Anticancer Activity of Scutellarein Against Several Cancer Types with Possible Mechanisms: A Mini Review

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Abstract: Scutellarein (STN), a bioactive flavone found in various medicinal plants such as *Scutellaria baicalensis* and *Scutellaria lateriflora*. It has a variety of pharmacological actions, including anticancer properties. This study explores STN's anticancer activity against various cancer cell lines. A literature review was conducted using databases such as PubMed, ScienceDirect, and Google Scholar, focusing on research evaluating STN's anticancer efficacy. The results showed that STN has significant anticancer properties against various types of cancer, such as blood, colon, colorectal, gastric, liver, lung, ovarian, and renal cancers. STN reduces cell growth by cell cycle arrest, triggers apoptosis through caspase activation, and inhibits metastasis by suppressing mitochondrial membrane potential (MMP) and epithelial mesenchymal transition (EMT) markers. It modulates important pathways such as ERK, Wnt/β-catenin, and PI3K/Akt/NF-κB. Together, these systems prevent the growth and metastasis of cancer cells. The compound has exhibited prominent cytotoxicity in diverse cancer cell lines.

Keywords: Scutellarein; Anti-cancer; Proliferation; Flavone

1. Introduction

Cancer is a group of illnesses defined by the unregulated development and proliferation of dysfunctional cells, which can infect adjacent cells and, in certain instances, cause metastasis to distant sections of the body (Hanahan & Weinberg, 2011). It arises from genetic abnormalities that disrupt cell cycle regulation, leading to uncontrolled growth, impaired cell death, and the spread to other tissues. These changes are driven by alterations in oncogenes and tumor suppressor genes, impairing important regulatory mechanisms such as cell cycle regulation, apoptosis, and cell signaling processes (Vogelstein et al., 2013; Hanahan, 2022; Noble & Pasi, 2010). Cancer may exhibit various signs and symptoms, including changes in bowel or bladder habits, unexpected weight loss, and prolonged difficulty sleeping (Berger et al., 2010).

Natural products, generally described as substances that originate from living organisms such as bacteria, marine organisms, plants, fungi, and animal, are frequently employed as medicinal products for treating illness and preserving health (Bontempo et al., 2023). Natural products have numerous pharmacological actions (Zhu et al., 2004), including cancer (Lichota & Gwozdzinski, 2018). *Nigella sativa* (black cumin) is a well-known medicinal plant with diverse biological activities, including anti-diabetic, antimicrobial, anticancer, and anti-inflammatory properties, among other biological activities (Aktar et al., 2024a). Natural chemicals that promote apoptosis, inhibit tumor development, and modify signaling pathways, such as flavonoids, polyphenols, and alkaloids, show potential in cancer treatment (Abotaleb et al., 2018; Millimouno et al., 2014). Their anti-inflammatory and antioxidant characteristics help prevent the spread of cancer by minimizing its negative consequences (Griffiths et al., 2016). Quercetin, a major flavanol, exhibits strong anticancer properties, while also demonstrating remarkable therapeutic benefits in degenerative diseases (Eity et al., 2024). Loganic acid, a plant component with a variety of uses, has been shown to have anti-inflammatory, antioxidant, and anticancer qualities (Aktar et al., 2024b).

Scutellarein (STN), a flavone found in various medicinal plants such as *Scutellaria baicalensis* and *Scutellaria lateriflora* (Nurul Islam et al., 2011). It has demonstrated a wide range of biological activities, including anticancer (Saralamma et al., 2020), anti-inflammatory (Sung et al., 2015), antioxidant (Spiegel et al., 2022), and neuroprotective effects (Han et al., 2022). Additionally, multiple *in vitro* and *in vivo* studies have demonstrated STN's potential as a chemo preventive agent for various types of cancer (Lang et al., 2021; Li et al., 2020).

This review explored STN's anticancer potential using data from earlier investigations.

2. Methodology

2.1. Search strategy

A detailed search was performed across widely reputable scientific databases, such as PubMed, Web of Science, Google Scholar, and ScienceDirect, between the years 2004 and 2024, utilizing the keywords STN, anticancer, and activity/effect.

2.2. Inclusion criteria

Specific criteria were applied to select studies for this review, focusing on the anticancer properties of various sources. Research

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conducted *in vivo*, *in vitro*, or *ex vivo*, with or without the use of experimental animals, was considered. Additionally, studies were included regardless of whether thy detailed the underlying mechanism of action.

2.3. Exclusion criteria

The exclusion criteria for this review were properly specified to ensure the significance of the research reviewed. Research was excluded if the title or abstract did not match the inclusion criteria or contained duplicate data. Furthermore, research on anticancer activity was excluded if additional findings eclipsed the main focus of the current investigation.

3. Results and discussion

3.1. Blood cancer

STN caused apoptosis in Namalwa cells by increasing caspase activity, arresting the cell cycle at the G0/G1 phase, and decreasing proliferation by downregulating cyclin D1 and CDK4 (Feng et al., 2012). *In vivo*, treatment of 15 mg/kg substantially suppressed lymphoma growth.

3.2. Colon cancer

STN demonstrated significant anticancer effects against several colon cancer cell lines (SW480, T84, and CL-40) by promoting apoptosis and cytotoxicity while inhibiting proliferation and angiogenesis indicators such as VEGF (Li et al., 2020).

3.3. Colorectal cancer

In colorectal cancer, it promoted apoptosis through Bax activation and inhibited the Wnt/β-catenin pathway, which reduced tumor growth, proliferation, and migration in HT-29 cells (Zeng et al., 2021). Additionally, PRPF38A suppression reduced migration and invasion in the CT116 and RKO cell lines (Xiong et al., 2020).

3.4. Gastric cancer

In gastric cancer cell lines AGS and SNU-484, STN induced apoptosis and G2/M phase arrest, upregulated p53 and Bax expression, and downregulated proliferation markers such as MDM2 and cyclin B1 at concentrations ranging from 25 to 100 μM (Gowda Saralamma et al., 2017).

3.5. Hepatocellular carcinoma

STN demonstrated strong anticancer activity against HepG2 and Huh-7 cells in a dose-dependent manner, producing cytotoxicity and G2/M phase arrest. It increased PTEN expression, prevented EMT, and decreased carcinogenic pathways such as PI3K/Akt/NF-κB. It also inhibited cell proliferation, metastasis, and migratory potential, which slowed tumor progression (Ha et al., 2021).

3.6. Liver cancer

STN inhibited hepatocellular cancer by blocking the PI3K/Akt/NF-κB pathway, causing cell cycle arrest in HepG2 and Huh-7 cells (Ha et al., 2021). It induced apoptosis in liver cancer (Hep3B cells) via Fas-FasL signaling and decreased cyclin B1 and cdc25C (Sang et al., 2019).

3.7. Lung cancer

In various lung cancer cell lines, including PC-9, H1975, and A549, STN induced apoptosis, autophagy, and cytotoxicity through the activation of ERK1/2 and inhibition of the Akt/mTOR pathway. In female BALB/c nude mice, oral administration of STN at doses of 30 –60 mg/kg significantly inhibited tumor growth *in vivo* (Sun et al., 2018a; Cao et al., 2019). Additionally, STN downregulated inflammatory mediators such as COX-2 and NF-κB (Cheng et al., 2014) and effectively suppressed tumor growth in NSCLC models.

3.8. Ovarian cancer

STN induced apoptosis and inhibited invasion and migration in ovarian cancer cell lines A2780 and SKOV-3 by suppressing the expression of EZH2 and FOXO1 and decreasing NF-κB signaling (Lang et al., 2021).

3.9. Renal cancer

In ACHN and 786-O cell lines, STN showed cytotoxicity by suppressing PI3K/Akt/mTOR signaling and increasing apoptosis and cell cycle arrest via enhanced Bax and caspase-3 activation (Deng et al., 2018).

The findings suggested that STN provides significant protection against a number of cancers (**Table 1**). It provides details on the

Table 1. Mechanism of anticancer activity of scutellarein.

Cancer types	Cell lines/ methods/ models	Dose/ concentrations (R/A)	IC_{50}	Results	References
Blood cancer	Namalwa cells, *in vitro* Female BALB/c nude mice, *in vivo* (n=5)	5, 10, 15, 20, and 30 μM 15 mg/kg, (i.p).	-	↑Caspases, lymphoma growth, cycle arrest at G0/G1, apoptosis ↓Proliferation, cyclin D1, CDK4	Feng et al., 2012
Colon cancer	SW480, T84, CL-40, *in vitro* BALB/c nude mice, *in vivo* (n=10)	20, 40, 60 and 80 μM 0.5 μg/g, (i.p).	40.9 μM	↑Cytotoxicity, apoptosis, CDC4, caspase3, caspase 7 ↓RAGE, clone formation, proliferation, p-p65, PKC, VEGF,	Li et al., 2020
Colorectal cancer	CRC HT-29 cell line, in vitro C57BL/6 mice, *in vivo*	60, 120, 180, 240, 300, 360 and 400 μM 25–100 mg/kg, (i.p).	-	↑BAX, apoptosis ↓Wnt/β-catenin, BCL-2, proliferation, migration.	Zeng et al., 2021
Colorectal cancer	CT116 and RKO cell lines, *in vitro* Female nude mice, *in vivo* (n=8)	- 50–300 mg/kg, (i.p).	117.8 and 255.1 μM	↑Apoptosis, cytotoxicity ↓Proliferation, tumor growth, migration, invasion, PRPF38A,	Xiong et al., 2020

Table 1. *Continued*

Cancer types	Cell lines/ methods/ models	Dose/ concentrations (R/A)	IC_{50}	Results	References
Gastric cancer	AGS, SNU-484, *in vitro*	-	62.88 and 49.18 μM, 59.45 and 52.91 μM	↑Apoptosis, p53, cytotoxicity, G2/M phase cell cycle arrest, caspase- 3, caspase-9, PARP, Bax ↓Proliferation, MDM2 cIAP1, cIAP2, XIAP, CDK1, CDC25C, cyclin B1, MMP,	Gowda Saralamma et al., 2017
Hepatocellular carcinoma	HepG2, Huh-7 cells line, *in vitro*	25, 50, 100, 150 and 200 μM	-	↑Cytotoxicity, PTEN EMT, cell cycle arrest, G2/M phase arrest ↓Cell proliferation, metastasis, PI3K/ Akt/NF-κB, E-cadherin, migration, colony formation,	Ha et al., 2021
Liver cancer	Hep3B cell line, *in vitro*	100, 200, 300, 400, 500 and 600 μM	-	↑Cycle arrest, cytotoxicity, cell cycle arrest, apoptosis, Fas FasL, caspase-8, caspase-3, PARP ↓Proliferation, Cdc25C, cdk1, Cyclin B1, DR4	Sang et al., 2019
Lung cancer	PC-9 and H1975, Hela, HepG2, Beas-2 cells line, *in vitro*	10, 20, 40, 80, and 160 μM	-	↑Apoptosis, autophagy, LC3-II, p-ERK1/2, MK-2206 cytotoxicity, ↓Proliferation, tumor growth, p-AKT	Sun et al., 2018a
	Female BALB/c nude mice, *in vivo* (n=8)	30–60 mg/kg, orally			
Lung cancer	A549 cell line, *in vitro*	200, 400 and 600 μM	-	↑Autophagy, apoptosis, G0/G1 phase arrest, Bax, 4EBP1, cleaved-caspase-3, ↓Metastasis, proliferation, (p)-mTOR, pan-AKT, mTOR, STAT3, BCL-XL, p-STAT3, cyclins E, cyclin D1, colony formation, BCL-XL, BCL-2	Cao et al., 2019
Lung cancer	A549 cell line, *in vitro*	5, 25 and 50 μM	-	↑m ERK and p-ERK ↓Proliferation, COX-2, pEGFR, p ERK, p NFκB	Cheng et al., 2014
NSCLC	A549, PC-9, H1975, and A549/DDP cell lines, *in vitro*	5, 10, 20, 40, 80 and 160 μM	-	↑Cytotoxicity, apoptosis, autophagy, ERK, p53, ↓p-AKT, c-met, tumor size	Sun et al., 2018b
	Female BALB/c nude mice, *in vivo* (n=8)	60 mg/kg, orally			
Ovarian cancer	A2780 and SKOV-3 cells line, *in vitro*	25, 50, 75 and 100 μM	-	↑Cytotoxicity, apoptosis ↓Proliferation, migration, invasion, EZH2, FOXO1, tumor growth, metastasis, tumorigenesis, H3K27me3, NF-κB	Lang et al., 2021
	Balb/c nude mice, *in vivo* (n=5)	0.05 and 0.5 μg/g, (i.p).			
Renal cancer	ACHN and 786-O cells line, *in vitro*	30, 60, 90, 120, 150, 180 and 210 μM	185.6, 183.6 μM; 149.3,	↑Cytotoxicity, cell cycle arrest, apoptosis, Bax, cleaved caspase 3, p21, PTEN,	Deng et al., 2018
	male BALB/c nude mice, *in vivo* (n=5)	30–60 mg/kg, (i.p).	131.5 μM; 92.5, 106.7 μM	↓Proliferation, cyclin D1, Bcl2, CDK2, MMP-2, MMP-9, P13K/AKT/mTOR, invasion, migration	

↑: Increase/Upregulate/Activation; ↓: Decrease/Downregulate/Inactivation; 4EBP1: Eukaryotic Translation Initiation Factor 4E-Binding Protein 1; AKT: Protein Kinase B; BAX: Bcl-2-Associated X Protein; BCL-2: B-cell Lymphoma 2; BCL-X: B-cell Lymphoma Extra Large; Cdc25C: Cell Division Cycle 25C; cdk1: Cyclin-Dependent Kinase 1; cIAP1: Cellular Inhibitor of Apoptosis Protein 1; cIAP2: Cellular Inhibitor of Apoptosis Protein 2; c-met: Mesenchymal-Epithelial Transition Factor; DR4: Death Receptor 4; EGFR: Epidermal Growth Factor Receptor; EMT: Epithelial-Mesenchymal Transition; ERK: Extracellular Signal-Regulated Kinase; EZH2: Enhancer of Zeste Homolog 2; FasL: Fas Ligand; FOXO1: Forkhead Box O1; H3K27me3: Histone 3 Lysine 27 Trimethylation; IC_{50}: Half Maximal Inhibitory Concentration; IKK: IκB Kinase; iNOS: Inducible Nitric Oxide Synthase; IκBα: Inhibitor of Nuclear Factor Kappa B Alpha; LC3-II: Microtubule-Associated Protein 1A/1B-Light Chain 3-II; MDM2: Double Minute 2; MMP-2: Matrix Metalloproteinase 2; MMP-9: Matrix Metalloproteinase 9; mTOR: Mechanistic Target of Rapamycin; NFκB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; p21: Protein 21; PARP: Poly (ADP-Ribose) Polymerase; p-ERK1/2: Phosphorylated Extracellular Signal-Regulated Kinase 1 and 2; PI3K: Phosphoinositide 3-Kinase; PKC: Protein Kinase C; p-mTOR: Phosphorylated Mechanistic Target of Rapamycin; p-p65: Phosphorylated p65; PRPF38A: Pre-mRNA Processing Factor 38A; p-STAT3: Phosphorylated Signal Transducer and Activator of Transcription 3; PTEN: Phosphatase and Tensin Homolog; RAGE: Receptor for Advanced Glycation End-products; STAT3: Signal Transducer and Activator of Transcription 3; TNF-α: Tumor Necrosis Factor Alpha; VEGF: Vascular Endothelial Growth Factor; Wnt/β-catenin: Wingless-related integration site/β-catenin signaling pathway; XIAP: X-linked Inhibitor of Apoptosis Protein;

tested cancer cell lines, experimental methods, dosage/concentration, IC_{50} values (if available), and key findings related to apoptosis, cell cycle arrest, metastasis inhibition, and pathway modulation. The findings highlight STN's potential as an anticancer agent by inducing apoptosis through caspase cascade activation, restricting proliferation via cell cycle arrest, and inhibiting metastasis by downregulating MMPs and EMT markers. Its anticancer effects are primarily mediated through key signaling pathways, including PI3K/Akt/NF-κB, Wnt/β-catenin, and ERK. *In vitro* studies have demonstrated its cytotoxic effects across various cancer cell types, suggesting its therapeutic potential. Further research should focus on optimizing its pharmacokinetics to enhance its efficacy and explore its clinical applications. **Table 1** summarizes the anticancer mechanisms of STN against several cancers while, **Fig. 1** illustrates how STN interacts with different cancer cell lines.

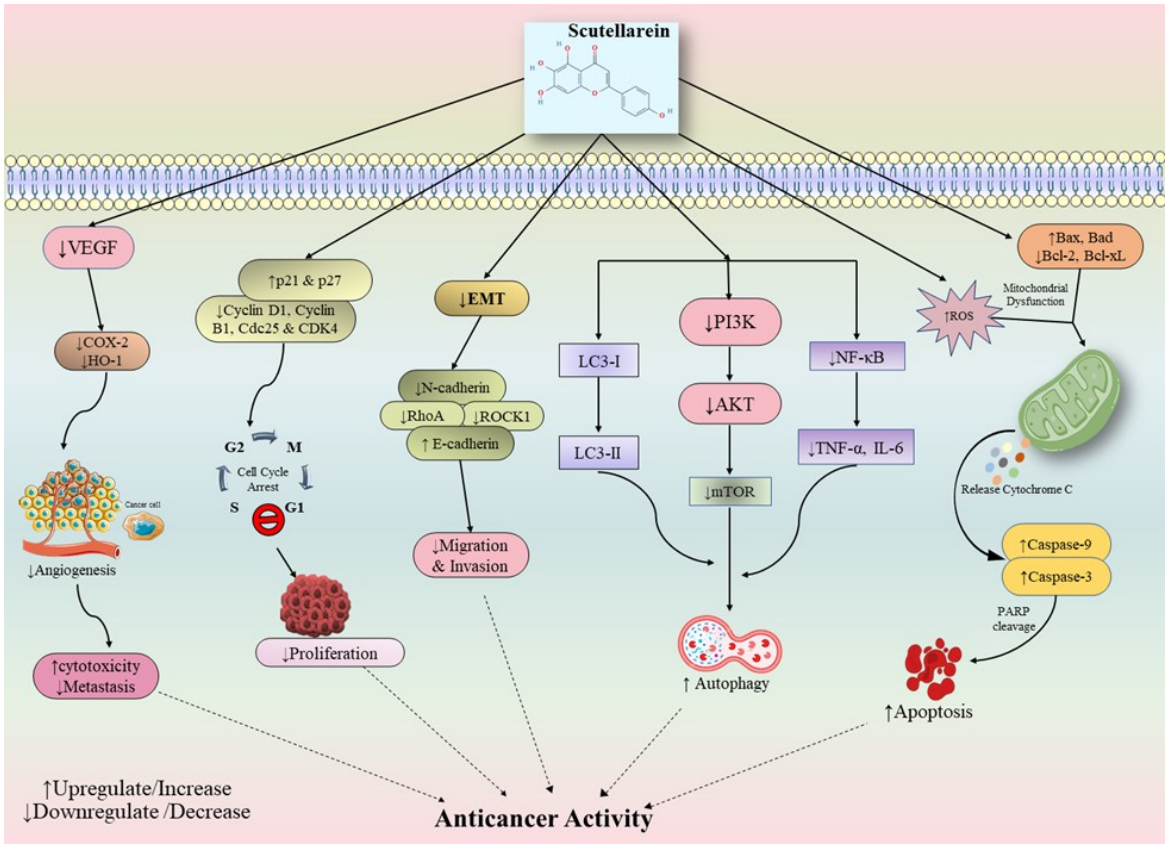

Fig. 1. Possible mechanism of the anti-cancer activity of scutellarein. [This figure illustrated the anticancer mechanisms of scutellarein. It inhibits angiogenesis by suppressing VEGF and prevents EMT by regulating N-cadherin, RhoA, ROCK1, and E-cadherin, thereby reducing cancer cell migration, invasion, and metastasis. Additionally, STN activates p21 and p22, leading to a decrease in cyclin D1, Cdc25, and CDK4, which induces cell cycle arrest and limits cancer cell proliferation. Moreover, STN promotes apoptosis by increasing pro-apoptotic factors Bax and Bad while decreasing anti-apoptotic factors Bcl-xL and Bcl-2. Apoptosis is further induced through activation of the caspase pathway. VEGF: Vascular endothelial growth factor; EMT: Epithelial-mesenchymal transition; N-cadherin: Neural Cadherin; RhoA: Ras Homolog Family Member A; ROCK1: Rho-Associated Coiled-Coil Containing Protein Kinase 1; Cdc25: Cell Division Cycle 25; CDK4: Cyclin-Dependent Kinase 4; Bax: Bcl-2-Associated X Protein; Bad: Bcl-2-Associated Death Promoter; Bcl-2: B-cell Lymphoma 2; Bcl-xL: B-cell Lymphoma-extra Large]

4. Conclusion

In conclusion, STN exhibits considerable potential as an anticancer agent across a diverse range of cancers, including blood, colon, colorectal, gastric, liver, lung, ovarian, and renal cancers. Its anticancer effects are primarily driven by the induction of apoptosis through caspase cascade activation, the suppression of cell proliferation via cell cycle arrest, and the inhibition of metastasis by downregulating MMPs and EMT markers. Its effects are mediated through key signaling pathways, such as PI3K/Akt/NF-κB, Wnt/β-catenin, and ERK. *In vitro* studies have consistently shown its cytotoxic impact on diverse cancer cell lines, highlighting its therapeutic potential. Further investigation should focus on optimizing STN's pharmacokinetics and exploring its clinical applications to improve cancer treatment strategies.

Conflict of interest

The authors declared that they have no conflict of interest.

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Authorship contributions

All authors significantly contributed to the work, including its conception, study design, execution, data acquisition, analysis, interpretation, and revisions or critical reviews. They also gave final approval for the manuscript, agreed on the journal for submission, and confirmed their accountability for all aspects of the work. All authors have read and approved the final version of the manuscript.

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