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Emerging roles of cardamonin, a multitargeted nutraceutical in the prevention and treatment of chronic diseases

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ABSTRACT

Although chronic diseases are often caused by the perturbations in multiple cellular components involved in different biological processes, most of the approved therapeutics target a single gene/protein/pathway which makes them not as efficient as they are anticipated and are also known to cause severe side effects. Therefore, the pursuit of safe, efficacious, and multitargeted agents is imperative for the prevention and treatment of these diseases. Cardamonin is one such agent that has been known to modulate different signaling molecules such as transcription factors (NF-κB and STAT3), cytokines (TNF-α, IL-1β, and IL-6) enzymes (COX-2, MMP-9 and ALDH1), other proteins and genes (Bcl-2, XIAP and cyclin D1), involved in the development and progression of chronic diseases. Multiple lines of evidence emerging from pre-clinical studies advocate the promising potential of this agent against various pathological conditions like cancer, cardiovascular diseases, diabetes, neurological disorders, inflammation, rheumatoid arthritis, etc., despite its poor bioavailability. Therefore, further studies are paramount in establishing its efficacy in clinical settings. Hence, the current review focuses on highlighting the underlying molecular mechanism of action of cardamonin and delineating its potential in the prevention and treatment of different chronic diseases.

1. Introduction

A remarkable progress in understanding the molecular mechanisms of chronic or non-communicable diseases such as arthritis, cancer, cardiovascular diseases, diabetes, liver cirrhosis, metabolic syndromes, neurological disorders, etc., and their modulation with different drugs, has been made over the past decades; however, these diseases still constitute the prime cause of mortality and morbidity worldwide (Kunnumakkara et al., 2018a, 2018b; Thakur et al., 2018; Bordoloi et al., 2018a; Parama et al., 2020). Many drugs have been developed for the treatment of these serious health complications; still, a large number of them affect the health and living conditions of patients due to chemoresistance, serious adverse side-effects, and high treatment costs (Kunnumakkara et al., 2019a, 2019b, 2019c; Bordoloi et al., 2016; Khatoon et al., 2020; Monisha et al., 2016). Therefore, with the increase in the incidence of chronic diseases, the development of highly efficacious and affordable drugs to impart a healthy and productive lifestyle to patients, without needless complications, becomes imperative. Hence, the challenge here is to develop clinically-productive compounds that would naturally blend into the body and improve the therapy, reduce long-term side effects and impart positive effects (Bulaj et al., 2016; Roy et al., 2016; Banik et al., 2018).

Fortunately, a deeper knowledge gained during the last couple of decades has helped us to delineate the complex network of molecular alterations which subsequently lead to the onset and progression of these diseases (Khwairakpam et al., 2015; Khwairakpam et al., 2020; Thakur et al., 2017; Padmavathi et al., 2018; Khwairakpam et al., 2019; Roy et al., 2019b; Sailo et al., 2019; Monisha et al., 2017; Shabnam et al., 2018; Bordoloi et al., 2019; Bordoloi et al., 2018b; Roy et al., 2019a). Overwhelming pieces of evidence have proven that the lack of physical activity, pollution, poor diet, obesity, regular intake of alcohol and tobacco, etc., are the prime risk factors contributing to the development of these diseases (Anand et al., 2008; Kunnumakkara et al., 2018a; Gupta et al., 2018). Numerous studies have established that these factors dysregulate multiple pathways/proteins, and different metabolic processes, which destroys the normal cellular homeostasis, and damage cells as well

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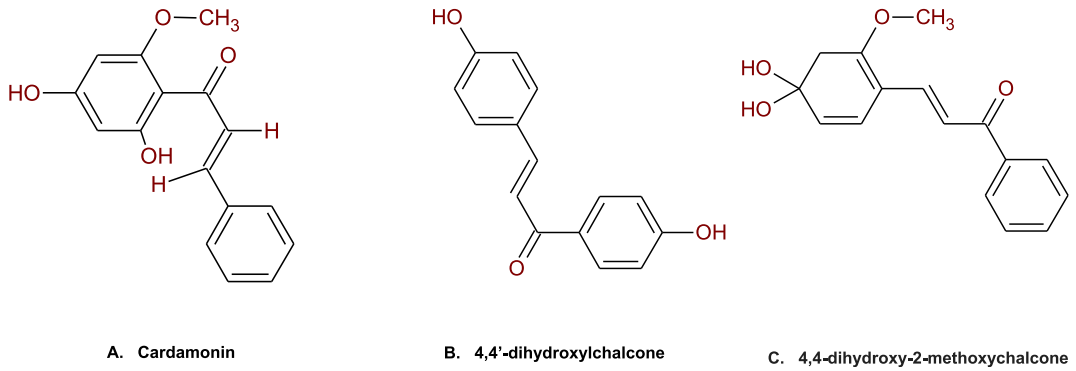

Fig. 1. Structure of cardamonin and its analogs.

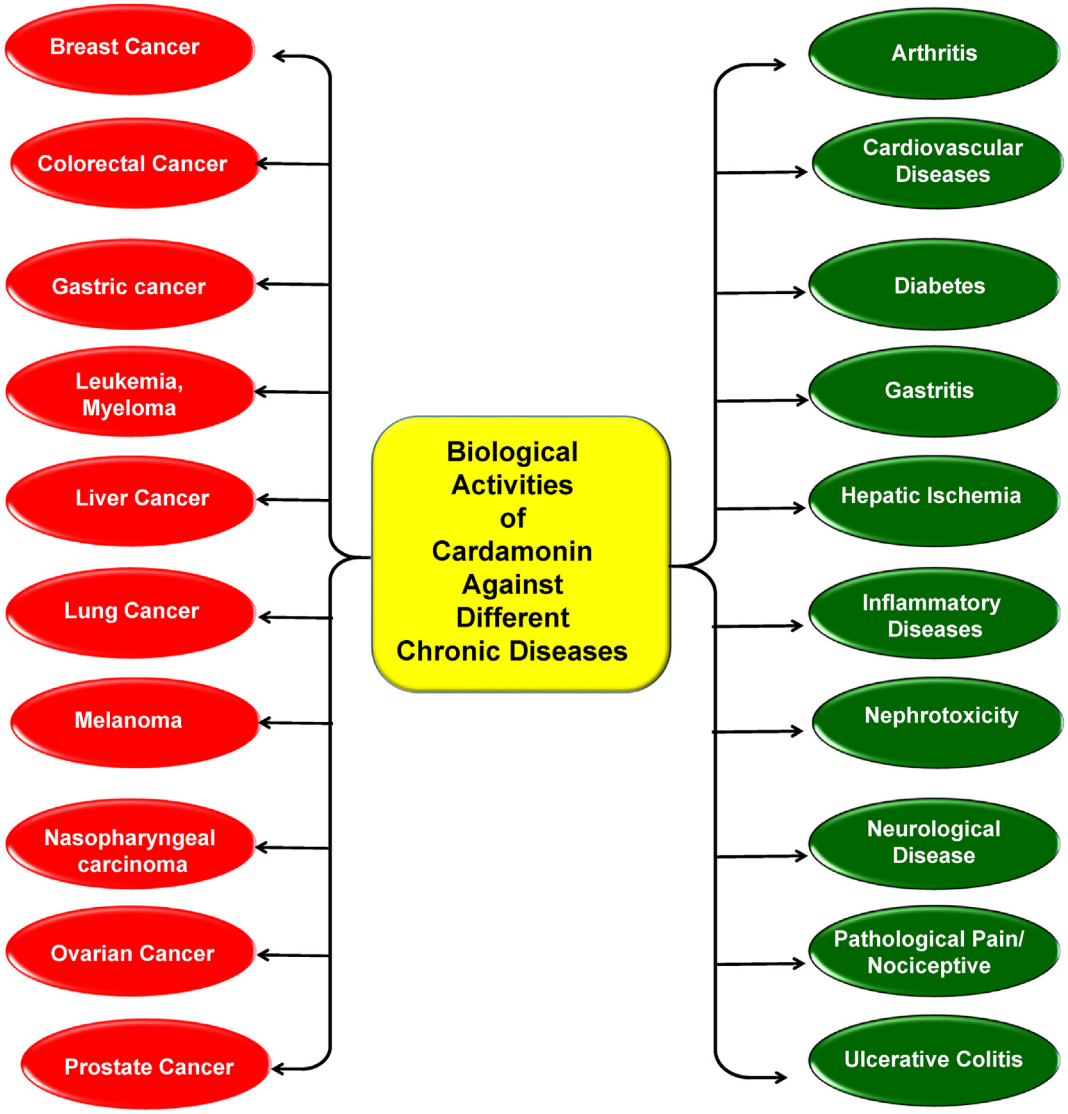

Fig. 2. Therapeutic potential and biological activities of cardamonin against different chronic diseases.

as tissues in due course of time, leading to the development of chronic diseases (Kunnumakkara et al., 2019a, 2020; Harsha et al., 2020). Therefore, targeting a particular pathway/protein/gene is not a sagacious idea in developing novel treatment modalities against these diseases (Kunnumakkara et al., 2008, 2017a, 2017b; Khwairakpam et al., 2018b; Sailo et al., 2018). Consequently, looking beyond conventionally used clinical drugs, multitargeted natural agents have gained the utmost attention as novel drug candidates in the emerging era of pharmaceutical sciences in combating these diseases (Ranaware et al., 2018; Harsha et al., 2017; Kunnumakkara et al., 2009, 2018a, 2018b; Singh et al., 2019). In fact, according to the World Health Organisation (WHO), almost 80% of the world's population relies on the use of phytomedicine

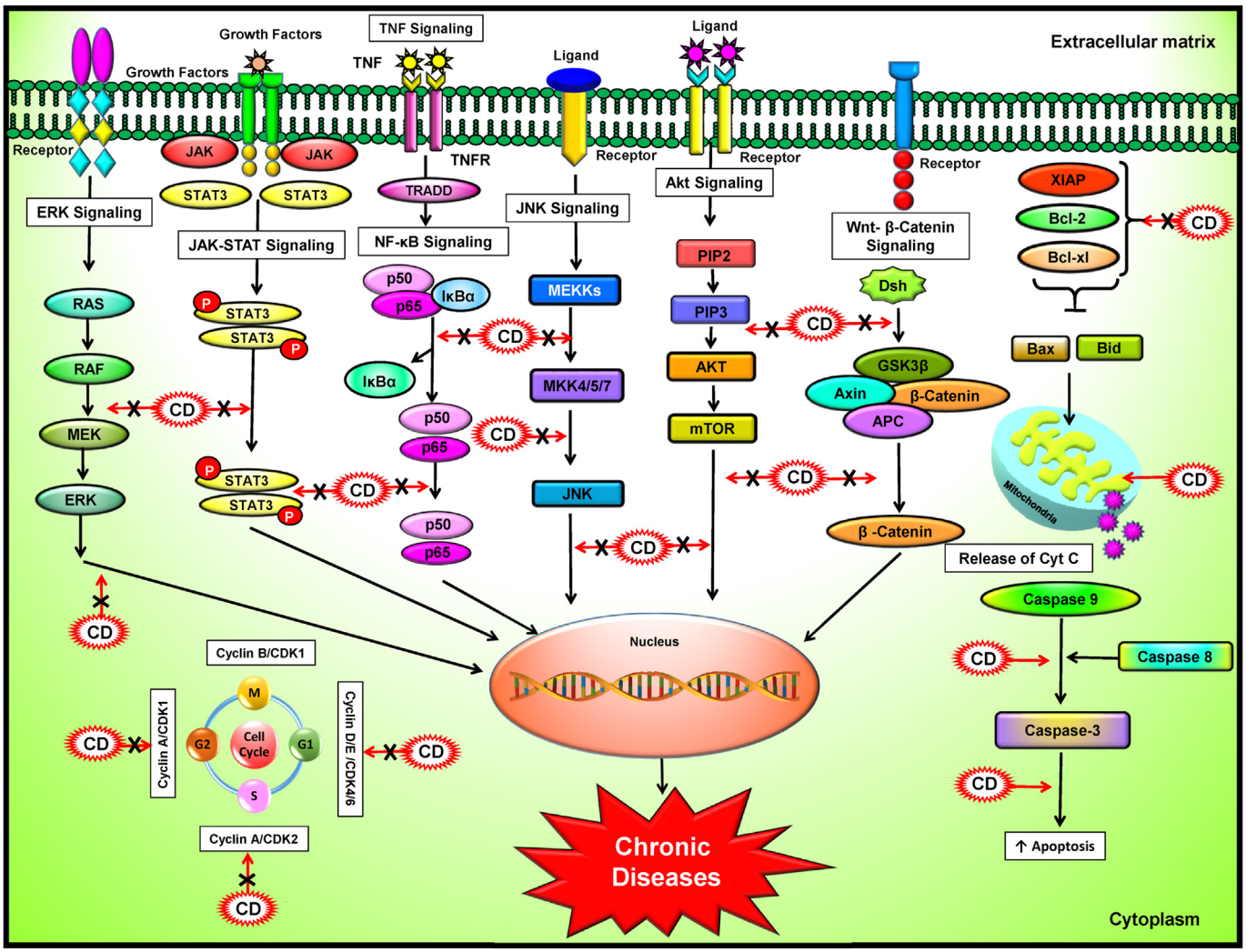

Fig. 3. Cardamonin regulates multiple signaling pathways involved in different chronic diseases.

for the management of various health problems (Roy et al., 2019b; Thakur et al., 2018). Additionally, it has been well-established that natural products have immense therapeutic potential in the prevention and treatment of many chronic diseases, primarily due to their safety, multitargeting properties, and affordability (Padmavathi et al., 2015, 2017; Babu et al., 2003; Kunnumakkara et al., 2012; Thomas et al., 2015; Girisa et al., 2019; Banik et al., 2019, 2020; Roy et al., 2019a; Moacă et al., 2019; Bordoloi and Kunnumakkara, 2018b; Khwairakpam et al., 2018a; Khwairakpam et al., 2018a, 2019; Henamayee et al., 2020). Cardamonin (CD) is one such agent that has gained remarkable attention recently due to its multitargeting properties and its significant potential in the prevention and treatment of many non-communicable diseases, as evidenced by various pre-clinical studies. The present review is an attempt to scientifically review the potential of this compound as a major drug lead for combating various chronic diseases and present the underlying mechanism involved in its action.

2. CD: chemistry and sources

CD is a chalcone, a member of the aromatic ketones' family. It is derived from plants belonging to the Zingiberaceae family (Hou et al., 2019; Nawaz et al., 2020). Different biological properties with its sources are listed in Table 1. This compound is characterized by the presence of an α, β-unsaturated ketone with two aromatic rings. The analogs of CD identified are 2′,4′-dihydroxy-6′-methoxy chalcone (DHMC), and 4, 4′-dihydroxylchalcone (DHC) (de Oliveira Cabral et al., 2017; He et al., 2014) (Fig. 1). CD can be isolated from *Piper aduncum*, *Ginkgo biloba*, *Boesenbergia pandurate, Elettaria cardamomum;* the rhizome of *Boesenbergia pandurata* and *Boesenbergia rotunda*, *Alpenia pricei, Kaempferia parviflora;* fruit of *Campomanesia reitziana;* fruit and the rhizomes of *Alpinia rafflesiana, Alpinia conchigera*, and leaves and seeds of *Carya cathayensis*, *Amomum subulatum*, *Cedrelopsis grevei* (Murakami et al., 1993; Voon et al., 2017; Tewtrakul et al., 2009; Nawaz et al., 2020; de Castro et al., 2015; Gonçalves et al., 2014; de Oliveira Cabral et al., 2017; Jaiswal et al., 2015; Liao et al., 2019; Qin et al., 2012; Ghosh and Rangan, 2013; Bisht et al., 2011; Chahyadi et al., 2014; Ongwisespaiboon and Jiraungkoorskul, 2017; Mingorance et al., 2008; de Souza Duarte et al., 2020; Tian et al., 2014; Sengottuvelu, 2011; Chan et al., 2007; Chaturapanich et al., 2008; de Almeida et al., 2009; Hseu et al., 2011; Ongwisespaiboon and Jiraungkoorskul, 2017).

3. Molecular targets of CD

Accumulating evidence has demonstrated the remarkable potential of CD in combating severe chronic disorders such as diabetes, cancer, cardiovascular diseases (CVD), ulcer, inflammatory diseases, etc., by modulation of multiple pathways (Nawaz et al., 2020) (Fig. 2). Several pre-clinical studies have illustrated the utmost potential of CD as an anti-inflammatory agent. CD significantly inhibits the expression of key pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α),

Table 1
Biological properties of different sources of cardamonin.

Sources	Parts of the Plant	Biological Properties	References
Alpenia conchigera	Leaves, stem, rhizomes	Antibacterial; Antifungal; Apoptotic; Anti-inflammatory	Ghosh and Rangan, (2013)
Alpenia pricei	Rhizome	Apoptotic, Anti-inflammatory	Ghosh and Rangan, (2013)
Amomum subulatum	Seeds	Analgesic activity; Anti-inflammatory; Antimicrobial; Antioxidant; Antiulcer; Cardio-adaptogen activity, Hypolipidemic activity	Bisht et al. (2011)
Boesenbergia pandurate	Rhizome	Antifungal; Antibacterial; Antioxidant	Chahyadi et al. (2014)
Boesenbergia rotunda	Leaf, stem, rhizomes	Anti-allergic; Antibacterial; Anticancer; Anti-inflammatory; Antioxidant; Antiulcer	Ongwisespaiboon and Jiraungkoorskul (2017)
Cadrelopsis grevei	Trunk-bark	Prevents blood pressure and age-related endothelial dysfunction	Minogrance et al. (2008)
Campomanesia areitziana	Fruits	Antinociceptive; Gastroprotective potential	de Souza Duarte et al., (2020)
Carya cathayensis	Leaves	Inhibit VEGF induced angiogenesis	Tian et al. (2014)
Elettaria cardamomum	Seeds	Anti-depressant; Treat heart disorders; Treat dysentery and diarrhea	Sengottuvelu, (2011)
Ginkgo biloba	Leaves	Free radical scavenging; Lower oxidative stress; Reduce neural damages; Lower platelets aggregation; Anti-inflammatory; Anti-tumor; Anti-aging; Anti-neural	Chan et al. (2007)
Kaempferia parviflora	Rhizomes	Increase spermatic blood flow	Chaturapanich et al. (2008)
Piper aduncum	Leaves	Anti-inflammatory; Treat intestinal disorders such as diuretic, pyelitis, cystitis, erysipelas; Wound healing	de Almeida et al., 2009

interleukin (IL)-1β, IL-6, and IL-15 (Ahmad et al., 2006; Kim et al., 2010; Voon et al., 2017; Chen et al., 2018a; Hou et al., 2019). It also decreases the mRNA expression of IL-15 and monocyte chemoattractant protein 1 (MCP-1) (Ren et al., 2015). CD also reportedly decreases the expression of the enzymes such as inducible NO) synthase (iNOS) and cyclooxygenase-2 (COX-2), thereby exerting an anti-inflammatory effect (Kim et al., 2010; Qin et al., 2012; Benchabane et al., 2018). Additionally, this compound also efficiently upregulated the expression of antioxidant enzymes such as superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT). Further, the remarkable antioxidant effect of CD was evinced through a CD-induced increase in levels of heme oxygenase 1 (HO1), NAD(P)H quinone dehydrogenase 1 (NQO1), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1 (NOX-1) (Qi et al., 2020). The antioxidant and anti-inflammatory properties of natural agents have been exploited for the prevention and treatment of chronic diseases in different studies (Babu et al., 2003; Khwairakpam et al., 2018a, 2018b). Therefore, the immense potential of CD in the prevention and treatment of several chronic diseases might be majorly endorsed by its antioxidant and anti-inflammatory properties.

Additionally, CD was shown to modulate the complex molecular network involved in cancer pathogenesis. For example, CD was shown to decrease the expression of caspase-3 which is known to be involved in the regulation of apoptosis in cancer cells (El-Naga, 2014; Qi et al., 2020). Other apoptotic regulators such as B cell lymphoma-2 (Bcl-2) and Bcl-2-associated X protein (Bax) were also modulated by CD treatment. (Shrivastava et al., 2017). Further, CD also suppressed the expression of cyclin D1 and cyclin E, involved in cell cycle regulation, and intercellular adhesion molecule 1 (ICAM-1) which play a vital role in the invasion of cancer cells (Lu et al., 2018; Kong et al., 2019; Qin et al., 2012; El-Naga, 2014). In another study, the expression of growth factors such as vascular endothelial growth factor (VEGF), a regulator of tumor angiogenesis was substantially suppressed by CD (Qin et al., 2012; El-Naga, 2014; Xue et al., 2016). Moreover, CD was shown to suppress different kinases such as interleukin-1 receptor-associated kinase-1 (IL-1R AK), inhibitor κB kinase-α/β, extracellular signal-regulated kinase (ERK), and c-Jun NH2-terminal kinase (JNK) levels which are the major key points in cancer signaling pathways (Ren et al., 2015).

In addition, the treatment with CD was shown to inhibit p-Akt (Akt/protein kinase B) expression, a key protein involved in cancer cell survival, proliferation, invasion, angiogenesis, metastases, chemoresistance, radio-resistance, etc. (Jin et al., 2019). Numerous studies have evidenced that CD effectively inhibits important transcription factors such as nuclear factor kappa B (NF-κB), hypoxia-inducible factor 1 (HIF-1α), microphthalmia-associated transcription factor (MITF), NF-κB, nuclear factor erythroid 2-related factor 2 (Nrf2) factor, octamer-binding transcription factor 4 (Oct-4), forkhead box O3 (FOXO3a), signal transducer and activator of transcription 3 (STAT3), etc. (Li et al., 2017; Cho et al., 2009; El-Naga, 2014; James et al., 2017; Lu et al., 2018; Jin et al., 2019; Kong et al., 2019; Zhang et al., 2017). Thus, several studies suggest that CD has a pivotal role in combating different chronic diseases by targeting various molecules, genes, and multiple pathways (Fig. 3).

4. Biological activities of CD

Recent studies have shed light on the remarkable pharmacological properties of CD in the prevention and treatment of various chronic diseases (Nawaz et al., 2020; Zhou et al., 2019). A critical evaluation of the potential of CD in combating these diseases can be obtained from Table 2, which provides a summary of the pharmacological properties of CD and its mechanism of action in different pre-clinical models. The biological activities of CD against various chronic diseases have been discussed below.

4.1. Cancers

Cancer is considered as the second largest cause of death and prime health concern in the present century. Lack of early diagnostic markers and the inefficacy of presently available therapies makes this disease one of the most dreadful diseases in the world. It is now well-established that cancer is a multistage disease and affects multiple organs of the body by the dysregulation of multiple pathways, genes, and proteins. Therefore, multitargeted agents have colossal potential in the prevention and treatment of this disease. Several lines of studies depicted the multi-targeting properties of CD in different experimental settings and its ability to suppress both solid tumors and hematological malignancies.

CD and solid tumors: The significant potential of CD in the prevention and treatment of different solid tumors were well demonstrated by different groups. Breast cancer is one of the most common cancers among women worldwide (Thakur et al., 2018; Roy et al., 2017). The potential of CD in combating breast cancer has been well studied using different pre-clinical models. CD was shown to suppress breast cancer cell survival, proliferation, epithelial-mesenchymal transition (EMT), etc. in different experimental settings. Triple-negative breast cancer (TNBC) is a rare type of breast cancer that accounts for approximately 10–20% of breast cancer cases and is considered as the most aggressive amongst all types of breast cancers due to high metastatic behavior and poor prognosis (Thakur et al., 2018). Treatment with CD was shown to exhibit chromatin condensation, nuclear shrinkage, suppression of Bcl-2 protein, overexpression of Bax

Table 2
Potential of cardamonin in the prevention and treatment of chronic diseases.

Chronic Diseases	*In vitro/In vivo In silico/Ex vivo*	Model	Mechanism	References
Cancers				
Breast Cancer	*In vitro*	SUM190, MCF-7, Cama-1	↓Colony forming ability, CSCs, ALDH1, Sox 2, ↓c-myc, OCT4, ↓SMYD3, IL-6, IL-8, MCP-1, NF-κB, IκB, STAT3 NANOG, EZH2, SETDB1	Jia et al. (2016)
	In vivo	SUM190 xenograft	↓Tumor growth, CSCs, ALDH1, Sox 2, OCT4, ↓NANOG	Jia et al. (2016)
	In vitro	MCF-7, MDA-MB-231,BT-549	↓Cell proliferation ↓Colony formation, ↑apoptosis, G2/M phase arrest, ↑Bax/Bcl-2, ↓β-catenine ↑E-cadherin, ↓N-cadherin, snail, slug, vimentin, ↓Wnt/β-catenin, cyclin D1, c-Myc, VEGF, CDK-4, ↓Akt-GSK3β	Shrivastava et al. (2017)
	In vivo	4T1 induced tumor	↓Tumor growth	Shrivastava et al. (2017)
	In vitro	MDA-MB-231, MCF-7	↓Cell proliferation, Bcl-2, GSH, ↑caspase-3, Bax, PARP, ROS, Apoptosis, ↑Foxo3a, p21, p27, Bim, p-JNK, G2/M phase arrest	Kong et al. (2019)
	In vivo	MDA-MB-231 xenograft	↓Tumor growth, cyclin D1, Bim, ↑caspase-3, p-JNK, FOXO3a, p21, p27	Kong et al.(2019)
	In vitro	MDA-MB-231 MCF-7, BT-549	↓Cell viability, ↑Apoptosis, Bax, caspase 3, ↓Bcl-2, ↓HIF-1α, PDHK1, LDHA, ↑OXPHOS, ↑ROS, ↓Nrf2, HO-1, NQO-1, mTOR/p70S6K	Jin et al. (2019)
	In vivo	MDA-MB-231 xenograft	↓Tumor growth, Bcl-2/Bax, ↓HIF-1α, ↓LDHA, p-PI3K, p-AKT, p-mTOR, p-P70S6K, ↓angiogenesis;, ↑caspase-3,	Jin et al. (2019)
CRC	*In vitro*	HCT-8	↓Cell viability	Jin et al. (2019)
	In vitro	SW480, LS1748, SW480, DLD-1, HCT116	↓Wnt/β-catenin, cyclin D1, c-myc, ↑G2/M phase arrest, cell viability	Park et al. (2013)
	In vitro	HT-29	↓Cell proliferation, clonogenicity, migration[A]	Memon et al. (2014)
	In vitro	HCT116	↓Cell proliferation, ↑G2/M phase arrest, autophagy, ↑p53/JNK	Kim et al. (2015)
	In vitro	HCT15, HCT116 SW480, SW620	↓Cell proliferation; ↑Apoptosis, S phase arrest, ROS, MD, Bax, p-JNK, p-p38	James et al. (2017)
	In vivo	AOM induced CRC	↓Tumor incidence, multiplicity, ↓NF-κB, p65, Ki-67, β-catenin	James et al. (2017)
	In vitro	HCT-116	↓Cell viability, ↑apoptosis, caspase-3/9, Bax, ↓c-myc, Oct4, cyclin E, NF-κB, TSP50	Lu et al. (2018)
	In vitro	HT-29, SW-460	↓Cell viability, IL-1β, TNF-α, ↓STAT1, STAT3, STAT5	Hou et al. (2019)
	In vivo	DSS + AOM induced CACC	↓IL-1β, TNF-α, p-JAK2, p-STAT1 ↓p-STAT3, p-STAT5	Hou et al. (2019)
Fibrosarcoma	In vitro	HT-1080	↓Tgase-2, ↓MMP-2, ↓NF- κB, ↓MMP-9, ↓cell migration & invasion	Park et al., (2013)
Gastric Cancer	*In vitro*	MGC803	↓Cell viability	Jin et al. (2019)
	In vitro	BGC-823, BGC-823/5-FU	↓Cell viability, ↑apoptosis, G2/M phase arrest, ↓CD44, ALDH1, OCT4, C-myc, β-catenin/TCF4 ↓cyclinD1, P-glycoprotein, Wnt	Hou et al. (2020)
	In vivo	BGC-823/5-FU xenograft	↓Tumor weight, volume	Hou et al. (2020)
	In vitro	AGS	↓Cell viability, ↑apoptosis, Bax, caspase-3, ↓Bcl-2 ↓colony formation, CDK1, Cyclin B1, CDC25 ↑p21, ↓cell migration, invasion, ↑E-cadherin, ↓snail, ↓α-SMA, STAT3, vimentin,	Wang et al. (2019a)
HCC	*In vitro*	HepG2	↓Cell viability, ↑G1 phase arrest, apoptosis, ↑caspase-3/7, −8, −9, Fas, TRAIL, H1F, FADD, ↑DR4, DR5, CD95, cyt *c*, p-p53, ↓ HSP-60, -27, −70, ↓XIAP, catalase, clusterin, survivin, TNF-α, NF-κB, ↑ROS	Badroon et al. (2020)
Leukemia	*In vitro*	WEHI-3	↑ROS, Ca2+, caspase-3, -8 and -9, Bax, cyt *c*, AIF, Endo G, GRP78, caspase-12, Fas, Fas-Ligand, FADD, DAP, TMBIM4, ATG5; ↓Bcl-2, DDIT3, DDIT4, BAG6, BRAT1	Liao et al. (2019)
	In vivo	WEHI-3 xenograft	↑CD19, ↓Mac-3, CD3, CD11b, ↑phagocytosis of macrophages, cytotoxicity of NK cells, ↑survival rate	Liao et al. (2020)
Lung Cancer	In vitro	A549, NCI-H1299, NCI-H460, NCI-H1688, NCI-H446, primary cell line 1,2	↓Cell viability[B]	He et al. (2014)
	In vitro	A549, NCI-H460	↑Apoptosis, ↑caspase-3, PARP, ↓IKKβ, NF-κB[B]	
	In vitro	LLC	↓Cell viability, invasion, migration, ↑E-cadherin ↓p-mTOR, p-S6K1, Snai1	Niu et al., (2015)
	In vivo	LLC transplant	↓Tumor growth, lung metastasis	Niu et al., (2015)
	In vitro	A549, H460, H292, H1299, H1975	↓Cell viability, EMT, ZEB1, Bcl-2 PI3K/Akt/mTOR, ↓Colony formation, N-cadherin, cyclin D1/CDK4, migration, invasion, ↑E-cadherin, G2/M phase arrest, apoptosis, caspase-3, Bax	Zhou et al. (2019)
	In vivo	H460 xenograft	↓Tumor growth, Ki-67, PI3K/Akt/mTOR	Zhou et al. (2019)
	In vitro	A549	↓Cell migration, G2/M phase arrest, ↑apoptosis, ↑caspase-3/7, ↑caspase-9, ↑PARP cleavage, ↓Mcl-1, ↓p-mTOR, ↓p-4EBP1[C]	Break et al., (2018)
Melanoma	*In vitro*	A375	↓Cell viability, invasion, ↑apoptosis, caspase-3, ↑PARP	Berning et al. (2019)
Myeloma	*In vitro*	RPMI 8226, U266, ARH-77, RPMI 8226	↓Cell proliferation ↑ Apoptosis, caspase-3, PARP, ↓Bcl-2, Bcl-xL, ↓ survivin, XIAP, cIAP-1, cIAP-2, NF-κB/p65, ↓IKK, IKKβ, p-IκBα, ICAM-1, COX-2, VEGF	Qin et al. (2012)
NPC	*In vitro*	HK1	↓Cell migration, G2/M phase arrest, ↑apoptosis, ↑caspase-3/7, ↑caspase-9, ↑PARP cleavage, ↓Mcl-1, ↓p-mTOR, ↓p-4EBP1[C]	Break et al., (2018)
Ovarian Cancer	*In vitro*	SKOV3	↓Cell viability, VEGF, HIF-1α, HIF-2α, ↓p-mTOR, p-S6K1	Xue et al., (2016)
	In vitro	SKOV3	↓p-Raptor, mTORC1, p-S6K1, Lamp2	Shi et al. (2018a)
	In vitro	SKOV3	↓Glycolysis, HK, LDH, ↑autophagy, LC3-II, ↑LAMP1, ↓p-S6K1, p-mTOR, HK2, ↑p-AMPK	Shi et al. (2018b)
	In vitro	SKOV3	↓Cell viability, ↑autophagy, ↑LC3-II, ↑apoptosis, ↑caspase-3, PARP, ↓Raptor, mTOR, S6K1	Shi et al. (2018c)
	In vitro	SKOV3, A2780 SKOV3	↓Cell viability, colony formation ↑G2/M phase arrest, ↓XIAP, survivin, Bcl-2, ↓mTOR, p70S6K	Niu et al. (2018)
	In vitro	SKOV3	↓Cell viability, S6 kinase 1, TNF-α, IL-6, NF-κB	Chen et al. (2018b)
PC	*In vitro*	DU145, LNCaP		Zhang et al. (2017)

(*continued on next page*)

Table 2 (*continued*)

Chronic Diseases	*In vitro/In vivo In silico/Ex vivo*	Model	Mechanism	References
			↓STAT3, JAK2, ↓cell proliferation, ↑apoptosis ↑caspase-3, -8, -9, PARP, ↓Bcl-xl, Bcl-2, Survivin, ↓ XIAP, VEGF, COX2, MMP9, Cyclin D1, CDK4, ↓Cyclin E, CDK2, ↓migration, invasion, ↑metastasis	
	In silico		↓STAT3, SH2 domain	Zhang et al. (2017)
	In vitro	PC-3	↓Cell growth, ↑apoptosis, ↓NF-κB1	Pascoal et al., (2014)
CVD	*In vivo*	Mesenteric arteries	↑CDR; ↓PIC, SCE, TCR	Wang et al., (2001)
	In vivo	Rat tail artery myocytes	↑ KCa1.1, ↓ICa(L), IBa(L), Cav1.2	Fusi et al. (2010)
	In vivo	DOX-induced cardiotoxicity	↑Nrf2, HO1, NAD(P), (NQO1), GCLM, SOD, GSH, CAT, ↓MDA, ROS, Caspase-3, NF-κB	Qi et al. (2020)
	In vitro	H2C9	↓4E-BP1, S6, mTOR-Raptor	You et al. (2018)
	In vivo	LPS treated C57 mice	↓Contractile defects, apoptosis, oxidative stress, ↓LPS induced Nrf2 signaling, inflammation, NK-κB	Tan et al. (2020)
Diabetes	*In vivo*	FEIR SD rats	↑ISI, ↓VSMC, VT, mTOR, HOMA-IR ↓4E-BP1, p-P70S6K1	Liao et al., (2010)
Gastritis	*In vitro*	EtOH/HCl induced gastric ulcer	↑LOOH, oxidative stress, SOD ↓ GSH	de Oliveria Cabral et al. (2017)
HI	*In vitro*	weight hanging method	↑NO, eNOS expression; ↓iNOS, ↓NF-κB, TNF-α, ↓Bcl-2,	Atef et al. (2017)
ID	*In vitro*	RAW264.7	↓TNF-α, IL-6, IL-1β, NF-κB, NO, PGE2, iNOS,COX-2 mRNAs, IL-1β mRNA, ROS	Kim et al. (2010)
	In vitro	HT-29, LS174T, RAW264.7	↓NF-κB, LPS, MAPK	Ren et al. (2015)
	In vivo	DSS induced colitis	↓iNOS, COX-2, MCP-1, TNF-α, IL-6, IL-15, NF-κB, MAPK, TLR4	Ren et al. (2015)
	In vitro	BMDMs, PBMCs	↓caspase-1, IL-1β, NLRP3	Wang et al. (2019b)
	In vivo	LPS induced septic shock	↓ NLRP3, caspase-1, IL-1β	Wang et al. (2019b)
Arthritis	*In vitro*	CFA Induced Cells	↓TNF-α, IL-1β, IL-6	Voon et al., (2017)
Pathological Pain/ Nociceptive	*In vitro*	MG63, RAW264.7	↑IκB; ↓Tgase-2, COX-2, p65,NF-κB	Park et al. (2014)
	In vivo	CIC	↓WR, COX-2, Tgase-2	Park et al. (2014)
	In silico	HEK293	↓TRPA1	Wang et al. (2016)
	In vivo	ACIAWR Model FIPL Model, Hot Plate Test GIPL Model	↓capsaicin-induced nociception	Ping et al. (2018)
Ulcerative colitis	*In vivo*	acetic acid induced	↓MPO, iNOS, NF-κB, TNFα, MDA, COX-2, caspase-3	Ali et al. (2017)
Nephrotoxicity	*In vivo*	cis induced *nephrotoxicity*	↓caspase-3, ↓Bax/Bcl-2, NOX-1, IL-1β, TNF-α, NF-κB, iNOS, MCP-1, ICAM	El-Naga (2014)
Neuropathic Pain	*In vitro*	PCI2	↑Nrf2, HO-1, NQO1, Trx1, TrxR1, GCLC, GCLM; ↓LDH, caspase-3, ROS	Peng et al. (2017)
Sjögren's Syndrome	*ex vivo*	BMCI-pSS	↓TNF-a, IL-6, NO, iNOS, NF-κB	Benchabane et al. (2018)

Notations.

[A]Dimethyl cardamonin or 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (DMC).

[B]Cardamonin analogs 4,4′-dihydroxylchalcone (DHC) and 4,4′-dihydroxy2′-methoxychalcone (DHMC).

[C]Cardamonin analog Compound 19.

Abbreviations: AAI Model = acetic acid-induced model; AE = Antihyperalgesic Effects; ALDH1 = aldehyde dehydrogenase 1; AP = activator prostratin; AOM = Azoxymethane; ATG5 = Autophagy related 5; AWR Model = abdominal writhing response model; BAG6 = BCL2-Associated Athanogene 6; BCL2L13 = BCL2-like 13 (apoptosis facilitator); BMCI-PSS = blood mononuclear cells isolated from pSS patients; BMDMs = bone-marrow-derived macrophages; BRAT1 = BRCA1-associated ATM activator 1; CA= Cold Allodynia; CAT = catalase; Cca = Cell Cycle Arrest; CCA = cardiac contractile abnormality; CCC = cancer cell migration; CCF = cancer cell colony formation; CCI = chronic constriction injury; CCP = cell cycle progression; CDK 4 = cyclin dependent kinase 4; CDR=Concentration dependent relaxation; CFA = complete Freund's adjuvant; CIC= Carrageenan-induced cells; CIS=Cisplatin; c-JNK = c-Jun N-terminal kinase; COX-2 = cyclooxygenase-2; CRC= Colorectal Cancer, CVD= Cardiovascular Diseases; cyt-C = cytochrome; DAP = Death Aassociated Protein; DDIT3 = DNA-Damage Inducible Transcript; DDIT4 = DNA-Damage-inducible Transcript 4; DSS = dextran sulfate sodium; DMC = dimethyl cardamonin; FEIR = fructose-enriched insulin resistant; FIPL Model = Formalin-Induced Paw Licking Model; FOXO3a = Forkhead box O3; 5-FU = 5-fluorouracil; G2/M CCA = G2 phase cell cycle arrest; GCLM = glutamate-cysteine ligase modifier subunit; GIPL model = glutamate-induced paw licking model; GSH = glutathione; HCC= Hepatocellular Carcinoma; HO1 = heme oxygenase-1; HI=Hepatic ischemia;; HOMA-HSP=High shock proteins; IR: = homeostasis model assessment for insulin resistance; ID=Inflammatory Diseases; IL = interlukin; iNOS = inducible nitric oxide synthase; ISI-=Insulin Sensitivity Index; JNKs = Jun N-terminal kinases; LAPE = lactic acid production and efflux; LOOH = lipidhydroperoxide, LIDCS = LPS-induced defect in cardiomyocyte shortening; LPS = lipopolysaccharide; MA = Mechanical Allodynia; MAPK = mitogen-activated protein kinase; MCD = Myocardial Contractile Dysfunction; MCP-1 = monocyte chemoattractant protein 1; MD = mitochondrial depolarization; MDA = malondialdehyde; MMP = matrix metalloproteinases; MOP = mitochondrial oxidative Phosphorylation; MPO = Myeloperoxidase; NAC=N-acetyl-cysteine; NC=Nuclear Condensation; NF-κB = Nuclear Factor kappa B; NO=Nitric Oxide; NLRP3 = NOD-LRR- and pyrin domain containing protein 3; NPC= Nasopharyngial carcinoma; NQO1 = NAD(P)H:quinone oxidoreductase 1; Nrf2 = nuclear factor erythroid-2 related factor 2; NT = nuclear translocation; OBTF 4 = octamer-binding transcription factor4; OS= Oxidative Stress; TSP50 = testes-specific protease 50;; p-Akt = phosphorylated-Akt; p-4EBP1 = phosphorylated 4E binding protein 1; PBMCs = human peripheral blood mononuclear cells; PC=Prostate Cancer; PGE2 = prostaglandin E2; PIC = phenylephrine induced contraction; PKB = protein kinase B; p-mTOR = phosphorylated-mTOR; pSS = Primary Sj¢ogren's syndrome; PVT1 = Plasmacytoma Varient Translocation 1; ROS = Reactive Oxygen Species; SCE=Sustained Contraction by Endothelin I; SOD = superoxide dismutase; Tgase-2 = .transglutaminase-2; S6K1 = S6 kinase 1 TH = Thermal Hyperalgesia; TMBIM4 = transmembrane BAX inhibitor motif containing 4; TNF-α = tumor necrosis factor-α;; TLR4 = toll-like receptor 4 signaling; TRPA1 = transient receptor potential ankyrin 1; TxB2 = thromboxane B2; UC=Ulcerative Colitis; VEGF= Vascular Endothelial Growth Factor; VSMC = vascular smooth muscle cells; VT = vascular thickening; WR=Writhing Response.

protein, and cleavage of caspase-3 in TNBC cells. CD also suppressed hypoxia inducible factor-1 (HIF-1)α and β-catenin and induced cell cycle arrest at the G2/M phase in TNBC cell lines and also suppressed the development of xenograft tumors in animals (Shrivastava et al., 2017). Another study showed that CD effectively abrogated Toll like receptor 3 (TLR3)activation-induced cancer stem cells (CSC) phenotypes *in vitro* and suppressed TLR3 stimulation-induced breast tumor growth in animals (Jia et al., 2015). The same group has also shown that CD in combination with 5-fluorouracil (5-FU), doxorubicin and paclitaxel suppressed breast CSCs through inhibition of the expression of cytokines such as IL-6, IL-8, and MCP-1 and transcription factors like NF-κB and STAT3 (Jia et al., 2016). Moreover, CD was found to sensitize breast cancer cells to doxorubicin *in vivo* (Jia et al., 2016). In another study, CD remarkably suppressed the proliferation of MDA-MB -231 and MCF-7 breast cancer cells through G2/M phase cell cycle arrest and induced apoptosis by increasing the nuclear translocation of Forkhead box O3 (FOXO3a) and its target genes, p21, p27, and Bim. Furthermore, CD downregulated cyclin D1 and activated caspase-3, and suppressed xenograft breast tumors in mice (Kong et al., 2019). Recent studies have shown that CD inhibited breast cancer cell growth and proliferation via targeting HIF-1α and mTOR/p70S6K pathway (Jin et al., 2019; Niu et al., 2020).

Many studies have demonstrated the potential of CD against colorectal cancer and gastric cancer. For example, a recent study demonstrated that CD inhibited cell proliferation of SW620 colorectal cancer cells by inducing S phase arrest and apoptosis via suppressing the NF-κB pathway (James et al., 2017). Studies have also shown that CD induced autophagy as well as G2/M phase arrest in HCT116 cells and inhibited Wnt/β-catenin pathway, cyclin D1, and c-myc expression in SW480 colon cancer cells (Kim et al., 2015; Park et al., 2013). Recently, it has been shown that CD induced apoptosis in chemotherapy-resistant HCT-116 colon cancer cells by increasing caspase 3/9 activity, Bax protein expression and downregulating c-myc, octamer binding transcription factor 4 (OBTF 4), cyclin E, testis-specific protease 50 (TSP50) as well as NF-κB protein expression which proves its chemosensitizing effect in cancer cells (Lu et al., 2018). Moreover, in a recent study, it was observed that CD enhanced the sensitivity of gastric cancer cells to 5-FU by downregulating the β-catenin signaling pathway (Hou et al., 2020). The anticancer effect of CD was again evident against GC cells where it was found to promote apoptosis by blocking the cell cycle progression at the G0/G1 phase. The expression of the apoptotic regulators such as Bax, Bcl-2, and caspase-3 was also modulated by CD. Further, it also inhibited the levels of p-STAT3 via the inhibition of the lncRNA, plasmacytoma variant translocation 1 (PVT1) (Wang et al., 2019a).

Accumulating lines of evidence suggest that CD has significant potential in the treatment of cancers of lung, skin, ovary, and prostate. . The mammalian target of rapamycin (mTOR) is the main cause of survival, proliferation, and invasion of lung cancer cells (Romaszko and Doboszyńska, 2018). Recent studies have shown that CD inhibited lung cancer cell proliferation, invasion, and migration via suppressing the expression of mTOR and Snail in lung cancer cells (Niu et al., 2015). Besides, CD remarkably inhibited tumor growth of H460 lung cancer cells induced xenografts, by suppressing Ki-67 and phosphoinositide 3-kinases (PI3K)/protein kinase B (Akt)/mTOR pathway, thus indicating its potential as an effective therapeutic agent (Zhou et al., 2019). Moreover, CD analogs, 4,4′-dihydroxylchalcone (DHC) and 4,4′-dihydroxy-20-methoxychalcone (DHMC), were observed to induce apoptosis in A549 and NCI-H460 cells by suppressing the NF-κB pathway (He et al., 2014). A couple of studies have demonstrated the role of CD in combating skin cancer. For instance, in an experimental study, CD derived from *Alpinia katsumadai* Hayata was shown to suppress pigmentation in melanocytes by inhibiting Wnt/β-catenin signaling pathway and it also repressed differentiation biomarkers such as MITF and tyrosinase (Cho et al., 2009). In addition, the treatment of CD was shown to induce apoptosis, suppress cell proliferation, invasion, etc. in human malignant carcinoma cell lines (Berning et al., 2019). These studies indicated the possible use of CD as a therapeutic agent against melanoma (Shannan et al., 2016).

Prostate cancer and ovarian cancer are some of the most common cancers in males and females respectively. Ovarian cancer stands the seventh most occurring cancer and the eighth leading cause of death in women suffering from cancer with a 5-year survival of less than 45% (Webb and Jordan, 2017). *In vitro* studies revealed that CD induces autophagy via the inhibition of mammalian target to rapamycin complex 1 (mTORC1) activity in ovarian cancer cells by decreasing the expression of raptor protein (Shi et al., 2018a, 2018b). Another study suggests that CD-induced autophagy by inhibiting the glycolysis pathway and the activity of mTORC1 in ovarian cancer cells (Shi et al., 2018b). CD also suppressed the protein expression of HIF-α and vascular endothelial growth factor (VEGF) in cobalt chloride (CoCl2)-mimicked hypoxic SKOV3 cells indicating its potency against ovarian cancer (Xue et al., 2016). Besides, CD in combination with cisplatin was shown to inhibit mTOR and anti-apoptotic proteins, which led to an enhanced anti-proliferative effect against ovarian cancer cell lines (Niu et al., 2018). Prostate cancer has been recognized as the second most occurring and heritable cancer worldwide (López-Abente et al., 2014; Barber et al., 2018). It has become very common in recent times among men. An *in vitro* study demonstrated that CD significantly regulated the STAT3 expression, an important transcription factor overexpressed in prostate cancer and plays a vital role in cancer cell survival, proliferation, invasion, angiogenesis, and metastases, in DU145 prostate cancer cells. Further, it was also shown to significantly inhibit STAT3 DNA binding activity and hinder the accumulation of STAT3 nuclear pool. In addition, CD also reduced cyclin D1, cyclin-dependent kinase 4 (CDK4), cyclin E, cyclin-dependent kinase 2 (CDK2) protein expressions, thus indicating suppression of the cell cycle. The upregulation of caspase-3, 8, and 9, and enhanced cleavage of poly ADP ribose polymerase (PARP) led to a high occurrence of apoptosis in prostate cancer cells. Further, the treatment of prostate cancer cell lines with CD inhibited proliferation, migration, and invasion of the cancer cells (Zhang et al., 2017).

Besides, CD was also shown to significantly inhibit other commonly occurring solid tumors such as hepatocellular carcinoma and nasopharyngeal carcinoma (NPC) in pre-clinical experimental settings. For example, it was shown that CD induced G1 phase arrest and inhibited the proliferation of HepG2 cells. It significantly enhanced the activities of caspase-3/7, −8, and −9 and inhibited the NF-κB pathway, and induced apoptosis by activating the intrinsic as well as extrinsic apoptotic pathways (Badroon et al., 2020). In another study, it was observed that CD analog decreased cell migration of HK1 cells by inducing apoptosis and induced cell cycle arrest at the G2/M phase. These results suggested that CD and its analogs are promising anticancer agents against nasopharyngeal carcinoma (NPC) (Break et al., 2018).

CD and hematological malignancies: The potential role of CD in combating leukemia and multiple myeloma, two commonly occurring hematological cancers, were studied by different groups. For example, a couple of studies have demonstrated the significant potential of CD in the treatment of leukemia. CD was shown to induce apoptosis in leukemic cells by regulating the expression of anti- and pro-apoptotic proteins such as Bcl-2 and Bax, respectively, *in vitro*. Moreover, it also substantially elevated the levels of reactive oxygen species (ROS) as well as Ca^{2+} and caused G0/G1 phase arrest in these cells (Liao et al., 2019). Also, the administration of CD was shown to enhance the survival rate of leukemic mice and improved the phagocytic capability of macrophages (Liao et al., 2020). In another study, it was observed that CD is capable of reducing tumor cell survival and inducing apoptosis in RPMI 8226, U266, ARH-77 myeloma cells by suppressing anti-apoptotic proteins like B-cell lymphoma 2 (Bcl-2), survivin, X-linked inhibitor of apoptosis protein (XIAP), cellular inhibitor of apoptosis protein 1 (cIAP-1) and -2, as well as intercellular adhesion molecule 1 (ICAM-1), COX-2 and VEGF as a result of the downregulation of the NF-κB pathway, the prime mediator responsible for carcinogenesis (Qin et al., 2012).

In addition, the effect of CD on chemotherapy-induced toxicities was also studied. For example, cisplatin, a chemotherapeutic drug used in the treatment of different types of cancer, is a well-known nephrotoxic agent.

Therefore, the agents that can inhibit cisplatin-induced nephrotoxicity has high potential in the treatment of cancer. Interestingly, CD was shown to attenuate cisplatin-induced nephrotoxicity and inflammation in an *in vivo* model by downregulating the cisplatin-induced expression of NOX-1. Furthermore, CD also suppressed the expression of caspase-3 and Bax/Bcl-2 ratio in this model. Thus, CD exhibited its potent therapeutic efficacy by enhancing the cytotoxic potential of cisplatin and simultaneously reducing its nephrotoxicity (El-Naga, 2014).

These studies showed that CD has high potential in the prevention and treatment of different cancers; however, further studies are warranted to validate and establish its role in pre-clinical and clinical settings.

4.2. Cardiovascular diseases (CVDs)

CVD is the leading cause of mortality in the world with around 17.7 million deaths annually (Nitsa et al., 2018). CVD mainly manifests heart attacks and strokes, which are responsible for taking a large number of lives every year (Nitsa et al., 2018). A study reported that CD acts as a bifunctional vasodilator by continuously suppressing I_{Ca} (L) and activating $K_{Ca}1.1$. Additionally, CD and alpinetin cumulatively induced relaxation of phenylephrine preconstructed arteries (Wang et al., 2001; Fusi et al., 2010). Further, CD also exerts cardioprotective effects against doxorubicin (DOX) induced cardiotoxicity *in vivo* by attenuating oxidative stress and inflammation. It exerted antioxidant effects by elevating the levels of enzymes associated with the antioxidant system such as HO1, NQO1, SOD, GSH, and catalase. Further, DOX-induced elevated levels of TNF-α, IL-1β, and IL-18 were attenuated by CD treatment (Qi et al., 2020). In addition, the effect of CD on myocardial infarction (MI) was also studied by using animal models. Administration of CD in lipopolysaccharide (LPS) induced mice showed protection against LPS-induced cardiac contractile dysfunction, oxidative stress, apoptosis, and inflammation occurring through Nrf2-and NF-κB-dependent mechanism (Tan et al., 2020). A study showed that the administration of CD in a MI *in vivo* model ameliorated cardiac dysfunction and hypertrophy. Further, a significant reduction in cardiac fibrosis, size of cardiomyocyte, as well as cell apoptosis was observed. Moreover, CD downregulated 4E-BP1 and S6 phosphorylation *in vitro* and *in vivo* and suppressed the mTORC1 signaling, thereby making it a potential lead for developing drugs against CVDs (You et al., 2018).

4.3. Diabetes

Diabetes is one of the most common metabolic diseases in the world. It is identified by the body's inability to process the glucose present in the blood and can be fatal in many instances. Therefore, the development of efficacious therapies is imperative for the clinical management of this disease. The administration of CD to a high fructose-fed rat diabetic model was shown to downregulate mTOR, P70S6K1, 4E-binding protein1 (4E-BP1), and ribosomal protein S6 kinase 1 (p-P70S6K1) involved in insulin resistance. This phenomenon is very common in diabetic patients, therefore, CD is a potential molecule in the prevention and treatment of diabetes (Liao et al., 2010).

4.4. Inflammatory diseases

Inflammatory diseases comprise over 100 different ailments such as arthritis, colitis, esophagitis, gastritis, pancreatitis, etc. Non-steroidal anti-inflammatory drugs and steroids are the conventional medications for the treatment of these diseases; however, their long-term uses are not devoid of disturbing side effects. Also, many of the inflammatory diseases are known to cause several non-communicable diseases. Therefore, the search for safe, affordable, and highly efficacious anti-inflammatory drugs is crucial, which would help us to effectively manage these diseases (Cipolla et al., 2002; Kunnumakkara et al., 2020). CD is one such compound that has been shown to have significant antioxidant and anti-inflammatory properties. Besides, CD was shown to suppress different inflammatory cytokines such as TNF-α, IL-6, etc. and different transcription factors involved in inflammation such as NF-κB and STAT3 (Hou et al., 2019; Kim et al., 2010; Wang et al., 2019b).

Pain is one of the most common pathological discomfort prevailing among the population of all ages. It plays an important role by warning the occurrence of a certain disease. A study reported that CD exhibits potent peripheral and central antinociception *in vivo*. Although the exact mechanism of the antinociceptive property of CD is poorly known, it was reported that CD modulate transient receptor potential cation channel subfamily V member 1 ($TRPV_1$), glutamate, and opioid receptors which would help in relieving the pain (Ping et al., 2018; Nesello et al., 2016). In another study, CD was shown to suppress inflammatory molecules and enzymes such as IL-1β-induced, COX-2, and transglutaminase (Tgase-2) expression in MG63 and Raw264.7 cell lines (Park et al., 2014). Transient receptor potential channels (TRP) are ion channels that modulate the pain signal transduction pathways. The transient receptor potential ankyrin 1 (TRPA1) is an ion channel associated with nociceptive transmission. In an *in silico* study, it was demonstrated that CD is a selective TRPA1 antagonist, suggesting novel insights into the target of its anti-nociceptive property (Wang et al., 2016). Besides, the potential of CD on Rheumatoid arthritis (RA), an autoimmune disorder that causes inflammation, pain, and swelling in the joints was also demonstrated in an *in vivo* model (Smolen et al., 2010, 2016; Voon et al., 2017). It is now well established that inhibitors of TNF-α have high potential in the management of this disease. Interestingly, a recent study has demonstrated that CD suppressed the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 and exerts potent anti-arthritic property in complete Freund's adjuvant-induced RA *in vivo* model (Voon et al., 2017).

Gastrointestinal (GI) diseases are a major health concern prevailing in the society. It affects a major portion of the population worldwide (de Oliveira Cabral et al., 2017). A study reported that the methanolic extract of *Campomanesia reitziana* fruits (MECR) containing CD showed a reduction of gastric lesions in an ethanol/hydrochloric acid (HCl)-induced gastric ulcer *in vivo* model. In addition, dimethyl cardamonin (DMC), an analog of CD isolated from MECR, exhibited a similar result. Further, MECR elevated the mucin content as well as the activity of SOD, suggesting its gastroprotective properties (de Oliveira Cabral et al., 2017). Moreover, the effect of CD in ameliorating ulcerative colitis (UC) was also investigated in the acetic acid-induced colitis *in vivo* model. This study reported that CD substantially reduced acetic acid-induced histopathological deterioration and inhibited the levels of myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), NF-κB, and TNFα. Moreover, the expression of COX-2 and caspase-3 was also downregulated by CD administration. Thus, the study suggested that CD is a potential candidate in the prevention and treatment of UC (Ali et al., 2017).

Hepatic ischemia-reperfusion (I/R) injury is a major complication that might be caused during transplantation or resection. It leads to the production of excessive oxidative stress which might induce detrimental effects on the cellular structure as well as the function of the liver (Gim and Koh, 2015). Atef et al. (2017) conducted an extensive study on the role of CD in a hepatic I/R injury-induced *in vivo* model. The study reported that CD exerted antioxidant effects by downregulating the level of MDA and increasing the expression of antioxidant molecules and enzymes such as GSH, catalase, etc. CD further inhibited inflammatory mediators such as NF-κB and TNF-α and downregulated iNOS expression but upregulated NO level by increasing endothelial nitric oxide synthase (eNOS) expression (Atef et al., 2017).

4.5. Neurological diseases

Neuropathic pain is a common medical condition prevailing at a rate of 7–10% among the general population (Zilliox, 2017). The condition is very complex and hard to be treated due to the ineffectiveness and unfavorable effects of the currently available medications. In a study, CD

was shown to inhibit chronic constriction injury (CCI)-induced neuropathic pain in a mouse model by using the Dynamic plantar anesthesiometer test, Cold plate test. Hargreaves plantar test and Randall-Selitto analgesiometer test. This study demonstrated CD as a potential lead component for the treatment of neuropathic pain (Sambasevam et al., 2017). Oxidative stress can damage the brain due to excess polyunsaturated fatty acids, which make it susceptible to free radical attacks. Excessive production of ROS is involved in the pathogenesis of a wide range of neurodegenerative (NDG) conditions like Alzheimer's and Parkinson's disease. Therefore, maintaining redox homeostasis in the brain is necessary to avoid NDG conditions. The Nrf2-antioxidant response element (Nrf2-ARE) pathway is an antioxidant defense responsible for maintaining redox homeostasis in the cells. CD is an antioxidant and therefore has a high potential in the prevention and treatment of neurodegenerative diseases. In a study, Peng et al. (2017) showed that the treatment of PC-12 with CD activated Nrf2, one of the key molecule involved in the amelioration of oxidative stress. This makes CD a powerful agent in the management of oxidative stress and associated NDG diseases (Peng et al., 2017).

5. Pharmacokinetic properties of CD

Despite the remarkable biological properties of CD, not many studies have been reported on the pharmacokinetic and pharmacodynamic activities. Jaiswal et al. (2015) conducted a study to evaluate the bioavailability of CD on male and female Sprague-Dawley rats using the Liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. In this study, CD was administered to both male and female rats intravenously as well as orally, and the results indicated poor systemic bioavailability of CD in both genders. However, bioavailability was higher in female rats, indicating better absorption of CD in female rats. The distribution and elimination of CD were also higher in female rats. It was inferred that CD being lipophilic in nature bound more to female rats because females possess more fat than males. From the study, it could be concluded that gender plays a significant role in the pharmacokinetic effect of CD in rats (Jaiswal et al., 2015). Another study by the same group (Jaiswal et al., 2017) showed that CD is a partially soluble and highly permeable compound. Further, it gets attached to plasma proteins and is uptaken by the RBCs in a very low amount. It is poorly absorbed and excreted outside the body in more quantity via feces rather than in urine. Though numerous pre-clinical studies have been carried out for assessing the efficacy of CD in a disease setting, it has yet to enter human clinical trials. Thus, there remains a scarcity of research on safety and bio-availability in human systems. Therefore, more studies are crucial for a proper understanding of the poor bioavailability of CD and seek better ways to improve its pharmacokinetic behavior in order to attain maximum clinical benefits (Jaiswal et al., 2017).

6. Conclusion and future prospects

CD, a natural chalconoid, has recently gained attention due to its profound pharmacological and medicinal value. Recent research has exhibited CD to possess anticancer, anti-inflammatory, antidiabetic, antinociceptive, and other protective features against various factors responsible for causing chronic diseases. Moreover, CD has been demonstrated to target multiple transcriptional factors, genes, proteins, etc. that are linked with the pathogenesis and progression of these disorders. It has shown a significant therapeutic and preventive effect in diseased cells by blocking inflammation-causing transcription factors, inhibiting cell proliferation, causing cell cycle arrest, suppressing malignant cell migration, inducing apoptosis, etc. in both *in vitro* and *in vivo* conditions. Thus, this review aims at highlighting the potential of CD in combating various chronic diseases like cancer, cardiovascular diseases, diabetes, neurological disorders, inflammation, rheumatoid arthritis, etc. Although CD is becoming relevant as a potential candidate in clinical therapeutics, still, all the underlying mechanisms of action of CD have not been unraveled. Thus, there exists a lacuna in the current research on the pharmacokinetics and bioavailability aspect of CD in human systems, which could be addressed with novel approaches like nanoparticle formulations, conjugation with other natural compounds, reformulating CD with oils, chemical modifications, etc. Therefore, further research warrants advanced techniques for enhancing the pharmacokinetic properties and designing suitable formulations of CD to increase its bioavailability in order to promote the use of this wonder molecule from bench to bedside.

Author contributions

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Ahmad, S., Israf, D.A., Lajis, N.H., et al., 2006. Cardamonin, inhibits pro-inflammatory mediators in activated RAW 264.7 cells and whole blood. Eur. J. Pharmacol. 538 (1–3), 188–194.
Ali, A.A., Abd Al Haleem, E.N., Khaleel, S.A.H., et al., 2017. Protective effect of cardamonin against acetic acid-induced ulcerative colitis in rats. Pharmacol. Rep. 69 (2), 268–275.
Anand, P., Kunnumakara, A.B., Sundaram, C., et al., 2008. Cancer is a preventable disease that requires major lifestyle changes. Pharm. Res. (N. Y.) 25 (9), 2097–2116.
Atef, Y., El-Fayoumi, H.M., Abdel-Mottaleb, Y., et al., 2017. Effect of cardamonin on hepatic ischemia reperfusion induced in rats: role of nitric oxide. Eur. J. Pharmacol. 815, 446–453.
Babu, B.H., Jayram, H.N., Nair, M.G., et al., 2003. Free radical scavenging, antitumor and anticarcinogenic activity of gossypin. J. Exp. Clin. Canc. Res. 22 (4), 581–589.
Badroon, N.A., Abdul Majid, N., Alshawsh, M.A., 2020. Antiproliferative and apoptotic effects of cardamonin against hepatocellular carcinoma HepG2 cells. Nutrients 12 (6), 1757.
Banik, K., Harsha, C., Bordoloi, D., et al., 2018. Therapeutic potential of gambogic acid, a caged xanthone, to target cancer. Canc. Lett. 416, 75–86.
Banik, K., Ranaware, A.M., Deshpande, V., et al., 2019. Honokiol for cancer therapeutics: a traditional medicine that can modulate multiple oncogenic targets. Pharmacol. Res. 144, 192–209.
Banik, K., Ranaware, A.M., Harsha, C., et al., 2020. Piceatannol: a natural stilbene for the prevention and treatment of cancer. Pharmacol. Res. 153, 104635.
Barber, L., Gerke, T., Markt, S.C., et al., 2018. Family history of breast or prostate cancer and prostate cancer risk. Clin. Canc. Res. 24 (23), 5910–5917.
Benchabane, S., Belguendouz, H., Behairi, N., et al., 2018. Cardamonin inhibits pro-inflammatory cytokine production and suppresses NO pathway in PBMCs from patients with primary Sjögren's syndrome. Immunopharmacol. Immunotoxicol. 40 (2), 126–133.
Berning, L., Scharf, L., Aplak, E., et al., 2019. In vitro selective cytotoxicity of the dietary chalcone cardamonin (CD) on melanoma compared to healthy cells is mediated by apoptosis. PloS One 14 (9), e0222267.
Bisht, V.K., Negi, J.S., Bh, A.K., et al., 2011. *Amomum subulatum* Roxb: traditional, phytochemical and biological activities-An overview. Afr. J. Agric. Res. 6 (24), 5386–5390.
Bordoloi, D., Banik, K., Shabnam, B., et al., 2018a. TIPE family of proteins and its implications in different chronic diseases. Int. J. Mol. Sci. 19 (10), 2974.

Bordoloi, D., Kunnumakkara, A.B., 2018b. The potential of curcumin: a multitargeting agent in cancer cell chemosensitization. Role Nutraceut. Chemoresistance to Canc. 31–60.
Bordoloi, D., Roy, N.K., Monisha, J., et al., 2016. Multitargeted agents in cancer cell chemosensitization: what we learnt from curcumin thus far. Recent Pat. Anti-Cancer Drug Discov. 11 (1), 67–97.
Bordoloi, D., Banik, K., Padmavathi, G., et al., 2019. TIPE2 induced the proliferation, survival, and migration of lung cancer cells through modulation of akt/mTOR/NF-κB signaling cascade. Biomolecules 9 (12), 836.
Break, M.K.B., Hossan, M.S., Khoo, Y., et al., 2018. Discovery of a highly active anticancer analogue of cardamonin that acts as an inducer of caspase-dependent apoptosis and modulator of the mTOR pathway. Fitoterapia 125, 161–173.
Bulaj, G., M Ahern, M., Kuhn, A., et al., 2016. Incorporating natural products, pharmaceutical drugs, self-care and digital/mobile health technologies into molecular-behavioral combination therapies for chronic diseases. Curr. Clin. Pharmacol. 11 (2), 128–145.
Chahyadi, A., Hartati, R., Wirasutisna, K.R., 2014. *Boesenbergia pandurate* Roxb., an Indonesian medicinal plant: phytochemistry, biological activity, plant biotechnology. Procedia Chem. 13, 13–37.
Chan, P.C., Xia, Q., Fu, P.P., 2007. *Ginkgo biloba* leave extract: biological, medicinal, and toxicological effects. J. Environ. Sci. Health C 25 (3), 211–244.
Chaturapanich, G., Chaiyakul, S., Verawatnapakul, V., Pholpramool, C., 2008. Effects of Kaempferia parviflora extracts on reproductive parameters and spermatic blood flow in male rats. Reproduction 136 (4), 515.
Chen, D., Li, H., Li, W., et al., 2018a. Kaempferia parviflora and its methoxyflavones: chemistry and biological activities. Evidence-Based Complement. Altern. Med. 2018, 4057456.
Chen, H., Shi, D., Niu, P., et al., 2018b. Anti-inflammatory effects of cardamonin in ovarian cancer cells are mediated via mTOR suppression. Planta Med. 84 (16), 1183–1190.
Cho, M., Ryu, M., Jeong, Y., et al., 2009. Cardamonin suppresses melanogenesis by inhibition of Wnt/β-catenin signaling. Biochem. Biophys. Res. Commun. 390 (3), 500–505.
Cipolla, G., Crema, F., Moro, E., et al., 2002. Nonsteroidal anti-inflammatory drugs and inflammatory bowel disease: current perspectives. Pharmacol. Res. 46 (1), 1–6.
de Almeida, R.R., Souto, R.N., Bastos, C.N., et al., 2009. Chemical variation in *Piper aduncum* and biological properties of its dillapiole-rich essential oil. Chem. Biodivers. 6 (9), 1427–1434.
de Castro, C.C.B., Costa, P.S., Laktin, G.T., et al., 2015. Cardamonin, a schistosomicidal chalcone from Piper aduncum L. (Piperaceae) that inhibits Schistosoma mansoni ATP diphosphohydrolase. Phytomedicine 22 (10), 921–928.
de Oliveira Cabral, C., Campos, A., Da Silva, L.M., et al., 2017. Gastroprotective potential of methanolic extract and dimethyl cardamonin from Campomanesia reitziana fruits in mice. Naunyn-Schmiedeberg's Arch. Pharmacol. 390 (6), 661–666.
de Souza Duarte, L., Pereira, M.T.M., Pascoal, V.D.Á.B., et al., 2020. Campomanesia genus–a literature review of nonvolatile secondary metabolites, phytochemistry, popular use, biological activities, and toxicology. EcléticaQuímica J. 45 (2), 12–22.
El-Naga, R.N., 2014. Pre-treatment with cardamonin protects against cisplatin-induced nephrotoxicity in rats: impact on NOX-1, inflammation and apoptosis. Toxicol. Appl. Pharmacol. 274 (1), 87–95.
Fusi, F., Cavalli, M., Mulholland, D., et al., 2010. Cardamonin is a bifunctional vasodilator that inhibits Cav1. 2 current and stimulates KCa1. 1 current in rat tail artery myocytes. J. Pharmacol. Exp. Therapeut. 332 (2), 531–540.
Ghosh, S., Rangan, L., 2013. Alpinia: the gold mine of future therapeutics. 3 Biotech 173–185.
Gim, S.A., Koh, P.O., 2015. Melatonin attenuates hepatic ischemia through mitogen-activated protein kinase signaling. J. Surg. Res. 198 (1), 228–236.
Girisa, S., Shabnam, B., Monisha, J., et al., 2019. Potential of zerumbone as an anti-cancer agent. Molecules 24 (4), 734.
Gonçalves, L.M., Valente, I.M., Rodrigues, J.A., 2014. An overview on cardamonin. J. Med. Food 17 (6), 633–640.
Gupta, S.C., Kunnumakkara, A.B., Aggarwal, S., et al., 2018. Inflammation, a double-edge sword for cancer and other age-related diseases. Front. Immunol. 9, 2160.
Harsha, C., Banik, K., Bordoloi, D., et al., 2017. Antiulcer properties of fruits and vegetables: a mechanism based perspective. Food Chem. Toxicol. 108, 104–119.
Harsha, C., Banik, K., Ang, H.L., et al., 2020. Targeting AKT/mTOR in oral cancer: mechanisms and advances in clinical trials. Int. J. Mol. Sci. 21 (9), 3285.
He, W., Jiang, Y., Zhang, X., et al., 2014. Anticancer cardamonin analogs suppress the activation of NF-kappaB pathway in lung cancer cells. Mol. Cell. Biochem. 389 (1–2), 25–33.
Henamayee, S., Banik, K., Sailo, B.L., et al., 2020. Therapeutic emergence of rhein as a potential anticancer drug: a review of its molecular targets and anticancer properties. Molecules 25 (10), 2278.
Hou, S., Yuan, Q., Yu, N., et al., 2019. Cardamonin attenuates chronic inflammation and tumorigenesis in colon. Cell Cycle 18 (23), 3275–3287.
Hou, G., Yuan, X., Li, Y., et al., 2020. Cardamonin, a natural chalcone, reduces 5-fluorouracil resistance of gastric cancer cells through targeting Wnt/β-catenin signal pathway. Invest. N. Drugs 38 (2), 329–339.
Hseu, Y.C., Chen, C.-S., Wang, S.-Y., 2011. Alpinia pricei rhizome extracts induce cell cycle arrest in human squamous carcinoma KB cells and suppress tumor growth in nude mice. Evidence-Based Complement. Altern. Med. 2011, 123815.
Jaiswal, S., Sharma, A., Shukla, M., et al., 2015. Gender-related pharmacokinetics and bioavailability of a novel anticancer chalcone, cardamonin, in rats determined by liquid chromatography tandem mass spectrometry. J. Chromatogr. B 986, 23–30.
Jaiswal, S., Shukla, M., Sharma, A., et al., 2017. Pre-clinical pharmacokinetics and ADME characterization of a novel anticancer chalcone, cardamonin. Drug Test. Anal. 9 (8), 1124–1136.
James, S., Aparna, J.S., Paul, A.M., et al., 2017. Cardamonin inhibits colonic neoplasia through modulation of MicroRNA expression. Sci. Rep. 7 (1), 1–16.
Jia, D., Tan, Y., Liu, H., et al., 2016. Cardamonin reduces chemotherapy-enriched breast cancer stem-like cells in vitro and in vivo. Oncotarget 7 (1), 771.
Jia, D., Yang, W., Li, L., Jia, D., Yang, W., Li, L., et al., 2015. β-Catenin and NF-κ B co-activation triggered by TLR3 stimulation facilitates stem cell-like phenotypes in breast cancer. Cell Death Differ. 22 (2), 298–310.
Jin, J., Qiu, S., Wang, P., et al., 2019. Cardamonin inhibits breast cancer growth by repressing HIF-1α-dependent metabolic reprogramming. J. Exp. Clin. Canc. Res. 38 (1), 1–16.
Khatoon, E., Banik, K., Harsha, C., et al., 2020. Phytochemicals in cancer cell chemosensitization: current knowledge and future perspectives. Semin. Canc. Biol. S1044–579X (20), 30150–30154.
Khwairakpam, A.D., Bordoloi, D., Thakur, K.K., et al., 2018a. Possible use of Punica granatum (Pomegranate) in cancer therapy. Pharmacol. Res. 133, 53–64.
Khwairakpam, A.D., Damayenti, Y.D., Deka, A., et al., 2018b. Acorus calamus: a bio-reserve of medicinal values. J. Basic Clin. Physiol. Pharmacol. 29 (2), 107–122.
Khwairakpam, A.D., Monisha, J., Roy, N.K., et al., 2019. Vietnamese coriander inhibits cell proliferation, survival and migration via suppression of Akt/mTOR pathway in oral squamous cell carcinoma. J. Basic Clin. Physiol. Pharmacol. 31 (3). /j/jbcpp.2020.31.
Khwairakpam, A.D., Banik, K., Girisa, S., et al., 2020. The vital role of ATP citrate lyase in chronic diseases. J. Mol. Med. 98 (1), 71–95.
Kim, Y.J., Ko, H., Park, J.-S., et al., 2010. Dimethyl cardamonin inhibits lipopolysaccharide-induced inflammatory factors through blocking NF-κB p65 activation. Int. Immunopharm. 10 (9), 1127–1134.
Khwairakpam, A.D., Shyamananda, M.S., Sailo, B.L., et al., 2015. ATP citrate lyase (ACLY): a promising target for cancer prevention and treatment. Curr. Drug Targets 16 (2), 156–163.
Kim, Y.J., Kang, K.S., Choi, K.-C., et al., 2015. Cardamonin induces autophagy and an antiproliferative effect through JNK activation in human colorectal carcinoma HCT116 cells. Bioorg. Med. Chem. Lett 25 (12), 2559–2564.
Kong, W., Li, C., Qi, Q., et al., 2019. Cardamonin induces G2/M arrest and apoptosis via activation of the JNK–FOXO3a pathway in breast cancer cells. Cell Biol. Int. 44 (1), 177–188.
Kunnumakkara, A.B., Anand, P., Aggarwal, B.B., 2008. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Canc. Lett. 269 (2), 199–225.
Kunnumakkara, A.B., Guha, S., Aggarwal, B.B., 2009. Curcumin and colorectal cancer: add spice to your life. Curr. Colorectal Canc. Rep 5 (1), 5.
Kunnumakkara, A.B., Sung, B., Ravindran, J., et al., 2012. Zyflamend suppresses growth and sensitizes human pancreatic tumors to gemcitabine in an orthotopic mouse model through modulation of multiple targets. Int. J. Canc. 131 (3), E292–E303.
Kunnumakkara, A.B., Bordoloi, D., Harsha, C., et al., 2017a. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. Clin. Sci. 131 (15), 1781–1799.
Kunnumakkara, A.B., Bordoloi, D., Padmavathi, G., et al., 2017b. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. Br. J. Pharmacol. 174 (11), 1325–1348.
Kunnumakkara, A.B., Sailo, B.L., Banik, K., et al., 2018a. Chronic diseases, inflammation, and spices: how are they linked? J. Transl. Med. 16 (1), 14.
Kunnumakkara, A.B., Banik, K., Bordoloi, D., et al., 2018b. Googling the guggul (commiphora and boswellia) for prevention of chronic diseases. Front. Pharmacol. 9, 686.
Kunnumakkara, A., Thakur, K.K., Rana, V., et al., 2019a. Upside and downside of tumor necrosis factor blockers for treatment of immune/inflammatory diseases. Crit. Rev. Immunol. 39 (6), 439–479.
Kunnumakkara, A.B., Bordoloi, D., Sailo, B.L., et al., 2019b. Cancer drug development: the missing links. Exp. Biol. Med. 244 (8), 663–689.
Kunnumakkara, A.B., Harsha, C., Banik, K., et al., 2019c. Is curcumin bioavailability a problem in humans: lessons from clinical trials. Expet Opin. Drug Metabol. Toxicol. 15 (9), 705–733.
Kunnumakkara, A.B., Shabnam, B., Girisa, S., et al., 2020. Inflammation, NF-κB, and chronic diseases: how are they linked? Crit. Rev. Immunol. 40 (1), 1–39.
Li, Y., Qin, Y., Yang, C., et al., 2017. Cardamonin induces ROS-mediated G2/M phase arrest and apoptosis through inhibition of NF-κ B pathway in nasopharyngeal carcinoma. Cell death & Dis. 8 (8) e3024–e3024.
Liao, Q., Shi, D.H., Zheng, W., et al., 2010. Antiproliferation of cardamonin is involved in mTOR on aortic smooth muscle cells in high fructose-induced insulin resistance rats. Eur. J. Pharmacol. 641 (2–3), 179–186.
Liao, N.C., Shih, Y.L., Chou, J.S., et al., 2019. Cardamonin induces cell cycle arrest, apoptosis and alters apoptosis associated gene expression in WEHI-3 mouse leukemia cells. Am. J. Chin. Med. 47, 635–656, 03.
Liao, N., Shih, Y., Ho, M., et al., 2020. Cardamonin induces immune responses and enhances survival rate in WEHI-3 cell–generated mouse leukemia in vivo. Environ. Toxicol. 35 (4), 457–467.
López-Abente, G., Mispireta, S., Pollán, M., 2014. Breast and prostate cancer: an analysis of common epidemiological features in mortality trends in Spain. BMC Canc. 14 (1), 874.
Lu, S., Lin, C., Cheng, X., et al., 2018. Cardamonin reduces chemotherapy resistance of colon cancer cells via the TSP50/NF-κB pathway in vitro. Oncol. Lett. 15 (6), 9641–9646.

Memon, A.H., Ismail, Z., Aisha, A.F.A., et al., 2014. Isolation, characterization, crystal structure elucidation, and anticancer study of dimethyl cardamonin, isolated from Syzygium campanulatum Korth. Evidence-Based Complement. Altern. Med. 2014, 470179.
Mingorance, C., Andriantsitohaina, R., de Sotomayor, M.A., 2008. *Cedrelopsis grevei* improves endothelial vasodilatation in aged rats through an increase of NO participation. J. Ethnopharmacol. 117 (1), 76–83.
Moacă, E.A., Pavel, I.Z., Danciu, C., et al., 2019. Romanian wormwood (Artemisia absinthium L.): physicochemical and nutraceutical screening. Molecules 24 (17), 3087.
Monisha, J., Padmavathi, G., Roy, N.K., et al., 2016. NF-κB blockers gifted by mother nature: prospectives in cancer cell chemosensitization. Curr. Pharmaceut. Des. 22 (27), 4173–4200.
Monisha, J., Roy, N.K., Bordoloi, D., et al., 2017. Nuclear factor kappa B: a potential target to persecute head and neck cancer. Curr. Drug Targets 18 (2), 232–253.
Murakami, A., Kondo, A., Nakamura, Y., et al., 1993. Possible anti-tumor promoting properties of edible plants from Thailand, and identification of an active constituent, cardamonin, of Boesenbergia pandurata. Biosci. Biotechnol. Biochem. 57 (11), 1971–1973.
Nawaz, J., Rasul, A., Shah, M.A., et al., 2020. Cardamonin: a new player to fight cancer via multiple cancer signaling pathways. Life Sci. 117591.
Nesello, L.A.N., Campos, A., Wagner, T., et al., 2016. Chemical composition and antinociceptive potential of campomanesia reitziana fruits. J. Med. Food 19 (5), 518–520.
Nitsa, A., Toutouza, M., Machairas, N., et al., 2018. Vitamin D in cardiovascular disease. In Vivo 32 (5), 977–981.
Niu, P., Shi, D., Zhang, S., et al., 2018. Cardamonin enhances the anti-proliferative effect of cisplatin on ovarian cancer. Oncol. Lett. 15 (3), 3991–3997.
Niu, P., Li, J., Chen, H., et al., 2020. Anti-proliferative effect of cardamonin on mTOR inhibitor-resistant cancer cells. Mol. Med. Rep. 21 (3), 1399–1407.
Niu, P.G., Zhang, Y.X., Shi, D.H., et al., 2015. Cardamonin inhibits metastasis of Lewis lung carcinoma cells by decreasing mTOR activity. PloS One 10 (5), e0127778.
Ongwisespaiboon, O., Jiraungkoorskul, W., 2017. Fingerroot, *Boesenbergia rotunda* and its aphrodisiac activity. Phcog. Rev. 11 (21), 27.
Padmavathi, G., Rathnakaram, S.R., Monisha, J., et al., 2015. Potential of butein, a tetrahydroxychalcone to obliterate cancer. Phytomedicine 22 (13), 1163–1171.
Padmavathi, G., Roy, N.K., Bordoloi, D., et al., 2017. Butein in health and disease: a comprehensive review. Phytomedicine 25, 118–127.
Padmavathi, G., Banik, K., Monisha, J., et al., 2018. Novel tumor necrosis factor-α induced protein eight (TNFAIP8/TIPE) family: functions and downstream targets involved in cancer progression. Canc. Lett. 432, 260–271.
Parama, D., Boruah, M., Kumari, Y., et al., 2020. Diosgenin, a steroidal saponin, and its analogss: effective therapies against different chronic diseases. Life Sci., 118182
Park, S., Gwak, J., Han, S.J., et al., 2013. Cardamonin suppresses the proliferation of colon cancer cells by promoting β-catenin degradation. Biol. Pharm. Bull. 36 (6), 1040–1044.
Park, M.K., Lee, H.J., Choi, J.K., et al., 2014. Novel anti-nociceptive effects of cardamonin via blocking expression of cyclooxygenase-2 and transglutaminase-2. Pharmacol. Biochem. Behav. 118, 10–15.
Pascoal, A.C.R.F., Ehrenfried, C.A., Lopez, B.G.C., et al., 2014. Antiproliferative activity and induction of apoptosis in PC-3 cells by the chalcone cardamonin from Campomanesia adamantium (Myrtaceae) in a bioactivity-guided study. Molecules 19 (2), 1843–1855.
Peng, S., Hou, Y., Yao, J., et al., 2017. Activation of Nrf2-driven antioxidant enzymes by cardamonin confers neuroprotection of PC12 cells against oxidative damage. Food Funct 8 (3), 997–1007.
Ping, C.P., Tengku Mohamad, T.A.S., Akhtar, M.N., et al., 2018. Antinociceptive effects of cardamonin in mice: possible involvement of TRPV1, glutamate, and opioid receptors. Molecules 23 (9), 2237.
Qi, W., Boliang, W., Xiaoxi, T., et al., 2020. Cardamonin protects against doxorubicin-induced cardiotoxicity in mice by restraining oxidative stress and inflammation associated with Nrf2 signaling. Biomed. Pharmacother. 122, 109547.
Qin, Y., Sun, C.Y., Lu, F.R., et al., 2012. Cardamonin exerts potent activity against multiple myeloma through blockade of NF-κB pathway in vitro. Leuk. Res. 36 (4), 514–520.
Ranaware, A.M., Banik, K., Deshpande, V., et al., 2018. Magnolol: a neolignan from the Magnolia family for the prevention and treatment of cancer. Int. J. Mol. Sci. 19 (8), 2362.
Ren, G., Sun, A., Deng, C., et al., 2015. The anti-inflammatory effect and potential mechanism of cardamonin in DSS-induced colitis. Am. J. Physiol. Liver Physiol. 309 (7), G517–G527.
Romaszko, A.M., Doboszyńska, A., 2018. Multiple primary lung cancer: a literature review. Adv. Clin. Exp. Med. 27 (5), 725–730.
Roy, N.K., Bordoloi, D., Monisha, J., et al., 2017. Specific targeting of Akt kinase isoforms: taking the precise path for prevention and treatment of cancer. Curr. Drug Targets. 18 (4), 421–435.
Roy, N.K., Deka, A., Bordoloi, D., et al., 2016. The potential role of boswellic acids in cancer prevention and treatment. Canc. Lett. 377 (1), 74–86.
Roy, N.K., Monisha, J., Padmavathi, G., et al., 2019a. Isoform-specific role of akt in oral squamous cell carcinoma. Biomolecules 9 (7), 253.
Roy, N.K., Parama, D., Banik, K., et al., 2019b. An update on pharmacological potential of boswellic acids against chronic diseases. Int. J. Mol. Sci. 20 (17), 4101.
Sailo, B.L., Banik, K., Padmavathi, G., et al., 2018. Tocotrienols: the promising analogss of vitamin E for cancer therapeutics. Pharmacol. Res. 130, 259–272.
Sailo, B.L., Banik, K., Girisa, S., et al., 2019. FBXW7 in cancer: what has been unraveled thus far? Cancers 11 (2), 246.
Sambasevam, Y., Farouk, A.A.O., Mohamad, T.A.S.T., et al., 2017. Cardamonin attenuates hyperalgesia and allodynia in a mouse model of chronic constriction injury-induced neuropathic pain: possible involvement of the opioid system. Eur. J. Pharmacol. 796, 32–38.
Sengottuvelu, S., 2011. Cardamom (*Elettaria cardamomum* Linn. Maton) seeds in health. Nuts Seeds Health Dis. Prevent. 285–291.
Shabnam, B., Padmavathi, G., Banik, K., et al., 2018. Sorcin a potential molecular target for cancer therapy. Transl. Oncol. 11 (6), 1379–1389.
Shannan, B., Perego, M., Somasundaram, R., et al., 2016. Heterogeneity in melanoma. Melanoma 1–15.
Shi, D., Niu, P., Heng, X., et al., 2018a. Autophagy induced by cardamonin is associated with mTORC1 inhibition in SKOV3 cells. Pharmacol. Rep. 70 (5), 908–916.
Shi, D., Zhao, D., Niu, P., et al., 2018b. Glycolysis inhibition via mTOR suppression is a key step in cardamonin-induced autophagy in SKOV3 cells. BMC Compl. Alternative Med. 18 (1), 1–8.
Shi, D., Zhu, Y., Niu, P., et al., 2018c. Raptor mediates the antiproliferation of cardamonin by mTORC1 inhibition in SKOV3 cells. OncoTargets Ther. 11, 757.
Shrivastava, S., Jeengar, M.K., Thummuri, D., et al., 2017. Cardamonin, a chalcone, inhibits human triple negative breast cancer cell invasiveness by downregulation of Wnt/β-catenin signaling cascades and reversal of epithelial–mesenchymal transition. Biofactors 43 (2), 152–169.
Singh, Y.P., Girisa, S., Banik, K., et al., 2019. Potential application of zerumbone in the prevention and therapy of chronic human diseases. J. Funct. Foods. 53, 248–258.
Smolen, J.S., Aletaha, D., Bijlsma, J.W.J., et al., 2010. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann. Rheum. Dis. 69 (4), 631–637.
Smolen, J.S., Aletaha, D., McInnes, I.B., 2016. Rheumatoid arthritis. Lancet (London, England). 388 (10055), 2023–2038.
Tan, Y., Wan, H., Sun, M., et al., 2020. Cardamonin protects against lipopolysaccharide-induced myocardial contractile dysfunction in mice through Nrf2-regulated mechanism. Acta Pharmacol. Sin. 1–10.
Tewtrakul, S., Subhadhirasakul, S., Karalai, C., et al., 2009. Anti-inflammatory effects of compounds from Kaempferia parviflora and Boesenbergia pandurata. Food Chem. 115 (2), 534–538.
Thakur, K.K., Saini, J., Mahajan, K., et al., 2017. Therapeutic implications of toll-like receptors in peripheral neuropathic pain. Pharmacol. Res. 115, 224–232.
Thakur, K.K., Bordoloi, D., Kunnumakkara, A.B., 2018. Alarming burden of triple-negative breast cancer in India. Clin. Breast Canc. 18 (3), e393–e399.
Thomas, D., Govindhan, S., Baiju, E.C., et al., 2015. Cyperus rotundus L. prevents non-steroidal anti-inflammatory drug-induced gastric mucosal damage by inhibiting oxidative stress. J. Basic Clin. Physiol. Pharmacol. 26 (5), 485–490.
Tian, S.S., Jiang, F.S., Zhang, K., et al., 2014. Flavonoids from the Leaves of *Carya cathayensis* Sarg. inhibit vascular endothelial growth factor-induced angiogenesis. Fitoterapia 92, 34–40.
Wang, S., Zhai, C., Zhang, Y., et al., 2016. Cardamonin, a novel antagonist of hTRPA1 cation channel, reveals therapeutic mechanism of pathological pain. Molecules 21 (9), 1145.
Voon, F.L., Sulaiman, M.R., Akhtar, M.N., et al., 2017. Cardamonin (2',4'-dihydroxy-6'-methoxychalcone) isolated from Boesenbergia rotunda (L.) Mansf. inhibits CFA-induced rheumatoid arthritis in rats. Eur. J. Pharmacol. 794, 127–134.
Wang, Z.T., Lau, C.W., Chan, F.L., et al., 2001. Vasorelaxant effects of cardamonin and alpinetin from Alpinia henryi K. Schum. J. Cardiovasc. Pharmacol. 37 (5), 596–606.
Wang, Z., Tang, X., Wu, X., et al., 2019a. Cardamonin exerts anti-gastric cancer activity via inhibiting LncRNA-PVT1-STAT3 axis. Biosci. Rep. 39 (5), BSR20190357.
Wang, Z., Xu, G., Gao, Y., et al., 2019b. Cardamonin from a medicinal herb protects against LPS-induced septic shock by suppressing NLRP3 inflammasome. Acta Pharm. Sin. B. 9 (4), 734–744.
Webb, P.M., Jordan, S.J., 2017. Epidemiology of epithelial ovarian cancer. Best Pract. Res. Clin. Obstet. Gynaecol. 41, 3–14.
Xue, Z.G., Niu, P.G., Shi, D.H., et al., 2016. Cardamonin inhibits angiogenesis by mTOR downregulation in SKOV3 cells. Planta Med. 82 (1–2), 70–75.
You, W., Wu, Z., Ye, F., et al., 2018. Cardamonin protects against adverse cardiac remodeling through mTORC1 inhibition in mice with myocardial infarction. Die Pharm. Int. J. Pharm. Sci. 73 (9), 508–512.
Zhang, J., Sikka, S., Siveen, K.S., et al., 2017. Cardamonin represses proliferation, invasion, and causes apoptosis through the modulation of signal transducer and activator of transcription 3 pathway in prostate cancer. Apoptosis 22 (1), 158–168.
Zhou, X., Zhou, R., Li, Q., et al., 2019. Cardamonin inhibits the proliferation and metastasis of non-small-cell lung cancer cells by suppressing the PI3K/Akt/mTOR pathway. Anti Canc. Drugs 30 (3), 241–250.
Zilliox, L.A., 2017. Neuropathic pain. Contin. Lifelong Learn. Neurol 23 (2), 512–532.