation in cells (Gaweł et al., 2004; Munisa et al., 2015).

Hepatoprotective activity of eugenol-rich fraction of *S. aromaticum* was reported by Ali et al. (2014), which can protect the liver against injury. They reported its action via *S. aromaticum* eugenol-rich fraction's ability to reverse the biochemical and histopathological changes in liver cirrhosis induced by thioacetamide (0.03%) and inhibit hepatic cell proliferation. Ding et al. (2017) reported a FASN inhibitor-alcohol extract of clove (AEC) using a fast microplate method whereby the AEC supplementation could significantly reduce body weight and abdominal adipose tissue weight, lowered lipid accumulation in the liver and epididymal adipose tissue when it was compared with the HFD control group. In addition, they confirmed that the AEC could regulate the content of total triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) in the serum lipid profiles. Rahman Alizadeh et al. (2017) investigated and reported that dietary administration of clove bud powder to hens given a low n-6 to n-3 ratio diet could modulate serum antioxidant indices and enzyme alterations in birds and improve the heightened susceptibility of hepatocytes to lipid peroxidation. Abdelrahman et al. (2018) reported that clove in combination with honey has antioxidant activity with the ability to reverse liver fibrosis via cytokines reduction (TGF-β, TNF-α, and EGF) and modulation of liver function enzymes including ALT, AST, and GGT activities (58.5, 56; 119, 121, and 6.1; 6.3) in comparison to the CCl_4 control group (97, 191, and 10.1).

3.11 Skin protective effect

Hwang et al. (2018) reported on the *S. aromaticum* role in resisting skin photoaging whereby a 50% ethanol extract of *S. aromaticum* and eugenol was tested for antiaging effects of UVB-irradiated normal human dermal fibroblasts (NHDFs) and hairless mice. The ethanolic extract of *S. aromaticum* significantly improved procollagen type I and elastin levels through TGF/Smad signaling. They further reported the histopathological effect of *S. aromaticum* extract and its ability to reduce wrinkles and increase filament aggregating protein (filaggrin), which is known to repair the skin barrier function and improve the skin's hydration.

3.12 Neuroprotection effect

In Ayurvedic medicine, clove oil has been used as a cognitive enhancer and nerves stimulant. The treatment of eugenol in the animal model led to improved cognitive impairment under oxidative stress conditions and overall improvement of the nervous system (Nunomura et al., 2001). The ethanol extract of *S. aromaticum* has been reported to possess a neuroprotective activity in Alzheimer's disease model via maintaining oxidative balance through Silence information regulator 1 (SIRT1) pathway whereby *S. aromaticum* extract was able to scavenge ROS and elevate the antioxidant enzymes percentage, alongside with the activation and elevation of the level of SIRT1 and downregulation of γ-secretase level (Shekhar et al., 2018a). SIRT1 is a member of the sirtuin family that targets histones and many nonhistone proteins and takes part in several physiological functions, including antioxidative effects and mitochondria protection (Khan et al., 2015), autophagy activation (Shekhar et al., 2018b), and neuroinflammation inhibition (Kauppinen et al., 2013) and more recently, their upregulation can slow down the progression of Alzheimer's disease (Corpas et al., 2017). Shekhar et al. (2018a) reported that *S. aromaticum* possesses a maximum level of oxygen radical absorbance capacity (ORAC) as it was reported by the National Institute on Aging in the National Institutes of Health (NIH) as per the published data by the United States Department of Agriculture (USDA). Another neuro-function of *S. aromaticum* is the stimulation of nerves due to vata pacification (Halder et al., 2011). They further emphasized that *S. aromaticum* can be considered an anticholinesterase (ACh) agent for the management of cognitive ailments such as Alzheimer's disease (AD) to make up for ACh deficiency during AD (Shekhar et al., 2018a). The anticholinesterase activity of the methanol extract of clove, eugenol, and clove oil has been reported with eugenol possessing higher inhibition of acetylcholinesterase

(AChE) and butyrylcholinesterase (BChE) than clove extract and its oil (Dalai et al., 2014). *S. aromaticum* can enhance catalase's catalytic activity in a dose-dependent manner and maintain the oxidative balance in cells under oxidative and proteotoxic stress by maintaining the level of ROS and oxidative enzymes that may lead to down-streaming the effect of SIRT1 pathway (Shekhar et al., 2018a) which promotes neuroprotection via the prevention of oxidative stress (Braidy et al., 2012).

3.13 Immunomodulation effects

Active compounds such as demethyldiisoeugenol that are responsible for clove extracts have been shown to modulate some of the immune responses such as anti-inflammatory effects (Ko et al., 1995), suppression of T cell cellular immunity, and enhancement of humoral immune responses with modulation of cytokine pattern and Th2 responses and humoral immunity cytokines acceleration (Dibazar et al., 2014). Dibazar et al. (2014) further indicated that researchers who studied clove benefits in traditional medicine settings proposed that its effects could be centralized on the immune system and its components. Previous studies on eugenol and its structural analog, isoeugenol by Park et al. (2007), reported the inhibition of IL-2 gene expression (typical T cell cytokine). Isoeugenol and its analogs (eugenol and allylbenzene) clove ingredients were reported to inhibit nitric oxide production and induce nitric oxide synthetase expression in a dose-dependent manner LPS-stimulated RAW 264.7 murine macrophages (Choi et al., 2007). The water-soluble part of the hydroalcoholic extract of clove demonstrated pro-inflammatory cytokines (IL-1beta and IL-6) production by macrophages of BALB/c mice, with eugenol being the major component of the clove extract responsible for the cytokine inhibition (Rodrigues et al., 2009).

Grespan et al. (2012) reported that eugenol in the mice model could reduce IFN- secretion in accordance with its ability to decrease the secretion of IFN- from T cells. The same compound (eugenol) enhanced the IL-10 cytokine production (Grespan et al., 2012). Bachiega et al. (2012) investigated the effect of clove water extract administration over a short term to BALB/c mice on T helper 1 (Th1, IFN-, and IL-2) and Th2 (IL-4 and IL-10) cytokine production with no influence on the Th1/Th2 cytokine balance been observed. They further confirmed that clove immunomodulatory/anti-inflammatory effects could be attributed to the LPS inhibition alongside another possible mechanism of action for eugenol involving suppressing the nuclear factor-κB pathway (Bachiega et al., 2012). Dibazar et al. (2015) reported the immunomodulatory effects of clove constituents isolated from the aqueous and ethanol extracts on the macrophages via in vitro evaluations. They demonstrated that clove extracts do not have a specific cytotoxic activity that impacts macrophage cytokine activity in a dose-dependent pattern.

4. Other health benefits

The aphrodisiac activity of 50% ethanol extracts of *S. aromaticum* and nutmeg in male mice yielded an enhanced sexual behavior in male Swiss mice with no adverse effect (Tajuddin et al., 2003). Hemphill (2006) reported on the culinary uses of clove, including meat flavoring, especially ham, stewed fruits, pickles, curries, pies, salads, and some spicy alcoholic beverages. They also have been added as food antioxidants to mayonnaise (Chatterjee and Bhattacharjee, 2015) and meat sausages (Zhang et al., 2017). Clove is used as a spice, and its extracts have a remarkable aroma, flavor, and vast beneficial health characteristics; therefore, they have been utilized in the food industries (Ramadan et al., 2013;

Idowu et al., 2021). Radha Krishnan et al. (2014) reported that the inclusion of clove extracts could lead to efficient oxidation-reduction, sensory properties enhancement, and prolongation of meat products' shelf life at refrigeration conditions during storage. Takahashi et al. (2004) reported on the ability of cloves to mask spoiled food smells via the interference in the odor maps in the olfactory bulb of the forebrain. Scientific literature has supported the health benefits of clove toward reducing microbial growth, improving nutrition values, diabetes symptoms, and neurological problems (Cortés-Rojas et al., 2014; Singletary, 2014). Studies have documented the contribution of *S. aromaticum* to counteract inflammation, oppose processes associated with cardiovascular disease, and inhibit oxidative stress (Batiha et al., 2020; Gülçin, 2011). Secondary metabolites in clove, such as eugenol, are likely to contribute to these actions and other health-promoting activities (Oliveira et al., 2016).

The pediculocidal activity using the *S. aromaticum* flower bud hexane extract against *Pediculus humanus capitis* was examined by direct contact and fumigant toxicity (closed- and open-container methods) bioassay (Bagavan et al., 2011). They reported that chavibetol (5-allyl-2-methoxyphenol) is the major compound (58.8%) of clove flower bud hexane extract. The flower buds of *S. aromaticum* are relieving flatulence, stimulant, natural anthelmintic, and antimalarial and used for dyspepsia, gastric trouble, nausea, and vomiting, as well as it is used to relieve toothache (Alqareer et al., 2006; Tanko et al., 2008; Gowri and Manimegalai, 2019). Chaula et al. (2019) demonstrated that clove extracts gave higher retention of *omega*-3 fatty acids and lower concentrations of secondary lipid oxidation products in comparison to the seaweed; *Kappaphycus alvarezii* showing its feasibility of pretreating whole, *omega*-3-rich small sardines (*Rastrineobola argentea*) with natural clove antioxidants to prevent lipid oxidation during preservation of the small sardines via sun drying. Saeed et al. (2021) reported that clove extracts were used as feed additives to manipulate rumen fermentation through its main bioactive compound, eugenol, via the propionate production increment, acetate and methane production reduction, altering the proteolysis pattern and peptidolysis, and the deamination of the amino acid in the rumen. Positive effects were also reported regarding cloves to broiler chicken diets on the performance, carcass, and production traits of broilers (Boyraz and Ozcan, 2006; Salman and Ibrahim, 2012; Suliman et al., 2021).

5. Conclusions

Clove is considered a viable plant with several agricultural, cosmetic, food, and pharmaceutical applications. Regardless of its pleasant aroma and nutritional values, literature has identified the anticancer, antidiabetic, anti-inflammatory, antinociceptive, antibacterial, antifungal, antiprotozoal, antioxidant, and antithrombotic properties of *S. aromaticum*. Clove extracts possess potent antibacterial and antioxidant activities; therefore, they have great potential to be used as natural food preservatives. In addition, clove is one of the richest sources of phenolic compounds such as eugenol, gallic acid, and tannins, with great potential for pharmaceutical and cosmetic applications. Due to its numerous pharmacological activities, clove can be considered a potential drug candidate for health-promoting activities.

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