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Review article

Anti-cancer effects of cinnamon: Insights into its apoptosis effects

Sahand Sadeghi [a], Amirhossein Davoodvandi [a, b], Mohammad Hossein Pourhanifeh [a, b], Nasrin Sharifi [a], Reza ArefNezhad [c], Roxana Sahebnasagh [d], Shirin Amiri Moghadam [e], Amirhossein Sahebkar [f, g, h, **], Hamed Mirzaei [a, *]

[a] Department of Nutrition, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[b] Student Research Committee, Kashan University of Medical Sciences, Kashan, Iran
[c] Department of Anatomy, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[d] Department of Molecular Medicine, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[e] Department of Community Medicine, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[f] Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[g] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[h] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Cancer is known as a leading cause of death worldwide. In the last two decades, the incidence of cancer has been dramatically increased mostly due to lifestyle changes. The importance of this issue has attracted further attention to discover novel therapies to prevent and treat cancers. According to previous studies, drugs used to treat cancer have shown significant limitations. Therefore, the role of herbal medicines alone or in combination with chemotherapy drugs has been extensively studied in cancer treatment. Cinnamon is a natural component showing a wide range of pharmacological functions including anti-oxidant, anti-microbial and anti-cancer activities. Impaired apoptosis plays critical roles in the initiation and progression of cancer. Increasing evidence indicates that cinnamon, as a therapeutic agent, has anti-cancer effects *via* affecting numerous apoptosis-related pathways in cancer cells. Here, we highlighted anticancer properties of cinnamon, particularly through targeting apoptosis-related mechanisms.

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1. Introduction

Cancer is one of the most threatening health problems in the world. In human body, new cells are continually generated in order to repair damaged tissues. Ordinarily, cell proliferation and death occur in a balanced manner. In cancerous conditions, cellular growth, division and death are deregulated. The result of such a deregulation is probably an unusual blood or lymph fluid in body,

* Corresponding Authors.Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran.
** Corresponding author. Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail addresses: sahebkara@mums.ac.ir (A. Sahebkar), mirzaei-h@kaums.ac.ir, h.mirzaei2002@gmail.com (H. Mirzaei).

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or formation of a mass known as tumor [1].

Apoptosis is a highly investigated process in pathological or normal conditions [1]. Due to the significant role of this process in different pathological conditions, it is important to understand its related mechanisms to discover novel therapies. In cancer, there is an imbalance between cell division and death. In fact, decisive cell death does not occur due to the lack of death signals [1,2].

Cinnamon, a traditional herbal medicine, has different biological properties such as anti-tumor, anti-diabetic, anti-inflammatory, anti-microbial and anti-oxidant activities. Also, it is able to affect apoptosis. This review describes the potential of cinnamon in the modulation of neoplastic processes through affecting different biochemical signaling pathways, especially apoptosis.

2. Cinnamon and cancer

It has been predicted by the International Agency for Research on Cancer (IARC) (2012) that despite all strategies used for cancer treatment, the world is experiencing an increasing burden of cancer. Notably, it has been reported that 8.2 million cancer-related deaths as well as 14.1 million newly diagnosed patients have been registered in 2012 worldwide. According to the estimations of Globocan 2012, the number of new cancer cases will reach 19.3 million by 2025 [3]. of the increasing trend in cancer occurrence calls for further research to find more efficacious drugs [4]. Chemotherapy, targeted therapies, radiotherapy, surgery, immunotherapy and other methods, such as transplantation of stem cells, are the main modalities for cancer treatment [4]. All these modalities have major barriers and limitations. The most frequently used cancer treatments (*i.e.* radiotherapy and chemotherapy) have two main hurdles including have recurrence and many side effects [4]. Fig. 1 shows a major difference between healthy and cancerous cells based on their attachment to basement membranes. One of the main research directions in the recent decades pertains to the discovery of novel strategies to fight against cancer *via* natural dietary elements including medicinal plants and phytochemicals [5].

Cinnamon is a spice that has been widely utilized from the ancient era [6]. This spice has been extensively studies with respect to its potential in improving human health. Cinnamon has anticancer activities that are exerted through multiple molecular mechanisms [7]. Fig. 2 indicates chemical structure of a number of main active components of cinnamon.

One of the most important properties of any potential anticarcinogenic compound is its ability to interfere with cancer cell viability. Numerous studies have indicated the anti-proliferative effects of cinnamon against various cancer cells. Significant antiproliferative function of cinnamon extract (CE) was shown in three hematological cancer cell lines *i.e.* U937, Wurzburg and Jurkat cells [8]. Each cell type exhibited a dose-dependent decrease in viability when treated with a dose range between 0.05 and 0.2 mg/mL of CE. Among the tested cells, it was observed that Wurzburg cells possessed the greatest sensitivity to CE. This finding suggests differential and cell-specific properties of cinnamon in regulating cell proliferation [8]. Moreover, anti-proliferative activity of CE was revealed in SiHa, a cervical cancer cell line, when treated with various concentrations of CE (10, 20, 40 and 80 μg/ml) [9]. In SiHa cells treated with CE at a concentration of 80 μg/ml, a dose-dependent decline in growth kinetics was observed compared with untreated cells. In addition, clonogenic assays confirmed the anti-proliferative potential of CE [9].

Due to the interrelationship between immunity and inflammatory processes contributing to cancer progression, immunotherapy is known as a potential therapy against cancer. Currently, there is an increasing interest to use natural products for strengthening the immune system. CD8+T cells, known also as killer T cells or cytotoxic T lymphocytes, function as major players in restricting the carcinogenic processes. Intra-tumoral injection or oral administration of CE significantly decreased tumor cell proliferation *via* acceleration of the cytolytic activities of CD8+T cells in vivo. Compared with the control group, cinnamon extract induced the expression of cytolytic mediators such as Tumor necrosis factor-α *(TNF-α)* and interferon gamma *(IFNc)*. It was shown that cinnamon significantly up-regulated perforin and granzymes B and C levels, thereby inducing apoptosis [7]. Due to its pivotal role in tumor cell metastasis, angiogenesis plays an important role in cancer progression. Hypoxia inducible factor 1 alpha (HIF-1α) and cyclooxygenase 2 (COX-2) contribute to the angiogenesis process. A significant down-regulation of HIF-1α and COX-2 expression was observed following treatment of Clone M3 and B16F10 melanoma cells with at different concentrations (0.1, 0.2, 0.3, 0.4 and 0.5 mg/ml) of CE for 24 h. CE completely blocked COX-2 expression at a dose of 0.5 mg/ml [10]. CE showed the same effects in mice treated by intra-tumoral injections (IT) or oral administration (OA) for 30 days. OA had greater capability in down-regulating both translation and transcription of HIF-1α and COX-2 compared with IT. COX-2 transcription was decreased by 40% in the IT group, while a 9% decrease was observed in the OA group [10].

When treating cancer, regulating the expression of growth factors is one of the most essential aims. CE significantly inhibited the transcription and translation of various growth factors (*e.g.* VEGF-α, FGF, EFG and TGF-β) in a dose-dependent (0.5 and 0.3 mg/ml) manner in melanoma cell lines Clone M3 and B16F10, while these effects were not seen when using similar concentrations of CE in healthy cells [10]. Also, the essential oil of cinnamon (EOC) has been shown to suppress EGFR-TK (epidermal growth factor receptor-tyrosine kinase) activities in laryngeal squamous cell carcinoma cell line Hep-2, which led to 43.5% decrease in tumor burden [11]. Essential oil of cinnamon bark (CBEO) also showed similar effects in pre-inflamed human dermal fibroblasts and significantly down-regulated plasminogen activator inhibitor-1 (PAI-1), epidermal

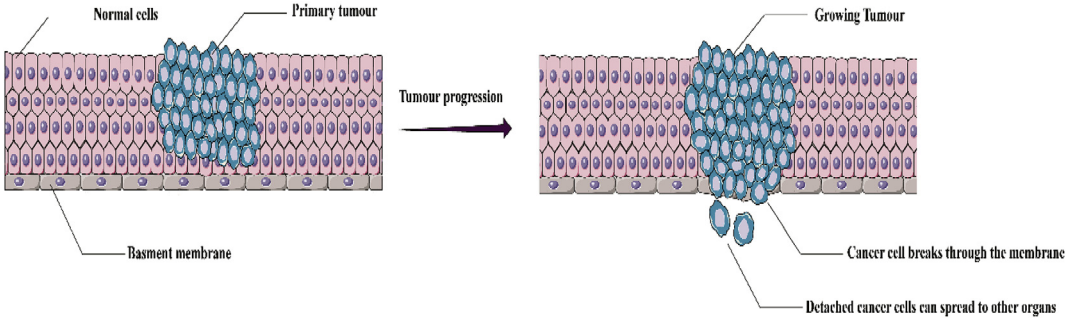

Fig. 1. Schematic presentation of the basic properties of cancer cells.

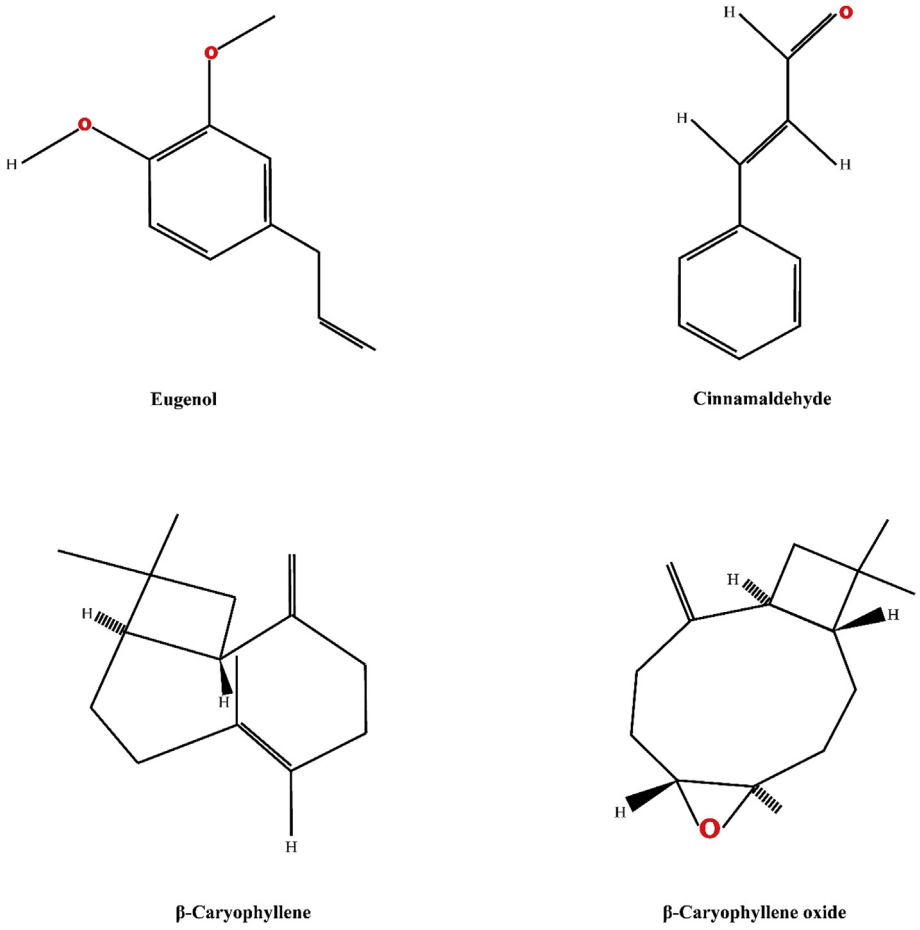

Fig. 2. Chemical structures of different active compounds of cinnamon.

growth factor receptor (EGFR) and matrix metalloproteinase 1 levels [12].

In addition to the anti-proliferative activities of cinnamon, individual changes in cancer cell morphology were shown following the use of cinnamon either as extract or as individual active constituent(s). Oral or intra-tumoral injection of CE to a mouse melanoma model significantly reduced tumor growth after 22 days of therapy as determined by tumor weight measurement. CE suppressed metastasis occurrence by decreasing weight and dimension of spleen drainage and lymph nodes compared to the control [10].

CBEO derived from *Cinnamomum zeylanicum* up-regulates the expression of some inflammatory cytokines including monocyte chemo-attractant protein-1, monokine induced by gamma interferon, interferon gamma-induced protein 10 and interferon-inducible T cell alpha chemo-attractant in the human dermal fibroblast system. Also, CBEO significantly reduced the level of macrophage colony-stimulating factor (M-CSF) as an immunomodulatory protein [12].

In addition to CE, various active compounds of cinnamon (*i.e.* eugenol, BCA, HCA and cinnamaldehyde) increased the cytotoxicity of different types of cancer cells. Eugenol is a compound which could be found in different plants including cinnamon, basil, lemon balm and nutmeg. Eugenol is a key compounds in cinnamon, which shows a wide ranges of pharmacological activities [13]. Following treatment with eugenol at a concentration ranged from 10 μM to 1 Mm for 24 h, the proliferation rate of HeLa cells was decreased. Although no cytotoxicity on normal lymphocytes was observed at 500 μM, a similar concentration caused a 50% suppression in the growth of HeLa cells [14]. Cytotoxic impact of eugenol was seen against colon cancer cells HT-29 and HCT-15, of which the former cell line had a higher sensitivity to eugenol [15]. Eugenol showed considerable anti-proliferative effects in HL-60 cell, a promyelocytic leukemia cell line, with an IC50 of 23.7 mM [16]. Using eugenol in combination with gemcitabine (a chemotherapy drug) showed a strong chemo-sensitizing impact. A combination of eugenol (150 μM; sublethal dose) and gemcitabine (15 mM) increased the cytotoxicity of both compounds in HeLa cells (47% viable cells) compared with anti-proliferative properties of using each compound alone (84% and 73% of viable cells for eugenol and gemcitabine, respectively) [14]. The chemo-sensitizing effect of eugenol was also reported in prostate cancer cells, in which the combination of 2-methoxyestradiol (2ME2) and eugenol synergistically increased the cytotoxic effects against androgen-independent PC-3 cell line. IC50 of 2-ME2 and eugenol, when used separately, were 82 μg/ml and 1 μM, respectively. Nevertheless, the combination (41 μg/ml eugenol + 0.5 μM 2ME2) showed a 50% growth suppression. In addition, the combination inhibited anchorage-independent growth of PC-3 cells; however, a considerable effect was not observed when either eugenol or 2-ME2 alone. Therefore, the combination efficiently declined anchorage-independent/dependent growth of prostate cancer cells [17].

In a DMBA croton oil-induced skin tumor animal model, neoplastic morphological alterations were inhibited at the pre-malignant phase following pre-treatment of animals with eugenol. It was found that the dimension of papillomas was 3 times

Table 1
Anti-cancer effects of cinnamon and its analogues.

Ref	Mechanism	Dose/Route	Cancer	Type of cinnamon
[20]	Inhibits transcriptionally MDR1 expression by suppression of AKT and STAT3pathway.	NA	Breast cancer, Lung cancer, and colon cancer	CB-PIC
[21]	Inhibits tumor growth in vivo, stimulates sub-G1 accumulation in hypoxic situations by inducing ERK and AMPKα, inhibits viability under hypoxia, suppresses the expression of AKT,HIF-1α, and mTOR in hypoxia	NA	Colon cancer	CB-PIC
[22]	Inhibits tumor growth, Stimulates cyclin B1 expression and G2/M cell cycle arrest	1.61–2.83 μg/mL	Breast cancer, Colon cancer	BCA (CB403)
[23,24]	Suppresses tumor growth and formation by down-regulation of the ROS scavengers, such as metallothionein1/2	NA	Hepatocellular carcinoma	BCA
[25]	Stimulates cell death by up-regulatingEGR1, Suppresses cell viability by nuclear translocalization of EGR1 via inducing importin-7	19.8–23.5	Prostate cancer	BCA
[26]	DJ-1 protects breast cancer cells against oxidative stress through inducing nuclear translocation-independent Nrf2 signaling pathway	46.57	Breast cancer	BCA
[27]	Stimulates stronger anti-proliferative activities in RK3E-ras than in RK3E cells.	>30 9.7	kidney cancer	BCA
[28]	Suppresses LPS and concanavalin A (Con A)-stimulated lymphocyte proliferation through arresting the cell cycle at the G1 phase, Stimulates T cell maturation.	NA	Mouse splenocyte cultures	BCA and HCA
[29]	Indicates anti-tumorigenic effects via stimulating G2/M phase arrest	<10	Breast cancer, Colon cancer	BCA and HCA
[30]	Suppresses growth of tumor cells in vivo and in vitro.	0.63–8.1 μg/mL	Colon cancer	BCA and HCA
[31]	Stimulates G2/M phase cell cycle arrest by induction of PARP cleavage expression, Suppresses tumor cell growth in vivo and in vitro.	16.8	Colon cancer	Hydroxylamine Derivatives
[32]	Suppresses tumor metastasis in vivo, stimulates EMT via inhibition of snail by GSK-3β nuclear translocalization and induction of E-cadherin, suppresses invasion via inhibition of the Sp1/Id-1 signaling pathway by KLF17up-regulation.	NA	Breast cancer	HCA
[33]	Suppresses cell invasion by pepsin clearance in a 2-macroglobulin-dependent manner via inducing the cysteine thiol oxidation condition of the LRP1 extracellular domain	NA	Breast cancer	HCA
[34]	Potently suppresses farnesyl protein transferase (FPTase)	NA	Colon cancer	HCA
[35]	Suppresses tumor growth in vivo	20.2–40.5	Oral squamous cell	HCA
[36]	Suppresses cell growth in vivo and in vitro.	NA	Various cancers	HCA
[37]	Suppresses protein isoprenylation, decreases proliferation of the tumor cells, decreases invasion by down-regulating collagenase, MMP2, HLA-A3 and type IV	1–4.5 mM	Lung carcinoma, Melanoma, Glioblastoma and Prostate cancer	Cinnamic acids
[38,39]	Suppresses estrogen and androgen generation by inhibition of 17β-HSD type 1and17β-hydroxysteroid dehydrogenase (AKR1C3)	NA	Hormone-dependent cancer	Cinnamic acids
[40]	Inhibits tumor growth in vivo, suppresses tumor cell proliferation, stimulates G2/M cell cycle arrest by suppressing Cdc25B phosphatase	0.6–10	Colon cancer, Breast cancer	Dimeric Cinnamaldehydes
[41]	Synergizes cytotoxic impacts of cytokine-stimulated killer cells to K562 cells	NA	Leukemia	Cinnamaldehyde
[42]	Stimulates oxidative stress reaction, increases SRXN1, TXNRD1, HMOX1, andCDKN1A expression, suppresses the TNF-α-stimulated expression of IL-8andthe NF-κB transcriptional function, inhibits invasiveness, tumor growth, and proliferation of melanoma cells	6.3	Melanoma	Cinnamaldehyde
[43]	Suppresses protein generation by trapping sulfhydryl-containing amino acid in cells	NA	Leukemia	Cinnamaldehyde
[44]	Inhibits cancer cell growth as well as suppresses the migration of tumor cells by MMP-2 down-regulation	0.36	Breast cancer	Cinnamaldehyde
[45]	Promotes efficacy OXA and 5-FU efficacy, causes a synergistic impact on apoptosis and inhibits the drug-metabolizing genes, such as ERCC1, TS, BRCA1 and TOPO1	9.12–9.48	Colon cancer	Cinnamaldehyde
[46]	Increases the expression of cyclin B1 as well as tubulin accumulation	1.2–86.4	Colon cancer, Breast cancer	Cinnamaldehyde, BCA, HCA, and FHCA
[47]	Increased PARP cleavage, increased PARP cleavage	9.76	Human hepatoma cells	Cinnamaldehyde
[48]	Compounds have reactive nucleophiles, including GSH and sulfhydryl groups, stimulates the expression of Nrf2, and suppresses thioredoxinreductase (TrxR)	1.6–7	Colon cancer	Cinnamaldehyde, BCA, HCA, and FHCA
[49]	Up-regulates Nrf2 protein, increases colon cancer cell protection and cellular glutathione against oxidative stress**,** activates an Nrf2 antioxidant response	NA	Colon cancer	Cinnamaldehyde, BCA, HCA, and FHCA
[50]	Stimulates cell cycle arrest at the G2/M phase	1.7–19.77	Cisplatin-resistant human ovarian cancer	Cinnamaldehyde
[51]	Induces MAPK pathway-related gene, such asERKp38andJNK, stimulates cell cycle arrest at the S phase	<0.5	Human hepatoma	Cinnamaldehyde
[52]	Stimulates G2/M cell cycle arrest through regulating two signaling proteins, inhibits cyclin B protein expression and induction of p38 MAPK expression	NA	Leukemia	CE
[53]	Down-regulates the expression of Her-2 oncoprotein, reduces cell migration by a decrease in the expression of MMP-2	NA	Cervical cancer	CE
[54]	Suppresses tumor growth and angiogenesis by inhibition of the VEGF2 signaling pathway	NA	Breast cancer	CE
[55]	Inhibits angiogenesis and tumor growth through down-regulating tumor-related growth factors such as HIF-1, Cox-2, TGF-β, VEGF-αand EGF, induces killing function of CD8+Tcells by up-regulating cytolytic molecules (TNF-α and IFN-γ)and granzymes B and C	NA	Melanoma	CE

CB-PIC: cinnamaldehyde derivative (E)-4-((2-(3-oxopop-1-enyl)phenoxy)methyl) pyridinium malonic acid; BCA: 2′-Benzoyloxycinnamaldehyde; HCA: 2′-hydroxycinnamaldehyde; FBCA: 5-fluoro-2-benzoyloxycinnamaldehyde; CE: Cinnamon extract.

smaller in the eugenol-treated mice compared with untreated tumor-bearing subjects. Eugenol significantly limited carcinogenesis at the dysplastic phase with a thickened epithelial layer or acanthosis, while the traits in the control group showed developed squamous cell carcinoma features including keratin pearl generation, acanthosis, and hyperkeratosis [18]. Significant changes in the cellular morphology were following combined treatment of prostate cancer PC-3 cells with 2-methoxyestradiol (0.5 μM) and eugenol (41 μg/ml) for 24 h, compared with each treatment alone [17].

IL-1β is an inflammatory cytokine that contributes to carcinogenesis. In HeLa cells, administration of eugenol suppressed IL-1β expression compared with the control group [14]. It has been indicated that pre-treatment with eugenol impedes tumorigenesis in vivo *via* a significant inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced up-regulation in the expression of pro-inflammatory mediators, including interleukin-6 (IL-6), prostaglandin E2 (PGE 2) and tumor necrosis factor-alpha (TNF-α). The expression of these factors was nearly similar to control levels when pre-treated with eugenol for 30 min prior to exposure to TPA [19]. The expression of COX-2 in HeLa cells was considerably diminished by eugenol treatment [14]. iNOS and COX-2 transcription levels in a TPA-induced skin cancer model were also limited by eugenol pre-treatment [19]. It was also demonstrated that pre-treating with eugenol hinders DMBA croton oil-mediated skin carcinogenesis in mice *via* a reduction in the translation and transcription levels of two oncogenes, c-Myc and H-ras. The expression was decreased by 40% for c-Myc and by 28% for H-ras compared with the controls.

Anti-tumor properties of cinnamon and its analogues in various cancers are listed in Table 1.

3. Apoptosis and cancer

Deregulation in programmed cell death or apoptosis contribute significantly to tumor pathogenesis by allowing neo-plastic cells to stay alive, even in the presence of oxidative stress and hypoxia [56]. Cancer may be regarded as an outcome of a series of genetic alterations that cause the transformation of normal cells to malignant cells [57]. Kerr et al. found an inverse association between apoptosis and tumor progression, hyperplasia and formation of abnormal cells [58]. Disturbed apoptosis contributes to carcinogenesis. Researchers have found numerous mechanisms by which an abnormal cell can suppress apoptosis and acquire apoptosis resistance. In general, causative mechanisms of apoptosis evasion are classified into three categories: i. impaired balance of pro-apoptotic and anti-apoptotic proteins, ii. decreased caspase activity, and iii. dysfunction in death receptors signaling. Fig. 3 summarizes the mechanisms contributing to apoptosis evasion and carcinogenesis.

It has been indicated that several proteins have pro-apoptotic or anti-apoptotic activities in cells. The ratio of pro- and anti-apoptotic proteins is pivotal in the modulation of cell death. In addition, it has been demonstrated that the modulation of apoptosis process through up- or down-regulation of particular genes (final modulatory proteins) plays an important role in carcinogenesis.

There are two general classes of caspases. One class, including caspase-1, -4, -5, -13, and −14 contribute to cytokine processing during inflammatory conditions. Another class including caspase-2, -3. −6, −7,-8, −9 and −10 has a major role in apoptosis. Nevertheless, it has been found that “initiator caspases” comprising caspase-2, -8, -9 and -10 initiate apoptosis, while caspase-3, -6 and -7, known as effector caspases, mediate the cleavage of cellular components during apoptosis [59]. Caspases play a significant role in initiating and executing apoptosis. Thus, dysfunction or deregulation of caspases can lead to impaired apoptosis and culminate in carcinogenesis. Down-regulation of caspase-9 is a frequent observation in patients with colorectal cancer and is associated with poor clinical outcomes [60]. Devarajan et al. reported that the levels of caspases-3 mRNA in commercially accessible total RNA samples from ovarian, cervical and breast tumors were either undetectable (cervical and breast) or significantly declined (ovarian). They also reported that through reinstating the expression of caspase-3, apoptosis sensitivity of caspase-3-deficient breast cancer cells (MCF-7) in response to anti-cancer drugs might be increased. This indicates that survival of breast cancer cells might be caused by

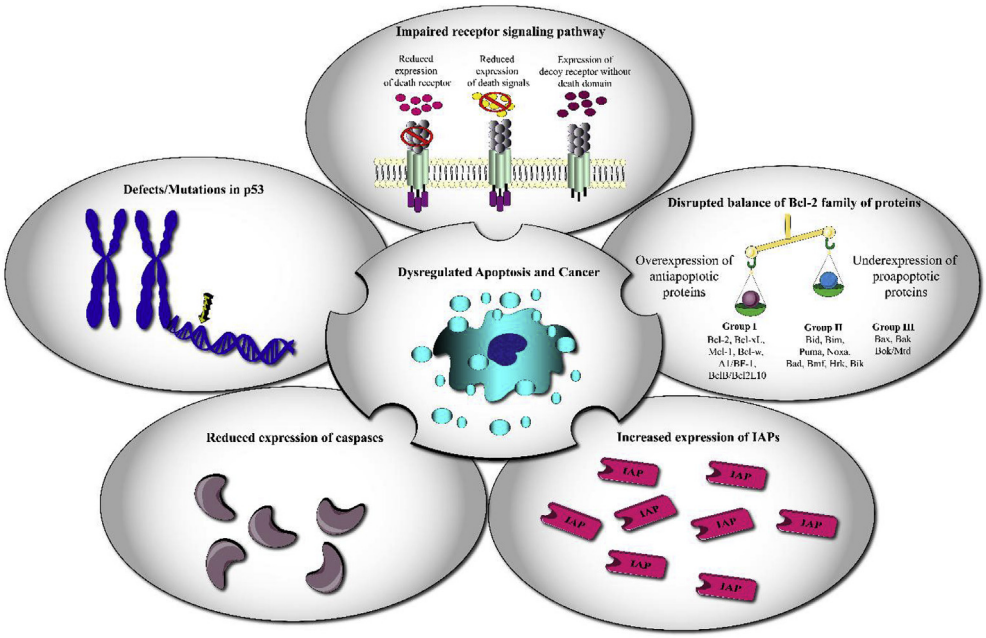

Fig. 3. Mechanisms that contribute to carcinogenesis and apoptosis evasion.

reducing caspases-3 performance and expression [61]. Sometimes, more than one caspase may be down-regulated involves in the progression and growth of tumour cells. Fong et al. found co-downregulation of capase-8 and -10. They suggested that this can play a role in the pathogenesis of choriocarcinoma [62].

Death receptors and their ligands play an essential role in the external pathway of apoptosis. TNFR1 that is referred to as Fas and DR1, is recognized by CD95 (also known as APO-1 or DR2). Other receptors are DR6, DR5 (or TRAIL-2), DR4 [or TNF-associated apoptosis, inducing ligand receptor 1 (TRAIL-1) or APO-2], DR3 (or APO-3), nerve growth factor receptor (NGFR), and ectodysplasin A receptor (EDAR) [61]. Following the stimulation of these receptors by death signals, some molecules bind to the death domain, leading to the activation of the related signaling processes. Nevertheless, death receptor ligands can also bind to decoy death receptors, which do not have a death domain [63]. Numerous abnormalities in death signaling pathways have been specified, which may result in evading from external pathway of apoptosis. Disorders are caused by down-regulation of death receptors, impairment of their functions or decreased death signals leading to decline in apoptosis. It has been indicated that down-regulation of the expression of surface receptors is a mechanism of acquired drug resistance. Also, down-regulation of CD95 expression contributes to therapy-resistant leukemia or neuroblastoma cells [64,65]. Moreover, it has been found that a decrease in the membrane expression of death receptors results in evading from the death signaling pathways in several cancers [66]. Reesink-Peters et al. conducted a study to examine whether modifications of the expression of death ligands and receptors within various phases of cervical carcinogenesis are associated with interaction between apoptosis and proliferation. They suggested that decrease in Fas expression and dys-regulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL),DR4, DR5, and FasL could cause cervical carcinogenesis in cervical intra-epithelial neoplasia (CIN)-cervical cancer sequence [67]. It should be noted that any disturbance in apoptosis machinery might have a detrimental impact, thus suggesting this process as a pivotal target for cancer treatment. Drugs or strategies restoring apoptotic signaling pathways toward normal patterns are potentially able to eliminate cancer cells.

4. Cinnamon targets apoptosis in cancer

Apoptosis or programmed cell death is a complex interaction between several molecules and pathways. Generally, CE and its active compounds can affect apoptosis progression in many cancers (Table 2, Fig. 4). It has been demonstrated that caspase-3 activity is stimulated by CE in an in vivo melanoma model and in B16F10 cells. However, the level of procaspase-3 (inactive form) did not change, and the expression of AP1 and NF-κB as well as transcription and translation of their target genes such as BcL-xL, Bcl-2 and survivin were significantly decreased [68].

Eugenol is one of the most significant active ingredient of cinnamon, which induces apoptosis in promyelocytic leukemia cell line HL-60 in a dose- and time-dependent manner *via* enhancement of DNA fragmentation and reduction of mitochondrial potential by generating ROS [16]. Also, eugenol increased ROS

Table 2
Targeting apoptosis by Cinnamon and its analogues.

Ref	Model	Dose/Route	Cancer	Type of cinnamon
[81]	In vitro	10, 20, 40, 80, 160 and 320 μg/ml	Cervical cancer	CE
[82]	In vitro	NA	Colon cancer	HCA
[83]	In vitro	12.5	Colon cancer	HCA
[84]	In vitro	3.3–70.8	Breast cancer, Colon cancer, Lung cancer	BCA
[7]	In vitro, in vivo	0.5 mg/ml,400 μg/g Oral	Lymphoma, melanoma, cervix cancer and colorectal cancer	Cinnamic aldehyde and cinnamylaldehyde
[85]	In vitro	NA	Human hepatoma cells	Cinnamaldehyde
[86]	In vitro	30.7	Leukemia	Cinnamaldehyde
[87]	In vitro	2 mmol	Human Nasopharyngeal Carcinoma Cells	Cinnamic Acid
[88]	In vivo	Cinnamon at a dose of 100 ml, Oral, 8 weeks	Colon cancer	Cinnamon
[89]	In vitro	2, 1, 0.1 and 0.01 mg/ml	Leukemia	*Cinnamon*
[90]	In vitro and in vivo	0 μM, 10 μM and 40 μM, injection of 200 μL	Hepatocellular carcinoma	*Cinnamon*
[91]	In vitro	5, 10, 50, 100, 200 and 300 μM	Prostate Cancer	PCB2
[92]	In vitro	5, 10, 25, 50, 75, and 100 μM	Leukemia	Cinnamon
[93]	In vitro	10–100 μg/mL	Breast cancer	CE
[94]	In vitro	500 μM	Cervical Cancer	Eugenol
[95]	In vivo and in vitro	5 or 20 mg/kg of	Leukemia and skin cancer	HCA
[96]	In vitro and in vivo	0, 10, 20, 40, 80 and 160 μM, Injection of 5, 10, or 20 mg/kg/day of cuminaldehyde	Colorectal Adenocarcinoma	Cuminaldehyde
[97]	In vitro	50 μM 00000	Prostate and Breast cancer	CPO
[98]	In vitro and in vivo	Different concentration, Injection of 10 mg/kg	Hepatocellular carcinoma	2-MCA
[99]	In vitro	0.5, 1, 5 and 10 mg/ml	Breast cancer	CPGF Nps
[100]	In vitro and In vivo	Different concentration, Injection of a 200 μL	Human Lung Adenocarcinoma	2-MCA
[101]	In vivo and in vitro	10 mg/ml, oral cinnamon 0.3 mg/g.	Ovarian cancer	Cinnamaldehyde
[102]	In vitro	1 mg/mL	Cervical cancer	CE
[103]	In vitro	various concentrations of cinnamon	Breast cancer	CE
[104]	In vivo and in vitro	Different doses of cinnamon, 400 μg/g oral	Melanoma	CE
[105]	In vitro	NA	Colon cancer, Melanoma	CE
[106]	In vivo	500 mg	Oral carcinogenesis	ACE
[107]	In vitro	2, 4, 6, 8, and 10 μm	Colon cancer	CE
[108]	In vivo and in vitro	120 mg/kg, 25 μM,	Melanoma	(CA
[109]	In vivo and in vitro	Different doses	Colorectal cancer	CA
[8]	In vitro	0.0, 0.05, 0.075, 0.10, and 0.20 mg/mL	Hematologic tumors	CE

BCA: 2′-Benzoyloxycinnamaldehyde; HCA: 2′-hydroxycinnamaldehyde; CE: Cinnamon extract; CA: Cinnamaldehyde; ACE: Aqueous cinnamon extract; CPGF Nps: Cinnamaldehyde-Magnetite Nanoparticles; 2-MCA: 2-Methoxycinnamaldehyde; CPO: b-Caryophyllene oxide; PCB2: Procyanidin-B2.

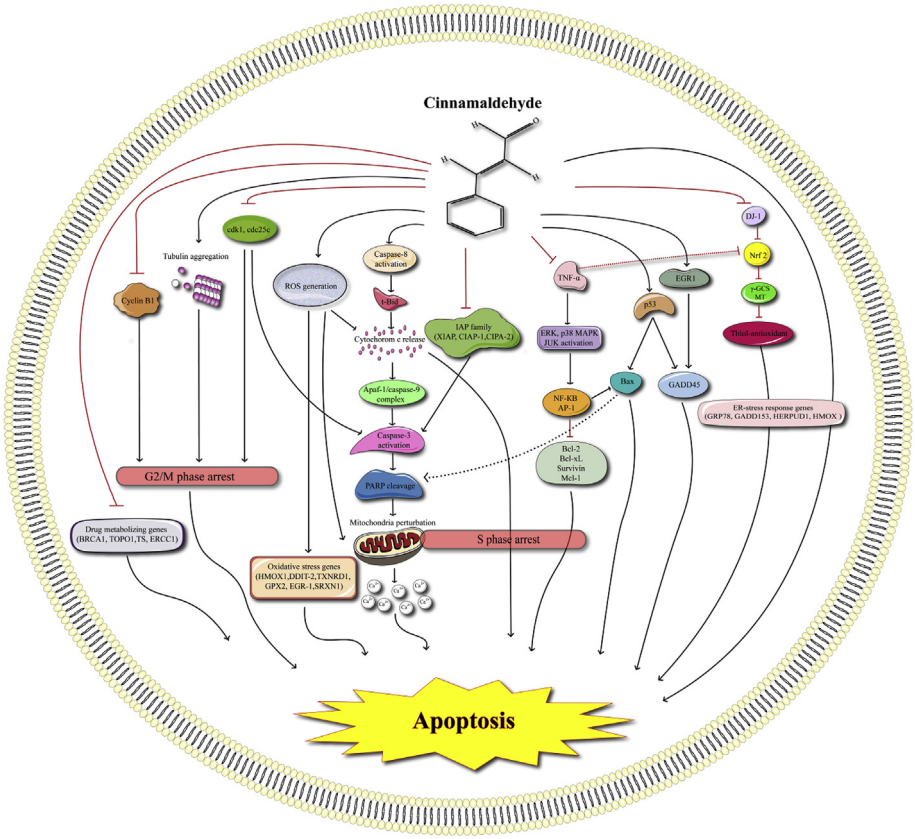

Fig. 4. Cinnamon and apoptosis in cancer.

production in colon cancer HT-29 and HCT-15 cells [15]. Treating HL-60 cells with 40 μM eugenol for 4 h led to significant DNA fragmentation through cleavage at inter-nucleosomal linker regions, which form a clear DNA ladder.

Apoptosis induction by eugenol is mediated by DNA fragmentation and proteolytic cleavage of caspase-3 and -9 from their inactive forms. Although a considerable depletion of the amount of bcl-2 protein and an increased cytochrome *c* release were observed at this concentration of eugenol, procaspase-8 cleavage had no significant impact [16]. An in vivo investigation showed that following pre-treatment with eugenol, the apoptotic index was increased 1.5 fold in DMBA/TPA induced murine skin carcinogenesis through up-regulation of p53 $p21^{WAF1}$ expression. Consequently, this study confirmed the effectiveness of eugenol in apoptosis regulation [19]. Moreover, eugenol potentially regulates the Bax:Bcl2 ratio and up-regulates caspase-3 activity in chemically induced murine skin carcinogenesis [18].

Eugenol also caused a dose-dependent up-regulation in the amount of caspase-3 activity in HeLa cells. Furthermore, eugenol had chemosensitizing effects and its combination with a conventional chemotherapeutic drug, gemcitabine (150 μM eugenol with 15 mM and 25 mM gemcitabine), synergistically amplified caspase-3 activities compared with each agent alone [14]. In addition, another study indicated the potential of eugenol in apoptosis induction; its administration with 2-methoxy-estradiol significantly down-regulated Bcl-2 protein, up-regulated pro-apoptotic protein Bax, and reduced mitochondrial membrane potential in prostate cancer PC-3 cell [17].

It was found that cinnamaldehyde (40 μM), similar to eugenol, induced apoptosis in HL-60 cells *via* inter-nucleosomal DNA fragmentation followed by chromatin condensation and degradation of nuclei. Moreover, it significantly up-regulated proteolytic cleavage of procaspase-3 and procaspase-9, increased caspase-9 and caspase-3 activation, declined mitochondrial transmembrane potential, and increased cytochrome *c* release into the cytosol [69]. At 30 μM, cinnamaldehyde showed significant anti-carcinogenic effects on liver cancer cell line HepG2 through reducing anti-apoptotic protein Bcl-XL and inducing pro-apoptotic proteins Bax and p53 in a time-dependent manner. After 24 h of treatment with cinnamaldehyde, the expression of Bcl-XL was fully inhibited. Moreover, cinnamaldehyde with the same dose up-regulated the expression of CD95 (APO-1/CD95) and cleaved poly (ADP-ribose) polymerase (PARP) [70]. It has been indicated that a low concentration of cinnamaldehyde (1 μM) induces apoptosis by up-regulating caspase-8, Bax and Bid activities, and reducing the expression of anti-apoptotic proteins (Mcl-1 and Bcl-2) in the hepatoma cell line PLC/PRF/5 in a time-dependent manner (6, 12, and 24 h) [71]. One of the cinnamaldehyde isomers called *trans*-cinnamaldehyde is able to enhance apoptosis in the myelogenous leukemia cell line K562, which is mediated by decreasing the mitochondrial *trans*-membrane potential. This isomers also contributes to the increased expression of Fas/CD95 [41]. Fig. 4 depicts the mechanisms through which cinnamaldehyde and its derivatives function as anti-carcinogenic agents [72].

It has been confirmed that cinnamaldehyde is an extremely unstable compound in serum due to its aldehyde group. Thus, modification of aldehyde group with hydroxylamine and synthesis of cinnamyl compounds without the aldehyde group were conducted by Shin et al. [73]. PARP and caspase-3 cleavage in SW620 and HCT116 colon cancer cells were increased by hydroxylamine derivatives at concentrations ranging from 20 to 40 μM [73]. Caspase-dependent apoptosis was induced by cinnamaldehyde

(40 μM) in HL-60 leukemia cell line *via* induction of ROS generation, cytochrome *c* accumulation in cytoplasm, activation of caspase-3 and caspase-9, and reduction of the mitochondrial *trans*-membrane potential [69].

2′-benzoyloxycinnamaldehyde (BCA) and 2′-hydroxycinnamaldehyde (HCA) are other cinnamon compounds which exert their therapeutic effects on various diseases such as cancer *via* affecting several biological mechanisms [6]. Gan et al. indicated that apoptosis is induced by BCA (40 μM) through caspase-dependent and caspase-independent pathways in HCT116 colon cancer cells [74].

In colon cancer cells, apoptosis is induced by HCA through extracellular signal regulated kinase (ERK)-dependent inactivation of NF-κB, or suppressing the DNA-binding activities of AP-1 and down-regulation of c-Fos and c-Jun expression [75,76]. Moreover, there is an association between HCA-induced and BCA-induced apoptosis with the inhibition of 26S proteasome activity in colon cancer cells [77]. Nevertheless, Gan et al. indicated that 26S proteasome suppression does not contribute to HCA-induced and BCA-induced apoptosis of HEK293 cells [74]. Previous investigations have demonstrated that BCA suppresses the proliferation of cells in a more effective manner than HCA [78]. Hitherto, in vitro and in vivo studies have shown that BCA is quickly hydrolyzed to HCA, and is subsequently transformed to *O*-coumaric acid during a few hours [79,80]. It was found that cell proliferation is more efficiently inhibited by BCA compared with HCA. This might be caused by variations in the cell permeability to compounds; the cell membrane is more permeable to BCA due to the existence of higher hydrophobic groups in this compound.

5. Conclusion

Due to the increasing prevalence of malignancies worldwide and side effects of the current therapies, finding novel therapies is an urgent medical need. Alternative or complementary treatments from herbal sources have been noticed owing to their potential safety and efficacy in interfering with the oncogenic molecular pathways. According to the extant data, cinnamon and its derivates are natural compounds that possess antitumor properties. This review highlighted the role of cinnamon in the regulation of apoptosis as an essential signaling pathway involved in cancer progression. However, further experimental studies should be conducted to substantiate the anticancer activity of cinnamon, particularly based on its apoptotic effects.

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