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Review Article

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Carnosic Acid as a Promising Anticancer Agent: Mechanisms of Action and Therapeutic Potential Across Multiple Cancer Types

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Abstract: Carnosic acid (CA) is a phenolic diterpene that has multiple pharmacological actions that include neuroprotective, anti-inflammatory, antioxidant, and anticancer actions. However, its anticancer activity remains underexplored, and this study aims to fill that gap. The process involves browsing through Google Scholar, ScienceDirect, Web of Science, and PubMed. According to our study, CA has strong anticancer properties against a variety of cancers like breast, colon, colorectal, lung, liver, leukemia, cervical, ovarian, and prostate cancer. It induces apoptosis by reducing anti-apoptotic Bcl-2 expression and increasing pro-apoptotic Bax and Caspase-3 levels. CA reduces cell growth and migration by suppressing key signaling pathways like Akt/mTOR, PI3K, and MAPK, while also inhibiting the cell cycle. Numerous cancer types have shown these effects in both *in vitro* and *in vivo* investigations. The results indicate that CA is a viable cancer therapeutic option that merits more research into its clinical uses and pharmacokinetics.

Keywords: Anticancer effects; Carnosic acid; Molecular mechanism; Phenolic diterpene

1. Introduction

Cancer is a pathological state that is defined by the uncontrollable and abnormal growth of cells within the human body (Bhat et al., 2023; Bhuia et al., 2025). Changes in digestive or bladder habits, long-term lack of sleep, unusual weight loss, and persistent discomfort that do not go away with standard treatment are just a few of the signs and symptoms related to cancer (Klein & Jodocy, 2021). Genetic abnormalities brought on by lifestyle decisions, pollution exposure, infections, and inherited predispositions lead to unchecked cell division and proliferation, which is how cancer develops (Parsa, 2012). Cancer treatment methods vary by type and grade, including chemotherapy, radiation, immunotherapy, targeted therapy, and hormone therapy, though chemotherapy has limitations like side effects and off-target effects (Debela et al., 2021). Natural products like polyphenols, flavonoids, and alkaloids that cause apoptosis, slow tumor development, and change signaling pathways may be used to cure cancer (Foroughi-Gilvaee et al., 2024; Aktar et al., 2024). Their antioxidant and anti-inflammatory qualities help stop the growth of cancer by minimizing negative consequences (Zappavigna et al., 2020).

Carnosic acid (CA) is a phenolic diterpene with the IUPAC name (4aR,10aS)-5,6-dihydroxy-1,1-dimethyl-7-propan-2-yl-2,3,4,9,10,10a-hexahydrophenanthrene-4a-carboxylic acid (Das et al., 2018). CA is common in the Lamiaceae family of plants found in the Mediterranean basin, specifically *Salvia fruticosa* and *Rosmarinus officinalis* (Matsingou et al., 2003; Cvetkovikj et al., 2013). CA exhibits of pharmacological activities, including antiviral (Shin et al., 2013), anti-inflammatory (Maione et al., 2017), neuroprotective (Mirza et al., 2023), antioxidant (Wei et al., 2021), and anticarcinogenic effects (Samarghandian et al., 2018). In addition to stimulating cyclin-dependent kinase inhibitor 1 (p21) expression, CA was previously shown to limit cell proliferation and induce a cell cycle arrest in B16F10 melanoma cells (Park et al., 2014). Furthermore, CA has been found to trigger G1-cell cycle arrest, thereby preventing the progression of human breast cancer cells that lack estrogen receptor expression (Einbond et al., 2012). Additionally, several *in vitro* and *in vivo* investigations have demonstrated that CA has the potential to be a chemopreventive drug for treating different types of cancer (Han et al., 2017; Borhan et al., 2025).

This review aims to analyze and summarize existing literature on the anticancer properties of the CA.

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2. Methodology

A thorough search was conducted using keywords such as anticancer, carnosic acid, and activity/effect across reputable scientific databases such as PubMed, ScienceDirect, and Google Scholar.

2.1. Inclusion criteria

The selection of studies was based on the following criteria: (1) Research from a variety of sources looking into anticancer effects. (2*) Ex vivo*, *in vitro*, or *in vivo* research, whether or not experimental animals are used. (3) Research that either provides or withholds information about the mechanism of action.

2.2. Exclusion criteria

The following criteria for exclusion were used: (1) Abstracts and/or titles that contained duplicate data or did not meet the inclusion requirements. (2) Studies on anticancer activity, during which the current study's focus is obscured by other findings.

3. Results and discussion

CA, a bioactive diterpene derived from *Rosmarinus officinalis* L., has demonstrated significant anticancer potential across multiple cancer types, primarily through apoptosis induction, cytotoxicity, inhibition of proliferation, and disruption of critical signaling pathways. However, in breast cancer (MDA-MB-453, MDA-MB-468, MCF-7, and T47D cell lines), it induced cytotoxicity, cell cycle arrest, and upregulated apoptotic markers (caspase-3, Bax, Bad, DcR1, and DcR2) while suppressing anti-apoptotic proteins (Bcl-2, Bcl-xL) and disrupting Akt/mTOR signaling and Na-K-ATPase activity (Einbond et al., 2012; Han et al., 2017; Borhan et al., 2025). On the other hand, CA promoted apoptosis via reactive oxygen stress (ROS) generation, c-Jun N-terminal kinase (JNK) pathway activation, endoplasmic reticulum (ER) stress induction, and caspase-3 activation in cervical cancer at 0–100 μM concentration (Su et al., 2016). Additionally, it enhanced apoptosis and cytotoxicity while activating the Nrf2 and extracellular signal-regulated kinase (ERK) pathways in colon cancer, highlighting its role in oxidative stress modulation (Yan et al., 2014). In addition, CA exhibited potent anticancer effects at concentrations ranging from 24 to 96 μM by increasing apoptosis and cytotoxicity while downregulating cyclooxygenase-2 (COX-2), proliferation, migration, protease activity, cell adhesion, metalloproteinases (MMPs), and urokinase plasminogen activator (uPA) (Barni et al., 2012). Moreover, it induced apoptosis via caspase activation and Akt/mTOR inhibition in gastric cancer (16.57–23.96 μg/mL) (El-Huneidi et al., 2021) and lung cancer (20–1000 μM) (Duran et al., 2024; O'Neill et al., 2024). It also suppressed the Akt/mTOR pathway and, stimulated cell cycle arrest, inhibited invasion in prostate and esophageal cancer (Jiang et al., 2021; Ossikbayeva et al., 2021; Nadile et al., 2024). Further, CA promoted apoptosis, autophagy, and cell cycle arrest via Beclin1, p21WAF1, and p27Kip1 regulation in liver cancer at 10 μM and leukemia at 2.5–200 μM concentration (Wu et al., 2020; Steiner et al., 2001; Liu et al., 2018).

Overall, CA demonstrates wide-ranging anticancer effects through various mechanisms, such as inducing apoptosis, causing cell cycle arrest, inhibiting proliferation, suppressing migration and invasion, and regulating critical survival pathways like Akt/mTOR, PI3K, and MAPK. These findings support its potential as a promising natural anticancer agent, warranting further clinical investigations to validate its therapeutic efficacy. Its novelty lies in the fact that no review has yet concluded on the anticancer activity of CA. Despite its potential, CA faces limitations due to variability in chemical concentrations, requiring standardized extraction techniques and quality control for consistent bioactive content. However, **Table 1** presents the anticancer activity of CA. **Fig. 1** describes the possible mechanism by which CA can work against various cancer cell lines.

Table 1. Mechanism of anticancer activity of carnosic acid.

Sources	Cancer types	Cell lines/ model	Dose / concentrations	IC_{50}	Results	References
-	Breast cancer	MDA-MB-453, MDAMB-468, MCF7 cell lines, *in vitro*	5–20 μg/mL	3 μg/mL	↑Apoptosis, cell cycle arrest ↓Transcription and cell cycle gene, Na-K-ATPase.	Einbond et al., 2012
-	Breast cancer	MCF-7, T47D, MCF 10A, L02 cell lines, *in vitro*	1–40 μM	-	↑Apoptosis, Caspase-3, Bax and Bad, DcR1 and DcR2, TRAIL ↓Bcl-2, Bcl-xl, proliferation, migration, cell growth	Han et al., 2017
-	Breast cancer	MCF-7, MDA-MB-231, and MCA10 cell lines, *in vitro*	5–80 μM	-	↑Cytotoxicity, ROS, caspase, apoptosis, autophagy ↓Akt-mTOR	Borhan et al., 2025
-	Colon cancer	HCT116 and SW480 cell line, *in vitro*	-	-	↑Apoptosis, cytotoxicity, Nrf2, ERK	Yan et al., 2014
Rosmarinus officinalis L.	Colorectal cancer	Caco-2, HT29 and LoVo cell lines, *in vitro*	1–388 μM	24–96 μM	↑Apoptosis, cytotoxicity ↓Cox-2, proliferation, migration, protease activity, cell adhesion, MMPs, uPA	Barni et al., 2012
-	Cervical cancer	male BALB/c nu/nu nude mice, *in vivo* (n=8)	5–100 μM (i.p.)	-	↑Apoptosis, ROS, JNK, caspase-3, ER stress ↓Proliferation	Su et al., 2016
-	Esophageal cancer	KYSE-150, and MIHA cell lines, *in vitro*	5–40 μM	29.87 ± 4.38 μM and >200μM	↑Apoptosis, cytotoxicity, Bax, caspase -3 and DNA damage ↓Cell proliferation, metastasis, invasion, migration, colony formation, MAPK, Bcl2	Jiang et al., 2021

Table 1. *Continued*

Sources	Cancer types	Cell lines/ model	Dose / concen-trations	IC_{50}	Results	References
Rosmarinus officinalis	Gastric cancer	AGS and MKN-45 cell line, *in vitro*	1–200 µg/mL	19.90, 18.93 and 16.57 µg/mL; 23.96, 20.39 and 17.76 µg/mL	↑Apoptosis, caspase-3, caspase-8, caspase-9 ↓Akt-mTOR, proliferation	El-Huneidi et al., 2021
-	Lung cancer	H1299 and H460 cell lines, *in vitro*	2.5–150 µM	47.3 and 27.1 µM; 89.6 and 67 µM	↑Cytotoxicity, caspase-3, BAX apoptosis, autophagy, Sestrin-2, LKB1, AMPK ↓PI3K/Akt/mTOR proliferation, Bcl-2	O'Neill et al., 2024
-	Lung cancer	H441, H520, and H661 cell line, *in vitro*	-	20 and 40µM	↑Apoptotic Bax, Bak, caspase-3, and p53 expression, ↓Antiapoptotic Bcl-2 and Bcl-XL expression	Duran et al., 2024
Rosmarinus officinalis	Leukemia cancer	KBM-7 cell line, *in vitro*	12.5–50 µM	25 µM	↑Apoptosis, cell cycle arrest, cytotoxicity ↓Proliferation, invasion, microRNA-780	Liu et al., 2018
-	Leukemia cancer	HL-60 and U937 cell lines, *in vitro*	2.5–10 µM	6–7 µM	↑Growth arrest, p^{21WAF1} and p^{27Kip1}, cytotoxicity ↓Proliferation, cell cycle progression	Steiner et al., 2001
-	Liver cancer	Huh7 and HCO2 cell line, *in vitro*	10 µM	-	↑Apoptosis, cytotoxicity, cytoplasmic vacuolation, Beclin1, Atg3, and LC3, autophagy and cytoplasmic vacuolation	Wu et al., 2020
Rosmarinus officinalis	Prostate cancer	PC-3, LNCaP and PNT1A cell lines, *in vitro*	5–150 µM	64, 21, and 139.4 µM	↑Sestrin-2-AMPK signaling, cytotoxicity, ACC ↓Proliferation, Akt, mTOR, p70S6K	Nadile et al., 2024
-	Prostate cancer	DU145 and PC-3 cell lines, *in vitro*	0.25–10 µM	-	↑Apoptosis, cytotoxicity, G0/G1 cell cycle arrest, cytosolic calcium levels ↓Proliferation, mRNA, SGK1 phosphorylation, mTOR	Ossikbayeva et al., 2021

↑: Increase; ↓: Decrease; ER: Endoplasmic Reticulum; AMPK: AMP-activated kinase; ACC: acetyl-CoA carboxylase; Bcl-2: B-cell lymphoma 2; BAX: Bcl-2-associated X protein; uPA: urokinase plasminogen activator; MMPs: Metalloproteinases; Ros: Reactive oxygen stress; JNK: c-Jun N-terminal kinase; DcR1: Decoy receptor 1; TRAIL; Tumor necrosis factor-related apoptosis-inducing ligand; LKB1: Liver kinase B1; MAPK: Mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase; Akt: Protein kinase B; mTOR: Mechanistic Target of Rapamycin; SGK1: Serum and Glucocorticoid-Regulated Kinase 1; i.p.: Intraperitoneal

4. Conclusion

In conclusion, CA has proven to be a promising anticancer agent, showing significant activity against a wide range of cancers, including breast, colon, colorectal, lung, liver, leukemia, cervical, esophageal, ovarian, gastric, and prostate cancers. Because of its capacity to trigger apoptosis, disrupt the advancement of the cell cycle, and prevent the growth of cancer cells, it is thought to have anticancer properties. It has been proven to alter several important signaling pathways that are important for tumor development and metastasis, including Akt/mTOR, PI3K, and MAPK. Its therapeutic promise is further shown by the fact that it inhibits the processes of metastasis. Its effectiveness in preventing tumor growth in a variety of cancer models has been repeatedly shown in preclinical research conducted both *in vitro* and *in vivo*. CA, based on these compelling findings, shows great promise as a potential therapeutic option for cancer treatment. To fully realize its promise in cancer therapy, more study is necessary to further clarify its pharmacokinetics, enhance its distribution, and investigate its clinical applications.

Conflict of interest

The authors declared no conflict.

Data availability

Data will be made available on request.

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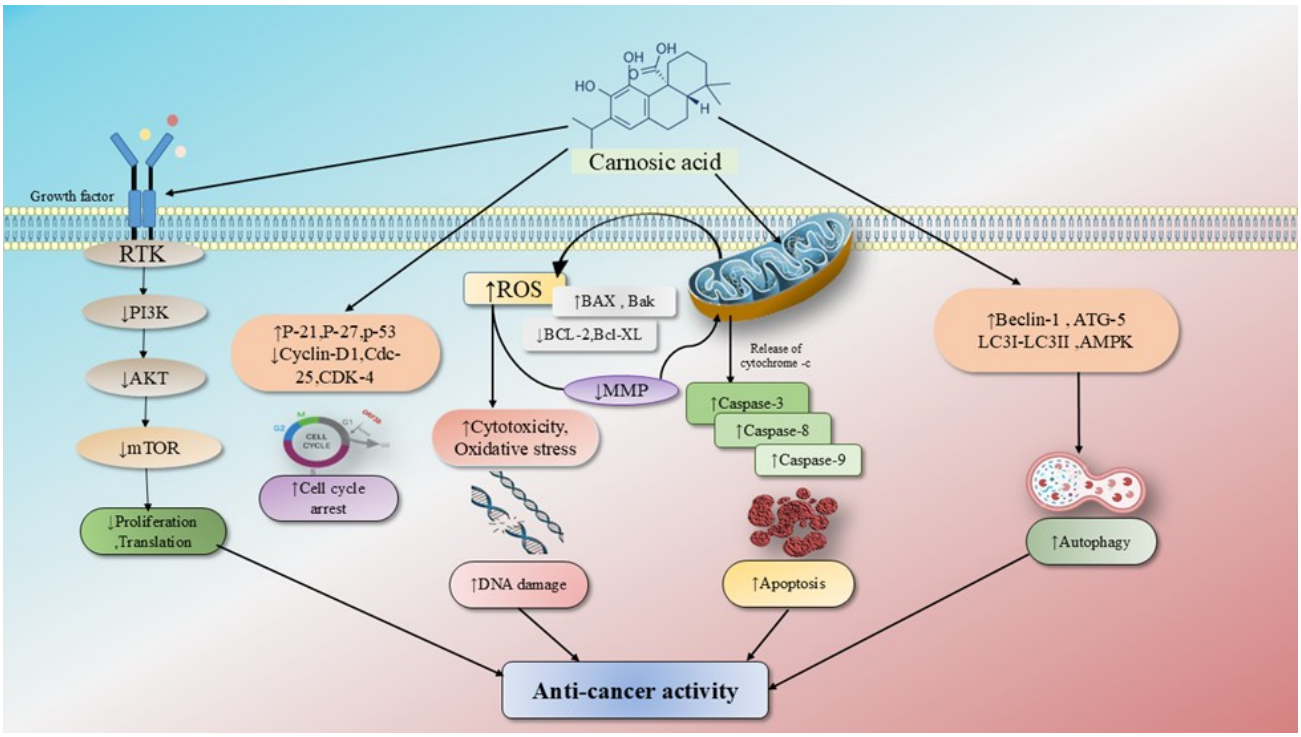

Fig. 1. Possible mechanism of anti-cancer activity of carnosic acid. [CA (Carnosic Acid) inhibits the Receptor Tyrosine Kinase (RTK) signaling pathway, thereby suppressing the Phosphoinositide 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/Akt/mTOR) pathway and reducing proliferation and translation. The chemical promotes cell cycle arrest by increasing Cyclin-Dependent Kinase Inhibitor 1 (P21), Cyclin-Dependent Kinase Inhibitor 1B (P27), and Tumor Protein P53 (P53) levels while decreasing Cyclin-D1, Cell Division Cycle 25 (Cdc-25), and Cyclin-Dependent Kinase 4 (CDK-4) expression. The substance increases Reactive Oxygen Species (ROS) formation, which enhances cytotoxicity and oxidative stress, leading to increased DNA damage. This pathway activates pro-apoptotic proteins Bcl-2-Associated X Protein (BAX) and Bcl-2 Homologous Antagonist Killer (Bak) while inhibiting anti-apoptotic proteins B-cell Lymphoma 2 (BCL-2) and B-cell Lymphoma-Extra Large (Bcl-XL). This results in caspase activation, ultimately leading to apoptosis. Carnosic Acid also enhances autophagy by upregulating Beclin-1, Autophagy-Related Gene 5 (ATG-5), Microtubule-Associated Proteins 1A/1B Light Chain 3 (LC3I-LC3II) conversion, and AMP-Activated Protein Kinase (AMPK) activation.]

Author's contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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