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Anticancer Potential of Xanthotoxol: Underlying Mechanistic Insights and Therapeutic Implications in Different Cancer Types

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Abstract: Cancer is a severe disease caused by genetic variations leading to uncontrolled cell proliferation and metastasis. Xanthotoxol (XTL), a bioactive furocoumarin from *Fructus Cnidii* and *Cnidium monnieri*, exhibits various pharmacological activities, including anticancer effects. However, its anticancer potential has not yet been specifically reviewed. This study explores its effects on various cancer cell lines through a literature review using PubMed, and Google Scholar. Findings reveal that XTL has significant anticancer activity against lung, skin, blood, and thyroid cancers. It induces apoptosis by activating pro-apoptotic factors like caspase 3, 7, 8, 9, and Bax while inhibiting proliferation, colony formation, DNA replication, migration, and invasion. Our study also showed that it exhibited good pharmacokinetic properties and reduced toxicity. However, most studies are limited to *in vitro* experiments, lacking *in vivo* and clinical evaluations. Further research is needed to validate its safety, bioavailability, and therapeutic efficacy in cancer treatment.

Keywords: Anti-cancer; Furocoumarin; Proliferation; Toxicological profile; Xanthotoxol

1. Introduction

Cancer is a condition when certain body cells proliferate out of control and spread to other bodily organs (Saini et al., 2020; Yana et al., 2025). It has been classified as a cellular disease caused by defects in genes that affect proliferation, differentiation, and death (Nia et al., 2020; Bhuia et al., 2023a). There are several indications and symptoms that cancer can exhibit, including changes in bowel or bladder habits, chronic lack of sleep, and unexpected weight loss (Scheel & Holtedahl, 2015). Genetic mutations that interfere with normal cell cycle regulation cause cancer by causing uncontrolled cell proliferation, avoiding organized cell death, and allowing cells to penetrate adjacent tissue and spread to additional tissues. These mechanisms, which produce the characteristics of cancer, are driven by changes in oncogenes and tumor suppressor genes (Noble & Pasi, 2010).

A natural product is a therapeutic chemical created by nature, such as plants, microbes, or marine life (Chowdhury & Al Hasan, 2025; Aktar et al., 2024; Hasan et al., 2025). Natural products have several pharmacological activities (Yu et al., 2018; Bhuia et al., 2023b), including cancer (Bhuia et al., 2025; Situ et al., 2025). Natural compounds that induce apoptosis, decrease tumor growth, and alter signaling pathways, such as polyphenols, flavonoids, and alkaloids, have promise in the treatment of cancer (Foroughi-Gilvaee et al., 2024). By reducing adverse effects, their anti-inflammatory and antioxidant properties assist in preventing the spread of cancer (Zappavigna et al., 2020).

Xanthotoxol (XTL), a bioactive linear furocoumarin, is primarily derived from the fruit of *Fructus Cnidii* (Ma et al., 2016). It is also found in *Cnidium monnieri* (L.). XTL has several pharmacological activities, including anti-cancer activity (Lin et al., 2022), anti-oxidant activity (Milanović et al., 2021), anti-fibrotic activity (Batiha et al., 2022), anti-microbial activity (Zhu et al., 2023), anti-inflammatory activity (He et al., 2013), and anti-diabetic activity (Karmase et al., 2013). Additionally, a number of *in vitro* studies have demonstrated XTL's potential as a chemopreventive treatment for a range of cancers (Kubrak et al., 2019; Grabarska et al., 2020).

This review explains how the XTL compound fights against cancer by collecting information from previous research.

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2. Methodology

2.1. Database study

2.1.1. Search strategy

On May 4, 2025, an extensive search was conducted throughout popular scientific resources, including PubMed, and Google Scholar. The literature search on XTL focused on its anticancer potential, toxicological profile, pharmacokinetics, and botanical sources. For anticancer activity, terms like "tumor," "anticancer activity," "cytotoxic activity," "apoptosis," and "in vivo/in vitro cancer studies" were used to assess its efficacy in cancer treatment. Toxicological concerns were explored using keywords such as "toxicity," "acute toxicity," "chronic toxicity," and "safety profile" to evaluate safety. Pharmacokinetics was examined with terms like "absorption," "metabolism," "bioavailability," and "pharmacokinetics" to understand its absorption and metabolism in the body. Additionally, the botanical sources of XTL were investigated using keywords like "plant sources," "natural sources," and "extraction" to identify its plant-based origins.

2.1.2. Inclusion criteria

Specific criteria were used to identify the studies for this review. It involved a study into the anticancer properties of diverse sources. Studies carried out *in vivo*, *in vitro*, or *ex vivo*, with or without experimental animals, were examined. Furthermore, studies were included regardless of whether they described the mechanism of action.

2.1.3. Exclusion criteria

The exclusion criteria for this review were carefully defined to ensure the relevance of selected studies. Research was excluded if the titles or abstracts did not meet the inclusion criteria or contained duplicate data. Additionally, studies on anticancer activity were not considered if other findings overshadowed the primary focus of the current study.

2.2. Determination of ADMET and Lipinski rule, pharmacokinetics, and drug-likeness properties

We predicted the pharmacokinetics and drug likeness properties in our investigation using the online tool SwissADME (Islam et al., 2025). Furthermore, we evaluated drug's absorption, distribution, metabolism, and excretion (ADME) properties using pkCSM (Al Hasan et al., 2025), another web tool.

3. Results and discussion

3.1. Database reports

An initial total of 1,834 records were screened from the Google Scholar and PubMed databases. Following a rigorous selection process based on title, abstract, duplication, data availability, and recency, 27 reports were included, while 1,807 were excluded. The final set of included reports consisted of studies spanning multiple domains. Specifically, five studies focused on anticancer properties, including investigations related to lung cancer (n= 1), blood cancer (n= 2), skin cancer (n= 1), and thyroid cancer (n= 1). Two studies addressed toxicological aspects, while 19 studies explored botanical sources. Additionally, one study examined the biopharmaceutical profile of the subjects. This distribution reflects the diverse nature of the selected literature and is visually summarized in the accompanying chart (**Fig. 1**).

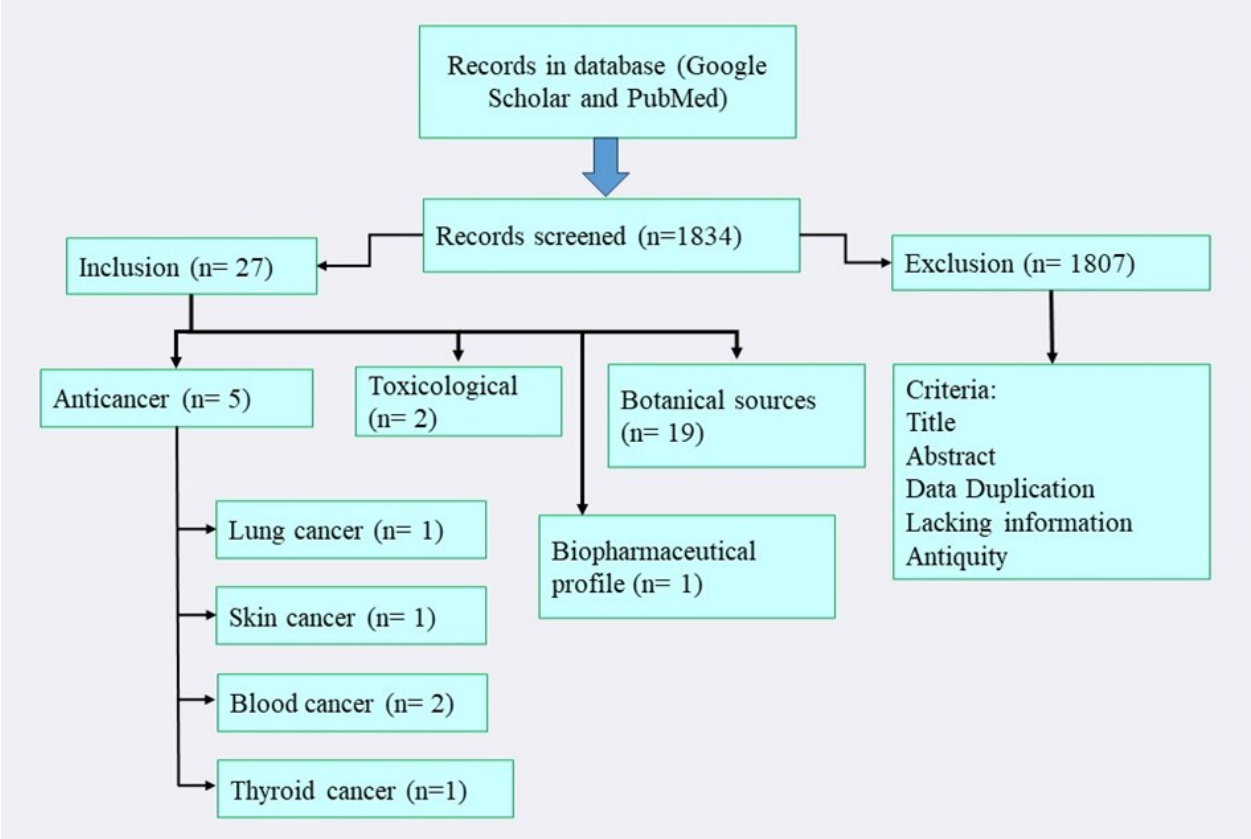

Fig. 1. Outline of data search, inclusion and exclusion of reported data .

3.2. Botanical sources of xanthotoxol

For centuries, plants have served as a source of medicine across various cultures, offering natural solutions for pain management, disease prevention, and treatment (Chaachouay & Zidane, 2024). XTL is primarily found in the fruits of *Cnidium monnieri*, which has been identified as a key source of this compound (Cai et al., 2000; Kim et al., 2013; Shin et al., 2011). Additionally, the root of *Angelica dahurica* also contains XTL, as documented in various studies (Shi et al., 2024). These two plant parts the fruits of *Cnidium monnieri* and the roots of *Angelica dahurica* are the primary botanical sources of XTL, emphasizing their significance in pharmacological research and therapeutic development (**Table 1**).

Table 1. Various botanical sources and plant parts of xanthotoxol

Sources	Plant parts	References
Ammi majus L.	-	Hehmann et al., 2004
Cnidium monnieri L.	-	Wei et al., 2004
	-	Sun et al., 2020
	Fruits	Cai et al., 2000
	Fruits	Kim et al., 2013
	-	Zhang et al., 2022
Saussurea obvallata	-	Wang et al., 2022
Angelica dahurica	-	Lin et al., 2022
	-	Yang & Li, 2023
	Root	Shi et al., 2024
	-	Li and Wu, 2017
	-	Yu et al., 2020
	-	Bai et al., 2016
	-	Chen et al., 2006
	-	Han et al., 2023
Cnidium monnieri	Fruits	Shin et al., 2011
Cnidii Fructus	-	Bai et al., 2025
	-	Xu et al., 2024
Trichomonas vaginalis	-	Yu et al., 2022

3.3. Beneficial effects of xanthotoxol against different cancers

3.3.1. Lung cancer

The compound XTL showed a significant effect against lung cancer. An *in vitro* study by Lin et al. (2022) showed that, in A549 and NCI-H460 lung cancer cell lines, the compound induces apoptosis, cell cycle arrest, and cytotoxicity. The study also showed that XTL also inhibits colony formation capacity, DNA replication, migration, and invasion (Lin et al., 2022). In A549, H1299 lung cancer cells (1.0-200 μM), the XTL increases apoptosis and cytotoxicity, which leads to a decrease in cell proliferation (Grabarska et al., 2020).

3.3.2. Skin cancer

The XTL also showed significant activity against skin cancer. Wróblewska-Łuczka et al. (2021) expressed that, in FM55P and FM55M2 cells, the compound at 25-250 μM increases apoptosis and cytotoxicity as well as decreases cell proliferation with IC_{50} values of 180 and 183 μM, respectively (Wróblewska-Łuczka et al., 2021).

3.3.3. Blood cancer

The XTL exhibited notable effectiveness against blood cancer. In HL60, HL60/MX1, and HL60/MX2 cells (10-1000 μM), it exhibited cytotoxicity leading to increased apoptosis by activating caspase 3, 7, 8 and 9, as well as decreased proliferation and p38 phosphorylation (Kubrak et al., 2019).

3.3.4. Thyroid cancer

Thyroid cancer arises from the follicular or parafollicular cells of the thyroid gland and represents the most prevalent endocrine malignancy (Prete et al., 2020). Its incidence has been steadily increasing worldwide, with differentiated thyroid cancers being the most common subtype (Weller et al., 2025). The TCTC cell line, derived from thyroid carcinoma, is frequently used in *in vitro* studies to evaluate anticancer potential (Kaczmarzyk et al., 2024). In one such study, TCTC cells treated with the XTL compound at concentrations ranging from 5-50 μM/ml showed a marked decrease in total cell protein content, mitotic index, colony formation, and overall cell proliferation, indicating strong antiproliferative activity (Gawron & Kruk, 1992).

Our overall result showed that XTL expressed a significant effect against several cancers, including lung cancer, skin cancer, thyroid, and blood cancer. It triggered apoptosis by activating several factors such as caspase 3, 7, 8, and 9, Bax while reducing cell proliferation, colony formation capacity, DNA replication, migration, and invasion. Several *in vitro* studies showed that the compound increased cytotoxicity toward different cancer cell lines. These results emphasize XTL's possibility as a therapeutic drug that regulates important processes associated with tumor formation. Further research should focus on improving its pharmacokinetic features in order to improve effectiveness and investigate its possibilities for clinical application.

However, **Table 2** presents the anticancer activity of XTL. The possible mechanism by which XTL can work against various cancer cell lines also describe in **Fig. 2**.

Table 2. Mechanism of anticancer activity of xanthotoxol, summary of key molecular pathways and cellular targets through which xanthotoxol exerts its anticancer effects.

Cancer types	Cell lines	Concentrations	IC_{50}	Results	References
Lung cancer	A549 and NCI-H460 cell lines, *in vitro*	-	-	↑Apoptosis, cell cycle arrest, cytotoxicity ↓EMT, colony formation capacity, DNA replication, migration, invasion	Lin et al., 2022
	A549, H1299 cell lines, *in vitro*	1.0-200 μM	-	↑Apoptosis, cytotoxicity ↓Proliferation	Grabarska et al., 2020
Skin cancer	FM55P, FM55M2 cell lines, *in vitro*	25-250 μM	180 μM, 183 μM	↑Apoptosis, cytotoxicity ↓Proliferation	Wróblewska-Łuczka et al., 2021
Blood cancer	HL60, HL60/MX1, HL60/MX2 cell line, *in vitro*	10-1000 μM	-	↑Cytotoxicity, apoptosis, caspase 3,7,8, and 9, Bax ↓Proliferation, p38 phosphorylation	Kubrak et al., 2019
Thyroid Cancer	TCTC cell, *in vitro*	5-50 μM/ml	-	↓Cell protein, mitotic index, colony formation, cell proliferation	Gawron & Kruk, 1992

Bax: Bcl-2-associated X protein; DNA: Deoxyribonucleic Acid; EMT: Epithelial-Mesenchymal Transition; IC_{50}: Half Maximal Inhibitory Concentration

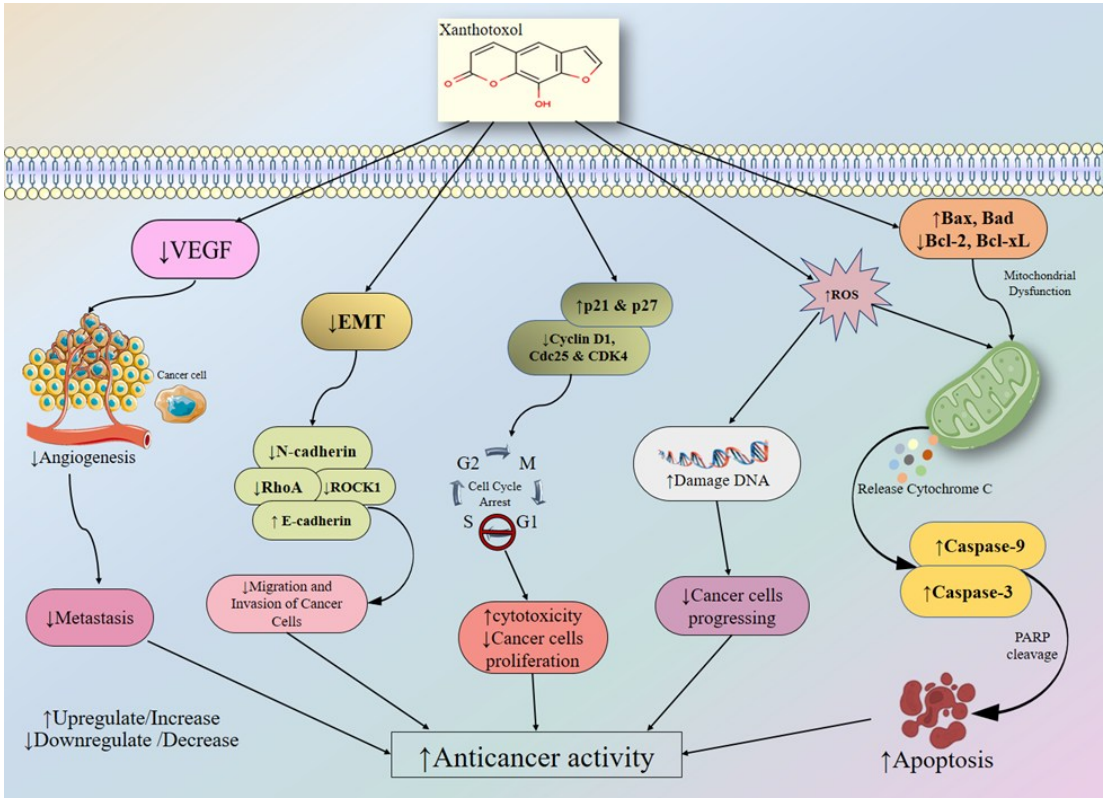

Fig. 2. Possible mechanism of the anti-cancer activity of xanthotoxol. [This figure demonstrates the anticancer mechanisms of XTL. It suppresses angiogenesis by inhibiting VEGF and inhibits EMT through modifying N-cadherin, RhoA, ROCK1, and E-cadherin, and lowering cancer cell migration, invasion, and metastasis. XTL activates p21 and p22, which decrease cyclin D1, Cdc25, and CDK4, promoting cell cycle arrest and reducing cancer cell proliferation. Additionally, XTL induces apoptosis by increasing pro-apoptotic factors Bax, Bad and decreasing anti-apoptotic factors Bcl-2 and Bcl-xL. Again, the caspase pathway also triggered apoptosis. 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]

3.4. Biopharmaceutical profile

Pharmacokinetics is the scientific study of ADME and their pharmacological, therapeutic, and toxic effects. It quantitatively analyzes these processes to determine the drug's time course and overall impact in the body (Jahan et al., 2025; Bithi et al., 2025). From the literature, we found that XTL metabolism involves CYP1A2, with V_{max} = 0.55 nmol·min^{-1}·mg^{-1}, K_m = 8.46 μM, CLint = 0.06 mL·min^{-1}·mg^{-1}, and CLH = 15.91 mLmin^{-1}kg^{-1}, strongly inhibiting CYP3A4 (IC_{50} = 7.43 μM) and CYP1A2 (IC_{50} = 27.82 μM) (Ma et al., 2016). In our computational ADME prediction, XTL is a soluble compound with moderate lipophilicity (log $P_{o/w}$ = 1.67) and excellent intestinal absorption (93.91%). It does not interact with CYP enzymes or P-glycoproteins and shows restricted brain distribution (log BB = 0.39). Primarily excreted through the kidneys, it has a total clearance of 0.676 log ml/min/kg. Additional details information and data are provided in **Table 3**, which provides a comprehensive visual representation of the relevant information for better understanding and analysis.

Table 3. Pharmacokinetic characteristics and drug-like properties of xanthotoxol.

Properties	Parameters	Xanthotoxol
Physicochemical properties	Formula	$C_{11}H_6O_4$
	Molecular weight (g/mol)	202.16
	Number of heavy atoms	15
	Number of aromatic heavy atoms	13
	Number of H-bond donors	1
	Number of H-bond acceptors	4
	Molar refractivity	54.28
Lipophilicity	Log $P_{o/w}$ (XLOGP3)	1.67
Drug-likeness	Lipinski	Yes; 0 violation
	Bioavailability score	0.55
Water solubility	Log S (ESOL)	–2.79
	Class	Soluble
Absorption	Caco2 permeability (log Papp in 10^{-6} cm/s)	0.954
	Intestinal absorption (human) numeric (% absorbed)	93.911
	Skin permeability (log Kp cm/h)	–2.83
	P-glycoprotein I inhibitor	No
	P-glycoprotein II inhibitor	No
Distribution	BBB permeability (log BB)	0.39
	CNS permeability (log PS)	–2.803
	VDss (human) (log L/kg)	0.197
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
Excretion	Total clearance (log ml/min/kg)	0.676
	Renal OCT2 substrate	No

CNS: Central nervous system; BBB: Blood brain barrier; H-bond: Hydrogen bond

3.5. Toxicological profile

Toxicity evaluation is essential to confirm the safety of newly developed drugs before their administration to humans (Blomme & Will, 2016). Toxicity assessments in test animals are crucial for identifying potential risks, ensuring safety, optimizing dosage, and detecting adverse effects of experimental compounds, including natural products (Sharma et al., 2025). Previous studies showed that in acute toxicity, XTL showed an LD_{50} of 468 mg/kg in mice following 48-hour acute toxicity testing with doses of 100–1000 mg/kg i.p. In a 6-month chronic toxicity study in rats, oral doses of 10, 40, and 80 mg/kg showed no side effects or abnormalities in reproductive activity or endocrine integrity (Sethi et al., 1992). Prior study, suggest that the LDH assay showed that imperatorin is non-toxic at concentrations ≤ 100 μM across four cell lines, with significant cytotoxicity observed only at 200 μM (Grabarska et al 2020).

4. Conclusion

In conclusion, XTL has shown significant potential as an anticancer drug, with great effectiveness against a number of cancer types, including lung cancer, blood cancer, thyroid and skin cancer. Its anticancer properties are connected to its ability to produce apoptosis and inhibit proliferation, colony formation capacity, DNA replication, migration, and invasion. It also induces cell cycle arrest and exhibits cytotoxicity against various cancer cell lines. Additionally, it also activates some factors such as caspase 3, 7, 8, 9 and Bax, which also influence apoptosis. Due to these beneficial outcomes, XTL could be a highly beneficial cancer treatment in the

future. Its favorable pharmacokinetics properties and lower toxicity further supports its potential as a cancer treatment. Further *in vivo* research is needed to investigate its safety and efficacy as an anti-cancer agent. However, it is necessary to understand how XTL is absorbed in the body, modify its administration methods, and investigate its potential in clinical therapies in order to enhance its effectiveness in cancer therapy.

Conflict of interest

The authors declared no conflict.

Data availability

Data will be made available on request.

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Not applicable.

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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