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Review Article

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Unveiling the Anticancer Mechanisms of Isorhamnetin: A Mini Review

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Abstract: Isorhamnetin (ISO), a flavonoid, exhibits significant anticancer properties; however, no review has been conducted on its anticancer activity. This mini-review evaluates the anticancer potential of ISO by summarizing its mechanisms of action based on studies from PubMed, Google Scholar, ScienceDirect and Web of Science. Research on breast, colon, lung, colorectal, gastric, prostate, skin, and gallbladder models, both *in vitro* and *in vivo*, supports ISO's anticancer properties. This review highlights its mechanisms of function, including cell cycle arrest, apoptosis induction, and inhibition of key oncogenic pathways such as mitogen-activated protein kinase (MAPK), epithelial-mesenchymal transition (EMT) and phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR). ISO also enhances reactive oxygen species (ROS) production, modulates mitochondrial pathways, and reduces metastasis by inhibiting matrix metalloproteinases (MMPs). Further research is needed on ISO's pharmacokinetics and clinical efficacy to establish this as an anticancer agent.

Keywords: Apoptosis; Cancer; flavonoid; Isorhamnetin; Proliferation

1. Introduction

Cancer, a complex illness caused by excessive development and a malfunctioning cell cycle, which results in abnormal cells that invade and move to different body parts (Neagu et al., 2019; Aktar et al., 2024; Bhuia et al., 2025; Mizan et al., 2025). Flavonoids are secondary metabolites of polyphenolic that give plant's their color, flavor, and pharmacological properties (Nabavi et al., 2020; Scarano et al., 2018). Flavones, flavonols, flavanones, anthocyanidins, isoflavones, and chalcones are the primary categories into which flavonoids can be divided. Flavonoids are mostly found in fruits and vegetables, but they are also frequently found in items made from cocoa, black and green tea, and red wine (Liu et al., 2018; Braicu et al., 2013). Flavonoids exhibit pharmacological activities, including anticancer (Kikuchi et al., 2019), anti-inflammatory (Pan et al., 2010), antioxidant (Shen et al., 2022), antimutagenic (Miyazawa & Hisama, 2003), antifungal (Kanwal et al., 2010), and antiviral activities (Badshah et al., 2021). ISO's methoxy (-OCH_3) group separates it apart from other flavonoids and affects its metabolism and bioactivity (Wang et al., 2018).

ISO, a chemically related compound to flavones, has been investigated for its potential therapeutic efficacy in the treatment of cancer because of its adverse effects on cancerous cells (Zhong et al., 2013; Gong et al., 2014; Eity et al., 2024). *Hippophae rhamnoides* L. along with *Ginkgo biloba* L. are two examples of plants that contain the chemical ISO in their leaves, blossoms, and fruits (Li et al., 2022a). Numerous studies have demonstrated that ISO has a major impact on immune system regulation, lowers inflammation, and fights against heart and brain disorders (Xu et al., 2020; Qi et al., 2018). Recently, ISO has gained attention because to its ability to reduce tumors in a range of human cancers, including as breast, skin, lung and colorectal cancers (Ruan et al., 2015; Kim et al., 2011; Hu et al., 2015). It has anti-tumor actions by preventing migration and proliferation of cells and encouraging apoptosis. Several investigations have demonstrated that ISO can halt the proliferation and invasion of cancer cells by triggering apoptosis, mainly via the PPAR-γ, mitochondria-cytochrome C-caspase-9, and ROS-mediated CaMKII/Drp1 pathway (Li et al., 2022a; Jiang et al., 2016). This review's objective is to summarize ISO's anticancer mechanisms based on experimental studies.

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2. Methodology

2.1. Literature search strategy

The information was gathered up until March 04, 2025, by using keywords like anticancer, isorhamnetin, and activity/effect, across reliable scientific resources like PubMed, ScienceDirect, and Google Scholar.

2.1.1. Inclusion criteria

The following standards were used to choose the studies: (1) Studies investigating anticancer effects from a range of sources. (2) *Ex vivo*, *in vitro*, or *in vivo* studies, regardless of the use of experimental animals. (3) Studies were included regardless of whether they described the mechanism of action.

2.1.2. Exclusion criteria

The given exclusion criteria were applied: (1) Titles and/or abstracts that didn't fit the inclusion criteria or contained duplicate data. (2) Research on anticancer activity while additional discoveries overshadow the subject of the current investigation.

3. Results and discussion

3.1. Anticancer activity of isorhamnetin

The anticancer effects of ISO have been evaluated across multiple cancer cell lines, demonstrating significant inhibitory activities on cell proliferation, apoptosis induction, and key signaling pathways involved in tumor progression.

3.1.1. Bladder cancer

T24 and 5637 cell lines treated with 10–200 μM exhibited IC_{50} values of 127.86 and 145.75 μM, respectively. The compound triggers cell cycle arrest and apoptosis during the G2/M phase via Cdk, p21WAF1/CIP1, p21, Fas/Fas ligand, cytotoxicity, and ROS upregulation, while reducing Wee1, cyclin B1, Bcl-2/Bax ratio, cytochrome c, and AMPK levels (Park et al., 2019).

3.1.2. Breast cancer

Treatment of T47D, MCF7, MDA-MB-231, BT474, BT-549 and MDA-MB-468 cell lines with 0.4–100 μM concentrations led to an IC_{50} of 10 μM. The study reported an increase in apoptosis, Bax expression, and cleaved caspase-3 levels, while reducing cell proliferation via inhibition of Akt/mTOR, MAPK kinase, and MEK/ERK pathways (Hu et al., 2015). Another study using MDA-MB-231 cells revealed that suppression of MMP-2, MMP-9, p38, MAPK, and STAT3 reduced migration, adhesion, and invasion (Li et al., 2015b). *In vivo* studies on BALB/c nude mice (5 mg/kg, i.p.), ISO demonstrated suppressed cancer cell growth (Yang et al., 2023).

3.1.3. Colon cancer

In vitro studies on HT-29, HCT116, and SW480 cell lines treated with 10–200 μmol/L of the compound exhibited IC_{50} values of 56.24, 54.87, and 43.85 μmol/L, respectively. The findings showed elevated expression of the cyclin B1 protein and cell cycle arrest at the G2/M phase. Conversely, a noticeable decrease in cell proliferation and suppression of the PI3K/Akt/mTOR pathway, along with decreased phosphorylation levels of Akt, 4E-BP1 protein, and p70S6 kinase was observed (Li et al., 2014).

3.1.4. Colorectal cancer

HT-29 cells treated with 5–150 μM exhibited an IC_{50} of 72 μM, significantly reducing cell proliferation, IL-8 production, mitochondrial and metabolic activity, and lysosomal function (Greifová et al., 2023).

3.1.5. Gallbladder cancer

NOZ and GBC-SD cell lines exposed to 40–100 μM yielded IC_{50} values of 162.5 μM and 147.1 μM, respectively. The compound promotes G2/M cell cycle arrest, apoptosis, and the overexpression of p53, cleaved PARP, Bax, and cleaved caspases 9, 3, while reducing proliferation, metastasis, PI3K/AKT signaling, migration, invasion, tumor growth, and expression of BCL-2, CDK1, N-cadherin, Slug, cyclin B1, p-PI3K, and p-AKT1 (Zhai et al., 2021).

3.1.6. Gastric cancer

AGS, SNU5, and MKN45 cell lines treated with 5–50 μM exhibited an IC_{50} of 5.98 μM, with an increase in cytotoxicity, PPAR-γ activity, and apoptosis, while reducing migration, invasion, and cell proliferation (Ramachandran et al., 2012). Another study using AGS -1 and HGC-27 cell lines (10–100 μM) showed increased apoptosis, Bax/Bcl-2 ratio, cytosolic cytochrome c, caspase-3 cascade activation, and ROS generation, leading to reduced cell proliferation, migration, mitochondrial potential, and cancer growth (Li et al., 2022b). *In vivo* studies in male nude mice (5 mg/kg, i.p.) corroborated these findings.

3.1.7. Lung cancer

Treatment of A549 cells with 2.5–10 μM showed increased E-cadherin protein expression and a reduction in cell proliferation, adhesion, invasion, migration, and EMT markers, including N-cadherin, vimentin, snail, and AKT/ERK1/2 pathways (Luo et al., 2019). Additionally, treatment with 5–320 μg/ml resulted in an IC50 of 44.5 μg/ml, increasing apoptosis via Bax, caspase-3, and p53 upregulation, while downregulating cell growth, Bcl-2, cyclin D1, and PCNA proteins (Li et al., 2015a).

3.1.8. Prostate cancer

DU145, PC3, and LNCaP cell lines received treatment with 2.5–20 μM concentrations, leading to an increase in apoptosis and lactate dehydrogenase (LDH) release. The compound significantly decreased cell growth, invasion, migration and expression levels of p-PI3K, p-Akt, p-mTOR, MMP-2, and MMP-9 (Cai et al., 2020).

3.1.9. Skin cancer

B16F10 cells treated with 10–100 μM displayed increased apoptosis and reduced proliferation, migration, and PI3K/Akt/NF-κB pathway activity (Duan et al., 2020). *In vivo* studies in C57BL/6 mice (20 mg/kg) supported these findings.

By triggering apoptosis, causing cell cycle arrest, and blocking migration, proliferation, and crucial signaling pathways like MAPK, PI3K/Akt/mTOR, and EMT, ISO demonstrated potent anticancer effects on several cancer cell lines, per these findings. Additionally, previous study reveals that ISO demonstrates the highest anticancer sensitivity against lung cancer cells, as confirmed by both *in vivo* and *in vitro* studies. These findings highlight the potential of these compounds for therapeutic applications, warranting further *in vivo* and clinical investigations to confirm their safety profile and effectiveness. However, the anticancer activity of ISO across various cancers, as reported in the literature, is summarized in **Table 1**, while its possible mechanism of action is illustrated in **Fig. 1**.

4. Conclusion and future perspectives

In conclusion, ISO has shown great potential as an anticancer agent, demonstrating significant efficacy against multiple cancer types, including prostate, skin, breast, colon, lung, colorectal, gastric, and gallbladder cancers. It expressed its anti-cancer activity by inducing apoptosis, inhibiting proliferation, and arresting cell cycle progression by regulating key pathways like PI3K/ Akt/ mTOR,

Table 1. Based on findings from various literature sources, the anticancer activity of isorhamnetin.

Cancer types	Cell lines / experimental methods	Dose/ concentrations (R/A)	IC_{50}	Results	References
Colon cancer	HT-29, HCT116 and SW480 cell line, *in vitro*	10 – 200 µmol/l	56.24, 54.87 and 43.85 µmol/l	↑Cell cycle arrest (G2/M phase), cyclin B1 protein ↓Cell proliferation, PI3K-Akt-mTOR pathway, phosphorylation levels of Akt, phosph-p70S6 kinase, phosph-4E-BP1 protein	Li et al., 2014
Prostate cancer	DU145, PC3 and LNCaP cells line, *in vitro*	2.5 – 20 µM	-	↑ Apoptosis, LDH release, MET, LDH release ↓Cell growth, migration, invasion, MMP-2, MMP-9, p-P13K, p-Akt, p-mTOR	Cai et al., 2020
Breast cancer	MCF7, T47D, BT474, BT-549, MDA-MB-231 and MDA-MB-468 cells line, *in vitro*	0.4 – 100 µM	10 µM	↑Apoptosis, Bax, cleaved caspase-3 ↓Cell proliferation, Akt/mTOR, MAPK kinase, MEK/ERK	Hu et al., 2015
Lung cancer	A549 cell line, *in vitro*	2.5 – 10 µM	-	↑E-cadherin protein expression ↓Cell proliferation, adhesion, invasion, migration, MMP-2, MMP-9, EMT markers, N-cadherin, vimentin, snail, AKT/ERK1/2 signaling pathways	Luo et al., 2019
Gastric cancer	AGS, SNU5, and MKN45 cell line, *in vitro*	5 – 50 µM	5.98 µM	↑Cytotoxicity, PPAR-γ activity, apoptosis ↓Migration, invasive, cell proliferation	Ramachandran et al., 2012
Bladder cancer	T24, 5637, 2531J and EJ cell line, *in vitro*	10 – 200 µM	127.86 µM and 145.75 µM	↑Cell cycle arrest (G2/M phase), apoptosis, Cdk, $p21^{WAF1/CIP1}$, p21, Fas/Fas ligand, cytotoxicity, ROS, ↓Wee1, cyclin B1, ratio Bcl-2/Bax, cytochrome c, AMPK,	Park et al., 2019
Gallbladder cancer	GBC-SD and NOZ cell line, *in vitro* Female BALB/c nude mice, *in vivo* (n = 5)	40 – 100 µM 1 or 5 mg/kg (i.p.)	162.5 µM and 147.1 µM	↑Apoptosis, Cell cycle arrest (G2/M) phase, BAX, cleaved PARP, cleaved caspases 9, p53, and cleaved caspases 3 ↓Cell proliferation, metastasis, PI3K/AKT signaling cascade, migration, invasion, tumar growth, BCL-2, N-cadherin, Slug, CDK1, cyclin B1, p-PI3K, and p-AKT1	Zhai et al., 2021
Gastric cancer	AGS-1 and HGC-27 cell line, *in vitro* Male nude mice, *in vivo*	10 – 100 µM 5 mg/kg (i.p.)	-	↑Apoptosis, cell growth, Bax/Bcl-2, cytosolic cytochrome c, caspase-3 cascade, PARP, ROS ↓Cell proliferation, migration, mitochondrial potential, tumor growth	Li et al., 2022b
Breast cancer	MCF7 and MDAMB-231 cell line, *in vitro*	10 – 50 µM	16.76 and 62 µg/ml, 0.23 and 0.16 µg/ml	↑Apoptosis, cell cycle arrest (G2/M), cleaved caspase 3, ROS, ↓Cell proliferation, migration, bcl 2,	Yang et al., 2023
Breast cancer	MDA-MB-231 cell lines, *in vitro*	10 – 40 µM	-	↓adhesion, migration, invasion, MMP-2, MMP-9, p38, MAPK, STAT3	Li et al., 2015b
Lung cancer	A549 cell line, *in vitro*	5 – 320 µg/ml	44.5 µg/ml	↑Apoptosis, Bax, Caspase-3 and P53 ↓Cell growth, Bcl-2, cyclinD1 and PCNA protein	Li et al., 2015a
Colorectal cancer	HT-29 cell line, *in vitro*	5–150 µM	72 µM	↓Cell proliferation, IL-8 production, mitochondrial, metabolic activity, lysosomal activity	Greifová et al., 2023
Lung cancer	Male C57BL/6 mice, *in vivo* (n=30)	50 mg/kg (i.p)	-	↑Endostatin expression. ↓tumor progression, VEGF, MMP-2,	Zhu et al., 2017
Skin cancer	B16F10 cell line, *in vitro* C57BL/6 mice, *in vivo* (n = 6)	10 – 100 µmol/L 20 mg/kg	-	↑ Apoptosis, ↓Proliferation, migration, PI3K/Akt pathway, NF-κB Pathways	Duan et al., 2020

Abbreviations: ↑:Increase/stimulation/up-regulation/initiation; ↓: decrease/inhibition/down-regulation/blocking; Akt: protein kinase; AMPK: adenosine 5′-monophosphate-activated protein kinase; Bax: Bcl-2 associated X protein; Bcl-2: B-cell lymphoma 2; Cdk: cyclin-dependent kinase; EMT: epithelial-to-mesenchymal transition; G2/M: gap 2/ mitosis; LDH: lactate dehydrogenase; MAPK: mitogen-activated protein kinase; MEK: mitogen activated protein; MET: mesenchymal–epithelial transition; MMP: matrix metalloproteinase; mTOR: mammalian target of rapamycin; p-Akt: phosphorylated Akt; PARP: poly ADP-ribose polymerase; PI3K: phosphatidylinositol 3-kinase; p-mTOR: phosphorylated mTOR; p-P13K: phosphorylated PI3K; PPAR-γ: peroxisome proliferator-activated receptor–γ; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor

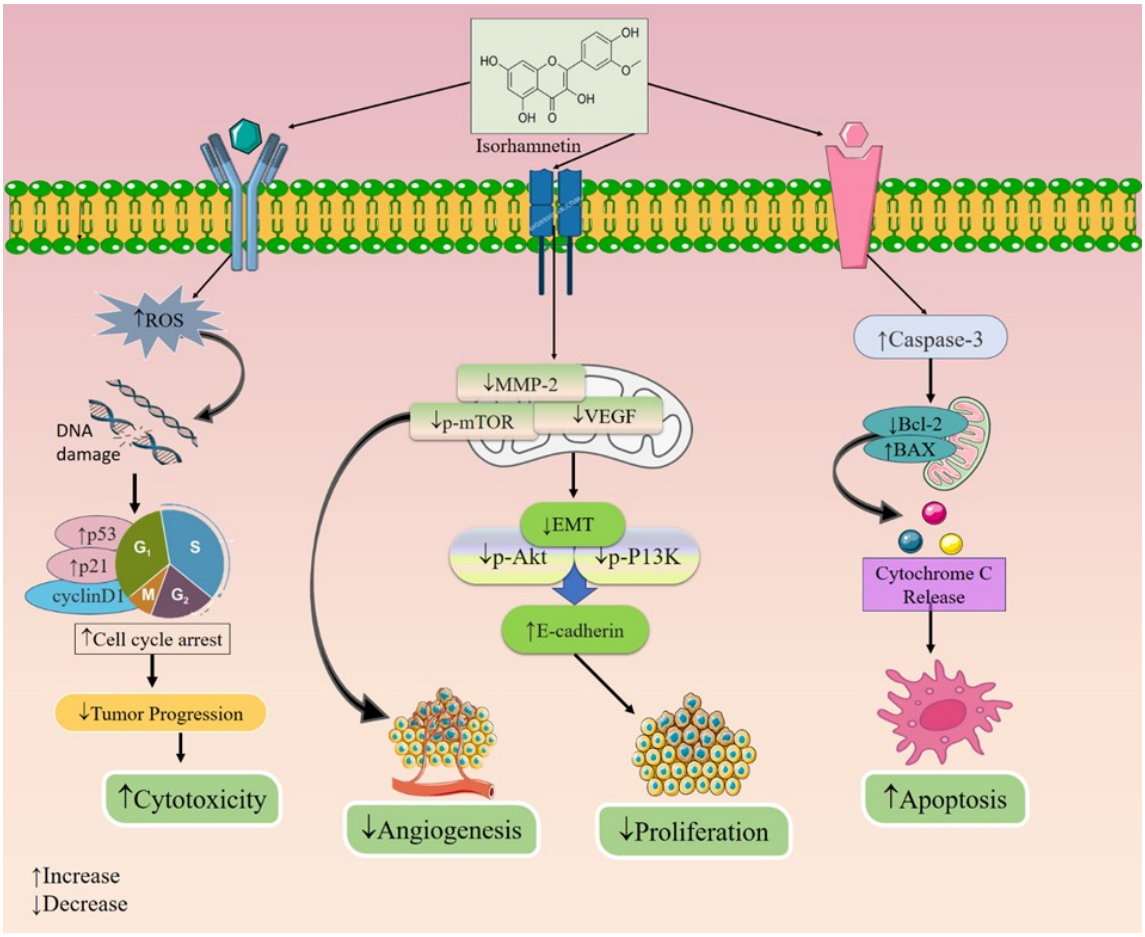

Fig. 1. Possible mechanism of anticancer activity of isorhamnetin. [This figure illustrates the anticancer mechanisms of ISO. It increases ROS, causing DNA damage that triggers p53 and p21, preventing cell growth. This leads to reduced tumor progression and increased cell death by affecting cyclin D1. It reduces the expression of MMP-2, phosphorylated mTOR (p-mTOR), and VEGF, thereby inhibiting angiogenesis and limiting tumor growth. It inhibits EMT by decreasing p-Akt and p-PI3K levels while boosting E-cadherin, thus preventing cell proliferation. Additionally, by activating caspase-3, increasing BAX, and reducing Bcl-2, ISO triggers cytochrome C release, promoting apoptosis in cancer cells. ROS: Reactive Oxygen Species; MMP-2: Matrix Metalloproteinase-2; p-mTOR: phosphorylated mammalian Target of Rapamycin; VEGF: Vascular Endothelial Growth Factor; EMT: Epithelial-Mesenchymal Transition; p-Akt: phosphorylated Protein kinase B; p-PI3K: phosphorylated Phosphoinositide 3-kinase; Bcl-2: B-cell lymphoma 2; BAX: BCL2 Associated X, Apoptosis Regulator; p53: Tumor protein p53; p21: Cyclin-dependent kinase inhibitor 1A]

MAPK, and EMT, leading to reduced migration and development of cancer. Additionally, both *in vitro* and *in vivo* investigation also showed its effectiveness in inhibiting tumor growth across various cancer models. Further research is essential to optimize its delivery, understand its pharmacokinetics, and explore clinical applications, ensuring its full potential in cancer therapy.

Conflict of interest

The authors declared no conflict.

Data availability

Data will be made available on request.

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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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