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REVIEW

Anticancer Potential of Bioactive Compounds in *Premna serratifolia*, *Premna odorata*, and *Premna tomentosa*: A Review of In Vitro Evidence

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Abstract: The genus *Premna* (Lamiaceae), widely distributed across tropical and subtropical regions, is renowned for its ethnomedicinal applications, including cardiotonic, antimicrobial, hepatoprotective, and antitumor properties. Despite these promising uses, the current body of literature relies predominantly on in vitro evidence, with limited knowledge regarding in vivo validation, metabolism, and bioavailability. This review synthesizes findings from the past decade on the *Premna serratifolia* group (*P. serratifolia, P. odorata*, and *P. tomentosa*), focusing on their bioactive compounds and mechanisms of in vitro anticancer activity. The compounds identified—such as flavonoids, terpenoids, and steroids—exhibit diverse actions, including cell cycle arrest, apoptosis induction, inhibition of metastasis, oxidative stress modulation, and autophagy. Key compounds like quercetin, kaempferol, and stigmasterol demonstrate multi-targeted actions, effectively regulating pathways such as PI3K/AKT and NF-κB while selectively targeting cancer cells. These findings underscore chemopreventive potential from *P. serratifolia* group and their ability to complement conventional cancer therapies, potentially reducing side effects and overcoming drug resistance. Furthermore, the review validates the ethnomedicinal use of *Premna* species and bridges traditional knowledge with modern oncology. However, the absence of comprehensive in vivo and clinical data warrants further research to fully harness these compounds' potential. This study highlights *P. serratifolia, P. odorata*, and *P. tomentosa* as promising sources for novel plant-derived anticancer agents, offering opportunities for future drug discovery.

Keywords: phytochemicals, natural product-based therapy, chemoprevention, cytotoxic activity, multi-target mechanisms

Introduction

Noncommunicable diseases, characterized by their chronic and complex nature, are responsible for more than 70% of global deaths annually, equating to approximately 41 million fatalities. Among these, cancer ranks as the second leading cause of death, following cardiovascular diseases.[1] According to GLOBOCAN 2020, a global cancer data source, new cancer cases are projected to rise significantly by 2040, representing a 47% increase compared to 2020.[2] Cancer includes a diverse group of over 277 diseases, generally defined by uncontrolled cell growth. Any somatic cell has the potential to undergo malignant transformation through a cascade of genetic mutations that disrupt normal cell functions.[3] This process, known as carcinogenesis, occurs in three stages: initiation, where genetic mutations occur; promotion, where mutated cells become malignant; and progression, marked by rapid, uncontrolled tumor growth. Additionally, metastasis —the spread of cancer cells to distant organs—is a major contributor to cancer-related.[4]

The growing global cancer burden highlights the urgent need for innovative, cost-effective chemopreventive, and therapeutic strategies that are accessible to populations worldwide. Natural products, with their unparalleled chemical diversity, provide a rich source of bioactive compounds with therapeutic potential.[5] Among these, phytochemicals have

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proven to be vital in the development of anticancer drugs, with more than 60% of current chemotherapeutic agents derived from these compounds.[6]

The genus *Premna*, first described by Linnaeus in 1771, comprises about 200 species found across Australia, Africa, Asia, and the Pacific Islands. The name Premna derives from the Greek word "premon", meaning tree stump, reflect the short and twisted trunks of *Premna serratifolia* L., the first species described in this genus. Typically, Premna species are shrubs or trees, though some exist as pyroherbs or lianas.[7] Morphologically, *Premna* species are divided into two groups based on their twig, calyx, and fruit characteristics: the *P. serratifolia* group and the *P. trichostoma* group. The *P. serratifolia* group includes commonly found species like *P. serratifolia, P. odorata*, and *P. tomentosa*. In contrast, the P. trichostoma group includes rarer, geographically restricted species.[8] The *P. serratifolia* group are renowned for their phytochemical richness, including compounds such as iridoid glycosides, diterpenoids, phenylethanoids, lignans, sesquiterpenes, ceramides, megastigmanes, and glyceroglycolipids. These metabolites contribute to the diverse bioactivities of *Premna* species, including immunomodulatory, antimicrobial, anti-hyperglycemic, anti-inflammatory, and cytotoxic effects.[9,10]

Despite these promising biological activities, current research predominantly consists of in vitro assays, and there remains a significant gap regarding the comprehensive understanding of anticancer mechanisms, bioactive constituents, and their therapeutic potential in clinical contexts. To bridge this gap, this review aims to summarize and evaluate the available in vitro data regarding the anticancer activities and mechanisms of bioactive compounds from *P. serratifolia, P. odorata*, and *P. tomentosa*. Emphasis is placed on identifying bioactive compounds, summarizing reported mechanisms of action, and discussing the implications of these findings for future research. Given the limited in vivo studies available, our review focuses primarily on in vitro cytotoxic, apoptotic, anti-metastatic, and related mechanistic data, while underscoring the necessity for further preclinical and clinical validation.

Materials and Methods

Search Strategy

We conducted literature search in PubMed, EBSCO, and Scopus from 2013 to 2023 to identify relevant studies on *Premna serratifolia, Premna odorata*, and *Premna tomentosa*. The primary search terms included "Premna serratifolia", "Premna odorata", "Premna tomentosa", combined with "bioactive compounds" and "anticancer activity". Only peer-reviewed articles presenting in vitro and/or in vivo evidence for the anticancer effects of bioactive compounds explicitly isolated from these three *Premna* species were included. Reviews or commentaries lacking primary data and studies on non-*serratifolia* group species were excluded.

Data Extraction and Validation

Two investigators (RMF and SNR) independently screened the titles and abstracts and then reviewed the full text of potentially relevant articles. Discrepancies were resolved through discussion with a third investigator (ITM). Extracted data included information on the experimental design, cell lines models, treatment doses, identified bioactive compounds, and reported outcome. The data were cross-verified to ensure consistency and accuracy.

Although the focus is on in vitro efficacy, some studies that mention initial in vivo experiments were considered if they provided substantial mechanistic or cytotoxic data. Potential conflicts of interest in the cited papers were not always explicitly stated; however, we acknowledge such factors may influence reported outcomes and interpretations.

Results and Discussion

Premna serratifolia, Premna odorata, and *Premna tomentosa* are widely distributed across tropical and subtropical regions and have been traditionally used to address a broad spectrum of ailments. Their phytochemical profiles, including flavonoids, sterols, and terpenoids, underline their potential as sources of bioactive compounds for therapeutic applications. Table 1 provides a comprehensive overview of three species within the *Premna serratifolia* group. Following, Table 2 summarizes recent in vitro anticancer studies examining the biological activities of various extracts and bioactive secondary metabolites derived from *Premna serratifolia, Premna odorata*, and *Premna tomentosa*. In the following

Table 1 Overview of Morphology, Distribution, Ethnopharmacological Uses, and Phytochemical Content of Premna Species

Name of the Plant	Plant Morphology	Plant Distribution	Ethnopharmacological Uses	Phytochemical Content *with Anticancer Activity*
Premna serratifolia	Small tree, 3–4 m in height, glabrous stem, ovate-cordate leaves with foetid odor, creamy-white flowers, black globose drupe.[11]	Tropical and subtropical regions, Marquesas Islands, Indonesia, Guam, Papua New Guinea.[11]	Cardiotonic, antibiotic, carminative, hepatoprotective, antitumor, treats canker sores, bad breath, leucorrhea, gonorrhea, asthma, malaria.	Flavonoids: quercetin, luteolin, casticin, diosmetin, linarin, tricin, pectolinaringenin, vitexin, kaempferide. Terpenoids: oleanolic acid, phytol, Phenylpropanoids: verbascoside, Fatty acids: hexadecenoic acid
Premna odorata	Evergreen small tree/shrub, up to 10 m tall, hairy green leaves, pale green/yellowish/white fragrant flowers.[12]	Philippines, temperate and tropical regions of Asia.[12]	Treats phlegm, stomach pain, headaches, cough, wounds, parasiticides, tuberculosis, heart disorders.	Flavonoids: Acacetin, diosmetin, Sterols: stigmasterol, β-sitosterol Phenylpropanoids: verbascoside, Terpenoids: β-caryophyllene,
Premna tomentosa	Medium-sized tree, 20 to 25 feet tall, Greyish-brown bark, ovate-cordate leaves, campanulate with two lobes calyx, dark purple to black ripe fruit.[13]	India, Bangladesh, Bhutan, China, Myanmar, Thailand, Cambodia, Vietnam, Malay Peninsula, Sumatra, Java, Philippines, East Timor.[14]	Treats stomach-related ailments, dropsy, wounds, and postpartum tonic.	Fatty acid: hexadecenoic acid.

paragraphs, we discuss anticancer mechanism of the bioactive compound such as induction of apoptosis, modulation of the cell cycle, inhibition of proliferation and migration, oxidative stress modulation, and autophagy induction. However, during compiling these findings, we recognized that certain references describing the anticancer mechanism of Premna species did not always provide in-depth of the identification of bioactive compound. To fill these gaps, we supplemented these mechanistic discussions with studies on the same compounds—albeit from other plant sources. While we acknowledge that subtle variations in phytochemical context can influence potency or synergy, the core biochemical pathways (eg, apoptosis, cell cycle arrest) generally remain consistent for well-characterized molecules. Thus, once a compound is structurally identified, its fundamental anticancer mechanism (eg, caspase activation, ROS modulation) is usually reproducible across different models.

Mechanism of Anticancer

The anticancer potential of the three species within the Premna serratifolia group—*P. serratifolia, P. odorata*, and *P. tomentosa*—is attributed to their diverse array of bioactive compounds that target multiple cancer-related pathways. The *Premna serratifolia* group, exhibits a rich diversity of bioactive compounds categorized into several major classes of secondary metabolites. These compounds include flavonoids, terpenoids, steroids, phenylpropanoids, and long-chain fatty acids, all of which contribute to their anticancer potential.[10] Among flavonoids, notable compounds such as quercetin, diosmetin, kaempferol-3-O-b-D-galactopyranoside, luteolin, and casticin have demonstrated potent anticancer activities through mechanisms like apoptosis induction, cell cycle arrest, and inhibition of proliferation and metastasis. Quercetin and kaempferol are particularly prominent for their ability to regulate oxidative stress and modulate signaling pathways such as NF-κB and PI3K/AKT.[65]

Table 2 Summary of Anticancer Mechanism of Premna Sp. Derived Bioactive Compound

Bioactive Compound	Group	Method/ Assay	Type of Cancer	In vitro Model	Dose and duration of treatment	IC50	Mechanism	Ref.
Quercetin	Flavonoid-flavonol	MTT assay	Breast cancer cells	MCF-7	0.5–100 μM; 48 h	50 μM/mL	↑apoptosis, Bax, caspase-3 ↓ Bcl-2	[15]
		MTT assay	Human Prostate cancer	LNCaP, DU-145, PC-3	5–160 μM; 24, 48, and 72 h	40 μM	↑apoptosis, MAPK, ↓Akt, and NF-κB; ↓ROS	[16]
Phytol	Diterpenes	MTT assay	Human lung cancer	A549	–; 48 h	16.97 ± 2.31 μM	↑apoptosis, ROS, TRAIL, FAS and TNF-α, caspase-9 and -3	[17]
Oleanolic acid	n-hexane fraction of methanol extract	MTT assay	Colon Cancer	HCT-116	0–120 μM; 72 h	29.8 μM	↑apoptosis, caspase-3 and PARP-1; ↑autophagy, Beclin-1, ATG5; ↑mitophagy, p62 and PINK1, ↓TOMM20; ↑cytotoxic activity, p38	[18]
Stigmasterol	Steroid	MTT assay	Human breast cancer	MCF-7	0–40 μM; 48 h	27.38 μM	↑apoptosis, Bax, p53, caspase-3 and −9 ↓ Bcl-2	[19]
			Human liver cancer	HepG2		25.80 μM		
		CCK8 assay, clone formation assay, and EdU proliferation assay	Gastric cancer cells	SGC-7901 and MGC-803	2.5–30 μM; 24, 48, and 72 h	20 μM	↓cell proliferation; ↑apoptosis, Bax, caspase-3 and PARP-1 ↓ p-Akt, Bcl-2; ↑autophagy, LC3-II, Beclin-1	[20]
		Migration assay	Ovarian Cancer Cell	ES2 and OV90	5, 10, and 20 μg/mL; 48 h	–	↑apoptosis, cytochrome c, BAK, BAX, caspase 3, and caspase; ↑Mitochondrial depolarization; ↑ROS generation; ↑Mitochondrial & cytosolic calcium levels ↓cell growth, pAKT, P70S6K, S6, ERK1/2, JNK, and P3 ↑subG1 phase	[21]
Linarin	Flavonoid-flavone	Cell cycle assay	Human Alveolar Basal Epithelial Cells	A549	0.1 to 10 μM; pretreatment 30 min, incubated 24 h	0.55 mg/mL	↑ cell cycle arrest in G1 phase; ↓ cell proliferation	[22]
		MTT assay	Human non-small-cell lung cancer	A549	5–500 μM; 24 h	282 μM	↓ NF-κB activation, MMP-9	[23]
		MTT assay, Eud analysis, flow cytometry assay	Glioma cells	A172 and U251	10–100 μM; 24 h	70 μM-80 μM	↑ apoptosis, p53, p21, Bax, Caspase-3, PARP-1, Survivin, p-Rb, Cyclin D; ↓ cell proliferation, ↓ NF-κB/p65	[24]

Pectolinarigenin	Flavonoids	MTT assay	Liver cancer cell	SK-HEP1	0–320 μM; 24 h	10 μM	↑autophagy, Beclin-1, LC3-I, and LC3-II; ↑cell cycle arrest in G2/M phase; ↓migration and invasive	[25]
		MTT assay	Gastric Cancer Cell	AGS MKN28	25, 50, 75, 100, 125, and 150 μM; 24 h	124.79 μM 96.88 μM	↑cell cycle arrest in G2/M phase, ↑apoptosis, caspase-3, PARP, ↓XIAP, ↑autophagy, LC3-II, ↓PI3K/AKT/mTOR pathway	[26]
Kaempferide	Flavonoids	SRB	Liver Cancer	HepG2	5, 10, and 20 μM; 24 h and 48 h	50 μM	↓lipid accumulation and oxidative stress, SREBP1, FAS, SCD-1, PPARγ, C/EBPβ, HO-1, Nrf2	[27]
Kaempferol	Flavonoid-flavonol	WST-1	Gastric Cancer Cells	GS, SNU-216, NCI-N87, SNU-638. NUGC-3 and MKN-7	25 μM, 50 μM, and 100 μM; 24 h	50 μM	↑ autophagy, LC3-I to LC3-II conversion ↓ p62	[28]
		WST-1	Head and Neck cancer	SCC-9, SCC-25, A-253	5 to 100 mm; 24, 48, and 72 h	SCC-9: 45.03 μM SCC-25: 49.9 μM A253: 47.49 μM	↑G2/M and S phases cell cycle arrest ↓ Bcl-2; ↑apoptosis, caspase-3, cytochrome c	[29]
Tricin	Flavonoids-flavone	MTT assay	Prostate Cancer	PC3	–; 48 h	117.5 ± 4.4 μM	↑metastasis, MiR-21; ↓cell proliferation	[30]
Casticin	Flavonoids	CCK-8	Nasopharyngeal carcinoma	S18	0, 2, 4, 8, 16 μM; 24, 48 or 72 h	8–16 μM	↑cell cycle arrest in G2/M phase, ↑apoptosis, Bax, ↓Bcl-2; ↓cell proliferation	[31]
		MTT assay	Lung cancer stem-like cells (LCSLCs)	A549	0.1, 1, 3, 10, and 30 μM; 48 h	0.4 μM	↓cell proliferation, ↓self-renewal and invasion, CD133, CD44, and ALDH1, MMP-9, pAKT	[32]
Diosmetin	Flavonoid	MTT assay	Human Colon Cancer	HCT-116	0–100 μg/mL; 24–72 h	11.92 ± 1.93 μM	↑cytotoxic effects towards HCT-116 CRC cells, ↑Fas, Bax, ↑cell cycle arrest in G2/M phase, ↓NF-ĸB translocation, ↓cell proliferation	[33]
		MTT assay	Prostate Cancer	LNCaP PC-3	0, 2.5, 5, 10, 20, 40, and 80 μM; 24, 48, and 72 h	40–80 μM	↑apoptosis, PARP, caspase-3, Bax, p27Kip1, FOXO3a, ↑cell cycle arrest in G0-G1 phase in LNCaP and PC-3 ↓X-linked inhibitor of apoptosis (XIAP), cyclin D1, Cdk2, Cdk4	[34]

(*Continued*)

Table 2 (Continued).

Bioactive Compound	Group	Method/ Assay	Type of Cancer	In vitro Model	Dose and duration of treatment	IC50	Mechanism	Ref.
Acacetin	Flavonoid-flavone	MTT assay	Oral squamous cell carcinoma	HSC-3	0, 6.25, 12.5, 25, 50, 100 mg/mL; 24h	25 μg/mL	↑apoptosis, MAPK, ↑sub-G1 cells and caspase-3 and PARP	[35]
		CCK-8 and colony formation assays	Osteosarcoma Cells	SJSA HOS	0, 15, 30, 45, and 60 μM; 72 h	28.91 μM 43.13 μM (24 h), 39.78 μM (48 h), and 28.72 μM (72 h)	↑apoptosis, caspase-3, − 8, and − 9, PARP, JNK signalling pathway ↓cell growth by activating the ROS/JNK signaling pathway	[36]
		CCK-8 assay	Gastric Cancer	MKN45	0, 3.125, 6.25, 12.5, 25, 50, 100 μmol/L; 24, 48, and 72 h	54.092 μM (24 h), 45.017 μM (48 h), and 36.961 μM (72 h)	↓cell proliferation, invasion and migration, ↓PI3K/Akt signalling and the phosphorylation levels of TGF-β1	[37]
				MGC803		48.357 μM (24 h), 33.449 μM (48 h), and 19.968 μM (72 h)		
		WST-1 assay	Glioblastoma cells	U87	0, 10, 20, 30, 50 μM; 24 h	43.73 ± 1.19 μM	↑apoptosis, Bax, caspase −9 and −3, and PARP, ↑cell cycle arrest in the G2/M, p21, ↓Cyclin-A1, Cyclin-B1, and Cdk-1	[38]
Luteolin	Flavonoid-flavone	MTS assay	Prostate Cancer	PC-3	3, 10, 30, 100 μM; 24 h	30 μM	↓proliferation and migration cells, ↓ANO1	[39]
		CCK8 assay	Human esophageal squamous cell carcinoma	EC1 KYSE450	0, 10, 20, 40, 80 μM; 48 and 72 h	20 μM 40 μM	↑apoptosis, caspase-3, p21 and p53; ↓cell proliferation	[40]
		Sulforhodamine B (SRB) Assay	Cholangiocarcinoma Cells	KKU-M156	1, 5, 10, 25, 50, 100 μM; 24 and 48 h	10.5 ± 5.0 μM (24 h), 8.7 ± 3.5 μM (48 h)	↑cell cycle arrest in G2/M phase, ↑apoptosis, ↓cell proliferation, ↓metastasic cells, Bcl-2 protein expression, JAK/STAT3 signaling pathway	[41]
		MTT assay	Lung cancer	A549	0–80 μM; 24 h	78.86 μM	↑cytotoxic effects, ↓migration and invasion, ↓FAK, Src, Rac1, Cdc42, and RhoA	[42]

Apigenin	Flavonoid-flavone	MTT assay	Colon Cancer	HCT-116 HT-29 DLD-1	0, 10, 20, 40, 60 μM; 24 h	27.9 ± 2.45 μM 48.2 ± 3.01 μM 89.5 ± 4.89 μM	↓cell proliferation, cell growth	[43]
		Sulforhodamine B (SRB) Assay	Malignant mesothelioma	MM-F1 (fibromatous)	12.5, 25, 50,100 μM; 48 and 72 h	56.31 ± 2.13 μM (48 h), 46.95 ± 1.69 μM (72 h)	↑cell cycle arrest in subG1 phase; ↑apoptosis, Bax/Bcl-2 ratio, p53, caspase-9, and -8, PARP-1; ↑ROS intracellular production; ↑DNA damage ↓cell proliferation, cell survival, pAKT, c-Jun expression and phosphorylation, and NF-κB nuclear translocation	[44]
				MM-B1 (biphasic)		64.23 ± 2.73 μM (48 h), 49.16 ± 2.52 μM (72 h)		
				H-Meso-1 (epithelioid)		46.44 ± 4.08 μM (48 h), 34.31 ± 1.55 μM (72 h)		
				The murine MM cell line #40a		60.39 ± 3.62 μM (48h), 56.82 ± 4.69 μM (72 h)		
		WST-1 assay	Glioblastoma cells	U-87	0–50 μM; 24 h	48.18 ± 1.37 μM	↑cell cycle arrest in G2/M phase; ↑apoptosis, caspase 8, Bid, Bax, caspase 9, caspase 3, and PARP; ↑ROS levels (2.5 fold)	[38]
		CCK-8 assay	Hepatocellular Carcinoma cells	HepG2	10, 20, and 40 μM 12 h; 20 μM 0, 6, 12, and 24 h.	>40 μM	↓ cell proliferation; ↑ apoptosis, Bax, caspase-3, PARP ↓ p-Akt, Bcl-2; ↑autophagy, LC3-II, Beclin-1	[45]
		WST-1 assay	Gastric Cancer Cells	AGS, SNU-216, NCI-N87, SNU-638, MKN-7, MKN-74	30, 50, 70, and 40 μM 12 h; 20 μM 0, 6, 12, and 24 h.	50 μM	↑autophagy, ATG5, LC3-II, phosphorylation of AMPK, ULK1 ↓ p-mTOR and p62	[46]

(*Continued*)

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Table 2 (Continued).

Bioactive Compound	Group	Method/ Assay	Type of Cancer	In vitro Model	Dose and duration of treatment	IC50	Mechanism	Ref.
Verbascoside	Phenylpropanoids	CCK-8 assay	Colorectal cancer cells	HCT-116 LoVo HT-29 SW620	12.5, 25, 50, 100, 150, or 200 μM; 72 h	63.51 μM 43.96 μM 66.68 μM 29.05 μM	↑apoptosis, HIPK2, p53, p-p53, Bax, ↓Bcl-2	[47]
		CCK-8 assay	Breast Cancer	MCF-7 MDA-MB-231 SKBR3	0, 20, 40, 80, 120, 160, 200, or 240 μM; 48 h	98.45 ± 7.63 μM 106.73 ± 9.34 μM 109.65 ± 9.62 μM	↑ apoptosis, Bax, caspase3/9, PARP1, Bcl-2, ↑ cell cycle arrest, CyclinB1, Cdc2	[48]
		MTT assay	Glioblastoma cells	U87	0, 10, 20, 40, 60, 80, 100 μM; 48 h	40 μM	↑apoptosis, SHP-1 expression ↓cell proliferation, migration, and invasion, phosphorylated (p)-STAT3 expression	[49]
β-amyrin	Triterpenoids	MTT assay	Colorectal carcinoma	Caco-2	20–80 μg/mL; 48 h	81 μg/mL	↑apoptosis, caspase-3; ↑cytotoxic activity	[50]
		MTT assay	Human liver cancer cells	HepG2	0, 3.12, 7.15, 12.5, 25, 50, 100 μM;	25 μM	↑apoptosis, Bax, p38 and JNK signalling pathways ↓Bcl-2	[51]
		MTT assay	Human prostate cancer cell line	PC3	–; 72 h	73.2 ± 1.02 μM	↑cytotoxic activities	[52]
			Human breast cancer cell line	Bcap-37		78.4 ± 0.93 μM		
			Human gastric cancer cell line	MGC-803		51.9 ± 0.87 μM		
Vitexin	Flavonoids	MTT assay	Chemo-resistant colorectal cancer cells	HCT-116(DR)	10, 25, 50 μM; 24 h	50 μM	↑apoptosis, Bax, cleaved caspase-3 and −9, BID	[53]
		CCK-8 assay	Human melanoma	A375 C8161	5, 10, 15, 20, and 25 μM; 48 h	16.85 μM 12.26 μM	↓migration and invasion, MMP-2, MMP-9, vimentin, Slug and Twist, ↑STAT3	[54]
α-amyrin	Triterpenoids	MTT assay	Human laryngeal cancer cell line	Hep2	10, 20, 40, 80,160, and 320 μmol/mL;	69.32 μmol/mL	↓cell proliferation, ↑cytotoxic effect	[55]

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β-Sitosterol	Steroid	Luminescent Cell Viability Assay	Hepatocellular cells	HepG2 Huh7	1.25–40 μg/mL; 48 h	6.85 ± 0.61 μg/mL 8.71 ± 0.21 μg/mL	↑apoptosis, caspase-3 and −9	[56]
		MTT assay	Human lung cancer cells	A549	0–200 μM; 72 h	24.7 μM	↑apoptosis, caspase-3 and −9, ROS, Bax, PARP; ↑cell cycle arrest in Sub-G1 phase	[57]
		MTT assay	Human colon adenocarcinoma	HT-29	0–100 μM; 24 and 48 h	79 μM	↑cell cycle arrest in G0/G1 phase, G2/M peak ↓ S peak; ↓proliferation ↑ LXR-α, LXR-β	[58]
Hexadecanoic acid/Palmitic acid	Long-chain fatty acids	MTT assay	Human colon adenocarcinoma	HT-29	5–320 μg/mL; 24 h	36.04 μg/mL	↑apoptosis, ↑ROS ↑cell cycle arrest in the G0/G1 phase	[59]
		MTT assay	Human breast cancer	MCF-7	0–256 μM; 24 h, 48 h, and 72 h	158.14 ± 0.27 (24 h), 118.87± 0.22 (48 h), and 94.64 ± 0.13 μM (72 h)	↑ apoptosis, caspase-3 and caspase-9, Bax, p53, ↓Bcl-2; ↓cell proliferation, NF-κB	[60]
β-caryophyllene	Sesquiterpene	MTT assay	Human pancreatic cancer	PANC-1	10–640 μM	27 μM	↓ cell proliferation ↑apoptosis, caspase-3, nuclear condensation and fragmentation ↓ motility and invasion ↓ colonization cells, PE	[61]
			Colorectal cancer	HCT-116 HT-29		19 μM 63 μM		
2α-hydroxyursolic acid/Corosolic acid	Triterpenoids	MTT assay	Human Breast Cancer	MCF-7 MDA-MB-231	5–50 μM; 24, 48, and 72 h	28.50 μM 20 μM	↓cell proliferation, NF-κB ↑apoptosis, caspase-8, 9, and −3	[62]
Maslinic acid	Triterpenoids	MTT assay	Murine melanoma cells	B16F10	0–212 μM; 24 h	42.3 μM	↓cell proliferation ↓ROS ↑SOD, GST and GPX	[63]
		Flow cytometry	Human cervix cancer	HeLa	0–45 μM; 48 h	35 μM	↑ DNA condensation, damage, fragmentation, p-ATMSer1981, p-ATRSer428, p53, p-p53Ser151, p-H2A.XSer139, BRCA1 and PARP ↓ NA-PK and MGMT	[64]

The terpenoid class is represented by compounds such as oleanolic acid and phytol which exhibit diverse anticancer mechanisms, including induction of apoptosis, autophagy, and modulation of mitochondrial function. Steroidal compounds such as stigmasterol and β-sitosterol play crucial roles in promoting apoptosis and disrupting cancer cell proliferation through mitochondrial depolarization and ROS generation. Phenylpropanoids, including verbascoside and pectolinarigenin, show remarkable potential in inhibiting cancer cell migration, invasion, and proliferation while promoting apoptosis and autophagy.[10] Additionally, long-chain fatty acids, particularly hexadecanoic acid, have been identified for their capability to enhance ROS levels, induce apoptosis, and arrest cell cycle progression in cancer cells.[66,67] A detailed overview of the anticancer mechanism of bioactive compounds extracted from Premna species focusing on their in vitro studies against various cancer types is presented in Table 2.

Induction of Cell Cycle Arrest

Dysregulation of the cell cycle is a hallmark of cancer, leading to unchecked proliferation. Compounds such as stigmasterol, linarin, kaempferol, and diosmetin derived from *Premna* species have been shown to arrest cancer cells at G0/G1, S, or G2/M phases, often accompanied by alterations in cyclin-dependent kinases and cell-cycle regulatory proteins. CDK inhibitors have emerged as promising therapeutic agents, forcing malignant cells into senescence or apoptosis by halting the cell cycle.[68] Cancer cells, like L1-LW6, are notably more susceptible to cell death caused by CDK inhibition compared to their normal counterparts.

Findings from various in vitro studies highlight the role of bioactive compounds in targeting specific phases of the cell cycle. For instance, stigmasterol-induced subG1 arrest in ES2 cells, signaling apoptosis.[21] Similarly, linarin disrupted the G1-to-S phase transition, resulting in G1 arrest in A549 cells.[22] Kaempferol −3-O-b-D-galactopyranoside exhibited dual effects by halting SCC-9 cells in the S-phase and arresting HT-29 and LNCaP cells in the G0/G1 phase, linked to the downregulation of cyclin D1, cyclin E, and CDKs.[29,59] Diosmetin also arrested the G1 and S phases in HCT-116 and PC-3 cells, respectively, by downregulating cyclin-dependent genes and increasing CDK inhibitors like p27Kip1, confirming its potential as a CDK inhibitor.[33,34]

Hexadecanoic acid and β-sitosterol significantly reduced the S and G2/M phases in HT-29 cells, suggesting these compounds arrest colon cancer cells in the G0/G1 phase.[58,59] Pectolinarigenin caused G2/M arrest in SK-HEP-1, AGS, and MKN28 cells through the downregulation of cyclin B1 and CDK1, along with the upregulation of p21 and p53.[25,26] Similarly, verbascoside-induced G2/M arrest in MCF-7 and MDA-MB-231 cells, which involved downregulating cyclin B1 and CDC2 and modulating the PI3K/AKT signaling pathway.[48]

Furthermore, casticin treatment-elevated p21 expression in S18 cells, further supporting its role in G2/M phase arrest.[31] Additionally, diosmetin-suppressed genes associated with mitotic division, such as ttk, pttg2, and mad2l2, while enhancing inhibitors of cyclin A and B, such as p21 and gadd45. This led to the inhibition of mitosis and accumulation of cells in the G2/M phase. These findings strongly suggest that compounds from the *P. serratifolia* group could effectively regulate the cell cycle and hold significant potential for developing anticancer therapies.

Inhibition of Proliferation

Cancer cells exhibit an abnormal ability to survive beyond their normal lifespan and proliferate uncontrollably, making the inhibition of proliferation a key strategy in cancer treatment. Targeting the high proliferative rate of cancer cells through specific interventions has proven effective in slowing or stopping cancer progression.[69] Several factors contribute to cancer cell proliferation, including epithelial-to-mesenchymal transition (EMT), dysregulated cell cycle proteins, and constitutive activation of signal transduction pathways such as Wnt, Notch, IGF, PI3K/Akt, NF-κB, and Hedgehog (Hh).[69] These factors promote uncontrolled cell proliferation, metastasis, and stem cell growth. Bioactive flavonoids like quercetin, linarin, casticin, and luteolin reduce cancer cell viability in in vitro assays, often by downregulating pro-survival signaling (eg, Akt, NF-κB) and upregulating cell cycle inhibitors (eg, p21, p27).

Genus *Premna* was reported rich in flavonoids such as quercetin, linarin, tricin, casticin, diosmetin, luteolin, acacetin, and apigenin. Flavonoids are known as key mediators of antiproliferative activity. Quercetin has been shown to inhibit prostate cancer (PCa) cell proliferation by modulating ROS production and interfering with MAPK, Akt, and NF-κB signaling pathways.[16] Similarly, linarin suppresses proliferation in human lung carcinoma (A549) cells by downregulating Akt

activation and upregulating cyclin-dependent kinase inhibitor p27Kip1.[22] In glioma cells, linarin exerts antiproliferative effects by upregulating p53 and downregulating NF-κB/p65, thereby inhibiting cell growth.[24]

Casticin effectively suppresses proliferation in lung cancer stem-like cells (LCSLCs) and nasopharyngeal carcinoma (NPC) cells by inducing G2/M arrest and selectively inhibiting PI3K pathways.[31,32] Diosmetin, a plant flavonoid, exerts antiproliferative effects on prostate and colon cancer cells by regulating proteins such as c-Myc, Bax, p27Kip1, and FOXO3a while inhibiting BMP and NF-κB pathways.[33,34]

Tricin reduces proliferation in prostate cancer cells by downregulating key proliferative markers, while luteolin exhibits antiproliferative activity through the suppression of migration and G2/M phase arrest, mediated by p21 and p53 regulation.[39,40] Additionally, luteolin inhibits metastasis in cholangiocarcinoma cells by regulating JAK/STAT3 signaling pathways.[41]

Beyond flavonoids, other classes of secondary metabolites, including triterpenoids, sesquiterpenes, phenylpropanoids, and fatty acids, also demonstrate antiproliferative effects. β-caryophyllene suppresses colorectal cancer cell growth by disrupting mitochondrial membrane potential and inducing apoptosis.[61] Hexadecanoid acid inhibits breast cancer cell proliferation by enhancing apoptosis-related proteins such as caspase-3, Bax, and p53 while downregulating anti-apoptotic protein Bcl-2.[60]

Stigmasterol inhibits gastric and ovarian cancer cell proliferation by targeting the PI3K and Akt/mTOR signaling cascades.[20,21] Verbascoside further demonstrates antiproliferative effects by inducing cell cycle arrest, apoptosis, and inhibiting glioblastoma cell migration and invasion through SHP-1 activation and STAT3 pathway inhibition.[48,49]

Inhibition of Migration, Invasion, and Metastasis

Metastasis accounts for a large percentage of cancer-related deaths. This process involves cancer cell migration, invasion, and eventual colonization of secondary tissues through intravasation into the blood or lymphatic systems.[70] The ability of cancer cells to migrate and invade tissues is a hallmark of metastatic progression and is largely driven by pathways such as STAT3 activation, which upregulates MMP-2 and promotes epithelial–mesenchymal transition (EMT).[71]

Flavonoids, a group of secondary metabolites abundant in *Premna* species, have demonstrated significant anti-metastatic properties in various in vitro cancer models. These effects are mediated by the regulation of signaling pathways and molecules associated with migration and invasion, including MMPs, TGF-β, and NF-κB.[72] Among the bioactive flavonoids in *P. serratifolia* leaves with demonstrated antimetastatic activity are linariin, pectolinaringenin, tricin, and casticin.

Linariin has been shown to significantly reduce IR-induced migration and invasion of A549 cells by downregulating MMP-9 expression and suppressing NF-κB activation through inhibition of NF-κB and IκB-α phosphorylation.[23] Pectolinaringenin inhibited the invasion and migration of human SK-HEP1 carcinoma cells, as evidenced by wound healing and transwell assays, further validating its anti-metastatic potential.[25] Tricin, through its ability to reduce MiR-21 overexpression, effectively decreased metastasis and chemoresistance in prostate cancer cells, indicating its potential in combating metastatic progression.[30] Similarly, casticin inhibited the invasion of sphere-forming cells (SFCs) derived from A549 lung cancer cells by reducing MMP-9 activity in a concentration-dependent manner.[32]

In addition to flavonoids, other secondary metabolites from *Premna* species have shown anti-metastatic effects. For instance, β-caryophyllene from *Aquilaria crassna* essential oil significantly reduced cell invasion in colorectal cancer, underscoring its potential as an anti-metastatic agent.[61] Similarly, verbascoside decreased glioblastoma cell migration and invasion by increasing SHP-1 expression, downregulating phosphorylated STAT3, and reducing MMP-2 and MMP-9 levels.[49]

Induction of Apoptosis

Apoptosis, or programmed cell death, is a tightly regulated process essential for maintaining cellular homeostasis, development, and the removal of damaged or unwanted cells. Unlike necrosis, apoptosis is a controlled and orderly mechanism that prevents inflammation and minimizes damage to surrounding tissues. Apoptosis occurs through two interconnected pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway, both of which involve the activation of caspase family proteases. Caspases serve as both initiators and executioners in the apoptotic process, breaking down cellular components to facilitate cell death.[73]

The intrinsic pathway is regulated by the BCL-2 protein family, which includes anti-apoptotic (eg, BCL-2, BCL-xL), pro-apoptotic (eg, BAX, BAK), and BH3-only proteins (eg, BIM, BID). Triggers for apoptosis increase BH3-only protein expression, leading to mitochondrial membrane disruption, cytochrome c release, and apoptosome formation, which activates caspase-9 and downstream executioner caspases-3 and -7. The extrinsic pathway involves death receptor ligands such as Fas-L and TNF binding to receptors, forming the death-inducing signaling complex (DISC) and activating caspases-8 and -10. These pathways converge to initiate apoptosis via cleavage of structural and regulatory proteins, aided by inhibitors such as XIAP and regulators like SMAC.[73,74]

Several bioactive compounds from the *Premna* genus (*P. serratifolia* group) have shown strong apoptotic effects in various cancer cell models. Quercetin, at a dose of 50 μM/mL, effectively activates the apoptotic signaling pathway in MCF-7 cells by increasing Bax and caspase-3 expression while downregulating Bcl-2 expression.[15] Similarly, stigmasterol enhances Bax expression, reduces Bcl-2 levels, and upregulates caspase-9 and -3 mRNA expression in a dose-dependent manner in ovarian and gastric cancer cells. It also increases mitochondrial depolarization and ROS generation in ES2 and OV90 cell line.[19,21]

Phytol induces apoptosis in A549 lung cancer cells via ROS-mediated activation of TRAIL, FAS, and TNF-α receptors and caspases-9 and -3, operating through both intrinsic and extrinsic pathways (Thakor, 2017). In colon cancer HCT116 cells, oleanolic acid activates cleaved caspase-3 and PARP-1, inducing apoptosis.[18] Linarin induces apoptosis in glioma cells by activating p53, Bax, and caspase-3 and cleaving PARP.[24] Pectolinaringenin decreases XIAP levels, activates caspase-3, and cleaves PARP in AGS and MKN28 gastric carcinoma cells.[26] Kaempferol −3-O-b-D-galactopyranoside induces apoptosis by triggering cytochrome c release and activating caspase-3 in head and neck cancer cells.[29]

Diosmetin activates apoptosis in colon and prostate cancer cells by upregulating Fas and Bax expression, releasing cytochrome c, and cleaving caspase cascades while inhibiting XIAP.[33,34] Acacetin induces apoptosis in oral squamous cell carcinoma, osteosarcoma, and glioblastoma through caspase activation, Bcl-2/Bax regulation, and mitochondrial depolarization.[35,36] Luteolin triggers apoptosis in cholangiocarcinoma cells by increasing p21 and p53 levels and activating caspase-3 and related pro-apoptotic proteins such as CYT-c and cPARP.[40]

Other flavonoids such as apigenin [ref] regulate apoptosis via the Bax/Bcl-2 ratio, p53 expression, and caspase-3 and PARP cleavage in colon and hepatocellular carcinoma cells.[45] Casticin increases Bax/Bcl-2 expression and decreases the Bcl-2/Bax ratio in nasopharyngeal carcinoma cells, promoting apoptosis.[31] Vitexin [ref] induces caspase-9 and −3 activation while upregulating pro-apoptotic proteins such as BID and Bax in colorectal cancer cells.[53] Verbascoside induces apoptosis by modulating apoptosis-related proteins, increasing pro-apoptotic factors such as HIPK2, p53, and cleaved PARP1 while reducing anti-apoptotic proteins like Bcl-2 and survivin in colorectal and glioblastoma cells.[48]

Additionally, β-sitosterol and hexadecenoic acid induce apoptosis by increasing ROS levels, modulating apoptotic signaling pathways, and activating caspase cascades in colon and breast cancer cells.[56,59] Furthermore, β-amyrin exerts its anticancer properties via apoptosis induction and activation of JNK and P38 signalling pathway.[50,51] β-caryophyllene disrupts mitochondrial membrane potential, promoting apoptosis via nuclear condensation and fragmentation.[61]

Effect on Oxidative Stress

Reactive oxygen species (ROS), known as partially reduced oxygen metabolites, exhibit potent oxidizing properties that, in high concentrations, can damage cellular components. However, at moderate levels, ROS play essential roles in cellular signaling and homeostasis. Elevated ROS levels in cancer cells can induce cell cycle arrest, senescence, and apoptosis through intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways. These effects are mediated by the activation of signaling cascades such as ASK1/JNK and ASK1/p38, which suppress anti-apoptotic factors and promote cell death. ROS also regulate apoptotic effectors, such as the Bcl-2 protein family and cytochrome c, leading to caspase activation, DNA fragmentation, and PARP cleavage, hallmark events in apoptosis.[75]

In cancer therapy, ROS can serve a dual role: while excessive ROS levels promote apoptosis in malignant cells, their suppression can protect normal cells from oxidative damage. Flavonoids, as polyphenolic compounds, play a critical role in modulating ROS levels and protecting cells against oxidative stress. Interestingly, flavonoids can also induce oxidative stress in cancer cells, triggering apoptosis. Several flavonoid compounds in the *Premna serratifolia* group, such as quercetin, kaempferide, acacetin, and apigenin, have demonstrated ROS-modulating properties in various cancer models.[27,38,44]

Quercetin demonstrated differential effects on ROS in prostate cancer cells, quenching ROS in LNCaP and PC-3 cells while elevating ROS levels in DU-145 cells, leading to the activation of Akt and NF-κB pathways and subsequent cancer cell death.[16] Acacetin induced ROS-mediated activation of the JNK/c-Jun signaling pathway in osteosarcoma cells, amplifying apoptotic signaling.[36] Similarly, apigenin induced a dose-dependent ROS increase in multiple myeloma (MM) and glioblastoma U87 cells, triggering apoptosis through caspase activation and DNA fragmentation.[38,44]

Steroidal compounds like stigmasterol and β-sitosterol also exhibit ROS-modulating activity. Stigmasterol induces ROS production in ES2 and OV90 ovarian cancer cells, contributing to mitochondrial depolarization and apoptosis.[21] β-Sitosterol triggers apoptosis in HT-29 colon cancer cells through ROS-mediated mitochondrial dysregulation, evidenced by caspase-3 and −9 activation, Bcl-2/Bax ratio alteration, and cytochrome c release.[57]

Other secondary metabolites from the *P. serratifolia* group also demonstrate ROS-related activities. Phytol induces ROS-mediated apoptosis in A549 lung cancer cells by activating TRAIL, FAS, and TNF-α receptors and caspase cascades.[17] Hexadecanoic acid significantly enhances ROS generation in HT-29 colon cancer cells, leading to apoptosis through mitochondrial pathways.[59]

Modulation of Autophagy

Autophagy, a cellular degradation process crucial for maintaining homeostasis, involves the sequestration and lysosomal degradation of damaged organelles and protein aggregates. This process, derived from the Greek words "auto" (self) and "phagia" (eating), is vital for cellular health and survival under stress conditions.[76] Autophagy is regulated by several upstream mechanisms, including the mTORC1 and AMPK pathways, which respond to cellular energy and nutrient levels. Under nutrient depletion, mTORC1 inhibition and AMPK activation promote autophagy initiation via phosphorylation of ULK1/2 and Atg13, enabling autophagosome formation. Dysfunctional regulation of autophagy has been implicated in cancer progression, where cancer cells bypass regulatory circuits to sustain high autophagic activity, promoting tumor survival.[77]

The role of natural products in modulating autophagy has been increasingly recognized in cancer therapy. Bioactive compounds from the *Premna serratifolia* group have demonstrated potent autophagy-regulating effects in various cancer models, either promoting autophagic cell death or inducing selective degradation of cellular components to inhibit tumor growth. Key autophagic markers such as LC3-I, LC3-II, and Beclin-1 are commonly evaluated to assess autophagy activation.

Oleanolic acid, a triterpenoid from leaf extract of *P. serratifollia* [ref oleanolic acid], induces autophagy by upregulating Beclin-1, ATG5, and LC3B expression, thereby promoting autophagosome formation. It also facilitates mitophagy by increasing p62 and PTEN-induced kinase 1 expression while reducing TOMM20 levels, which contributes to oxidative stress mitigation and cancer inhibition.[18] Apigenin enhances autophagy in HepG2 cells by increasing LC3-II levels and GFP-LC3 puncta, alongside upregulating ATG5 and AMPK phosphorylation and downregulating p-mTOR and p62 in gastric cancer cells, leading to autophagic cell death.[45,46]

Kaempferol-3-O-b-D-galactopyranoside exhibits similar effects by increasing LC3-II expression and decreasing p62 levels in gastric cancer cells. It activates the IRE1-JNK-CHOP signaling pathway, inducing an ER stress response and autophagic cell death.[28] Pectolinaringenin and stigmasterol modulate autophagy by inhibiting the PI3K/AKT/mTOR signaling pathway, reducing p-4EBP1, p-p70S6K, and p-eIF4E levels. These effects are associated with increased Beclin-1, LC3-I, and LC3-II expression, alongside the formation of autophagosomes and acidic vesicular organelles, as observed via electron microscopy.[20,25,26]

Table 3 summarizes the diverse anticancer mechanisms of bioactive compounds identified in the *Premna serratifolia* group, categorized into six major pathways. Cell cycle arrest is mediated by compounds like β-sitosterol, casticin, diosmetin, kaempferol-3-O-b-D-galactopyranoside, and linarin, which target cyclin-dependent kinases, leading to disruption in the G1, S, or G2/M phases. Induced apoptosis, a critical pathway for eliminating cancer cells, involves compounds such as apigenin, diosmetin, and stigmasterol. These compounds trigger both intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways through the activation of caspases and modulation of pro- and anti-apoptotic proteins. The modulation of oxidative stress plays a dual role in cancer treatment, where compounds like quercetin and acacetin either mitigate oxidative damage in normal cells or induce excessive ROS production in cancer

Table 3 Mechanism-Based Classification Table for the Bioactive Compounds Derived from Premna Serratifolia Group

Anticancer Mechanism	Bioactive Compounds
Induction of Apoptosis	Quercetin, Phytol, Oleanolic acid, Stigmasterol, Linarin, Pectolinarigenin, Kaempferol, Casticin, Diosmetin, Acacetin, Luteolin, Apigenin, Verbascoside, β-Amyrin, Vitexin, β-Sitosterol, Palmitic acid, β-Caryophyllene, 2α-Hydroxyursolic acid (Corosolic acid), Maslinic acid
Inhibition of Cell Proliferation	Quercetin, Stigmasterol, Linarin, Pectolinarigenin, Kaempferol, Tricin, Casticin, Diosmetin, Acacetin, Luteolin, Apigenin, Verbascoside, β-Amyrin, α-Amyrin, β-Sitosterol, Palmitic acid, β-Caryophyllene, 2α-Hydroxyursolic acid (Corosolic acid), Maslinic acid
Modulation of Oxidative Stress	Quercetin, Phytol, Kaempferide, Acacetin, Apigenin, Maslinic acid, Palmitic acid, β-Sitosterol
Induction of Autophagy	Oleanolic acid, Stigmasterol, Pectolinarigenin, Kaempferol, Apigenin, Verbascoside
Suppression of Migration/ Invasion/Metastasis	Linarin, Pectolinarigenin, Tricin, Casticin, Acacetin, Luteolin, Apigenin, Verbascoside, β-Caryophyllene, Vitexin
Cell-Cycle Arrest	Linarin, Pectolinarigenin, Kaempferol, Casticin, Diosmetin, Acacetin, Luteolin, Apigenin, Verbascoside, β-Sitosterol, Palmitic acid

cells to promote apoptosis. Autophagy regulation, a process that facilitates cellular homeostasis, is influenced by compounds such as kaempferol-3-O-b-D-galactopyranoside, oleanolic acid, and pectolinagerin, which target mTOR and AMPK signaling to promote autophagic cell death in cancer cells. Compounds such as β-caryophyllene, tricin, and stigmasterol inhibit migration, invasion, and metastasis by suppressing key signaling pathways like NF-κB and matrix metalloproteinases (MMPs), thereby reducing the metastatic potential of cancer cells. Finally, the inhibition of cell proliferation is achieved by compounds like diosmetin, verbascoside, and luteolin, which regulate oncogenic pathways such as PI3K/AKT and Wnt. Collectively, the *Premna sp*. represents a promising avenue toward the development of innovative, targeted, and less toxic cancer therapies that meet the goals of modern oncology.

However, although the bioactive compounds from the Premna serratifolia group exhibit promising anticancer effects in vitro, their clinical translation requires careful assessment of pharmacokinetics and toxicology in in vivo models. Key parameters such as absorption, distribution, metabolism, excretion (ADME), and bioavailability strongly influence therapeutic efficacy. Many flavonoids, terpenoids, and steroids, for instance, undergo extensive metabolic modifications (eg, glucuronidation, sulfation) that can attenuate or alter their cytotoxic potential. Moreover, limited water solubility and rapid clearance often hamper systemic availability in animal models. To date, only a few studies have addressed these aspects in detail for Premna species. Future research should include well-designed in vivo experiments to validate anticancer efficacy and examine optimal delivery methods, pharmacokinetic profiles, and potential toxicity. Ultimately, incorporating both metabolic and bioavailability investigations will more definitively position these compounds for clinical application.

Limitations of the Study

Although the present review provides comprehensive insights into the anticancer potential of bioactive compounds from *Premna serratifolia, P. odorata*, and *P. tomentosa*, several limitations need to be acknowledged. First, most of the evidence presented relies on in vitro studies, and there is a notable scarcity of robust in vivo data and clinical studies to confirm efficacy, safety, pharmacokinetics, and therapeutic relevance in more complex biological systems. Secondly, variability in the experimental design—such as differences in cell lines, experimental conditions, concentrations, and methodologies—may introduce inconsistencies or biases into the interpretation of results. Furthermore, the pharmacokinetic properties and bioavailability of identified compounds remain largely unexplored, posing challenges for translating laboratory findings into clinical applications. Thus, future research should incorporate standardized methods, systematic evaluation of pharmacokinetics and toxicity in animal models, and eventually clinical validation to substantiate the therapeutic utility of these promising natural compounds.

Conclusion

This review highlights the in vitro anticancer potential of bioactive compounds from the *Premna serratifolia* group, encompassing *P. serratifolia, P. odorata*, and *P. tomentosa*. Flavonoids, terpenoids, and steroids present in these species

exhibit varied mechanisms of action—inducing cell cycle arrest, promoting apoptosis, inhibiting metastasis, modulating oxidative stress, and regulating autophagy—making them valuable prospects for the development of novel plant-based anticancer drugs. Compounds such as quercetin, kaempferol, and stigmasterol stand out for their ability to target multiple pathways in tumorigenesis. Nevertheless, the current evidence is predominantly from in vitro research, and thorough in vivo and clinical evaluations remain necessary to confirm therapeutic utility. By investigating pharmacokinetics, toxicity, and long-term safety, future studies can help realize the chemopreventive and therapeutic potential of these *Premna* species, potentially overcoming drug resistance and minimizing side effects in conventional cancer treatments.

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