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TRADITIONAL, PHYTOCHEMICAL AND BIOLOGICAL ACTIVITIES OF *ELETTARIA CARDAMOMUM* (L.) MATON – A REVIEW

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ABSTRACT: The *Elettaria* Maton genera belonging to the Zingiberaceae family is native to South India to West Malesia. From ancient times this genus has been largely explored for its biological properties. Various pharmacological properties such as anti-inflammatory, analgesic, antioxidant, and antimicrobial effects have been related to this genus. *E. cardamomum* also acts as an Ayurvedic aphrodisiac and remedy in case of digestive problems, asthma, bronchitis, and urinary complaints, and several other human ailments; this review aims to provide a critical and comprehensive evaluation of the traditional and current medical uses of *E. cardamomum*, and compare these applications with modern research studies. Cardamom contains various chemical constituents such as proteins, minerals, lipids, carbohydrates, terpenoids and carotenoids, flavonoids, and essential oils, and its capsules is widely used as a spice and flavoring ingredient in foods. This critical review also discusses the botanical distribution, phytochemical constituents, and biological activities of its extracts and essential oil.

INTRODUCTION: *Elettaria cardamomum* (L.) Maton known as green cardamom, small cardamom, or true cardamom, is grown in India, Sri Lanka, Guatemala, Nepal, Indonesia, Mexico Costa Rica, and Tanzania [1]. In India, it is mostly cultivated in 900-1400 m above MSL (mean sea level) covering Kerala, Karnataka, and Tamil Nadu. In Kerala, it is mainly cultivated in the Indian Cardamom Hills, which designated as Cardamom Hill Reserves [2]. The name *Elettaria cardamomum* is originated from the Tamil word "Elettari" which refers to the seeds of cardamom [3].

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E. cardamomum is called "Queen of Spices" in India and "Hel" in Iran that used as a flavor agent (spice) in a variety of foodstuffs [4]. Cardamom (*E. cardamomum*), a member of the Zingiberaceae family, belongs to the sweet spices group. It is widely cultivated and occupies second or third place in world trade. It is mostly used for baked goods, flavor sweets, and coffee, particularly in the Arab countries and in Asian countries. Various studies explored its clinical [5-10], traditional and pharmacological properties [11-19].

Its seed powder is commonly used in the treatment of gastrointestinal disorders and as a digestive, stomachic, breath freshener, anti-emetic and carminative agent [20]. The available information on this species was collected from scientific databases such as PubMed, Sci Finder, Science Direct, Scopus, Web of Science, and Google Scholar. The search terms used for this review included *Elettaria*

cardamomum, phytochemical composition, essential oils, traditional uses, activity, pharmacology, and toxicity. No limitations were set for languages.

Traditional Uses: Traditionally, it is used for controlling asthma, teeth and gum infections, digestive and kidney disorders [21, 22], cataracts, cardiac disorders, nausea, and diarrhea [23, 24], asthma and constipation, bronchitis [25, 26], carminative, cold, cough, congestion of lungs, diuretic, kidney disorders, teeth and gum infections, urinary and pulmonary tuberculosis and irritation of eyelids [21, 22, 27], bladder infections, constipation, stomach ache and dysentery in children [28, 29], in manufacturing of some plant-based hand creams and soaps [30], digestive ailments, headaches and inflammation [31], controlling cold and related symptoms [32], improves the eyesight [33].

Botanical Description: Herbaceous perennial plant, 2-5 m in height, leaves 30-35 cm long and 7-10 cm wide, lance late, acuminate, dark green in colour [34] inflorescences panicle, possessing a long cane-like peduncle having nodes and internodes, 2 - 4 panicles emerge from the swollen base of tillers; flowers white with the central lip streaked with pink [35], bisexual, irregular, labellum oval and indistinctly 3 lobed; calyx tubular, split about ¼ of its length on one side and shortly 3 toothed; corolla unequally three-lobed with the larger one at the posterior side; anthers two-lobed; stigma funnel-shaped with cilia around a small cavity; ovary inferior, trilocular with axial placentation, ovules numerous in each carpel [36].

Chemical Constituents: 1, 8-cineole (28.94%), α-terpinyl acetate (26.7%), α-terpineol (14.6%), sabinene (13.5%), nerol (5.0%) and α-pinene (2.4%) [37] α-terpinyl acetate, 1, 8-cineole and α-terpineol [38] α-terpinyl acetate, 1, 8-cineole, sabinene, linalyl acetate, linalool [39] limonene (2.9%), 4-terpineol (1.4%), α-pinene (1.1%), β-pinene (0.8%), myrcene (0.8%), octanal (0.2%), δ-3-carene (0.4%), p-cymene (0.7%), (E)- nerolidol (0.7%) cis-sabinene hydrate (0.6%), geranylacetate (0.3%), cis-sabinene hydrate acetate (0.2%), β-caryophyllene (0.2%), β-selinene (0.2%), γ-cadinene (0.2%), translinalooloxide (0.1%) [40] α-tocopherol, γ-tocopherol, δ-tocopherol, oleic acid, palmitic acid, linoleic acid [41] α-terpinyl acetate, 1,8-cineole, Linalyl acetate, Sabinene 42; α-terpinyl acetate, Linalool, Sabinene, α-terpineol, Geraniol [43] α-terpinyl acetate, Linalool, 1,8 Cineole, β-terpineol [44] 4-terpineol, 1,8-Cineol, α-terpene, Linalool [45].

Pharmacological Profile:

1. Anti-Alzheimer Activity: The petroleum ether extract of *E. cardamomum* fruits was evaluated for Alzheimer-like alterations induced by high fructose and high-fat diet coupled with a single small dose of STZ (25 mg/kg) on type 2 diabetes mellitus (T2DM) on Wistar rats by measuring behavioral tests, immune histochemical examination, biochemical analysis and gene expression determination. The extract significantly decreased hippocampal level of AChE activity, caspase-3 activity and reduced Aβ and p-tau accumulation. The extract suppressed glutamate receptor expression (AMPA GluR1 subunit and NMDA receptor subunits NR1, NR2A, NR2B), reduced hippocampal lipid peroxidation marker malondialdehyde (MDA) and augmented antioxidant defensive system, including superoxide dismutase (SOD) and reduced glutathione (GSH). It lowered hippocampal TNFα, IL β1, but not IL6, and reduced GSK3β in brain T2D rats. It was concluded that the extract could ameliorate Alzheimer disease-like alterations in T2DM rats through activation of blunted insulin signal transduction in the brain, attenuation of associated oxidative stress, and neuroinflammation [46].

2. Analgesic Activity: Cardamom oil from seeds of *E. cardamomum* (133-400 µl/kg) was evaluated for analgesic activity by using the p-benzoquinone-induced writhing method and compared with standard drug aspirin (50-175 mg/kg). It was observed that aspirin (175 mg/kg) and cardamom oil (400 µl/kg) prevented the writhing in treated mice by 100% protection of control values [25].

3. Anti-cancer Activity: The aqueous extract (1, 10, 50 and 100 µg/ml) from seeds of *E. cardamomum* was evaluated for the anti-cancer activity of NK cells against YAC-1 lymphoma cells by using JAM assay. The extract showed significant dose-dependent stimulation of NK cells and possess no direct cytotoxic activity against YAC-1 tumor cells. The extract showed synergistic stimulatory effect on the activity of NK cells

against YAC-1 tumor cells and displayed a more potent stimulatory effect on activity of NK cells [47].

4. Anti-convulsant Activity: The methanolic extract (1, 1.5, and 2 g/kg) and essential oil (0.25, 0.50, 0.75 and 1 ml/kg) from *E. cardamomum* seeds were evaluated for anti-convulsant activity against seizures induced by pentylentetrazole (PTZ) or electrically (maximal electroshock; MES) in NMRI male mice. The essential oil (1 ml/kg) significantly delayed the onset of clonic seizures and increased the onset time of tonic convulsions at all doses in PTZ model and significantly reduced (dose - 1 ml/kg) the percentage of hind limb tonic extension (HLTE) in MES-induced seizure model. Methanolic extract raised the onset time of tonic seizures at all doses and prevented tonic convulsions by 33% at a dose of 1.5 g/kg. The extract and essential oil showed significant neurotoxicity in the rotarod test (dose - 1.5 g/kg and 0.75 ml/kg). These results concluded that anti-convulsant effects were negligible against the seizures induced by pentylentetrazole and maximal electroshock but showed significant neurotoxicity [48].

5. Anti-hypercholesterolemic Effect: Whole cardamom powder, de-oiled cardamom powder, and cardamom oil from seeds of *E. cardamomum* were evaluated for anti-hypercholesdterolemic effect against hypercholesterolemia induced Wistar rats at the dose of 50 g/kg. Cardamom oil reduced total blood cholesterol (31%), LDL cholesterol (44%), total serum cholesterol (17%) and LDL cholesterol (28%), respectively. Serum cholestrol exhibit a decrease in triglycerides by 42% and 24% by cardamom oil and whole cardamom. Whereas elevated serum cholesterol: phospholipid ratio in hypercholesterolemic rats was significantly countered by dietary intervention with cardamom oil (27%), atherogenicity index in serum was brought down from 2.92 in hypercholesterolemic rats to 1.38 and 2, respectively by cardamom oil and whole cardamom. Cholesterol content of cardiac muscle was lowered by 39% with administration of cardamom oil and elevated hepatic cholesterol: phospholipid ratio was beneficially countered by dietary cardamom oil, which reduced the same by 22%. Moreover, treatment with de-oiled cardamom as well as cardamom oil countered the diminished activity of catalase in hypercholesterolemic animals *i.e.*, 50.25 and 40.94 mmol/min/mg proteins, respectively. Cardamom also enhanced the activity of heart superoxide dismutase in hypercholesterolemic situation. Ascorbic acid concentration in circulation was significantly increased by the dietary interventions with cardamom or its fractions both in hypercholesterolemic and normal situations. In conclusion, a significant reduction of athero-genicity index by dietary intervention with cardamom powder and cardamom oil indicates the potential cardioprotective effect of cardamom [49].

6. Anti-inflammatory Activity: Cardamom oil from seeds of *E. cardamomum* (175-280 µl/kg) was evaluated for anti-inflammatory activity against carrageenan-induced hind paw oedema in male albino rats and indomethacin at 30 mg/kg, i.p. (76% inhibition) was used standard drug. Cardamom oil (280 µl/kg) exhibited 86.4% inhibition, while at 175 µl/kg oil showed 69.2% inhibition, concluded that cardamom oil (175 µl/kg) provoked a significant suppressive action on carrageenan-induced oedema but to a slightly lesser extent than indomethacin. However, at a dose of 280 µl/kg, oil exerts a more potent anti-inflammatory effect than indomethacin [25].

7. Anti-microbial Activity: Essential oil from E. cardamomum was evaluated for anti-microbial activity against Candida tropicalis, *C. parapsilosis, C. krusei, C. glabrata, C. guilliermond, C. albicans, Saccharomyces cerevisiae* (Fungal strains), *Bacillus cereus, B. subtilis, Enterococcus faecalis, Listeria monocytogenes, Micrococcus luteus, Staphylococcus aureus* MR (B2), *S. aureus, S. epidermidis, Escherichia coli, E. coli* ATCC 25922, *Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabils, Shewanella putrefaciens, Salmonella typhimirium, Shigella flexenerii, Vibrio alginolyticus* ATCC 17749, V. alginolyticus ATCC 33787, V. cholerae, V. parahaemolyticus ATCC 17802, V. parahaemo-lyticus ATCC 43996, V. vulnificus ATCC 27562, *V. vulnificus* ATCC 33149 and *Serratia marcescens* (Bacterial strains) by using disc diffusion and microdilution assays. Amphotericin B (ZOI - 10.33 to 14.66 mm) and ampicillin (ZOI - 7 to 30.33 mm) were used as reference drug at 10 mg/ml against fungi and bacteria, respectively. The essential oil showed highest inhibition against C. *parapsilosis*

(21.67 mm) and *M. luteus* (40.33 mm). On the other hand, essential oil and its isolated components (10-400 µg/ml) were evaluated for anti-quorum sensing activity against Chromobacterium violaceum CV026 and *P. aeruginosa* PAO1. The essential oil at 10 µg/ml concentration showed more than 50% of inhibition of elastolytic and proteolytic activities in *P. aeruginosa* PAO1, whereas, highest diameter of violacein inhibition was noted for 1,8-cineole about 28 mm at 2 mg/disc. Moreover, 1, 8-cineole attenuated the expression of the tested QS-controlled virulence factors (violacein pigment production, elastase and protease production, and motility) in a dose-dependent manner. It concluded that oil has effectively reduced/stopped bacterial and fungal growth and may have potential use in clinical settings for microbial infections [50].

The ethanol and acetone extract was evaluated against multi-drug resistance against Candida species by assessing virulence factors such as MDR-biofilm, protease, phospholipase activity, anti-fungal susceptibility, and hydrophobicity, using disc diffusion and tube methods. *C. albicans* showed 95.94% resistance to fluconazole; C. glabrata showed 94.33% resistance to fluconazole, clotrimazole and ketoconazole; *C. parapsilosis* showed 95.45% resistance to fluconazole and clotrimazole; *C. dubliniensis* exhibited 100% resistance to clotrimazole and itraconazole and *C. tropicalis* showed 100% resistance to fluconazole and itraconazole.

Whereas, in biofilm production, *C. dubliniensis* (75%) showed strong biofilm-producing activity, followed by *C. glabrata* (67.9%), *C. albicans* (58.11%), *C. tropicalis* (53.33%), and *C. parapsilosis* (45.45%), while 100 µl of acetonic extract showed anti-biofilm activities against *C. albicans* isolates (inhibition zone: 15 mm), compared to the ethanolic extracts (10 mm). However, *C. parapsilosis* (75%) showed the highest percentage of protease production, followed by *C. albicans* (68.92%), *C. glabrata* (64.15%), *C. tropicalis* (40 %), *and C. dubliniensis* (37.5%). Moreover, *C. glabrata* (98.33%) showed the most significant adherence followed by *C. albicans, C. parapsilosis, C. dubliniensis* and *C. tropicalis*. These results concluded that the acetonic extract majorly inactivated pathogenic *C. albicans* and this plant could be used as a therapeutic option for the inhibition of biofilm-forming Candida species [51]. The aqueous, ethanol, methanol, ethyl acetate, and hexane dry fruits showed *in-vitro* anti-microbial activity against Escherichia coli, Salmonella typhi, *Bacillus cereus*, *Bacillus subtilis*, *Streptococcus pyogenes* and *Staphylococcus aureus* by using agar well diffusion assay, while tetracycline (5 µg/ml) was used as a standard antibiotic (zone of inhibition 25.83-34 mm). It observed that all the extract except hexane extract possess activity ranged from 10.88 to 20.63 mm (aqueous extract), 10.83 to 19.80 mm (ethyl acetate extract), 11.46 to 15.80 mm (methanol extract), and 09.06 to 14.80 mm (ethanol extract) among which ethyl acetate extract and aqueous extract showed maximum inhibition against *S. aureus i.e.*, 20.63 and 19.80 mm, respectively. It proves that *E. cardamomum* seems to have significant antimicrobial activity [52].

Karadağ and coworkers evaluated *in-vitro* anti-bacterial activity of *E. cardamomum, Lavandula angustifolia* and *Salvia fruticosa* essential oils in mouthwashes formulated with different combinations such as 0.1/0.25/0.1; 0.2/0.25/0.1; 0.3/0.1/0.1 in 10 mL (v/v) by using the disc diffusion method against human pathogenic *S. aureus* ATCC 6538, *E. coli* NRLL B-3008, *B. cereus* ATCC 14579 and *S. typhii* (clinical isolate), respectively. Among the tested bacteria, *S. typhii* (8mm) was the most sensitive, while *E. coli* and *S. aureus* (7mm) both respectively were the most less resistant pathogens against *E. cardamomum* in the applied mouthwash formulations [53].

8. Anti-oxidant Activity: The hexane extract was evaluated for in vitro anti-oxidant activity by using DPPH radical scavenging, reducing power assay, metal chelating, and total anti-oxidant activity. BHA, ascorbic acid, EDTA, and gallic acid were used as standard. Results revealed that extract (ERH) exhibited DPPH and metal chelating activity with IC50 464 µg/ml and 199 µg/ml, respectively, whereas the reducing power and antioxidant activities were found to be 289 AAE/mg, 468 GAE/mg. These results concluded that the extract of this plant possesses anti-oxidant activity [54]. The methanolic extract from seeds evaluated for anti-oxidant activity by using DPPH radical scavenging assay and ascorbic acid (IC50 22.78 µg/ml) was used as standard.

The extract exhibited low anti-oxidant activity with IC_{50} 217.43 µg/ml [P20] and about 50% inhibition at higher concentration of 100 µg/ml [55]. The ethanolic extract of *E. cardamomum* and phytoconstituents were evaluated for Fe3+ reducing ability by FRAP assay and hydrogen donating ability by DPPH assay. Ferrous sulfate ($FeSO_4$) was used as a calibration standard to calculate FRAP values as µmolFe2+/ml of FeSO4 equivalents per µg/µM of extract alpha-terpinyl acetate, respectively. Both the extract and alpha-terpinyl acetate showed low antioxidant potential due to low Fe^3+ reducing ability and DPPH percentage scavenging activity. The low antioxidant and free radical scavenging activity of alpha-terpinyl acetate, a menthane monoterpene is due to its chemical nature [56].

9. Anti-spasmodic Activity: Cardamom oil from seeds (200-900 nl) was evaluated for anti-spasmodic activity in rabbits, using acetylcholine as an agonist. The oil inhibits the stimulant action of acetylcholine in a dose-dependent manner. The atropine (3 µg) and cardamom oil (400 nl) produced a 50% reduction of the stimulant action of acetylcholine. In conclusion, cardamom oil exerts its anti-spasmodic action through muscarinic receptor blockage [25].

10. Anxiolytic Activity: The methanolic extract (200, 400, and 800 mg/kg) was evaluated for anxiolytic activity in Wistar rats (group I- single prolonged stress (SPS), Group II post-stress (received saline or extract 30 min after establishment of post-traumatic stress disorder (PTSD)) by using open field, elevated plus-maze and rotarod test. Results revealed that at the dose of 400 mg/kg, grooming, rearing, time spent in perimeter, and time spent in center were significantly altered in SPS group and PTSD group, mobility increased in SPS group.

Whereas, in elevated plus-maze, at the doses of 200 and 400 mg/kg had a significant increase in time spent in the open arms and showed reduced time spent in closed arms. Moreover, a significant reduction was observed in the time spent by the rats treated with the extract at the dose of 800 mg/kg in SPS and PTSD groups. The anxiolytic properties are because of high flavonoid content, especially quercitin [57].

11. Cardioprotective Effect: Cardamom extracts (100 and 200 mg/kg) from fruits of *E. cardamomum* (cardamom) was evaluated for cardio-protective effect against isoproterenol (ISO)-induced myocardial infarction (MI) in Wistar male albino rats. The result showed that ISO injections induced a significant decrease in heart rate and systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP), decrease in myocytes grievance indicator enzymes, creatinine kinase-myocardial bundle (CK-MB), lactate dehydrogenase (LDH) enzymes, significant fall in reduced glutathione (GSH) content and induction of lipid peroxidation as evidenced by increased malondialdehyde (MDA) level in the heart and decreased the activities of endogenous antioxidant enzymes; superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSHPx) in heart as compared to the normal control group.

However, treatment with cardamom (100 and 200 mg/kg) significantly prevented the ISO-induced decline of arterial pressure indices, SAP, DAP, MAP, prevented the depletion of myocardial enzymes, and has prevented the reduction in the activities of antioxidant enzymes; SOD, CAT, and GSHPx. Whereas, treatment with cardamom only at 200 mg/kg dose significantly prevented (+) lessened ventricular dynamics LVdP/dtmax in comparison to ISO-induced diseased control group. Cardamom treatment at both doses (100 and 200 mg/kg) significantly improved (+) LVdP/dtmax significantly attenuated the raised LVEDP as compared to ISO control group treatment with cardamom. Moreover, the protective effects were strengthened by improved histopathology and ultrastructural changes, which specifies the salvage of cardiomyocytes from the deleterious effects of ISO. Cardamom significantly protects the myocardium and exerts cardio-protective effects by free radical scavenging and antioxidant activities [58].

12. Chemopreventive Effect: *E. cardamomum* was evaluated for chemopreventive effect against benzo (α) pyrene [B(α)P]-induced for stomach papilloma genesis in mice. The treatment with cardamom [(B(α)P + cardamom] reduced tumor incidence and multiplicity significantly by 41.67% and 74.55%, respectively, compared to that of the B (α) P control group and showed a significant

enhancement in the hepatic activities of glutathione-S-transferases, superoxide dismutase, glutathione peroxidase and catalase in mice treated with cardamom compared with the control. Moreover, the nonenzymatic antioxidant glutathione was significantly increased in the cardamom-treated group, whereas the lipid peroxidation level along with lactate dehydrogenase activity exhibited a significant reduction with cardamom treatment compared to the control. In conclusion, cardamom has the potential to become a pivotal chemopreventive agent against fore-stomach cancer [59].

The aqueous suspension was studied against (DMBA)-induced skin carcinogenesis in Swiss albino mice by evaluating tumor incidence, tumor burden, tumor yield, the cumulative number of papillomas, average latency period and was also assessed for its modulatory effect on lipid peroxidation (LPO) and reduced glutathione (GSH) levels. Results showed chemopreventive effect with a significant reduction in the incidence of tumors, tumor yield, average latency period and tumor burden when compared with the carcinogen control group. Whereas, tumor weight and tumor size were significantly reduced in DMBA-induced and croton oil–promoted skin tumor genesis in Swiss albino mice. Moreover, a significant decrease in hepatic LPO was observed, and GSH levels were significantly elevated when compared with control group (LPO 4.90 nmol/mg, GSH 2.60 nmol/g). The chemopreventive activity of cardamom was due to its modulation of LPO level and enhancing glutathione content and might be useful for reducing cancer incidence and tumor burden [20].

The aqueous suspension was evaluated for chemopreventive effect against azoxymethane (AOM) induced colonic aberrant crypt foci (ACF) in Swiss Albino mice by studying cell proliferation, apoptosis, COX-2, and iNOS expression. The total number of ACF was significantly lowered by 48.33% in the 0.5% cardamom treated group, while mean numbers of ACF, consisting of 4 or more aberrant crypts in each group were significantly lowered by 97% in mice. Whereas reduction in ACF was accompanied by suppression of cell proliferation (mean Brdu LI in carcinogen control was 13.91, and 0.5% cardamom was 2.72) and induction of apoptosis (mean AI in carcinogen control was 1.55 and 0.5% cardamom was 6.61). Moreover, reduction of both COX-2 and iNOS expression was also observed [60].

13. Diuretic Activity: Crude extract (1, 3, and 10 mg/kg) from fruit was evaluated for diuretic activity in Sprague–Dawley rats, where 10 mg/kg of furosemide (urinary output 6.93 ml) was used as a reference diuretic drug. Results revealed that extract at 1, 3, and 10 mg/kg increased the urinary volume to 4.13, 5.05, and 5.54 ml, respectively, indicating diuretic effect and also enhanced Na+ and K+ excretion. Whereas, Na+ and K+ contents in pooled urine samples were 0.63, 0.69, 0.84 mmol and 0.16, 0.14, 0.20 mmol at the doses 1, 3 and 10 mg/kg, respectively and compared to furosemide 0.88 and 0.19 mmol, respectively 23.

14. Gastroprotective Effect: The crude methanolic extract (TM), essential oil (EO), petroleum ether soluble (PS) and insoluble (PI) fractions of methanolic extract (100–500, 12.5–50, 12.5–150, and 450 mg/kg, respectively) from the fruit were evaluated against gastric lesions induced by aspirin, ethanol and pylorous ligature in Wistar albino rats, where, ranitidine (50 mg/kg.) were used as a reference standard. The TM was more active in reducing lesion by 73.1% inhibition in the EtOH-induced ulcer model at 500 mg/kg. Whereas, PS fraction at 50 and 100 mg/kg reduced the lesions by 50 and 53.3% inhibition, respectively, with similar effect than the PI fraction (450 mg/kg) 54.1% inhibition. Moreover, the aspirin-induced gastric ulcer model showed that the best gastro-protective effect was found in the PS fraction, which inhibited lesions by nearly 100% at 12.5 mg/kg proved to be more active than ranitidine 69.1% inhibition [61].

15. Hepatoprotective Effect: The ethanolic extract was evaluated for hepato-protective effect against high carbohydrate high fat (HCHF) diet-induced obese Male Wistar rats. It observed that HCHF diet feeding in rats developed glucose intolerance, increased peritoneal fat deposition, dyslipidemia, increased fat deposition, and inflammation in the liver compared to control rats. Also, the HCHF diet increased lipid peroxidation, decreased antioxidant enzymes activities, and increased advanced protein oxidation product level significantly in plasma and liver tissue. Whereas supplementation of cardamom improved the glucose intolerance significantly and

prevented the rise of lipid parameters significantly, and prevented abdominal fat deposition in HCHF diet-fed rats. Whereas, increased fat deposition and inflammatory cell infiltration in liver, ALT, AST, and ALP enzyme activities in plasma were also normalized by cardamom powder supplementation in HCHF diet-fed rats. Moreover, cardamom powder supplementation ameliorated the fibrosis in liver of HCHF diet-fed rats. These results concluded that cardamom powder supplementation can prevent dyslipidemia, oxidative stress and hepatic damage in HCHF diet-fed rats [62].

16. Immunomodulatory Activity: The aqueous extract (1, 10, 50, and 100 µg/ml) was evaluated for immunomodulatory activity by using ELISA. The aqueous extract significantly enhances splenocyte proliferation in a dose-dependent, synergistic fashion. ELISA revealed that extract significantly enhances and suppresses T helper (Th)1 and (Th)2 cytokine released by splenocytes. Whereas, experimental evidence suggested that extract exert pro-inflammatory and anti-inflammatory roles. Moreover, nitric oxide production by macrophages was significantly augmented and reduced. It is strongly suggested that seeds of this plant exert immunomodulatory roles and hence manifest themselves as natural agents that can promote the maintenance of a healthy immune system [47].

The protein extract and total extract from *E. cardamomum* (0.1 mg/ml PBS) were evaluated for immunomodulatory activity on the proliferation of splenocytes by using colorimetric MTT assay, and concanavalin-A (Con-A) (7 µg/ml) was used as a positive control. The cell proliferation in the presence of total extract was 102% and cell proliferation induced by Con-A was 93.8%. Whereas cell proliferation in the presence of protein extract was 129%, cell proliferation induced by Con-A was 83.7% 63.

17. Protective Effects on Lungs: *E. cardamomum* was evaluated for protective-effect on lungs against pan masala induced damage in the lung of male Swiss mice by using biochemical assay (pNPP kinetic, α- napthylphosphate kinetic and IFCC method). The pan masala treated group (PMT) exhibited marked lung histopathological abnormalities, characterized by a fusion of alveoli and adenocarcinoma with compressive and destructive growth. Extensive fibrosis in peribronchial region and increased thickness of bronchial smooth muscle due to accumulation of collagen. Whereas, on cardamom treatment in the PMT and pan masala with cardamom treated (PMCT) mice, congestion of lungs was mild with almost no medullary hemorrhage. Moreover, enzymatic activities significantly decreased during amelioration, when the treatment groups were exposed only to cardamom, and the values reached almost near the control [64].

18. Sedative Activity: Crude extract (30–300 mg/kg) from fruit was evaluated for sedative activity against pentobarbital-induced sleeping time in Swiss albino mice were diazepam (5 mg/kg) (sleeping time 348.01 min) was used as a reference sedative agent. Results revealed that at doses of 30, 100, and 300 mg/kg, extract prolonged sleeping time to 162.5, 202.75, and 277.4 min, respectively. In conclusion, extract caused prolongation of pentobarbital-induced sleeping time in mice [23].

19. Stimulatory Effect: Crude extract (3-10 mg/ml) and its aqueous fraction from fruit were evaluated for stimulatory effect by measuring the contractile effect in Guinea-pig ileum, where acetylcholine chloride (ACh) was used as a positive control. The extract caused a concentration-dependent contractile effect. The efficacy of the stimulant effect was 9.3, 49.48, and 70.61%, respectively at concentrations of 3, 5, and 10 mg/ml when compared to ACh, while histamine response remained unchanged [23].

20. Clinical Study: A clinical study was conducted to determine the effects of *E. cardamomum* (green cardamom, GC) supplementation on blood glucose indices, lipids, inflammatory profiles, and liver function by examining irisin, paraxonase-1 (PON1) and sirtuin-1 (Sirt1) in obese patients with nonalcoholic fatty liver disease (NAFLD). The intervention involves taking two 500 mg GC capsules three times per day with meals for 3 months. Results showed that GC significantly increased Sirt1 and decreased hs-CRP, TNF-α, IL-6, ALT, and the degree of the fatty liver while the differences in weight, body mass index, and aspartate transaminase were not significant.

The study concluded that *E. cardamomum* supplementation could improve some biomarkers related to fatty liver, including inflammation, ALT, and Sirt1 in overweight/obese NAFLD patients [65]. Another clinical study was conducted to evaluate the effects of *E. cardamomum* supplementation on serum lipids, glycaemic indices, blood pressure, oxidative stress, and inflammatory biomarkers in overweight and obese 80 pre-diabetic women.

The stratified randomization method was used to control the age and BMI (age in the range of ≤40 and 41–70 years; BMI in the range of 25–29.9 and 30–39.9 kg/m2). The intervention involves taking one capsule of either cardamom or placebo powder three times a day with a meal for 8 weeks. It was observed that after 8 weeks, cardamom supplementation reduced serum hs-CRP, hs-CRP: IL-6 o (P=0.008) ratio, and reduced serum MDA levels. However, a complete restoration of inflammatory, oxidative stress parameters was not achieved and did not show the influence of cardamom on PC, TAC, SOD, or GR levels. In conclusion, cardamom could improve some parameters of inflammation and oxidative stress in pre-diabetic subjects. Thus, increased cardamom consumption may be useful in reducing diseases associated with inflammation, such as cardio-vascular diseases, in pre-diabetic subjects [8].

21. Toxicological Profile: The methanolic extract (1, 1.5 and 2 g/kg) and essential oil (0.25, 0.50, 0.75 and 1 ml/kg) from seeds of *E. cardamomum* were evaluated for toxicological activity in NMRI male mice. No mortalities were observed up to the doses of 2 g/kg and 0.75 ml/kg for the extract and essential oil [P3]. Crude extract from fruit did not cause any mortality up to the dose of 10 g/kg when evaluated for toxicological activity in Swiss albino mice [23].

22. Anti-scabies: Sharma and coworkers examined the anti-scabies activity of *E. cardamomum* essential oil for their *in-vitro* anti-scabies potential against Sarcoptes scabiei mites.

The essential oil demonstrated scabicidal potential as its 10% concentration caused 100% mortality within 60 min, whereas 5% diluted solution took 80 min to kill all the mites. It was found that Permethrin (reference) killed all the mites within 60 min, but in the negative control group, mortality was only 1.58%, and most of the mites remained alive after 80 min of treatment [66].

CONCLUSION: In this review, we have briefly summarized the ethnopharmacological properties and phytochemical constituents that have been isolated from *E. cardamomum*. Further research should be conducted to explore new potential therapeutic agents and their ethnopharmacological properties of *E. cardamomum* to treat life-threatening diseases.

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