Cinnamaldehyde: Pharmacokinetics, anticancer properties and therapeutic potential (Review)

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Abstract. Cancer incidence is increasing globally, presenting a growing public health challenge. While anticancer drugs are crucial in treatment, their limitations, including poor targeting ability and high toxicity, hinder effectiveness and patient safety, requiring relentless scientific research and technological advancements to develop safer and more effective therapeutics. Cinnamaldehyde (CA), an active compound derived from the natural plant cinnamon, has garnered attention in pharmacological research due to its diverse therapeutic applications. CA has potential in treating a wide array of conditions, including cardiovascular diseases, diabetes, inflammatory disorders and various forms of cancer. The present review comprehensively summarizes the physicochemical and pharmacokinetic profiles of CA, and delves into the latest advancements in elucidating its potential mechanisms and targets across various cancer types. CA and its derivatives have antitumor effects, which encompass inhibiting cell proliferation, arresting the cell cycle, inducing apoptosis, limiting cell migration and invasion, and suppressing angiogenesis. Additionally, the present review explores targeted formulations of CA, laying a scientific foundation for further exploration of its implications in cancer prevention and treatment strategies.

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1. Introduction

Cinnamon is widely used because of its culinary uses. The medicinal value of cinnamon has attracted the attention of more and more researchers (1). Cinnamaldehyde (CA) is a main ingredient extracted from the bark of the cinnamon tree (2), with a broad range of pharmacological effects, including anti-inflammatory (3), antioxidant (4), antiviral (5), anti-bacterial (6), antithrombic (7), hypoglycemic (8), hepatoprotective (9), anti-diabetic (10), neuroprotective (11) and anticancer effects (12), which largely contribute to the prevention and treatment of various diseases such as inflammatory diseases, neurodegenerative diseases, cardiovascular disease, diabetes mellitus and cancer. Advancements in cancer research have highlighted the promising potential of CA in restricting the growth of cancer cells (3-12). As demonstrated in a previous study, CA has shown a marked ability to impede cancer cell proliferation (13), prompting a surge in scientific interest in exploring its potential role in cancer therapy. Furthermore, to address issues such as the poor targeting and high toxicity of anticancer drugs, targeted formulations based on CA are also under constant research. These can enhance the effectiveness of anticancer drugs and ensure patient safety. Therefore, researchers utilize techniques such as structural modification and nano-carriers to optimize the performance of CA, aiming to improve its efficacy and safety in targeted cancer therapy (14-18). This progress lays the foundation for further investigation into the effects of CA in cancer prevention and therapy to identify potential effective and targeted treatment options in the future.

Therefore, the relevant literature in the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Science Direct (https://www.sciencedirect.com/) and China National Knowledge Infrastructure (https://www.cnki.net/) databases was searched using the main keywords 'cinnamon', 'CA', 'antitumor', 'pharmacological activity', 'pharmacokinetics' and 'toxicity', and their combinations. The present study systematically reviews the pharmacokinetics, antitumor activity and toxicity of CA, which provides a theoretical basis and direction for further research and clinical expansion.

2. Physicochemical and pharmacokinetic characteristics of CA

Physical and chemical properties of CA. The physicochemical characteristics of CA have been extensively studied (19-22). Peters and Caldwell (19) demonstrated that CA naturally exists in the form of trans-CA. CA (C_9H_8O; Fig. 1) is also known as cinnamon aldehyde, 3-phenyl-2-propenalin and trans-CA (20). CA is a yellow oily liquid with low solubility in water, and soluble in ethanol and chloroform (21). Due to its aldehyde structure, when CA comes into contact with air and light, it gradually oxidizes into cinnamic acid (21). Zinn *et al* (22) demonstrated that there may be four possible stereoisomers of CA.

Research on the pharmacokinetics of CA. To comprehend the mechanism of action of the drug and provide guidance for clinical practice, it is crucial to investigate pharmacokinetic parameters. Furthermore, ensuring the safety and effectiveness of the drug in clinical settings is imperative.

Bickers *et al* (23) revealed that CA is an active aldehyde that can be converted to cinnamyl alcohol. As a result, CA is unstable in the body and has the potential to be metabolized to cinnamic acid and converted to cinnamyl alcohol (23). In addition, Vasconcelos *et al* (24) demonstrated that, *in vivo*, it is possible that trans-CA decomposes to cinnamic acid by enzyme catalysis before it can elicit its antibacterial activity, and thus, could be considered unstable in blood. In a study by Zhao *et al* (25), the pharmacokinetics of CA in rats were assessed using a highly sensitive gas chromatography-mass spectrometry technique. The rats in the experiment received CA orally at a dose of 500 mg/kg and intravenously at a dose of 20 mg/kg. The results indicated that the bioavailability of intravenous administration of CA was superior to that of oral administration (25). In another study, the researchers utilized gas chromatography-mass spectrometry to measure the concentration of CA and its metabolite cinnamyl alcohol in rat tissues at the same time and investigated their distribution patterns. According to the study findings, the spleen exhibited the highest concentrations of both CA and cinnamyl alcohol among the major organs of rats, including the heart, liver, spleen, lungs, kidneys and brain. Additionally, there was no detectable long-term buildup of CA in the rat tissues (26).

To improve the stability and bioavailability of CA, researchers have designed a series of new dosage forms (27-32). For example, Zhao *et al* (27) developed a novel intravenous submicron CA (SME-CA) emulsion that not only successfully improved the solubility and absorption of CA, but also had lower toxicity and higher antitumor effects. Furthermore, SME-CA improved the tissue distribution in the kidney, liver, spleen and brain, and a 27% higher concentration was found in the brain compared with CA (27).

The advantages of convenience and good adherence make oral administration the preferred route for drug delivery (28). Researchers have mainly considered oral administration when studying CA dosage forms. For example, Wu *et al* (29) made CA into CA solid lipid nanoparticles, which increased the oral bioavailability of CA by >1.69 times. Furthermore, CA-solid lipid nanoparticles had a higher absorption rate under intestinal pH conditions compared with CA (29). Liu *et al* (30) developed a self-emulsifying drug delivery system (SEDDS) containing CA to overcome the shortcomings of poor solubility and limited absorption of CA. Compared with the free CA group, the CA-SEDDS group exhibited higher accumulation of CA and cinnamic acid in various tissues, especially in the kidney (30). In addition, Cai *et al* (31) investigated the ability of SEDDS to deliver lipophilic aldehyde CA-SEDDS in rat mucus, mucin solution, and Caco-2 and Caco-2/HT29 co-culture monolayers. The results of the study showed that CA-SEDDS exhibited excellent mucus permeability in mucus and mucin solutions, which was 5.1- and 2.8-fold higher, respectively, than that in the free CA group. CA-SEDDS penetration increased by 2.5-fold compared with that of free CA when using the mucus-secreting co-culture cell model as a barrier. The relative oral bioavailability of CA-SEDDS was 242% compared with CA (31).

Furthermore, Dong *et al* (32) examined the oral bioavailability of CA from the perspective of a microemulsion-mucus system. CA microemulsion (CA-ME) was prepared, and the results demonstrated that CA-ME had the highest absorption in the ileum compared with CA solution. Pharmacokinetic experiments indicated that the relative bioavailability of CA-ME was 2.5 times higher than that of CA solution (32).

Overall, these studies (29-32) have demonstrated the potential of various drug delivery systems, such as solid lipid nanoparticles, SEDDSs and microemulsions, to enhance the oral bioavailability and absorption of cinnamic acid.

3. Antitumor effects of CA in different types of cancer

According to the latest Global Cancer Statistics report released in 2022, there were nearly 20 million new cancer cases globally, with 9.7 million associated deaths in this year (33). According to forecasts, cancer is expected to surpass cardiovascular disease as the leading cause of premature death in most countries (34). In 2022, the five main types of cancer diagnosed in China were lung, colorectal, stomach, liver and breast cancer (35).

Application of CA in lung cancer. In 2022 globally, there were nearly 2.5 million new cases and over 1.8 million deaths from lung cancer (33). By 2022, lung cancer had become a leading cause of both incidence and mortality (33). The global burden of lung cancer is increasing. By 2035, China will become the country with the highest number of new cases (36). Therefore, in addition to controlling the incidence factors of lung cancer, finding novel chemotherapy drugs is also the key to solving the problem.

Using a 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone induced rasH2 mouse lung cancer model, it was demonstrated that CA reduced the combined incidence of lung adenocarcinoma and cancer. Specifically, in male rasH2 mice, the incidence decreased from 86 to 31%. The underlying mechanism may be to reduce the proliferation of tumor-initiating cells (37).

A previous study (38) provided evidence that suggested a combination of berberine and CA could reduce the susceptibility of mice to ammonia-induced lung cancer. The combined treatment activated AMP-activated protein kinase (AMPK), and inhibited the proliferation and growth of tumor cells in

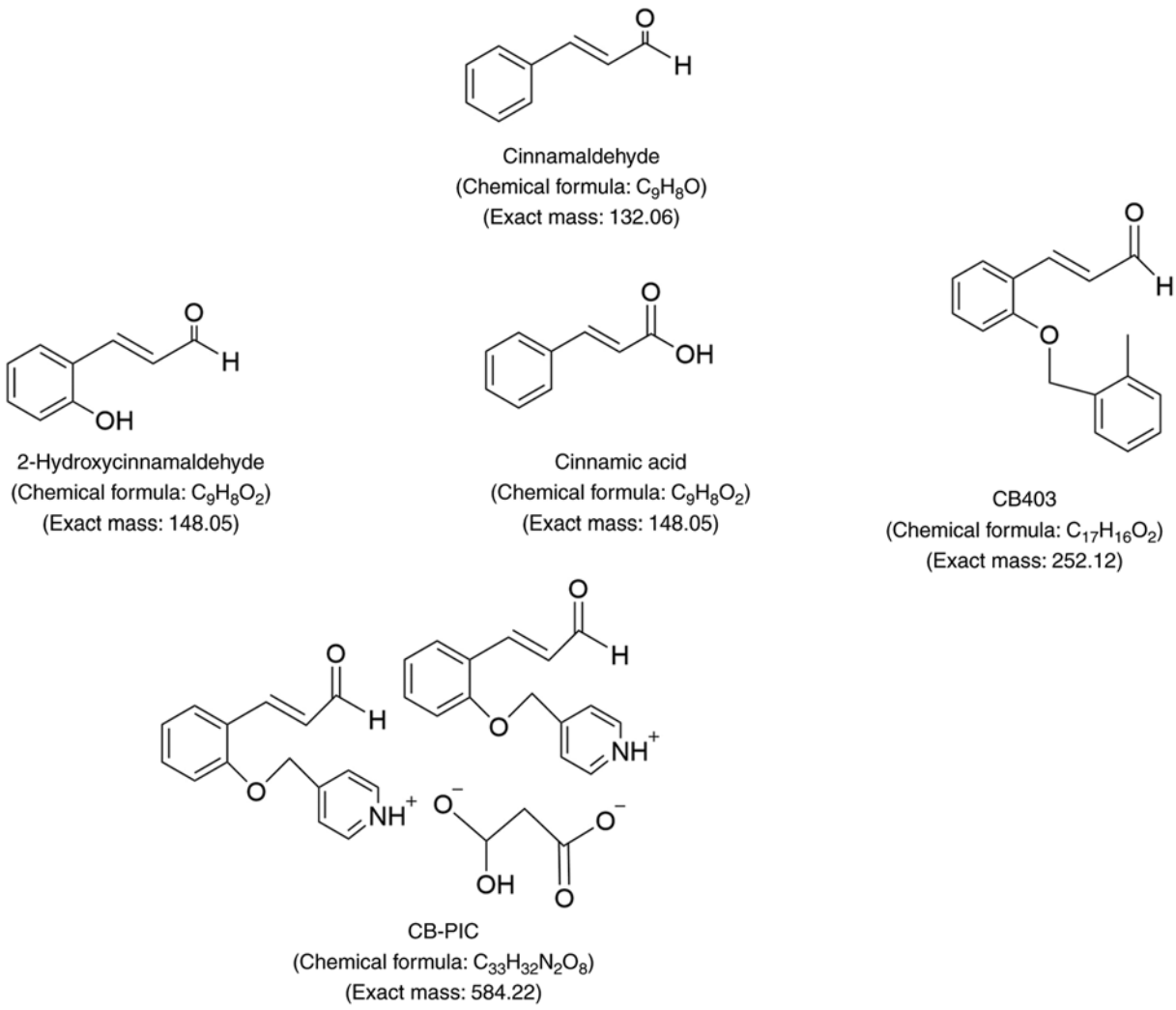

Figure 1. Chemical structures of cinnamaldehyde and its derivatives.

mice with methane-induced lung cancer. Additionally, the combined treatment effectively targeted the mTOR signaling pathway, which is a critical signaling pathway for cell proliferation and survival, thereby blocking tumor cell proliferation and survival (38). Furthermore, it has been observed that the combination of berberine and CA induced apoptosis of A549 cells, and inhibited cell proliferation, autophagy and wound healing, while upregulating AMPK and downregulating aquaporin 1 *in vitro* (38). A549 and NCI-H460 lung cancer cell lines were found to respond well to CA treatment. Additionally, CA treatment led to the induction of apoptosis in these cells, with the degree of induction being dependent on the concentration of CA used. Notably, the researchers observed a substantial increase in the expression levels of circular RNA hsa_circ_0043256 following CA treatment (39). This upregulation was found to serve a crucial role in triggering apoptosis in the cells (39). Furthermore, CA has the potential to disrupt abnormal cell growth, promote apoptosis and effectively hinder the advancement of lung cancer cells by interfering with the Wnt/β-catenin signaling pathway (40). Another study explored the effects of combining CA with hyperthermia on non-small cell lung cancer cells, specifically A549 cells. The research results indicate that the combination therapy of CA and hyperthermia could inhibit the growth and proliferation of A549 cells, and induce cell apoptosis by regulating the activity of reactive oxygen species (ROS) and the mitogen-activated protein kinase family. Especially when combined with hyperthermia therapy at 42˚C and 43˚C, CA could inhibit cell proliferation (41). Furthermore, CA induces apoptosis in non-small cell lung cancer cells by regulating Janus kinase/STAT, the NF-κB signaling pathway and RNA degradation (42).

Overall, these findings (37-42) suggest that CA possesses chemo-preventive properties and may have potential therapeutic benefits in lung cancer treatment. However, these studies were conducted *in vitro* or on animal models, and further clinical trials are required to validate the effectiveness and safety of these treatments in humans.

Application of CA in colorectal cancer (CRC). In 2022, there were over 1.9 million new cases of colorectal cancer (including anal cancer) and 904,000 associated deaths globally (33). Surgery for patients with CRC is considered to be the most effective approach, but postoperative complications can affect the quality of life to a certain extent (43). In addition, Sargent *et al* (44) demonstrated that patients with colon cancer

still have relatively low 5-year survival rates in chemotherapy, with high recurrence rates. The 1-5 year recurrence rates are 12, 14, 8, 5 and 3%, respectively. The median time from recurrence to death is 12 months (44). Therefore, in addition to controlling the factors of direct bowel cancer incidence, research and development of novel chemotherapy drugs is also the key to solving this problem.

CB403 (Fig. 1) is a cinnamaldehyde derivative that inhibits the activity of cyclin-dependent kinases (CDKs), particularly CDK1, CDK2 and CDK4, thereby halting cell cycle progression. Simultaneously, CB403 also suppresses the expression of cyclin D1, exerting antitumor effects (45). In addition, Lee *et al* (46) demonstrated that 2-hydroxycinnamaldehyde (HCA; Fig. 1) inhibits the growth of SW620 colon cancer cells by reducing the expression of c-Jun and c-Fos, inhibiting the DNA binding activity of activator protein 1, and inducing cell apoptosis (46). The CA derivative CB-PIC (Fig. 1) has marked cytotoxicity and induces apoptosis in SW620 human colon cancer cells by activating the AMPKα and ERK signaling pathways (47). Furthermore, CB-PIC is able to overcome drug resistance in chemotherapy cancer cells by inhibiting multidrug resistance protein 1 and its upstream STAT3 and AKT signaling pathways (48). At the same time, combining CA with chemotherapy drugs has shown promise in enhancing the sensitivity of cancer cells to these drugs. For instance, when CA is combined with 5-fluorouracil (5-FU), CA increases the sensitivity of CRC cells to 5-FU by reducing the expression of thymidylate synthase, ERCC1, DNA topoisomerase 1 and BRCA1, increasing the percentage of apoptotic cells to 92.7% (49). This finding suggests that utilizing CA as an adjunct therapy with 5-FU may lead to improved treatment outcomes for patients with CRC.

Research has indicated that CA exerts its antitumor effects by activating nuclear factor erythroid 2-related factor (Nrf2) (50). A study has found that inhibition of the PI3K/AKT signaling pathway can inhibit tumor cell proliferation and promote apoptosis (51). For example, researchers have found that CA can induce apoptosis in colon cancer cells by inhibiting the PI3K/Akt signaling pathway. Additionally, CA upregulates the expression of E-cadherin while downregulating the expression of matrix metalloproteinase-2 (MMP2) and MMP9 (52). Furthermore, Zhang *et al* (53) demonstrated that CA induced cell apoptosis by inhibiting the PI3K/Akt signaling pathway. In addition, the study revealed a decrease in Ki-67 expression in the CA group, along with the accumulation of numerous apoptotic cells (53). Nguyen and Kim (54) reported that HCA, a derivative of CA, induced apoptosis in colon cancer cells via heat shock transcription factor 1-mediated BAG cochaperone 3 expression. An inhibitory effect of CA on the hypoxia-activated Wnt/β-catenin pathway has been observed, leading to an augmented sensitivity of CRC cells to oxaliplatin, and enhancing the apoptosis of cancer cells (55). The presence of *Escherichia coli* has been linked to the advancement of colon cancer. A study conducted by Kosari *et al* (56) revealed that CA exhibited regulatory effects on the expression of the clbB gene, thereby mitigating the biofilm-forming capability of *E. coli*. CA (75 μM) treatment could induce apoptosis, necrosis and cell cycle slowing in Caco-2 and SW-620 cells after 72 h of treatment (57). Nile *et al* (13) revealed that, after cinnamaldehyde-rich cinnamon extract treatment, the number of HCT116 and HT-29 cells in the G_1 phase was decreased, the number of cells in the sub-G_1 phase was increased, and the number of cells in the G_2 phase was stagnant compared with the number of untreated cells. In addition, CA was also able to induce apoptosis in cancer cells by increasing intracellular ROS levels (13).

These findings suggest the potential of CA and its derivatives to inhibit colon cancer growth and promote apoptosis of colon cancer cells.

Application of CA in breast cancer. In 2022, there were ~2.3 million new cases of breast cancer in women globally, with 666,000 associated deaths (33).

Jeong *et al* (45) demonstrated that CB403, a derivative of CA, arrested breast cancer cells in mitosis by increasing the expression levels of cyclin B1. In addition, CB403 did not affect mouse body weight, while inhibiting tumor growth (45). A research team has synthesized biocompatible CA functionalized magnetic nanoparticles (CPGF NPs), which inhibit the proliferation of breast cancer cells by inducing apoptosis. The IC_{50} of CPGF NPs was found to be 0.363 and 0.368 μM in MDA-MB-231 and MCF7 cells, respectively, while the IC_{50} of free CA for MDA-MB-231 and MCF7 cells was 192.3-fold and 773.6-fold higher than that of CPGF NPs. This indicated that the CPGF NPs formulation of CA was substantially more effective in inhibiting the growth of breast cancer cells compared with free CA alone (58). In a study by Rad *et al* (59), it was demonstrated that cinnamon extract induced apoptosis in MCF7 and MDA-MB-231 cell lines by modulating antioxidant enzyme activity and activating the caspase pathway. Compared with healthy individuals, patients with breast cancer exhibit visibly elevated plasma visfatin concentrations, and lower survival rates are observed in patients with increased visfatin gene expression levels (60). However, the promotional effects of visfatin on breast cancer can be curtailed by the inhibitory actions of CA (60). By conducting experiments on breast cancer cells, researchers have demonstrated that CA stimulated the apoptosis of cancer cells by inhibiting their proliferation, invasion and migration (61). Through *in vitro* experiments, researchers revealed that cinnamon bark extract could inhibit the proliferation of breast cancer cells and induce apoptosis (62). Researchers have designed a reasonable co-loading drug formulation, using simple but practical graphene oxide to encapsulate mesoporous silica nanoparticles, modify hyaluronic acid (HA), and realize the co-delivery of CA and doxorubicin (DOX) to enhance their combined therapeutic effect on tumor cells and reduce their application defects (63). The combined use of CA and DOX exhibited higher cytotoxicity against MCF7 human breast cancer cells, which was related to CA-induced activation of the intrinsic apoptotic pathway in MCF7 cells (63). Through cell cycle analysis, it was found that the combined treatment of measles virus with baicalein or CA can induce apoptosis in breast cancer cells, thereby further enhancing therapeutic efficacy (64). Compared with monotherapy, combination therapy has a stronger inhibitory effect on breast cancer cells (63). Schuster *et al* (65) revealed that CA in combination with chlorogenic acid could disrupt the mitochondrial integrity of breast cancer cells, thereby promoting breast cancer cell death. At the same time, it did not affect the growth of normal breast epithelial cells (65). In one study, docetaxel

(DTX)/arginine-glycine-aspartic nanoparticles were prepared by nanoprecipitation/self-assembly using CA-Oxi-αCD material as a carrier (66). Through the endogenous ROS and acidic environmental stimulation of nanoparticles, the acetal bond between CA and αCD in the nanoparticles is broken to achieve the efficient release of the drug DTX. The selective and complete release of the drug is realized, and the accumulation and therapeutic effect of the drug in the tumor site are improved (66).

Research indicates that CA holds promise for the treatment of breast cancer. It has the potential to impede the growth and survival of breast cancer cells, and induce apoptosis through various mechanisms. Additional research and clinical trials are needed to establish the exact role and effectiveness of CA in breast cancer treatment and advance its development as a potential therapeutic option.

Application of CA in liver cancer. In 2022, liver cancer claimed the lives of >750,000 individuals worldwide, ranking it as the third highest cause of cancer-related death (33). Natural compounds have fewer side effects and lower toxicity than traditional chemotherapy drugs and are expected to be a potential treatment option for liver cancer (67).

CA promotes the apoptosis of cancer cells. CA induces cell apoptosis by upregulating Bax expression, and downregulating Bcl-2 and X-linked inhibitor of apoptosis (XIAP) expression (68). However, when CA is combined with vitamin E, the promoting effect of CA on the release of apoptotic factors in the mitochondria of hepatocellular carcinoma cells can be inhibited by vitamin E, thereby inhibiting apoptosis (68). A study has indicated that 2'-benzoyloxycinnamaldehyde and HCA, derivatives of CA, inhibit the activity of farnesyl transferase, thereby delaying the onset of liver cancer (69). There is evidence to suggest that CA activated the ERK1/2, Akt and JNK signaling pathways, which in turn led to Nrf2 nuclear translocation, which ultimately increased the expression of phase II enzymes, making them exert effective chemoprevention effects (70). CA induces apoptosis in HepG2 cells by downregulating the expression levels of Bcl-XL, and upregulating the expression levels of CD95 (apolipoprotein A-I), p53 and Bax proteins (71). Researchers have identified that CA instigated apoptosis in human hepatocellular carcinoma cells by triggering the mitochondrial death pathway. Following CA treatment, there was a decrease in the protein levels of anti-apoptotic factors XIAP and Bcl-2, while the protein levels of the pro-apoptotic factor Bax were elevated (72). 2-Methoxycinnamaldehyde inhibits the activity of DNA topoisomerases I and II, thereby inhibiting the proliferation of Hep 3B cells. In addition, it can also induce lysosomal vacuolization, increase the volume of acidic organelles and promote apoptosis of cancer cells (73). A study has shown that cinnamon oil could reduce the incidence of hepatocellular carcinoma, and reduce liver damage and tumor growth (74). A derivative of CA, known as CB-PIC, can hinder the phosphorylation of STAT3 and diminish the expression of genes associated with STAT3. This process subsequently induces apoptosis in hepatocellular carcinoma cells (75).

In summary, CA and its derivatives may have potential anti-proliferative and apoptosis-inducing effects on hepatocellular carcinoma cells. However, further research is required to fully understand the mechanisms involved and to determine the therapeutic potential of these compounds in the treatment of hepatocellular carcinoma.

Application of CA in prostate cancer. In 2022, there were ~1.4 million new cases of prostate cancer globally, with ~375,000 associated deaths (33).

CA prompts apoptosis in cancer-associated fibroblasts (CAFs) by reducing the mitochondrial membrane potential, while simultaneously increasing the levels of endogenous ROS within CAFs and activating caspase-9 and caspase-3 (76). Mei *et al* (77) also studied prostate CAFs and found that CA acted on CAFs via a Toll-like receptor 4-dependent signaling pathway and regulated their function so that they no longer inhibit the proliferation of T cells, thus CA plays a certain role in the treatment of tumors. The proteasome is an anticancer target, and proteasome inhibition can promote apoptosis and inhibit tumor growth (78,79). Gopalakrishnan and Ismail (80) found that cinnamon compounds can inhibit the activity of the proteasome, leading to the accumulation of p27 protein, thereby inhibiting the proliferation of prostate cancer cells. Meanwhile, cinnamon compounds also lead to downregulation of vascular endothelial growth factor A (VEGFA) and VEGF receptor, thereby inhibiting the angiogenic capability of tumor cells. Gopalakrishnan *et al* (81) revealed that cinnamon and its active compounds enhanced the activity of apoptotic markers caspase-8 and caspase-3, leading to the promotion of cancer cell death. This provides a scientific basis for cinnamon as a potential chemoprevention agent for prostate cancer (81).

Current research on using CA for prostate cancer treatment is still limited and further experiments and clinical trials are required to ascertain its specific role and effectiveness. However, the initial results present an encouraging outlook for CA as a prospective therapeutic approach and provide valuable guidance for further investigations related to prostate cancer treatment.

Application of CA in leukemia. As early as 1983, Moon and Pack (82) observed the cytotoxic effect of CA on L1210 mouse leukemia cells and found that the aldehyde group of the CA molecule directly reacted with amino acids containing thiol groups in the cell, thereby blocking the utilization of amino acids contained in the thiol group in the cell and blocking protein synthesis, resulting in the inhibition of L1210 cell growth (82). In a previous study, researchers found that CA was an effective inducer of cell apoptosis, inducing white blood cell apoptosis through ROS-mediated mitochondrial permeability transition and cytochrome c release, as well as activating cascading reactions of cysteine protease-9 and cysteine protease-3 (83). In addition, CA can also induce apoptosis in leukemia K562 cells by reducing the mitochondrial transmembrane potential via mitochondrial-mediated pathways (84). Furthermore, CA can also inhibit cell proliferation by affecting the cell cycle. Water extract of cinnamon activates p38 MAPK kinase, reduces the expression of cyclin B1 protein and induces G_2/M blockade, and thus, affects the proliferation of cell lines (85). CA exerts its anti-leukemic effect by downregulating the transcription levels of the BCR-ABL gene and reducing the expression of the C-MYC protein (86). There has also been a study indicating that HCA interferes with the growth and transformation

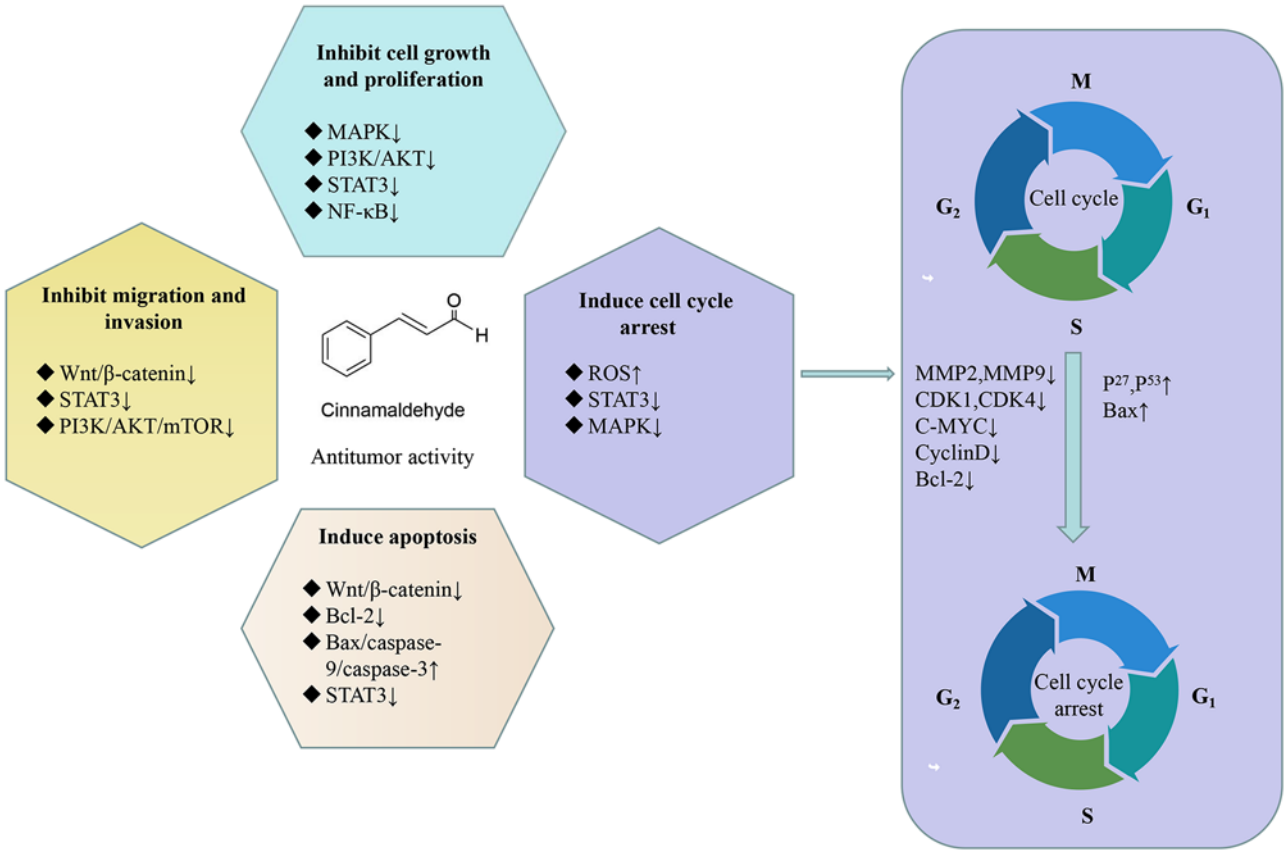

Figure 2. Summary of the major cellular signaling pathways involved in the anticancer activity of CA. ↓, inhibitory effect of CA; ↑, promotion effect of CA; CA, cinnamaldehyde; CCNA, cyclin A; CCNE, cyclin E; ROS, reactive oxygen species.

process of leukemia cells by inhibiting the activity of Pim-1, thus having an anti-leukemia effect (87). To summarize, while CA shows potential for leukemia treatment, more extensive research is still needed. These findings provide a direction for future research regarding leukemia treatments.

Summary. CA exhibits antitumor efficacy against various types of tumors, such as non-small cell lung cancer (41), colon cancer (45), breast cancer (58), liver cancer (73), prostate cancer (78) and leukemia (84). Extensive research has confirmed that the antitumor effects of CA are primarily achieved through the following mechanisms: Inhibiting cell growth and proliferation (37), arresting the cell cycle (45), inducing apoptosis (46), and inhibiting cell migration and invasion (63). A summary of the major cellular signaling pathways involved in the anticancer activity of CA is shown in Fig. 2. Table I shows the antitumor effects of cinnamaldehyde in different types of cancer.

4. CA preparations in cancer

The first objective for cancer treatment is to achieve high treatment outcomes and reduce side effects. Therefore, with advancements in targeted therapy and immunotherapy, the clinical treatment of patients with cancer has improved (88).

Nanodrug particles have low systemic toxicity *in vivo* and do not cause significant damage to normal tissues (89). Therefore, researchers have linked 5-FU and CA through acetal and ester bonds to prepare carrier-free nanodrug particles, and a synergistic effect of chemotherapy drugs was observed, the antitumor effect was improved and the systemic toxicity was reduced, indicating good application prospects (15). To enhance the permeability of the blood-brain barrier and mitigate drug toxicity, researchers combined trypsin (Try) and CA through an imine condensation reaction to form a novel small molecule nano prodrug and emulsified it into nanoparticles (Try-CA-NPs). Try-CA-NPs could achieve specific uptake of glioma cells by specifically binding to upregulated 5-hydroxytryptamine receptors (5-hydroxytryptamine receptor 1A and 5-hydroxytryptamine receptor 2) and improve cytotoxicity through endosomal escape, efficient drug release, and synergistic effects between Try and CA (16).

ROS levels are one of the unique hallmarks of cancer, and the levels of ROS in cancer cells are much higher than those in normal tissues (90). A study has shown that apoptosis and necrosis of cancer cells occur when ROS levels exceed the tolerance threshold of cancer cells (91). CA directly kills tumor cells by producing ROS (83).

Zhou *et al* (14) utilized cinnamaldehyde-modified chitosan hybrid nanoparticles for delivering the chemotherapy drug DOX. Cinnamaldehyde can generate ROS to directly kill tumor cells, thereby synergizing with DOX to exert antitumor effects (14). To improve the preparation process of nanomedicines, researchers have prepared CA-copper-polydopamine (CA-Cu-PDA) nanomedicines through a simple one-step polymerization reaction. The experimental results showed

Table I. Antitumor effects of cinnamaldehyde in different types of cancer.

A, Lung cancer

First author/s, year	*In vivo*	*In vitro*	Mechanisms	Methods	(Refs.)
Imai *et al*, 2002	Mouse model of lung cancer induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone	-	Reduces the proliferation of tumor-initiating cells	-	(37)
Meng *et al*, 2017	Urethane to induce lung adenocarcinoma model	A549 cells	↑AMPK; ↓AQP-1; ↓mTOR	Western blot analysis	(38)
Tian *et al*, 2017	Nude mouse model induced by NCI-H460 cells	A549 and NCI-H460 cells	↑Circular RNA hsa_circ_0043256	-	(39)
Wu *et al*, 2017	Mouse lung cancer model induced by A549 cells	A549 cells	↓Wnt/β-catenin pathway	RT-qPCR analysis; western blot analysis	(40)
Park and Baek, 2020	-	A549 cells	↑ROS; ↓MAPK	Western blot analysis	(41)
Chen *et al*, 2020	Mouse lung cancer model induced by A549 cells	A549, NCI-H1650, SK-MES-1 and NCI-H226 cells	↓JAK/STAT3; ↓NF-κB	RT-qPCR analysis; western blot analysis	(42)

B, CRC

Jeong *et al*, 2003	Mouse colon cancer model induced by SW620 cells	SW620 and MCF7 cells	↓Cyclin D1	Western blot analysis	(45)
Lee *et al*, 2007	-	SW620 cells	↓AP-1	Western blot analysis	(46)
Cho *et al*, 2013	-	H460/PT, HCT15/cos and MCF7/Adr cells	↑AMPK; ↑ERK	Western blot analysis	(47)
Yun *et al*, 2015	-	HCT15/cos cells	↓MDR1; ↓STAT3; ↓AKT	RT-PCR analysis; western blot analysis	(48)
Yu *et al*, 2014	-	LoVo and HT-29 cells	Induces apoptosis in tumor cells	RT-qPCR analysis	(49)
Long *et al*, 2015	Mouse colon cancer model induced by azoxymethane/dextran sulfate sodium	HCT116 cells	Promotes the expression of Nrf2 target genes	PCR analysis	(50)
Li *et al*, 2016	-	LoVo, SW480, and HCT116 cells human CRC cell lines	↓PI3K/Akt	Western blot analysis	(52)

Table I. Continued.

B, CRC

First author/s, year	*In vivo*	*In vitro*	Mechanisms	Methods	(Refs.)
Zhang *et al*, 2023	Mouse colon cancer model induced by HCT116 cells	HCT116 cells	↓PI3K/Akt; ↓Ki67	Western blot analysis	(53)
Nguyen and Kim, 2017	-	SW480 and SW620 cells	↑BAG3	RT-PCR analysis; western blot analysis	(54)
Wu *et al*, 2019	Mouse colon cancer model induced by HCT116 cells	HCT116 and SW480 human CRC cell lines	↓Wnt/β-catenin pathway	RT-qPCR analysis; western blot analysis	(55)
Kosari *et al*, 2020	-	*E. coli*	↓clbB gene	RT-qPCR analysis	(56)
Petrocelli *et al*, 2021	-	NCM-460, Caco-2 and SW620 cells	Induces apoptosis in tumor cells	-	(57)
Nile *et al*, 2023	-	HCT116 and HT-29 cells	↑ROS	-	(13)
C, Breast cancer					
Wani *et al*, 2014	-	MDA-MB-231 and MCF7 cells	↑VEGF; ↑caspase-3	Western blot analysis	(58)
Rad *et al*, 2015	-	MDA-MB-231 and MCF8 cells	↑Caspase-8	RT-qPCR analysis; western blot analysis	(59)
Chiang *et al*, 2019	Mouse model of breast cancer induced by MDA-MB-231-GFP cells	MDA-MB-231-GFP cells	↓Visfatin	Western blot analysis	(60)
Liu *et al*, 2020	-	MDA-MB-231 cells	Induces apoptosis in tumor cells	-	(61)
Kubatka *et al*, 2020	N-nitroso-N-methylurea-induced rat breast cancer model	MDA-MB-231 and MCF7 cells	Inhibits tumor cell proliferation	-	(62)
Dong *et al*, 2020	-	H9c2 and MCF7 cells	Induces apoptosis in tumor cells	-	(63)
Kuo *et al*, 2021	-	MCF7 cells	Induces apoptosis in tumor cells	-	(64)
Schuster *et al*, 2022	-	MCF7, MDA-MB-231 and HCC1419 cells	Prompts cancer cell apoptosis	-	(65)
Yao *et al*, 2023	4T1 breast cancer model mice	MDA-MB-231 cells	↑ROS	-	(66)

Table I. Continued.

First author/s, year	*In vivo*	*In vitro*	Mechanisms	Methods	(Refs.)
D, Liver cancer					
Wu *et al*, 2004	-	PLC/PRF/5 cells	↑Bax; ↓Bcl-2; ↓ XIAP	Western blot analysis	(68)
Moon *et al*, 2006	H-ras12V transgenic mouse model	-	↓Farnesyl transferase	-	(69)
Huang *et al*, 2011	-	HepG2 cells	↑ERK1/2; ↑Akt; ↑JNK; ↑Nrf2	Western blot analysis	(70)
Ng and Wu, 2011	-	HepG2 cells	↓Bcl-XL; ↑CD95 (APO-1); ↑p53; ↑Bax	Western blot analysis	(71)
Lin *et al*, 2013	-	PLC/PRF/5 cells	↓XIAP; ↓Bcl-2; ↑Bax	Western blot analysis	(72)
Perng *et al*, 2016	Mouse liver cancer model induced by Hep 3B cells	Hep 3B cells	↓DNA topoisomerases I and II	Western blot analysis	(73)
Aly *et al*, 2019	Male albino rats	-	Reduces tumor growth	PCR analysis	(74)
Kim *et al*, 2022	-	Huh7 and HepG2 cells	↓STAT3	RT-qPCR analysis; western blot analysis	(75)
E, Prostate cancer					
Han *et al*, 2020	-	Prostate cancer-associated fibroblasts	↓ΔMψ; ↑ROS; ↓Bcl-2; ↑Bax	Western blot analysis	(76)
Mei *et al*, 2020	C57 mice	Prostate cancer-associated fibroblasts	↑TLR4	Western blot analysis	(77)
Gopalakrishnan and Ismail, 2021	-	LNCaP, PC3	↑P^{27}	RT-qPCR analysis; western blot analysis	(80)
Gopalakrishnan *et al*, 2023	Mouse prostate cancer model induced by testosterone propionate	-	↑Caspase-8; ↑caspase-3	RT-qPCR analysis; western blot analysis	(81)
F, Leukemia					
Moon and Pack, 1983	-	L1210 cells	Inhibits tumor cell growth	-	(82)
Ka *et al*, 2003	-	HL-60 cells	↑ROS	-	(83)
Zhang *et al*, 2010	-	K562 cells	↓ΔΨm	-	(84)

Table I. Continued.

F, Leukemia					
First author/s, year	*In vivo*	*In vitro*	Mechanisms	Methods	(Refs.)
Schoene *et al*, 2009	-	CD45 Jurkat clone, Wurzburg cells	↑p38; ↑MAPK; ↓cyclin B1	Western blot analysis	(85)
Liu *et al*, 2001	-	K562 cells	↓BCR-ABL;↓C-MYC	RT-qPCR analysis; western blot analysis	(86)
Kim *et al*, 2015	Mouse tumor model induced by HEL cells	HEL, HaCaT and A431 cells	↓Pim-1	-	(87)

ΔMψ, mitochondrial membrane potential; AMPK, AMP-activated protein kinase; AP-1, activator protein 1; APO-1, apolipoprotein A-I; AQP-1, aquaporin 1; BAG3, BAG cochaperone 3; CRC, colorectal cancer; GFP, green fluorescent protein; JAK, Janus kinase; MDR1, multidrug resistance protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; RT-qPCR, reverse transcription-quantitative PCR; RT-PCR, reverse transcription-PCR; TLR4, Toll-like receptor 4; XIAP, X-linked inhibitor of apoptosis.

that CA-Cu-PDA was able to release copper ions and CA in tumor cells, and weakened the antioxidant system by binding to glutathione (GSH), which in turn produced additional ROS, thereby inducing enhanced oxidative stress effects (17). In addition, researchers have produced a self-amplifying degradable polymer composed of ROS-responsive thioacetal groups and CA, which could not only achieve sustained drug release but could also trigger immunogenic cell death in cancerous cells (18).

A previous study demonstrated that excess GSH promotes tumor progression (92). Researchers have synthesized a tumor-targeted oxidative stress nanoamplifier using CA as the ROS generator, β-phenethyl isothiocyanate as the GSH scavenger and HA as the carrier for targeting tumors. This could synergistically enhance oxidative stress and suppress tumor growth, and exhibited favorable biological safety (93). In addition, researchers have synthesized Fc-CA-PCN-HA nanoparticles coated with sodium hyaluronate, which not only have improved biocompatibility and targeting but can also incrementally H_2O_2 levels (94). *In vivo* experiments in nude mice revealed that sodium hyaluronate-coated Fc-CA-PCN-HA nanoparticles had antitumor effects under the synergistic effect of photodynamic therapy and chemodynamic therapy, and had no obvious toxic side effects on the overall health of nude mice (94).

Despite being in the early stages of research as a targeted agent, CA has shown some promising results. Future studies will continue exploring its potential, and optimizing its pharmacological properties and therapeutic effects to better address the challenges in treating diseases, particularly cancer.

5. Safety of CA

Data have validated the safety of CA, demonstrating its non-carcinogenicity even at the highest exposure level of 4,100 ppm over an extended period (95). In a study spanning 3 months to 2 years utilizing microencapsulated trans-CA in both male and female F344/N rats and $B6C3F_1$ mice, no tumors linked to its exposure were observed in either species (96). Oral administration of CA in various animals has been proven to be safe, exemplified by its median lethal dose values of 2,220 mg/kg in rats (20) and 2,301 mg/kg in mice (7). Notably, Anand *et al* (97) revealed that even at 20 times the effective dose (20 mg/kg), CA did not induce significant abnormalities in physiological parameters. Consistent with these findings, another study has demonstrated that CA does not exhibit genotoxic or carcinogenic effects on the body (98).

CA is widely acknowledged for its exceptional safety profile, and research advancements indicate that CA possesses the ability to mitigate the toxic side effects of chemotherapy drugs (99,100). Specifically, CA has demonstrated a capacity to alleviate cardiotoxicity induced by DOX (99), and exhibits cytoprotective effects, safeguarding against cardiorenal toxicity triggered by cyclophosphamide (100).

6. Conclusions

There has been a steady rise in the occurrence of cancer, posing great risks and challenges to human survival. With the continuous development and utilization of natural

products, they occupy an increasingly important position as anticancer drugs. CA is an active ingredient found in the natural medicine cinnamon. There is evidence that CA and its derivatives not only have a positive effect on cancer prevention and treatment but can also produce synergistic anticancer effects when used in combination with different chemotherapy drugs, and alleviate the adverse effects of chemotherapy drugs (38). A large number of studies have demonstrated that CA and its derivatives exert their antitumor activity by inhibiting cell growth and proliferation (37), arresting the cell cycle (13), inducing apoptosis (57), inhibiting cell migration and invasion (52), and inhibiting angiogenesis (101). Although CA is not soluble in water, recent studies on various nanomedicine delivery systems for CA have effectively improved drug stability, targeting capability and bioavailability (18,90-92).

Although studies have hinted at the potential of CA as an anticancer agent, particularly in suppressing tumor growth and metastasis (38,39,41), its mechanisms of action during tumor initiation, progression and treatment remain largely unexplored. A crucial step forward lies in elucidating its interactions with tumor cell signaling pathways and the impact on gene expression. Furthermore, research should uncover novel therapeutic targets for CA in cancer therapy, coupled with advancements in drug optimization and synthesis techniques to yield more potent and safer derivatives. Chromatin immunoprecipitation (ChIP) cDNA expression chip [or similar ChIP technologies such as ChIP-chip or ChIP sequencing (seq)] and assay for transposase-accessible chromatin with sequencing (ATAC seq) can provide in-depth research on the mechanisms of genomic regulation and expression of drugs (102-105). However, to the best of our knowledge, there are no reports of results related to the aforementioned technologies for CA. Therefore, in future research, techniques such as ChIP cDNA expression chip (or similar ChIP technologies such as ChIP-chip or ChIP seq) and ATAC seq can be used to further investigate the antitumor effects of CA.

Additionally, emphasis should be placed on investigating combination therapy strategies, utilizing CA alongside other anticancer agents to enhance therapeutic efficacy and minimize drug resistance. As clinical trials advance and translational research progresses, CA may emerge as a pivotal component in future cancer therapeutics, offering patients more effective treatment options and improved quality of life.

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Availability of data and materials

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Authors' contributions

RH and XL wrote the original draft of the manuscript. GL and XG reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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