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 preclinical 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 (Balaj et al., 2016; Roy et al., 2016; Banik et al., 2019).

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...
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. 1. Structure of cardamonin and its analogs.](image1)

![Fig. 2. Therapeutic potential and biological activities of cardamonin against different chronic diseases.](image2)
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; Moac et al., 2019; Bordoloi and Kunnumakkara, 2018b; 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’-dihydroxychalcone (DHC) (de Oliveira Cabral et al., 2017; He et al., 2014) (Fig. 1). CD can be isolated from *Piper aduncum*, *Ginkgo biloba*, *Boesenbergia pandurata*, *Elettaria cardamomum*; the rhizome of *Boesenbergia pandurata* and *Boesenbergia rotunda*, *Alpinia pricei*, *Kaempferia parviflora*; fruit of *Campomanesia reitziana*; fruit and the rhizomes of *Alpinia raflesiana*, *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; Sengottuvelu, 2011; Chan et al., 2007; Chaturapanich et al., 2008; de Almeida et al., 2009; Hseu et al., 2011; 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),...
The antioxidant quinone dehydrogenase 1 (NQO1), and nicotinamide adenine dinucleotide (NADPH) oxidase 1 (NOX-1) (Qi et al., 2020). Further, the remarkable antioxidant effect of CD was evinced through a superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT). 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 x 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., 2019; Jin et al., 2019; de Souza Duarte et al., 2020). Moreover, CD was shown to suppress different kinases such as interleukin-1 receptor-associated kinase-1 (IL-1R AK), inhibitor x 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).

Table 1

| Sources | Plant | Biological Properties | References |
|---------|-------|-----------------------|------------|
| Alpinia officinarum | Leaves, stem, rhizome | Anti-inflammatory | Ghosh and Rangan, (2013) |
| Alpinia officinarum | Rhizome | Anti-inflammatory | Ghosh and Rangan, (2013) |
| Alpinia officinarum | Leaves | Anti-inflammatory | Ghosh and Rangan, (2013) |
| Piper nigrum | Leaves | Anti-inflammatory | Ghosh and Rangan, (2013) |
| Piper nigrum | Rhizomes | Anti-inflammatory | Ghosh and Rangan, (2013) |
| Piper nigrum | Seeds | Anti-inflammatory | Ghosh and Rangan, (2013) |
| Piper aduncum | Leaves | Antioxidant | Ghosh and Rangan, (2013) |
| Piper aduncum | Rhizomes | Antioxidant | Ghosh and Rangan, (2013) |
| Piper aduncum | Seeds | Antioxidant | Ghosh and Rangan, (2013) |
| Piper aduncum | Leaves | Antioxidant | Ghosh and Rangan, (2013) |
| Piper aduncum | Rhizomes | Antioxidant | Ghosh and Rangan, (2013) |
| Piper aduncum | Seeds | Antioxidant | Ghosh and Rangan, (2013) |

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 multisite 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 multitargeting 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 protein.
Table 2: Potential of cardamonin in the prevention and treatment of chronic diseases.

| Chronic Diseases | In vitro/In vivo | Model | Mechanism | References |
|------------------|------------------|-------|-----------|------------|
| **Cancers**      |                  |       |           |            |
| Breast Cancer    | In vitro         | SUM190, MCF-7, Cama-1 | Colony formation ability, CSOs, ALDH1, Sox 2, | Jia et al. (2016) |
|                  |                  | SUM190 xenograft | | |
|                  |                  | MCF-7, MDA-MB-231, BT-549 | Cell proliferation, cell formation, apoptosis, G2/M phase arrest, | Jia et al. (2016) |
|                  |                  | 4T1 induced tumor | Tumor growth | Shrivastava et al. (2017) |
|                  | In vivo          | MDA-MB-231, MCF-7 | Cell proliferation, Bcl-2, GSH, J-caspase-3, Bax, PARP, ROS, Apoptosis, | Kong et al. (2019) |
|                  |                  | HCT-116 | Tumor growth, cyclin D1, Bim, J-caspase-3, p-JNK, FOXD3a, p21, p27, | Kong et al. (2019) |
|                  | In vivo          | SW480, LS1748, SW480, DLD-1, SKOV3 | Wnt/J-catenin, cyclin D1, c-Myc, | Park et al. (2013) |
|                  |                  | HT-29 | Cell proliferation, clonogenicity, migration | Memon et al. (2014) |
|                  | In vivo          | HCT116 | Cell proliferation, G2/M phase arrest, autophagy, J-p53/JNK | Kim et al. (2015) |
|                  |                  | AOM induced CRC | Cell proliferation, Apoptosis, S phase arrest, ROS, MD, Bax, p-JNK, p-p38 | James et al. (2017) |
|                  | In vivo          | HCT-116 | Tumor incidence, multiplicity, J-caspase-3, p65, Ki-67, J-catenin | James et al. (2017) |
|                  |                  | HT-29, SW-460 | Cell viability, IL-1β, TNF-α, STAT1, STAT3 | Hou et al. (2019) |
|                  | In vivo          | DSS + AOM induced CACCC | Cell viability, IL-1β, TNF-α, p-JNK, p-STAT3 | Hou et al. (2019) |
|                  | In vivo          | BGC-823, BGC-823/5-FU | Cell viability, apoptosis, G2/M phase arrest, IC50, 12H1, C4, C-Myc, J-catenin/TCF4, CYC1D1, P-glycoprotein, Wnt | Hou et al. (2020) |
|                  | In vivo          | BGC-823/5-FU xenograft | Cell viability | Wang et al. (2019) |
| **HCC**          | In vivo          | HepG2 | Cell viability, J-phase growth arrest, apoptosis, J-caspase-3-7, 8, 9, Fas, TRAIL | Badroo et al. (2020) |
| **Leukemia**     | In vivo          | WEHI-3 | ROS, Ca2+, J-caspase-3, 8 and 9, Bax, c-jun, AIF, Endo G, GRP78, caspase-12, Fas, fas-ligand, FADD, DADD, TMBM4, ATG5 | Liao et al. (2019) |
|                  | In vivo          | WEHI-3 xenograft | CD19, J-mac-3, CD11b, phagocytosis of macrophages, cytotoxicity of NK cells, cell survival rate | Liao et al. (2020) |
| **Lung Cancer**  | In vivo          | A549, NCi-H1299, NCi-H460, NCi-H1168 | Cell viability | He et al. (2014) |
|                  | In vivo          | A549, NCi-H460 | J-apoptosis, | Niu et al. (2015) |
|                  | In vivo          | LLC | Cell viability, invasion, migration, J-catenin, p-JP-mTOR, S6K1, Snail1 | Niu et al. (2015) |
|                  | In vivo          | LLC transplant | Tumor growth, lung metastasis | Niu et al. (2015) |
|                  | In vivo          | A549, H460, H292, H1299, H1975 | Cell viability, EMT, ZEB1, Bcl-2 PI3K/Akt/mTOR, J-catenin formation, N-catenin, cyclin D1, CDK4, | Zhou et al. (2019) |
|                  | In vivo          | BGC-823 | Cell viability, migration, invasion, G2/M phase arrest, apoptosis, caspase-3, Bax | Zhou et al. (2019) |
| **Melanoma**     | In vivo          | A549 | Cell migration, G2/M phase arrest, J-apoptosis, | Break et al. (2018) |
|                  | In vivo          | A575 | Cell viability, invasion, J-apoptosis, caspase-3, J-PARP | Berning et al. (2019) |
| **Myeloma**      | In vivo          | RPMI 8226, U266, ARH-77, RPMI 8226 | Cell proliferation J-apoptosis, caspase-3-PARP, J-Bcl-2, Bcl-xL, J-survivin, XIAP, caspase-1, J-CLAP-2, NF-κB, J-ILK, | Qin et al. (2012) |
| **NPC**          | In vivo          | HK1 | Cell migration, G2/M phase arrest, | Break et al. (2018) |
| **Ovarian Cancer**| In vivo         | SKOV3 | Cell viability, VEGF, J-catenin, J-HIF-1α, J-PI3K, J-mTOR, S6K1 | Shi et al. (2018a) |
|                  | In vivo          | SKOV3 | Cell viability, | Shi et al. (2018c) |
|                  | In vivo          | SKOV3, A2780 SKOV3 | Cell viability, colony formation J-G2/M phase arrest, J-XIAP, survivin | Niu et al. (2018) |
| **PC**           | In vivo          | DU145, LNCaP | Cell viability, | Chen et al. (2018b) |

(continued on next page)
Table 2 (continued)

| Chronic Diseases | In vitro/In vivo | Model | Mechanism | References |
|------------------|-----------------|-------|-----------|------------|
|                  | In silico/Ex vivo |       |           |            |
| CVD              | In vivo         | Mesenteric arteries | STAT3, SH2 domain | Zhang et al. (2017) |
|                  | In vivo         | Rat tail artery myocytes | Cell growth, apoptosis, NF-κB1 | Wang et al. (2001) |
|                  | In vivo         | DOX-induced cardiotoxicity | [κCa1.1, [Ca(II)], Cav1.2 | Fusi et al. (2010) |
|                  | In vivo         | HI2C9 | 4E-BP1, S6, mTOR-Raptor | Qi et al. (2020) |
|                  | In vivo         | LPS treated C57 mice | Contractile defects, apoptosis, oxidative stress, LPS induced Nrf2 signaling, inflammation, NK-κB | You et al. (2018) |
| Diabetes         | In vivo         | FEIR SD rats | LOOH, oxidative stress, SOD, GSH | Tan et al. (2020) |
| Gastritis        | In vivo         | EsOH/HCI induced gastric ulcer | | de Oliveria Cabral et al. (2017) |
| HI               | In vivo         | weight hanging method | [NO, eNOS expression; iNOS, NF-κB, TNF-α, Bcl-2, [TFN-α, II-6, IL-1], NF-κB, NO, PGE2, iNOS,COX-2 mRNAs, IL-1β mRNA, ROS | Atef et al. (2017) |
| ID               | In vivo         | RAW264.7 | NF-κB, LPS, MAPK | Kim et al. (2010) |
|                  | In vivo         | 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 vivo         | BMDMs, BMDCs | caspase-1, IL-1β, NLRP3 | Wang et al. (2016) |
|                  | In vivo         | LPS induced septic shock | LNL3P3, caspase-1, IL-1β | Wang et al. (2019b) |
| Arthritis        | In vivo         | CFA Induced Cells | [TFN-α, II-6, IL-6 | Voon et al. (2014) |
| Pathological Pain/ | In vivo         | GM63, RAW264.7 | [IKb; Tγase-2, COX-2, p65,NF-κB | Park et al. (2014) |
| Nociceptive      | In vivo         | CIC | [WR, COX-2, Tγase-2 | Park et al. (2014) |
|                  | In silico       | HEK293 | TRPA1 | Wang et al. (2016) |
|                  | In vivo         | ACIAWR Model F1PL Model, Hot Plate Test G1PL Model | capsacin-induced nociception | Ping et al. (2018) |
| Ulcerative colitis | In vivo        | acetic acid induced | [MPO, iNOS, NF-κB, TNFs, MDA, COX-2, caspase-3 | Ali et al. (2017) |
| Nephrotoxicity   | In vivo         | cis induced nephrotoxicity | [caspase-3, [jax/Bl-2, NOX-1, IL-1], TNF-α, NF-κB, iNOS, MCP-1, ICAM | El-Naga (2014) |
| Neuropathic Pain | In vivo         | PCIC | [Nrf2, HO-1, Tγase-1, Tγase, COX-2, iNOS, PGE2, COX-2 mRNAs, IL-1, NO, PGE2, COX-2, iNOS, PGE2 | Peng et al. (2017) |
| Sjogren's Syndrome | ex vivo       | BM3c-pSS | IL-6, II-6,benosin | Benchabane et al. (2018) |

Notations.

4Dimethyl cardamon in or 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC).
5Cardamon analog 4',4'-dihydroxylchalcone (DHC) and 4',4'-dihydroxy-2'-methoxychalcone (DHMC).
6Cardamom analog Compound 19.

Abbreviations: AAI Model = acetic acid-induced model; AE = Antihyperalgesic Effects; ALDH1 = aldehyde dehydrogenase 1; AP = activator prostratin; AOM = Azoxymethane; ATGS = 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; CCA = Cell Cycle Arrest; CCA = cardiac contractile abnormality; CCC = cancer cell migration; CCF = cancer cell colony formation; CCI = chronic constriction injury; CFP = 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 = cyclooxygenase; CRC = Colorectal Cancer; CVD = Cardiovascular Diseases; cyt-C = cytochrome C; DAP = Death Associated Protein; DDIT3 = DNA Damage Inducible Transcript; DDIT4 = DNA Damage-inducible Transcript 4; DSS = dextran sulfate sodium; DMC = dimethyl cardamom; FEIR = fructose-enriched insulin resistant; F1PL 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; HR = homeostasis model assessment for insulin resistance; ID = Inflammatory Diseases; IL = Interleukin; iNOS = inducible nitric oxide synthase; IS = Insulin Sensitivity Index; JNKs = Jun N-terminal kinases; LAPE = lactic acid production and efflux; LOOH = lipidperoxidation; LDECS = LPS-induced defect in cardiomycyte shortening; LPS = lipopolysaccharide; MA = Mechanical Allodynia; MAPK = mitogen-activated protein kinase; MCD = Myocardial Contractile Dysfunction; MOP = monocytone chemoattractant protein 1; MD = mitochondrial deloparization; 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; OBT4F = octamer-binding transcription factor 4; 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; p65 = Primary Sjogren's syndrome; PVT1 = PlasmaDysplasia Variant Translocation 1; ROS = Reactive Oxygen Species; SCA = Sustained Contraction by Endothelin 1; 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; Tx2B = thromboxane B2; UC = Ulcerative Colitis; VEGF = Vascular Endothelial Growth Factor; VSMC = vascular smooth muscle cells; VT = vascular tone; WR = Writhing Response.
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 of 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 (Lopez-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 Grx-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 (cIAP1) 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 ICAM-1 and activating Kv3.1. Additionally, CD and alpinetin cumulatively induced relaxation of phenylephrine preconstricted 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 lipo-poly saccharide (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-kB 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 (TRPV1), 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 Campomamusa reitiana 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-kB, 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 antioxidative 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-kB 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 Nr2f-antioxidant response element (Nr2f-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 Nr2f, 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 better 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.

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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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