DOI: 10.55522/jmpas.V13I4.6236 **ISSN NO. 2320 – 7418**

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Review on medicinal properties of large Cardamom constituents towards cardiovascular diseases

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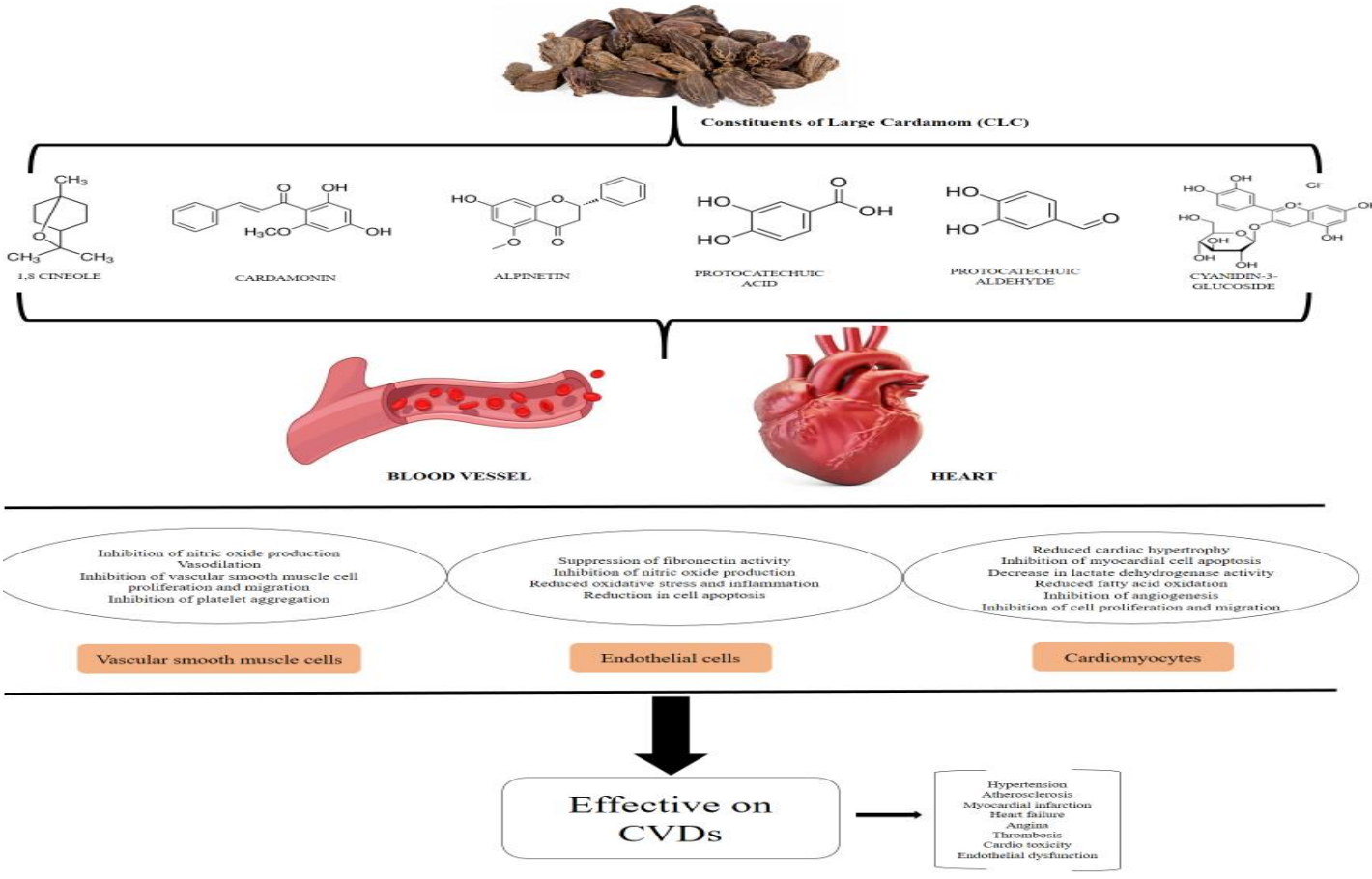
Received - 30-01-2024**, Revised** - 17-06-2024, **Accepted** - 13-08-2024 **(DD-MM-YYYY)**

Refer This Article

VS Arya, T Tamilanban, 2024. Review on medicinal properties of large Cardamom constituents towards cardiovascular diseases. Journal of medical pharmaceutical and allied sciences, V 13 - I 4, Pages - 6669 – 6680. Doi: https://doi.org/10.55522/jmpas.V13I4.6236.

ABSTRACT

Dietary factors have a significant impact on the onset and prevention of many disorders, including cardiovascular diseases (CVDs). The discovery of medical plants which are pharmacologically effective with few side effects when used in preventative medicine is currently a concern.



Spices have been used worldwide for culinary purpose, because of its high nutritional value. Many research has been done to assess the possible health advantages of different spices, especially in terms of preventing cardiovascular diseases. The current review probe to examine the effectiveness of *Amomum subulatum* Roxb, and its constituents for the management of heart diseases, that will be beneficial for defining affordable and cost-effective interventions for the cure and control of CVDs. Information on the biological activities of bioactive constituents of large cardamom was obtained from databases including Science Direct, Web of Science, PubMed, and Scopus, and published as original research papers from 2000 to 2022. Even though there is empirical support for the claim that some spices can promote heart health, further research is required to fully understand the particular dietary exposures, required to cause a response. More thorough clinical trials are required to investigate the potential negative impacts of spices on long term use, then it will be easy to identify the best intervention strategies with these spices, that enable the achievement of greatest benefits on cardiovascular health while minimising the adverse effects.

Keywords: Cardiovascular diseases, large cardamom, Cardamonin, Alpine tin, 1, 8 Cineole.

INTRODUCTION

Cardiovascular diseases (CVDs) are the collective term for a number of pathophysiological conditions that affect the blood vessels and heart, which include deep vein thrombosis, pulmonary embolism, cerebrovascular disease, rheumatic and congenital heart disease [1]. Cardiovascular problems are a leading global cause of death and a major public health concern [2].

Most of the cardiovascular problems are mainly associated with genetic make-up and lifestyle modification [3]. Drastic progressive changes are occurring in the medical field for the diagnosis, control and cure of CVDs but, low and middle-income countries bare a huge burden of the disease because of low-level awareness and poor socioeconomic status [4]. Hence, the recent researchers are mainly focusing on natural remedies ie, an affordable health care system with fewer side effects, to put proper control over the diseases. Recently, studies describing the therapeutic efficacy, pharmacological activity, cellular and molecular mechanisms of natural medicines are available in the field of various CVDs [5].

Historically, India has a rich tradition of using herbs and spices for treating various human ailments. Indian system of traditional medicine describes that the herbs and spices are having medicinal properties such as being, hypoglycaemic, antithrombotic, ant atherosclerosis, hyperlipidemic, anti-inflammatory, antihypertensive, ant arthritic, etc. since, effective in modulating the cardiovascular system activities as well [6-7]

Amomum subulatum, commonly known as Black cardamom, is a dried ripe fruit of perennial herbaceous plant *Amomum subulatum* Roxb, family Zingiberaceae. It is mostly grown in eastern Sikkim, Nepal, and some areas of the Darjeeling district in West Bengal, India, and southern Bhutan. It is native to the eastern Himalayas and widely used in culinary because of its strong flavour. Major bioactive constituents of the spice include Cardamonin, alpine tin, Protocatechuic acid and aldehyde, Glucosides like cyaniding and petunidin 3-glucoside and the essential oil fraction contains 1, 8-cineole, α-terpineol etc. [8-9].

Aqueous extract of large cardamom has shown antihypertensive activity aginst Nω-Nitro-L-arginine methyl ester (L-NAME) induced hypertensive rats [10]. However, a comprehensive review highlighting the activities of large cardamom constituents on various CVDs and associated risk factors are lacking in the literature. Hence, we aim to sort out the effectiveness of pharmacologically active constituents of large cardamom in various disorders associated with the cardiovascular system. This review will help in identifying the biological activities of large cardamom constituents on heart and blood vessels and hence, hence aid in the development of a cost effective therapeutic strategy for the management of CVDs.

Biological activities of constituents on CVDs

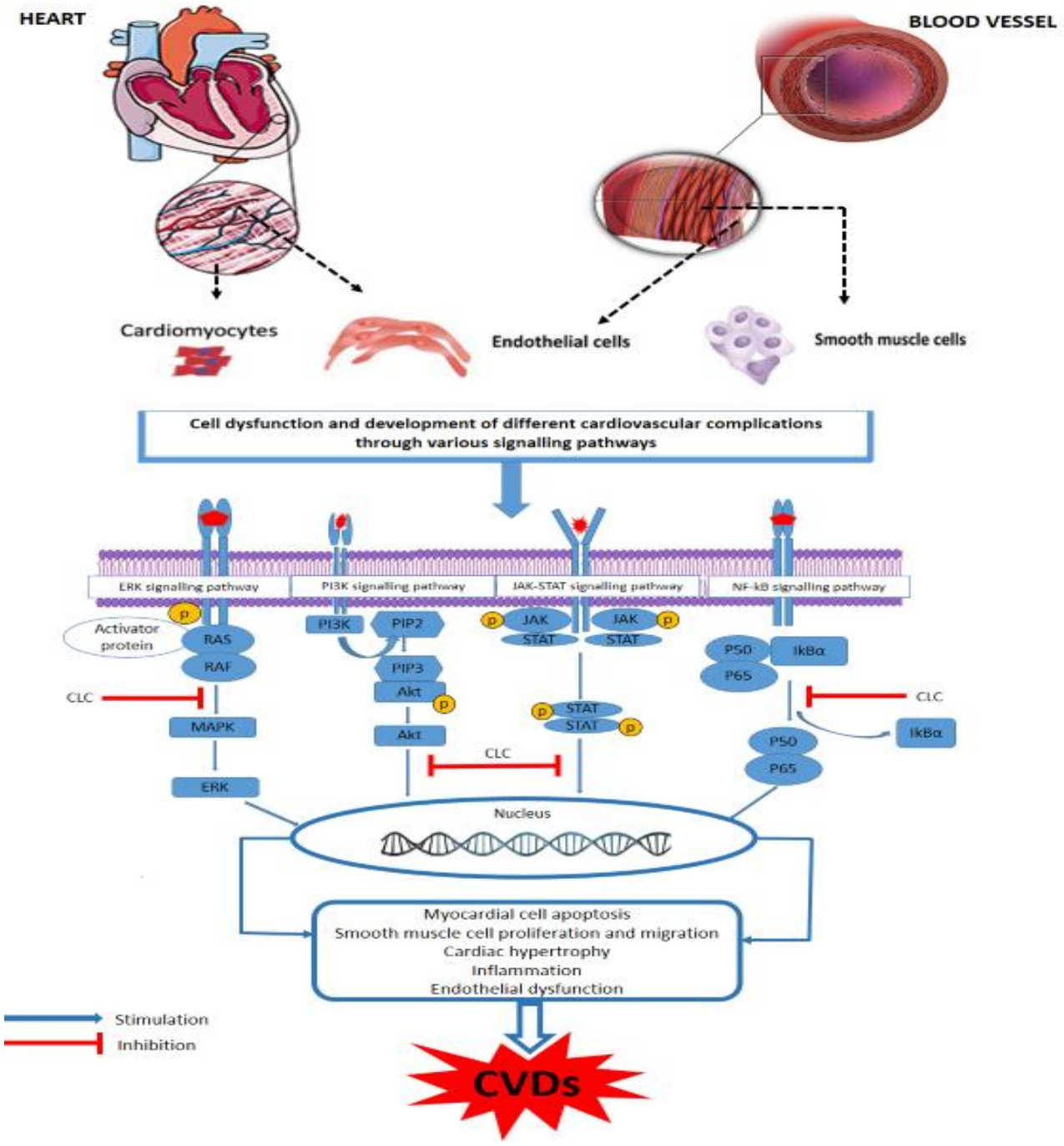
CVDs are ailments of the heart and circulatory system. Chronic CVDs might go undiagnosed for a very long time. Furthermore, CVDs represent a significant concern to public health since they are the primary cause of morbidity and mortality globally. Molecular mechanism that favours the cell death, inflammation, endothelial dysfunction and atherosclerosis are the major triggering factors of hypertension and other complications (Figure 1) [11]. Most of the bioactive constituents of large cardamom have shown some beneficial effect on CVDs pathology by altering several molecular mechanisms. Biological activities of bioactive constituents and the elucidated mechanism were summarized in Table 1

Hypertension

Hypertension is one among the major significant and modifiable risk factor for the premature CVDs. It accounts for about 47% of all ischemic heart disease and 54% of all stroke's events worldwide [12]. Rats treated with an aqueous extract of large cardamom demonstrated antihypertensive efficacy due to vasorelaxation and an antioxidant impact on models of hypertension produced by L-NAME [10]. Protocatechuic acid and 1, 8 cineole are two of the main bioactive components that have been shown to have antioxidant and antihypertensive properties. In hypertensive rats exposed to nicotine, 1, 8 cineole has been shown to reduce SBP by raising plasma nitrate content [13]. Furthermore, intravascular injection of 1, 8 cineole produced a hypotensive state in both conscious and anaesthetized normotensive rats, mostly due to the active relaxation of the vascular

smooth muscles [14]. Another active ingredient, Protocatechuic acid, demonstrated antioxidant and antihypertensive properties in rat models of hypertension produced by deoxycorticosterone acetate-salt (DOCA) and glucocorticoids [15]. The injection of DOCA salt led to elevated levels of malondialdehyde and hydro peroxides, a significant reduction in the activity of the antioxidant enzymes catalase and glutathione, oxidative stress, and elevated SBP [16]. In hypertensive mice, protocatechuic acid showed some positive effects and improved the changed parameters. All of the study's findings when combined imply that supplementing with large cardamom, which contains bioactive components like protocatechuic acid and 1, 8 cineole, may be helpful in preventing hypertension and oxidative status. This can lower the risk of developing CVDs and enhance the quality of life for those who are afflicted.

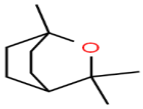
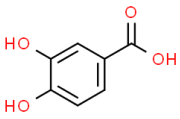
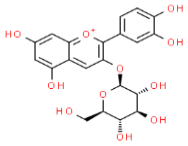
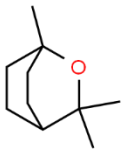
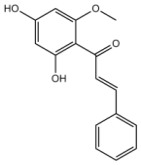
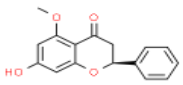
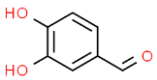
Figure 1: CLC regulates multiple signalling pathways involved in the development of different CVDs

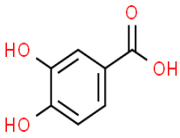
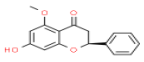
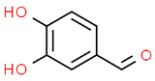
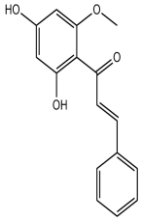
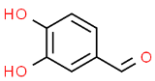


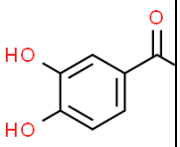
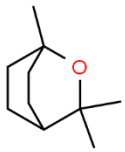
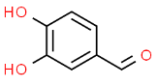
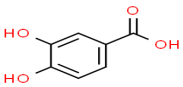
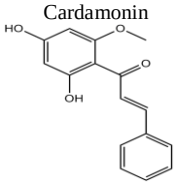
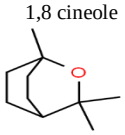
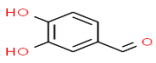
(ERK: Extracellular signal regulated kinase, PI3K: Phosphatidylinositol 3-kinase, JAK-STAT: Janus kinase/signal transducers and activators of transcription, NF-kB: Nuclear factor kappa light chain enhancer of activated B cells, PIP2: Phosphatidylinositol 4,5-bisphosphate , PIP3: Phosphatidylinositol-3,4,5-triphosphate , Raf: Rapidly accelerated fibrosarcoma (proto-oncogene serine threonine protein kinase), Akt: Protein kinase B (serine/threonine specific protein kinase), IkBα: NF-kB inhibitor

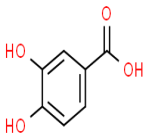
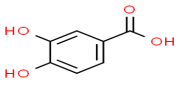
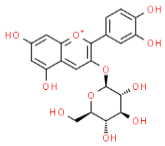
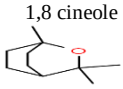
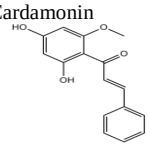
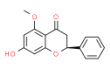
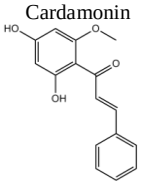
alpha, CVDs: Cardiovascular diseases, CLC: Constituents of large cardamom).

Table 1: Effect of large cardamom constituents on various CVDs

Antihypertensive activity				
Constituent	**Animal/Cell line/Tissue**	**Animal model/Inducing agent**	**Results**	**Reference**
1,8 cineole 	Male Sprague Dawley rats (100-120 g)	0.8 mg/kg/day nicotine for 21 days, followed by 3 mg/kg nicotine the next day(IP)	↓ SBP and plasma MDA level and ↑plasma nitrite level	13
	Male Wistar rats (250–320 g)	Normotensive rats	↓ mean arterial pressure (MAP) and heart rate (HR)	14
Protocatechuic acid 	Male albino Wistar rats (200 ± 20 g)	Dexamethasone (30 µg/kg, s.c.) for 14 days	↓ SBP, plasma H_2O_2 level, ↑ plasma ferric reducing antioxidant power	15
	Male Wistar rats	Deoxycorticosterone acetate (DOCA) (25 mg/kg, s.c.) twice weekly and 1% NaCl in drinking water for 4 weeks	↓SBP, serum sodium and chloride, raised serum potassium level. ↑serum catalase activity, total antioxidant capacity and glutathione concentration and ↓ MDA and hydro peroxides levels. Improved organ weight changes, ↓ water intake and moderately prevented histopathological changes of kidney and heart	16
Cyanidin-3- Glucosides 	SHR and WKY rats as the normotensive control group		Ameliorated cardiac hypertrophy and diastolic dysfunction	43
Anti-atherosclerotic activity				
1,8 cineole 	Hypercholesterolemia Zebra fish	4% cholesterol, for 3 weeks	↓serum lipid, serum amyloid A and interleukin 6 levels and lipid accumulation in liver	18
Cardamonin 	Rat vascular smooth muscle cells (VSMCs)	Angiotensin II	Inhibited angiotensin II induced vascular smooth muscle cell proliferation and migration by down regulating p38 MAPK, Akt, and ERK phosphorylation.	44
Alpinetin 	Rat aortic smooth muscle cells	H_2O_2 (100 µmol L-1)	Inhibited smooth muscle cells proliferation and migration	45
		TNFα (200 U ml-1)	Inhibited the production of NO in cultured VSMC	
Protocatechuic Aldehyde 	Isolated thoracic aortic smooth muscle cells of Sprague–Dawley rats (200–250 g)		Down-regulated mitogen activated protein kinase (MAPK) and the phosphatidylinositol 3- kinase (PI3K)/Akt pathways. Inhibited the migration and proliferation of vascular smooth muscle cells. Suppressed the expression of cyclin D2 and induced the S-phase arrest of	19

			the vascular smooth muscle cell cycle.	
	Human umbilical vein endothelial cells (HUVEC)	TNF-α 2 ng/ml for 6 hrs	Suppression of ibronectin activity through the down regulation of ROS/JNK and NF-κB activation	20
Protocatechuic Acid 	Male ApoE−/− mice	High-cholesterol diet (21% crude fat, 0.15% cholesterol, and 20% casein)	Reduction of atherosclerotic lesion formation and inflammatory responses. Inhibition of the phosphorylation of NF-κB pathway.	46
	Mouse-Macrophage Cell Line (J774 Cells) and Mouse-Bone Marrow-Derived Macrophages (BMDMs)		Inhibition of macrophage 1 (M1) polarization via the PI3K−Akt−NF-κB−SOCS1 Pathway. Enhancement of macrophage 2 (M2) polarization by PCA via the STAT6−PPARγ pathway. Alleviated atherosclerosis by inhibiting M1 polarization and promoting M2 activation	
Effect on Myocardial infarction				
Alpinetin 	Myocardial cells of male Sprague Dawley rat	myocardial apoptosis induced by serum deprivation	Activated δ receptor and protected myocardial cells from apoptosis via the PKC/ERK signalling pathway.	22
Protocatechuic aldehyde 	Male Sprague–Dawley rats	Ligation of the left anterior descending coronary artery	Reduction of myocardial Infarct size and serum CK MB and cTn-I level. Reduction in serum level of inflammatory mediators like TNF-α, IL-6, and ICAM-1. Modulated NF-κB Signaling Pathway to produce anti-inflammatory effect.	40
	Neonatal rat cardiomyocytes		↓ Activity of LDH and cTn I in culture. Protection against apoptosis. Reduced production of inflammatory mediators. Modulated NF-κB Signaling Pathway	
Effect on Heart Failure				
Cardamonin 	C57BL/6 male mice	Transverse aortic constriction (TAC)	↓ left ventricular weight, Reduced thickness of the anterolateral and interventricular septal wall. ↓ TAC-induced cardiac fibrosis, alleviated TAC induced apoptosis, inhibited TAC-induced oxidative stress	24
	Rat myocardium derived cardio myoblast H9C2	Angiotensin-II	Inhibition of oxidative stress and apoptosis	
Protocatechuic aldehyde 	Neonatal rat cardiomyocytes	Isoproterenol treatment (ISO, 10 μM for 24 h)	Protect against cardiac hypertrophy by the inhibition of the JAK2/STAT3 signalling pathway	26
	Male Sprague–Dawley rats	Isoproterenol 1.5mg/kg/day for 7 days (SC)	Reduced mRNA and protein expression of hypertrophy markers, including ANF and β-MHC. Altered histological abnormalities. Protection against cardiac hypertrophy	
Antinational activity				
Protocatechuic acid	Isolated rat heart		Reduced fatty acid oxidation	29

				
Antithrombotic activity				
1,8 cineole 	Human platelet cells	CRP-XL, collagen, thrombin and ADP	Inhibition of platelet aggregation	31
Protocatechuic aldehyde 	Thoracic aortic smooth muscle cells of Sprague Dawley rat	Platelet-derived Growth factor (PDGF)- BB 20 ng/ml for 24 hrs.	Inhibition of ROS . Production and PDGF-BB induced smooth muscle cell proliferation and migration. Inhibition of PDGF-BB stimulated AKT and ERK 1/2 pathways. Prevention of platelet aggregation	47
Protocatechuic acid 	Isolated human platelet	High shear stress (>10,000 s (-1))	Inhibited the higher shear stress induced platelet aggregation.	32
Cardamonin 	Human whole blood	Arachidonic acid- (AA), collagen- and ADP	Inhibition of platelet aggregation	47
Effect on Endothelial Dysfunction				
1,8 cineole 	Male Kunming mice	LPS 1 mg/ kg for one day (IP)	↓expression of VCAM-1 in thoracic aorta, ↑ PPAR-γ and decreased the phosphorylation of NF-κB. Attenuated vascular endothelial cells injury via PPAR-γ dependent modulation of NF-κB.	34
Protocatechuic aldehyde 	Male Sprague Dawley rats	Common carotid balloon injury	Promoted re endothelization in balloon injured arteries. ↑ G Protein Coupled Estrogen Receptor 1 expression. Inhibited Angiogenesis. Inhibited noontime formation in injured carotid arteries Improved the anti-oxidative capacity in HL-1 cells. Inhibited inflammatory response in HL-1 cells	35
	Mouse cardiomyocytes HL-1			
	Human umbilical vein endothelial cells (HUVEC)	8 ng/mL vascular endothelial growth factor (VEGF)	Inhibition of cell proliferation, migration, and angiogenesis regulation of miR-21 expression	52
Protocatechuic acid	Male Sprague–Dawley rats	Single i.p. injection of 50 mg/kg streptozotocin (STZ)	Produced cardiac protective effect and improved cardiac function.	42

	Male Sprague Dawley rats (280–310 g) Human umbilical vein endothelial cells (HUVECs)	2,3,7,8-Tetracholorodibenzo p-dioxin (TCDD) 2 mg/kg/week orally for 45 days	↑levels of glutathione, catalase, glutathione Peroxidase and superoxide dismutase. Prevented Oxidation, necrosis and Haemorrhage of heat tissue. Provided protection for heart tissue against TCDD induced toxic effects ↑ G Protein-Coupled Estrogen Receptor-1 expression, ↓ ROS production. Down regulated VCAM-1, ICAM-1 and CD40 expression	53
	Human umbilical vein endothelial cells (HUVECs)	Lipopolysaccharide 15 µg/ml for 30 hrs.	Inhibited cell apoptosis in dose dependent manner. Inhibited caspase-3 activation	48
Protocatechuic acid 	Aging spontaneously hypertensive rats (SHR).		Improved the endothelium dependent-vasorelaxation induced by insulin and IGF 1 by amplifying the PI3K– NOS–NO pathway	36
Cyanidin-3-Glucoside 	Bovine artery endothelial cells (BAECs)		↑ eNOS expression and escalated NO production via an Src-ERK1/2-Sp1 signalling pathway in vascular endothelial cells.	49
	Human endothelial cells	TNF-α	Reduced oxidative stress and inflammation in endothelial cells by down regulating NF-κB pathway.	50
Vascular Activity				
1,8 cineole 	Male Wistar rats left ventricular papillary muscles		Relaxation of the contracted muscles majorly by Ca2+ channel blocking	51
Cardamonin 	Rat isolated mesenteric arteries		Endothelium dependent and -independent relaxation	37
	Rat tail artery myocytes		Vasodilation by inhibiting the voltage dependent Cav2.1 channel and stimulating the calcium activated KCa1.1 channel	38
Alpinetin 	Rat isolated mesenteric arteries		Endothelium dependent and -independent relaxation	37
Cardio protective effect				
Cardamonin 	Male C57BL/6J mice	Doxorubicin (5mg/kg/week) for 4 weeks	Alleviated cardio toxicity. ↓ Oxidative stress. Attenuated inflammatory response. Inhibited apoptosis	39
	Rat myocardium derived cardio myoblast H9C2 and	Doxorubicin	↑ Expression of Nrf2 and elevated Nrf2 nuclear Translocation in HL-1 cells.	

Atherosclerosis

Heart failure, myocardial infarction, peripheral vascular disease, and stroke are among the CVDs that are most commonly caused by atherosclerosis, a chronic inflammatory condition of the blood vessels [17]. In hypercholesteraemic zebra fish, 1, 8 cineole has been shown to have anti-inflammatory and lipid-lowering properties. In the liver of zebra fish, 1, 8 cineole demonstrated antioxidant action,

prevented oxidation and glycation-associated changes to the lipoproteins, and decreased fat buildup [18]. In addition, it has been shown that 1, 8 cineole and protocatechuic aldehyde exhibit notable alterations in atherosclerotic lesions, mostly through the down-regulation of the PI3K/Akt and mitogen-activated protein kinase (MAPK) pathways. Furthermore, it has been documented that protocatechuic aldehyde inhibits the production of cyclin D2 and induces S-phase arrest in the cell cycle of vascular smooth muscle cells [19]. Protocatechuic aldehyde was used in an *in vitro* investigation to decrease the production of ofibronectin in human umbilical vein endothelial cells (HUVEC) triggered by tumour necrosis factor-α (TNF-α) by downregulating ROS/JNK and activating NF-κB [20].

Myocardial Infarction (MI)

Myocardial infarction or Heart attack is one of the most common conditions among the coronary heart diseases. It usually results from an imbalance between oxygen demand and supply. Atherosclerosis is remains as a predominant risk factor for MI. In addition, hypertension, high cholesterol, obesity, cigarette smoking, exercise, LDL, triglyceride levels are also directly or indirectly will favor the development and progression of the disease [21]. However, MI is a medical emergency require stents and bypass surgery in severe cases, but can manage the disease development at an early stage by adopting healthy diet and life style modifications. One of the bioactive constituents of large cardamom Alpinetin has been reported to possess protective effect against myocardial cell apoptosis. Myocardial cell apoptosis is the pathological hallmark in MI and will affect the normal structure and functions of the heart and will lead to number of cardiovascular complications. Alpinetin inhibited myocardial cell apoptosis in Sprague Dawley rats myocardial cells by activating the δ receptor instead of the μ and κ receptors through the PKC/ERK signaling pathway because, these δ receptors are majorly involved in the protection of myocardial cells from trauma [22].

Heart Failure (HF)

Heart failure or congestive heart failure is a complex clinical syndrome of ventricular dysfunction that results when the heart fails to supply enough volume of blood to meet the metabolic needs of the body [23]. Comparing with other agents the effects of Cardamonin is extensively studied in this field using different models. Cardamonin alleviated the cardiac remodelling and dysfunction by inhibiting oxidative stress and apoptosis in aortic constricted mice via mitochondria-dependent pathways [24]. Additionally, Cardamonin prevented cardiac remodelling in myocardial infarcted mice by inhibiting the mTORC1-dependent signaling pathway [25]. Cardiac hypertrophy is an adaptive response during mechanical stress to maintain the normal functions of the heart. Sustained cardiac hypertrophy will result in heart failure. Intragastrically administration of protocatechuic acid for 7 days alleviated the isoproterenol treatment induced cardiac hypertrophy in rats by modulating the the JAK2/STAT3 signaling pathway [26].

Angina

The clinical manifestation of myocardial ischemia known as angina is primarily characterized by discomfort or pain in the chest, as well as dyspnea brought on by an inadequate oxygen supply to the heart muscles. Angina can be caused by a number of factors, including cigarette smoking, eating a diet high in saturated fat and cholesterol, hypertension, obesity, stress, diabetes, atherosclerosis, and coronary spasms, which restrict the blood flow to the heart muscles [27].

Studies that describing the anti-anginal effects of constituents of large cardamom are limited. Cao Y et al. investigate the activity of a single ingredient, protocatechuic acid, in an isolated rat heart in this setting. The heart muscles often rely on mitochondrial fatty acid oxidation to continue functioning when they are oxygen-deficient. However, research indicates that partial inhibition of fatty acid oxidation is advantageous in oxygen-deficient states, as the heart can function more effectively with glucose oxidation at a given oxygen level than with fatty acid oxidation [28]. In the published work, the scientists demonstrated that protocatechuic acid can reduce fatty acid oxidation, allowing the heart to prefer glucose over fat as an energy source [29]. This is particularly helpful when myocardial ischemia is present. There is a dearth of empirical information supporting the effectiveness of big cardamom's bioactive ingredients in treating angina. Therefore, in order to determine the potential for therapeutic benefit in this area, a thorough investigation of all other constituents using appropriate models is necessary.

Thrombosis

Thrombosis involves the obstruction of blood flow through the circulatory system due to the formation of blood clots inside the blood vessels. Consistent thrombosis with in the veins and arteries will results in most serious complications like heart attack, pulmonary embolism and stroke [30]. Usually, the inappropriate activation of platelets will result in thrombus formation. Hence, the consumption of natural agents with anti-thrombotic property will be a better remedy for the prevention of impending cardiovascular complications. 1, 8 cineole have been reported to possess antithrombotic effect on human platelets by preventing platelet aggregation [31]. Anti-thrombotic effect of protocatechuic acid was confirmed by Kim K et al using rat arterial thrombosis model and suggested the practicality of using protocatechuic acid for preventing the onset of thrombus formation, since protocatechuic acid showed the positive impact without enhancing the bleeding risk [32].

Endothelial dysfunction

It is now known that the endothelium functions as a useful barrier and is a crucial regulator of blood flow between the micro- and microvasculature. The abnormality in the vascular endothelium is a

well-established response to risk factors of CVDs and precedes the development of numerous complications like hypertension, atherosclerosis, thrombosis, diabetes and other cardiovascular ailments [33]. The endothelial cells continue to act as the cardiovascular system's gatekeeper. Thus, managing the pathophysiology of CVDs and the emergence of ensuing life-threatening consequences from the outset will be made easier by preventing endothelial dysfunction.

A few substances, such as 1, 8 cineole, protocatechuic acid, cyanidin-3-glucoside, and protocatechuic aldehyde, have been discovered to be effective against the modulation of endothelial dysfunctions. By modifying the PPAR-γ dependent NF-κB activation, 1, 8 cineole has been shown to drastically alter the endothelial injury and inflammation that was produced by lipopolysaccharides in HUVEC cell line and in Kunming mice [34]. Protocatechuic aldehyde produced protective effect against endothelial dysfunction both in *in vivo* and *in vitro* studies by modulating G Protein-Coupled Estrogens Receptor-1[35]. Furthermore, Masodsai K et al. in 2019 used aged spontaneously hypertensive rats to investigate the effects of protocatechuic acid on vascular endothelial function and antioxidant activities. They found that administering protocatechuic acid for 12 weeks to these rats significantly improved the endothelium dependent-vasorelaxation by amplifying the PI3K–NOS–NO pathway [36]. Based on available data, a small number of components may be able to restore normal endothelium physiology and hence help control the development of CVDs from the very beginning.

Vascular activity

In rat isolated mesenteric arteries, Alpinetin and Cardamonin have demonstrated a vasodilatory effect through a variety of pathways, including endothelial independent relaxing through the suppression of calcium ion influx and endothelium dependent relaxation through the mediation of nitric oxide release [37]. Cardamonin has been shown to have a bifunctional effect on the myocytes in the rat tail artery by simultaneously stimulating the KCa1.1 current and inhibiting the Cav1.2 current [38].

Miscellaneous

Cardamonin has been reported to produce cardio protective effect against doxorubicin induced cardio toxicity in mice by preventing the oxidative stress, inflammation and apoptosis [39]. In a left anterior descending coronary artery ligated rat model, protocatechuic aldehyde prevented myocardial ischemia and reperfusion injury by inhibiting nuclear factor-kappa B activation [40]. Numerous *in vitro* and *in vivo* investigations have demonstrated the cardio protective action of protocatechuic acid in myocardial injury [41]. Furthermore, on streptozotocin-induced diabetic rats, combined insulin and protocatechuic acid treatment resulted in cardio protection and enhanced heart function [42].

Clinical applications of Large Cardamom and its constituents on various CVD

Since ancient times, greater cardamom has been associated with positive effects on cardiovascular health. Supplementing the diet with large cardamom powder for a period of 12 weeks resulted in notable improvements in the antioxidant and fibrinolytic activity, as well as alterations in the lipid profile, among patients diagnosed with ischemic heart disease [43].

Novel Drug Delivery Approaches with bioactive constituents on CVD

Antioxidant, anti-inflammatory, and cholesterol regulating actions of 1, 8 cineole make it highly promising for inhibiting the advancement of atherosclerosis. Nevertheless, the considerable volatility and instability of 1, 8 cineole led to a diminished ability to be absorbed orally and a brief duration of effectiveness, thereby restricting its practical use in clinical settings. A nano emulsion with Polysaccharide-Protein/Protein Complex as emulsifier and Vitamin B12 as ligand facilitated the therapeutic effect of 1,8 cineole on atherosclerosis **[44].**

CONCLUSION

Multiple studies have shown the therapeutic advantages of the major constituents of large cardamom in treating cardiovascular disorders. Pharmacological analysis uncovered fascinating results for substances that affected many disease development pathways, including those associated with low blood pressure, prevention of blood clotting, prevention of plaque buildup in arteries, relief of chest pain, and protection of the heart. Modifying the primary pathways of disease progression can significantly enhance cardiovascular health, as indicated in Figure 1. These positive results will help increase public awareness about the benefits of large cardamom's bioactive components for cardiovascular health and its use in food preparation. Thus, incorporating the inclusion of substantial quantities of cardamom, known for its bioactive constituents, into a typical dietary regimen can serve as a cost-effective and effective means of enhancing cardiovascular well-being. Nevertheless, the range of clinical studies and novel drug delivery techniques in this domain is limited, presenting a chance for additional substantial investigation.

Consent for Publication: Not applicable.
Funding: None.
Conflict of Interest
The authors declare no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENT

Declared none.

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