Therapeutic Interventions of Cardamom in Cancer and Other Human Diseases

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Authors’ contributions

This work was carried out in collaboration among all authors. Author SQ conceptualized and wrote the first draft of the manuscript. Authors MAK and SMA reviewed the literature on the chemical composition and biological activities. Authors MS and AYA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Cardamom, a dietary phytoproduct, is the most popular spice in the world, and its beneficial health properties are gaining more and more attention. Small cardamom [Elettaria cardamomum (L.) Maton. (Family: Zingiberaceae)] has been used for traditional therapeutic applications, including the management of asthma, teeth and gum infections, cataracts, nausea, diarrhea and heart, digestive and kidney disorders. Numerous studies have demonstrated the biological activity of cardamom and its polyphenols, including antioxidant, anti-tumor, anti-inflammatory, and metabolic control. 1,8-cineole, and its esters, Limonene, α-terpinyl acetates are the most abundant bioactive constituents in cardamom. They are known to be multifunctional compounds that can be efficient in the prevention or treatment of various types of cancers, Cardiovascular diseases, chronic inflammatory conditions, digestive disorders, as well as infectious bacterial and fungal diseases. In this review, we summarized the up-to-date research and underlying molecular mechanisms of cardamom and its active components.

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1. INTRODUCTION

Spices and medicinal plants play an essential role since time immemorial, in the management of various diseases, including cancer and cardiovascular diseases [1,2]. Cardamom belongs to *Elettaria* and *Amomum* genera of the ginger family Zingiberaceae. Both forms have small spindle-like seedpods, but *Elettaria* is more modest and light green, whereas *Amomum* is big and blackish-grey in appearance.

*Elettaria cardamomum* (L.) Maton is generally referred to as small cardamom or green cardamom and is cultivated and grown in some Asian countries, including Nepal, Costa Rica, Guatemala, Indonesia, Sri Lanka, India, Tanzania, and Mexico [3]. It is also recognized as "Hel" in gulf countries like Kuwait, Saudi Arabia, United Arab Emirates, Iran, Iraq, and other regions [4]. *Elettaria cardamomum* is botanically named originated from the Tamil word "Elettari" which refers to cardamom seed [5].

Among several prominent spices, cardamom (*Elettaria cardamomum* (L.) Maton), commonly called as the "Queen of Spices" is a distinctive aromatic spice that is often used in Eastern, Arab, Scandinavian and even Western cuisines for its distinct aroma. It is a pioneer in foodstuffs and continues to have tremendous commercial value for finding a way into the dietary habits of millions of people worldwide [6]. Cardamom seeds have multifunctional properties. They have aromatic, sweet, cooling cardiac, carminative, deodorant, digestive, diuretic, expectorant, purgative, stimulant, thirst reliever, and tonic properties. Moreover, it is useful in asthma, burning sensation, cold and cough, diseases of bladder and kidney, flatulence, heart weakness, indigestion, scanty urine, and piles [7].

In recent years, a huge interest in the abundant health-promoting properties of cardamom had led to numerous pharmacological studies (in-vitro and in-vivo) as well as the identification and quantification of various classes of phytochemicals [8-11]. The protective effects of cardamom against chronic diseases are ascribed to bioactive non-nutrient called phytochemicals. Phytochemicals have gained increased interest among several investigators due to their antioxidant activity, cholesterol-lowering properties, and other potential health benefits, including chemoprevention of cancer and cardiovascular diseases [8,12].

Cardamom has exhibited anticancer [13] gastroprotective [14], antihypertensive [15], anti-inflammatory [16] and immunomodulatory [17] antifungal and antibacterial properties [18] in numerous experimental studies (Fig. 1).

The main ingredients of cardamom are 1,8-cineole (representing 50% or more), limonene, terpineol, citronellol, -phellandrene, sabinene, myrcene, borneol, terpenyl acetate, and neryl acetate camphor, terpinene, p-cymene, terpinolene, linalool, and α-Pinene [19]. In this review, we summarized the beneficial health properties of cardamom and also listed the bioactivities of the ingredients of cardamom and the possible mechanisms of its primary elements.

2. CANCER PREVENTION AND ANTI-TUMOR EFFECTS OF CARDAMOM

Cancer is the most widely recognized reason for human mortality [20-22]. Plant-derived natural products currently comprise a significant proportion of commercially available antineoplastic drugs. Chemoprevention with food phytochemicals is meanwhile considered as one of the most critical strategies for cancer control [23,24].

Acting on multiple targets in the cellular signaling pathways and the regulation of critical molecules in carcinogenesis by food phytochemicals and natural products was effective in Counteracting, preventing, delaying, or reducing the risk of cancer [25]. As suggested by experimental evidence and phytochemical composition, cardamom can have potential health benefits against many types of cancer.

Anticarcinogenic effects of the essential oil of cardamom are revealed through in vitro studies. As it inhibited the damage to adult DNA by aflatoxin B1 in a microsomal enzyme intermediated reaction [26]. This could be attributed to bioactive components in an essential oil that has possible anti-cancer functions. Bhattacharjee et al. [13] stated that the phytochemicals components of cardamom oil such as limonene and 1,8-cineole had shown a preventive effect against cancer progression.
Fig. 1. Shows multiple benefits of cardamom that can be beneficial for human health

The activation of the detoxification enzymes is a basic feature in the impacts of cardamom in antagonizing diverse chemical-induced carcinogenesis. The detoxifying enzyme system plays a critical role in determining the final destiny of carcinogens/procarcinogens and its consequent effect on carcinogenesis [27]. Regulation of different detoxifying enzymes is mediated by the transcription factor Nrf2 (nuclear factor erythroid 2–related factor 2) binding to the antioxidant response element (ARE)/electrophilic response element (EpRE) located in the promoter region of related genes to trigger the expression of antioxidant and cell-protective genes [28]. Ingestion of cardamom has been shown to rescue the nuclear expression of Nrf2 in the mouse skin of DMBA-treated mice, which suggests that the cardamom treatment might trigger activation of Nrf2 despite the deleterious effects of DMBA, to maintain cellular homeostasis during oxidative stress. In addition to Nrf2 activation, oral administration of cardamom to 7,12-dimethylbenz[a]anthracene (DMBA)-treated mice up-regulated the phase II detoxification enzymes, such as glutathione-S-transferase, glutathione peroxidase glutathione reductase, superoxide dismutase, and catalase as well as reduced glutathione via activation of nuclear factor erythroid-2-related factor 2 transcription factor in mice and blocked NF-kB activation and down-regulated cyclo-oxygenase-2 expression [29]. It has been shown that cardamom extract or geraniol as a component of cardamom oil was highly effective in preventing diethylnitrosamine (DENa)-induced hepatocellular carcinoma through blocking oxidative stress, decreasing pro-inflammatory cytokines such as TNF-α and IL-1β and NF-kB, and also decreasing ornithine decarboxylase (ODC) [30]. The potential for cardamom extract chemoprevention may be attributed to the synergistic influence of the Phytomolecules in the extract. Many anticarcinogenic compounds that could serve as potential NF-kB inhibitors are now being developed for anti-cancer therapy [31].

We earlier reported the strong potential of the anti-tumor potential of cardamom in a mouse skin model of carcinogenesis. Ingestion of cardamom delayed skin tumorigenesis, reduced incidence, and the number of skin papilloma and size in DMBA-treated mice through activation of antioxidant enzymes, detoxification enzymes, and decreased lipid peroxidation [32]. Consistent with the results in the skin cancer model, cancer chemopreventive potential of an aqueous
Cancer Foundation (MCF results in the maximum inhibition of Michigan Cardamom seed oil concentration of 500 μg / mg been reported to significantly increase in vitro. Eugenol, an active component of cardamom, has significantly increased the level of lymphocytes, CD4 +, and CD8 + in a dose-dependent manner. Cardamom extracts increase the cytotoxic activity of natural killer cells significantly, suggesting their possible anti-cancer. Raksamiharja et al. [38] reported that in doxorubicin-treated rats, cardamom oil has significantly increased the level of lymphocytes, CD4 +, and CD8 + in a dose-dependent manner. Eugenol, an active component of cardamom, has been reported to significantly increase in vitro proliferation of cell-mediated lymphocytes [39]. Cardamom seed oil concentration of 500 μg / mg results in the maximum inhibition of Michigan Cancer Foundation (MCF-7) cells, an Estrogen Receptor (ER)-positive cell line that increases abnormal monolayers cell growth. Cardamom contains phytochemicals such as IC3 (indole-3-carbinol) and DIM diindolylmethane) that promote increased development of various white blood cells, including natural killer cells and also inhibit hormone receptor-positive breast cancer cells. Cardamom chemopreventive activity (20 mg/ml) results in a decreased activity of cancer in the cell lines MCF and HEP-G2 [40].

Phytochemicals such as limonene and 1,8-cineole have been shown to be protective against cancer progression and to inhibit cyclooxygenase-2 and cytochrome P450 activities and to get many signal transduction molecules down-regulated [41].

3. EFFECTS OF CARDAMOM ON CARDIOVASCULAR DISEASES

Cardiovascular disease (CAD) is becoming the world's main cause of death. Cardiovascular disease is related to numerous factors such as elevated serum total cholesterol, decreased LDL, and increased LDL oxidation, increased platelet aggregation, high blood pressure, and smoking [42-43].

In clinical trials, patients with primary stage 1 hypertension provided with 3g powdered cardamom for 12 weeks achieved a significant reduction in blood pressure along with fibrinolysis and enhancing antioxidant properties that can be beneficial as a dietary supplement to these patients [15,44]. Cardamom has two mechanisms to lower blood pressure: through the cholinergic pathway and the control of calcium ion channels. In experimental animal studies, Lahlou et al. [45] measured cardiovascular function of 1,8-cineole and reported intravenous bolus injections of 0.3–10 mg/kg (1,8-cineole) induced a dose-dependent decrease in aortic pulse pressure. Myocardial infarction (MI) is the most commonly encountered ischemic heart disease and remains the world’s leading cause of death and disability. Hemodynamic, biochemical, and histopathological alternations are observed together with changes in blood pressure indices, heart rate, ventricular dysfunction, and decreased endogenous antioxidants as well as the escape of cardiac injury markers and lipid peroxidation. [46]. Such changes are due to the increasing ROS, including superoxide anion and hydroxyl radicals in ischemic tissues, which lead to oxidative damage to membrane lipids, proteins,
carbohydrates, and DNA [47]. Therapeutic advantages by antioxidants can, therefore, help to prevent the initiation and future consequences of ischemic cardiac diseases [48, 49]. Cardamom has been found to have cardioprotective against isoproterenol (ISO)-induced myocardial infarction (MI) by attenuating hemodynamic and left ventricular weakness, thwarting lipid peroxidation, and enhancing endogenous antioxidant defense system along with histological and ultrastructural preservation of cardiomyocytes evidenced by reduced leakage of the myocyte injury marker enzymes [12]. This indicates that cardamom possesses the ability and potential to prevent oxidative stress-mediated heart dysfunction in ISO-induced experimental MI in rats. The phytoconstituents, sterols, phenolic acids, flavonoids, and flavanols present in cardamom have been described to be potential cardioprotectants against overt oxidative damages [50]. The long-term dietary supplementation of cardamom has also been found to modify the lipid profile favorably and to significantly improve fibrinolytic activity and the overall status of antioxidants in ischemic heart disease patients, which may be favorable for athero-thrombotic coronary artery disease patients. Cardamom treatment showed significant aorta plaque size regression in rabbits fed with a high cholesterol diet for 90 days (500 mg/kg.b.wt./day) [15].

It has been reported that oral administration of cardamom extract to Wistar rats fed a high-fat diet significantly reduced total, LDL, and very-low-density lipoprotein (VLDL) cholesterol and triglycerides that may contribute to reducing the risk of CAD [51]. Rats treated with cardamom for 30 days experienced less heart damage after a heart attack and retained higher levels of antioxidants. That was due to the free radical scavenging and antioxidant activity of cardamom [12].

In addition to antioxidant activity, hypotensive, fibrinolytic, vasorelaxant, and antiplatelet properties are also reported [52], which can contribute significantly to its cardioprotective activity. The inhibitory activity of cardamom extract was also studied on human platelets, obtained from the blood of healthy volunteers. The extract significantly inhibited the platelet aggregation induced by ADP (adenosine diphosphate) and epinephrine [52]. It may, therefore, be said that aqueous cardamom extract may have components that protect platelets against aggregation that may prevent heart attack or stroke.

4. EFFECTS OF CARDAMOM IN CHRONIC INFLAMMATORY DISEASES

Chronic inflammation, a key element in many human chronic diseases that include rheumatoid arthritis, allergy, Alzheimer’s disease, cardiovascular disease (CVD), inflammatory bowel disease (IBD), diabetes, Parkinson’s disease, and cancer, remains the leading cause of disability and death worldwide [53-55]. The real hazard factors related with these illnesses are poor and unhealthy lifestyle choices, including psychosocial stress, poor nutrition, and consumption of diets high in saturated fats and sugars, tobacco use, excessive alcohol consumption, lack of physical activity, and infection with lethal pathogenic microorganisms. It is now well known that these factors induce inflammation and dysregulate one or more of inflammatory pathways, which lead to the development of inflammation-associated chronic diseases [54]. Therefore, targeting specific inflammatory pathways has high potential to prevent and eradicate these fatal diseases [53]. Cardamom, or its extract or its active components, was recorded in several experiments in animal models. The principal property of these cardamom anti-inflammatory effects is by inhibiting NF-KB [56]. NF-KB is a transcription factor that plays an essential role in inflammation because of its ability to induce the transcription of various pro-inflammatory genes. The NF-KB is highly active in inflammatory sites in various inflammatory conditions and triggers transcription of pro-inflammatory cytokines, chemokines, adhesion molecules and matrix metalloproteinases (MMPs), cyclo-oxygenase-2 (COX-2) and inducible nitric oxide (iNOS) [57]. Consequently, anti-inflammatory agents modulating NF-KB and its regulated products can have a significant potential to prevent and treat chronic inflammatory diseases. Inflammatory cytokines also affect transcription factors such as nuclear factor erythroid 2-related factor-2 (Nrf2), which serves as a mediator for cellular responses to oxidative stress [58]. Cardamom was found to activate transcription factor Nrf2, which boosts and up-regulates a series of enzymes with protective, antioxidant, and detoxification effects including enzyme for glutathione biosynthesis and metabolism to maintain glutathione levels [27]. Activating Nrf2 also decreases the inflammatory response mediated by NF-κB [59], which plays a vital role in cardamom anti-inflammatory effects.
Similarly, eugenol, an active component of cardamom, has been reported to significantly inhibit secretion of the pro-inflammatory mediators IL-1β and IL-6 [60], inhibitory NO synthase and NO [61] and cyclooxygenase-2. Interestingly, oral administration of the aqueous extract of cardamom is accompanied by a significant reduction in cyclooxygenase-2 and inhibitory NO synthase expression in murine models of colon cancer [33]. Moreover, cardamom was shown to have anti-inflammatory activity against acute carrageenan-induced plantar edema in albino rats [16].

One major constituent of cardamom, 1,8-Cineole, has been extensively studied for its antioxidant and anti-inflammatory effects in various disease models [62]. A study [63] in mice showed that 1,8-Cineole suppressed lipopolysaccharide-induced pro-inflammatory cytokine production through the actions of nuclear factor (NF)-κB, TNF-α, IL-1β, and IL-6. Cineole has been shown to downregulate NO synthase-2, COX-2, and NF-κB, hence explaining its potential as an anti-inflammatory agent [64]. Moreover, Cineole also attenuated the colonic damage in trinitrobenzene sulfonic acid (TNBS)-induced colitis in rats; decreased acute pulmonary inflammation in vivo; ameliorated acute pancreatitis in vivo via downregulation of cytokines, oxidative stress and NF-κB [63,65].

Several components of inflammatory signaling pathways such as free radicals, cytokines, NF-κB, signal transducer and activator of transcription-3 (STAT-3), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), prostaglandins, and vascular endothelial growth factor (VEGF), have been shown to contribute in the progression of multi-forms of cancer [66]. Cardamom exerts its anti-cancer effects by modulating several signaling pathways, including the inflammatory signaling pathway. TNF-in the regulatory machinery of immune cells and, in advance of systemic inflammation, make a significant contribution. Impairment of a regulatory mechanism in the production of TNF-α has been shown to cause a variety of inflammatory diseases, as well as cancer [67].

5. GASPROTECTIVE EFFECTS

Despite a great emphasis on cancer prevention in phytochemical research, several herbal products are being used and/or studied for a variety of gastrointestinal problems [68]. Cardamom, Elettaria cardamomum Maton fruit is used for the treatment of digestive disorders. The gastroprotective effects of cardamom and its main aroma constituent viz.1,8 -cineole were identified in the following studies. Methanolic extract (TM), essential oil (EO), petroleum ether soluble (PS) and insoluble (PI) fractions of methanol extract of cardamom have been tested for their ability to inhibit aspirin and ethanol-induced gastric lesions in rats at doses 100-500, 12.5-50, 12.5-150 and 450 mg/kg, respectively. The gastric lesions were substantially inhibited by all fractions (TM, EO, PS, PI) [14].

The gastro-protective effect of 1,8-cineole on ethanol-induced rat mucosal damage was examined. 1,8 –cineole(50-200 mg/kg), given orally 1 hour before 1 ml of pure ethanol, significantly reduced ethanol-induced gastric injury [69].

Results from yet another study support the potential value of 1,8-cineole as a dietary flavoring agent in gastrointestinal ulceration prevention. In animals pretreated with 1,8-cineole following trinitrobenzene sulfonic acid (TNBS) colitis in rats, a marked reduction in the gross damage scores and wet weights (mg/cm) of colonic segments was evident [65]. It has been shown that the free radical scavenging, antioxidant, and anti-inflammatory activities of cardamom may have contributed to the observed gastro-protective effects.

6. ANTIMICROBIAL EFFECTS

Natural antimicrobials attract a lot of attention to a variety of pathogen control issues. Several of the benefits include reducing antibiotic demand, controlling microbial contamination in food, creation of technologies to increase shelf-life to remove unwanted microbes and/or retarding microbial spoilage, reducing antibiotic resistance by microbial pathogens or improving human immune cells [70]. In addition to their taste and aroma qualities, many spices and herbs used today are valued for their antimicrobial activities and medicinal effects.

Several investigators have documented the antibacterial activity of cardamom extracts using different solvents against several bacterial species such as Pseudomonas aeruginosa, Klebsiella pneumonia, [71], Staphylococcus aureus [71,72], methicillin-resistant Staphylococcus aureus [73], Escherichia coli [72], Salmonella typhi [74], Salmonella...
typhimurium [74] and Shigella sonnei [71]. It has been shown that the use of various solvents can lead to extracts having different chemical profiles and activities [72].

The five specific cardamom antimicrobial compounds, a-Pinene, cineole, limonene, linalool, and geranyl acetate, have been effective against certain food bore pathogens and antibiotic-resistant Staphylococcus aureus, Bacillus cereus, Escherichia coli, and Campylobacter jejuni. [75,76]. Cardamom oil (10 mg/ml) exhibited significant antibacterial property toward S. aureus, E. coli, S. typhi, Streptococcus mutans and C. albicans [18], Bacillus pulmilus and Listeria monocytogenes [77]. According to Mejdi et al. [78], Cardamom oil has potential wide range antibacterial and antifungal properties that might be used to prevent damage caused by food-borne microorganisms and food spoilage pathogen. Candida is an opportunistic fungal pathogen with high mortality and morbidity levels among immunocompromised people, and Candida albicans is the fourth leading cause of nosocomial infections worldwide.

Formulated extracts from nutmeg and cardamom have demonstrated antifungal activity against Candida albicans clinical isolates by showing growth inhibition of more than 80% at respective concentrations of 50 μl/ml and 100 μl/ml (v/v). Treated cells have shown reduced ergosterol content, altered cell morphology, cell wall thickening, membrane distortions, and cytoplasm displacement that appear to lead to the development of new therapeutic approaches for candidiasis therapy [79].

7. SUMMARY AND CONCLUSION

In summary, cardamom and its extracts have many health-promoting properties backed by a multitude of in vitro and in vivo studies evidence as well as clinical trials of humans. In-vitro and in-vivo cardamom studies and several aqueous and organic cardamom solvent extracts have been found to have many health-enhancing effects; including antioxidant stress properties, free radical scavenging ability, prevention of coronary heart disease, anti-inflammatory gastroprotective, antimicrobial, and anti-cancer activities.

Given the effects of oxidative modification of low-density lipoprotein cholesterol in atherosclerosis development, the antioxidant properties of cardamom are of particular interest. Given that several metabolic diseases and age-related degenerative disorders are closely linked to oxidative processes in the body, the application of cardamom as a source of antioxidants to counter oxidation needs further attention. Immediate research should focus on the validation of cardamom's antioxidant potential and on testing its effect on oxidation markers. It will work in conjunction with clinical trials aimed at recognizing antioxidants as mediators of disease prevention. While cardamom is being examined in animals for anticarcinogenic properties, the challenge is to incorporate this information to determine whether any effects in humans can be observed. With growing interest in chronic inflammation treatment alternatives to non-steroidal anti-inflammatory drugs, research work is developing on the use of food items like cardamom. As shown by experimental evidence and phytochemical composition, cardamom can have potential health benefits against many types of cancer.

Cardamom and its polyphenols have a crucial molecular action through the activation of the Nrf2 transcription factor, which regulates detoxification and antioxidant enzymes. Such work could also contribute to the inhibition NF-κB, the major transcription factor that controls inflammation. All these different actions are the scientific basis for promoting the use of cardamom or its extract for cancer prevention and the treatment of various inflammatory and metabolic diseases.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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