Multi-target Anticancer Mechanisms of Spathodea campanulata Phytoconstituents in Ovarian Cancer: A Comprehensive Review

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***Abstract*—Ovarian cancer remains one of the most aggressive gynaecological malignancies and is a leading cause of cancer-related mortality among women worldwide. Despite advances in surgical interventions and platinum-based chemotherapy, the prognosis of advanced-stage ovarian cancer remains poor due to late diagnosis, frequent recurrence, and the emergence of chemoresistance. Consequently, there is growing interest in identifying novel therapeutic agents with improved efficacy, reduced toxicity, and the ability to target multiple molecular pathways simultaneously.**

Medicinal plants have gained considerable attention as valuable sources of bioactive compounds with diverse pharmacological activities. Spathodea campanulata (African tulip tree), belonging to the family Bignoniaceae, possesses a wide range of phytoconstituents, including flavonoids, phenolic compounds, triterpenoids, and phytosterols, which have demonstrated significant antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Major phytochemicals such as quercetin, kaempferol, and β-sitosterol exhibit potent anticancer activity through modulation of multiple cellular and molecular targets.

This review comprehensively summarizes the phytochemical composition of Spathodea campanulata and critically discusses the molecular mechanisms underlying its anticancer potential against ovarian cancer. The reported mechanisms include induction of mitochondrial-mediated apoptosis, regulation of oxidative stress, inhibition of tumour cell proliferation, cell cycle arrest, suppression of angiogenesis, and modulation of key signalling pathways including PI3K/Akt, MAPK, p53, and VEGF. Furthermore, available in vitro and in silico evidence supporting the therapeutic potential of these phytoconstituents is discussed, together with current challenges and future perspectives for drug development.

Overall, the collective evidence indicates that Spathodea campanulata represents a promising natural source of multi-target anticancer agents. Further pharmacological investigations, animal studies, and well-designed clinical trials are required to validate its therapeutic efficacy and facilitate its translation into novel phytopharmaceutical interventions for ovarian cancer management.

***Index Terms*—Spathodea campanulata, Ovarian cancer, Phytochemicals, Multi-target therapy, Apoptosis, Molecular docking, PI3K/Akt signalling, VEGF, Anticancer activity, Natural products**

I. Introduction

Ovarian cancer is one of the most aggressive and life-threatening gynecological malignancies, accounting for a substantial proportion of cancer-related mortality among women worldwide[1]. According to the Global Cancer Observatory (GLOBOCAN) 2022 estimates, ovarian cancer remains among the leading causes of cancer-associated deaths in women because of its asymptomatic progression, advanced-stage diagnosis, and limited therapeutic success. The disease is characterized by remarkable biological heterogeneity, high metastatic potential, and the frequent development of resistance to conventional chemotherapy, all of which contribute to poor long-term survival rates [2].

Epithelial ovarian cancer (EOC) represents nearly 90% of all ovarian malignancies and is further classified into high-grade serous, endometrioid, mucinous, and clear-cell carcinomas, each possessing distinct molecular and pathological characteristics. Among these subtypes, high-grade serous ovarian carcinoma is the most prevalent and is associated with mutations in BRCA1, BRCA2, TP53, and other genes involved in genomic instability. Unfortunately, more than 70% of patients are diagnosed at advanced stages (FIGO stage III or IV), when tumour dissemination has already occurred within the peritoneal cavity, significantly reducing the effectiveness of therapeutic interventions [3].

Current management strategies primarily involve cytoreductive surgery followed by platinum-based chemotherapy, frequently combined with taxane derivatives. Recent advances, including targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors, angiogenesis inhibitors, and immune checkpoint inhibitors, have improved clinical outcomes in selected patient populations. Nevertheless, treatment-associated toxicity, tumour recurrence, multidrug resistance, and limited responsiveness to targeted therapies remain major clinical challenges [4]. Therefore, identifying safer and more effective therapeutic agents capable of simultaneously modulating multiple oncogenic pathways has become an important objective in ovarian cancer research.

Natural products have historically played a pivotal role in anticancer drug discovery, serving as sources for several clinically approved chemotherapeutic agents. Medicinal plants are particularly attractive because they contain structurally diverse phytochemicals capable of interacting with multiple molecular targets while generally exhibiting lower toxicity than many synthetic drugs [5]. Bioactive plant-derived compounds possess antioxidant, anti-inflammatory, antiproliferative, antiangiogenic, and pro-apoptotic properties, making them promising candidates for the development of novel anticancer therapies.

Spathodea campanulata P. Beauv., commonly known as the African tulip tree, belongs to the family Bignoniaceae and is widely distributed throughout tropical and subtropical regions. Traditionally, different parts of the plant—including the bark, leaves, flowers, and stem—have been used in folk medicine for the treatment of inflammation, microbial infections, wounds, gastrointestinal disorders, and several other ailments [6]. Phytochemical investigations have demonstrated that the plant contains numerous biologically active constituents, including flavonoids, phenolic compounds, triterpenoids, phytosterols, iridoids, and glycosides, many of which exhibit potent pharmacological activities.

Among these phytochemicals, quercetin, kaempferol, β-sitosterol, ursolic acid, and oleanolic acid have attracted considerable scientific attention because of their ability to regulate multiple signalling pathways involved in carcinogenesis[7]. These compounds have been reported to induce apoptosis, arrest cell cycle progression, suppress angiogenesis, inhibit oxidative stress-mediated tumour progression, and modulate critical intracellular signalling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR), and tumour protein p53 (TP53). Their multi-target mode of action suggests significant therapeutic potential against ovarian cancer and other malignancies [8].
In recent years, advances in computational biology have further accelerated natural product research. Molecular docking, molecular dynamics simulations, and other in silico approaches have enabled researchers to predict the binding affinity and interaction profiles of phytochemicals with cancer-associated molecular targets before experimental validation. Simultaneously, in vitro investigations using ovarian cancer cell lines, including A2780, SKOV3, and OVCAR-3, have demonstrated the cytotoxic and antiproliferative activities of several plant-derived compounds, thereby supporting their potential application in anticancer drug development [9].

Although increasing evidence supports the pharmacological potential of Spathodea campanulata, comprehensive reviews specifically focusing on its multi-target anticancer mechanisms in ovarian cancer remain limited. Integrating phytochemical evidence with molecular pharmacology, in vitro findings, and in

silico investigations is therefore essential for understanding its therapeutic significance and identifying future research opportunities.

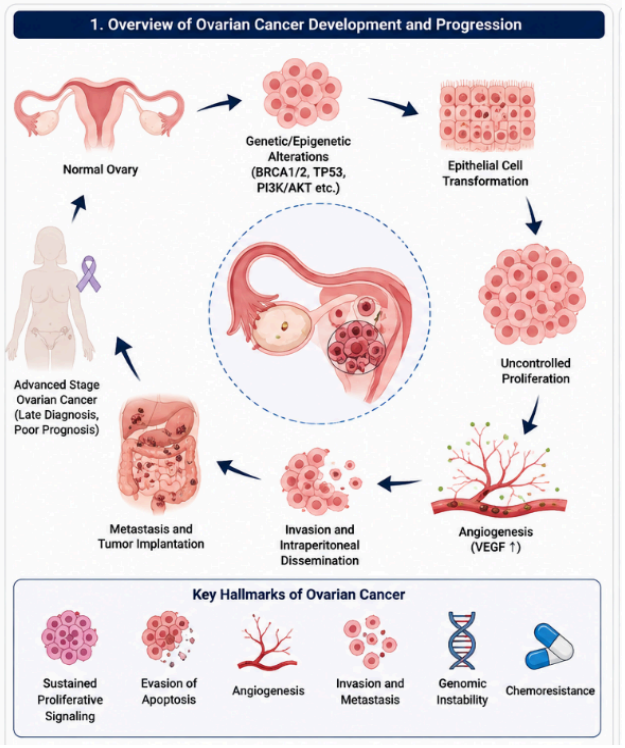

Figure 1. Overview of Ovarian Cancer Development and Progression

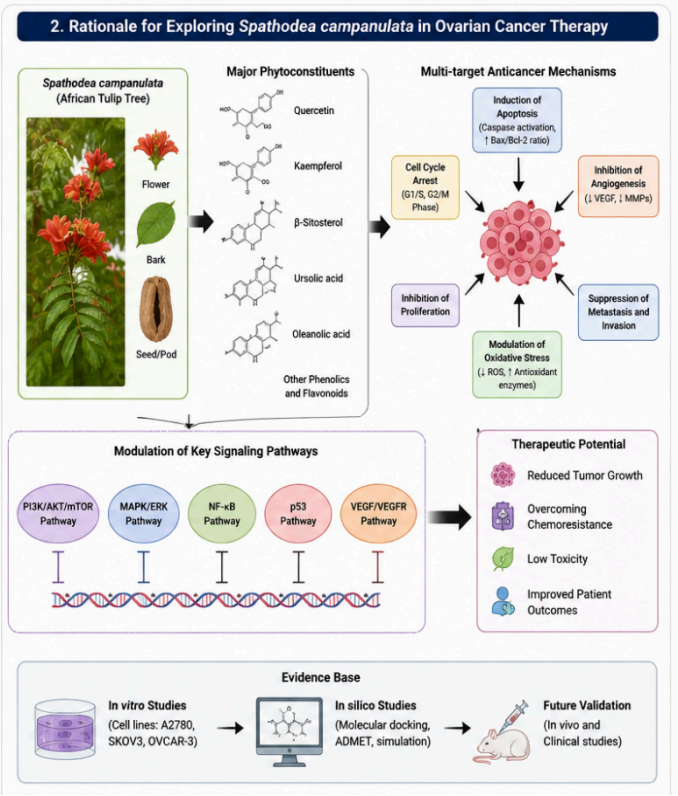

Figure 2. Rationale for Exploring Spathodea campanulata as a Multi-target Anticancer Agent in Ovarian Cancer

Aim of the Review

The present review aims to comprehensively summarize the phytochemical composition of Spathodea campanulata and critically evaluate its multi-target anticancer mechanisms against ovarian cancer. Particular emphasis is placed on apoptosis induction, regulation of oxidative stress, inhibition of tumour proliferation and angiogenesis, modulation of key signalling pathways, and the contribution of in vitro and in silico studies. Furthermore, this review highlights existing research gaps and discusses future perspectives for translating these phytoconstituents into effective phytopharmaceutical interventions for ovarian cancer management.

II. Overview of Ovarian Cancer Biology

Ovarian cancer is a heterogeneous malignancy comprising several histopathological subtypes that differ in their molecular characteristics, biological behaviour, and clinical outcomes. Among these, epithelial ovarian cancer (EOC) accounts for approximately 90% of all ovarian malignancies and remains the most frequently diagnosed subtype. Based on histological and molecular features, EOC is further classified into high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, mucinous carcinoma, and clear-cell carcinoma[10]. High-grade serous ovarian carcinoma (HGSOC) is the predominant subtype and is responsible for the majority of ovarian cancer-related deaths due to its aggressive nature, extensive genomic instability, and propensity for early metastasis.

The pathogenesis of ovarian cancer is a multistep process involving the accumulation of genetic and epigenetic alterations that disrupt normal cellular homeostasis. Mutations in tumour suppressor genes such as **TP53**, **BRCA1**, and **BRCA2**, together with aberrant activation of oncogenic pathways including **PI3K/Akt**, **MAPK**, and **NF-κB**, promote uncontrolled cellular proliferation, resistance to apoptosis, enhanced angiogenesis, and metastatic dissemination [11]. These molecular abnormalities enable tumour cells to evade growth-regulatory mechanisms and acquire characteristics that favour disease progression.

Several environmental, hormonal, and genetic factors contribute to ovarian carcinogenesis. Increasing age, family history of ovarian or breast cancer, inherited BRCA1/BRCA2 mutations, Lynch syndrome, infertility, endometriosis, obesity, and prolonged exposure to ovulation are well-established risk factors [12]. In contrast, the use of oral contraceptives, pregnancy, breastfeeding, and prophylactic salpingo-oophorectomy in genetically predisposed women have been associated with a reduced risk of disease development.

One of the major challenges in ovarian cancer management is the absence of specific clinical manifestations during the early stages of disease. Initial symptoms are often vague and nonspecific, including abdominal discomfort, pelvic pain, bloating, early satiety, urinary frequency, and gastrointestinal disturbances. Consequently, nearly 70% of patients are diagnosed only after the disease has spread beyond the ovaries, resulting in poor prognosis and reduced five-year survival rates [13].

Tumour progression is driven by several interconnected biological processes collectively referred to as the hallmarks of cancer. Ovarian cancer cells exhibit sustained proliferative signalling, evasion of programmed cell death, replicative immortality, genomic instability, induction of angiogenesis, activation of invasion and metastasis, immune evasion, and metabolic reprogramming [14]. These hallmarks are regulated by a complex network of intracellular signalling pathways that coordinate tumour growth and survival.

Among these pathways, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signalling pathway plays a pivotal role in promoting cell survival, proliferation, metabolism, and resistance to apoptosis [15]. Hyperactivation of this pathway has been observed in a significant proportion of ovarian cancers and is closely associated with poor clinical outcomes. Similarly, the mitogen-activated protein kinase (MAPK) pathway regulates cellular differentiation, proliferation, and migration, whereas activation of nuclear factor-kappa B (NF-κB) promotes chronic inflammation and tumour progression. Dysregulation of the tumour suppressor protein p53 impairs DNA repair mechanisms and apoptosis, thereby facilitating genomic instability and malignant transformation [16].

Angiogenesis represents another critical event in ovarian cancer progression. Rapidly proliferating tumour cells require a continuous supply of oxygen and nutrients, which is achieved through the formation of new blood vessels. This process is primarily mediated by vascular endothelial growth factor (VEGF), one of the most important angiogenic mediators in ovarian cancer [17]. Elevated VEGF expression is associated with increased tumour vascularization, ascites formation, metastatic dissemination, and poor patient prognosis.

Metastatic dissemination of ovarian cancer differs from that of many other solid tumours. Instead of spreading primarily through the bloodstream, ovarian cancer cells frequently detach from the primary tumour and disseminate throughout the peritoneal cavity via peritoneal fluid. These exfoliated tumour cells subsequently adhere to mesothelial surfaces, invade surrounding tissues, and establish secondary tumour nodules on the omentum, bowel, liver capsule, and diaphragm. This unique pattern of transcoelomic metastasis contributes significantly to disease recurrence and treatment failure [18].

Although cytoreductive surgery combined with platinum- and taxane-based chemotherapy remains the current standard of care, the development of chemoresistance continues to be a major obstacle in successful treatment. Several mechanisms have been implicated in drug resistance, including increased drug efflux mediated by ATP-binding cassette transporters, enhanced DNA repair capacity, epithelial-mesenchymal transition (EMT), alterations in apoptotic signalling, cancer stem cell survival, and activation of pro-survival pathways such as PI3K/Akt and MAPK. These limitations highlight the urgent need for alternative therapeutic strategies capable of simultaneously targeting multiple molecular pathways involved in ovarian carcinogenesis [19].

Recent advances in natural product research have demonstrated that plant-derived phytochemicals possess the ability to regulate numerous oncogenic signalling pathways simultaneously. Such multi-target therapeutic approaches may overcome several limitations associated with conventional chemotherapy, thereby reducing drug resistance while improving therapeutic efficacy. Consequently, medicinal plants such as *Spathodea campanulata* have attracted increasing attention as potential sources of novel bioactive compounds for ovarian cancer prevention and treatment [20].

Histological subtype	Approximate frequency	Key molecular alterations	Clinical characteristics
High-grade serous carcinoma	~70%	TP53, BRCA1/2	Highly aggressive; advanced-stage presentation
Low-grade serous carcinoma	<10%	KRAS, BRAF	Slow-growing; relatively chemo resistant
Endometrioid carcinoma	~10%	PTEN, PIK3CA	Frequently associated with endometriosis
Clear-cell carcinoma	5–10%	ARID1A, PIK3CA	Resistant to conventional chemotherapy
Mucinous carcinoma	3–5%	KRAS	Rare; often diagnosed at an early stage

Table 1. Histological classification of epithelial ovarian cancer and their major molecular characteristics.

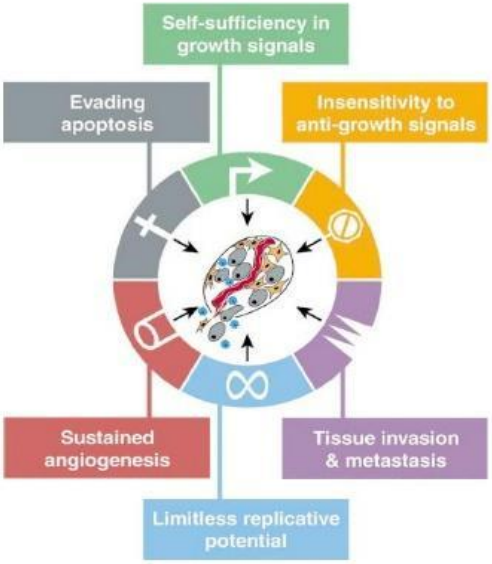

Figure 3 Hallmarks of Ovarian Cancer

III. Botanical profile of Spathodea campanulate

Spathodea campanulata P. Beauv., commonly known as the African tulip tree, is a tropical flowering plant belonging to the family **Bignoniaceae**. The species is native to tropical Africa but has been extensively introduced into Asia, South America, and other tropical and subtropical regions as an ornamental tree because of its striking scarlet-orange flowers and rapid growth [21]. Besides its ornamental importance, *S. campanulata* has gained considerable attention in recent years owing to its rich phytochemical composition and diverse pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, wound-healing, and anticancer properties.

The tree is medium to large in size, typically attaining a height of 15–25 m with a broad, dense canopy. The bark is greyish-brown and rough, while the leaves are opposite, imparipinnate, and dark green in colour. The flowers are large, bell-shaped, and bright orange to scarlet-red, arranged in terminal clusters, making the plant easily distinguishable from other members of the family [22]. The fruit is an elongated woody capsule containing numerous winged seeds that facilitate wind-mediated dispersal.

Traditionally, various parts of the plant have been utilized in African and Asian folk medicine for the management of several ailments. The bark has been employed to treat malaria, dysentery, gastrointestinal disorders, and microbial infections, whereas leaf extracts have been used for wound healing, inflammation, skin diseases, and diabetes [23]. Flower extracts possess antioxidant and antimicrobial activities, while different plant parts have also demonstrated analgesic and anti-ulcer effects in experimental studies [7,19]. These traditional applications provide valuable ethnopharmacological evidence supporting the medicinal significance of *S. campanulata*.

Phytochemical investigations have revealed that *S. campanulata* is a rich reservoir of secondary metabolites. Major classes of bioactive compounds identified from different plant parts include flavonoids, phenolic compounds, triterpenoids, phytosterols, iridoids, saponins, tannins, alkaloids, glycosides, and polysaccharides [24]. Among these, flavonoids such as quercetin and kaempferol, together with β-sitosterol and other triterpenoids, have attracted significant scientific interest because of their potent antioxidant and anticancer properties. These phytoconstituents are capable of modulating multiple molecular pathways involved in carcinogenesis, thereby exhibiting considerable therapeutic potential.

Several pharmacological studies have demonstrated that extracts obtained from the leaves, bark, flowers, and stem bark of *S. campanulata* exhibit remarkable biological activities. These include free radical

scavenging activity, inhibition of inflammatory mediators, antimicrobial effects against pathogenic microorganisms, hepatoprotective activity, antidiabetic effects, and cytotoxic activity against various cancer cell lines [25]. The observed pharmacological activities are primarily attributed to the synergistic interaction of multiple phytoconstituents rather than the action of a single bioactive compound.

In recent years, increasing attention has been directed toward investigating the anticancer potential of *S. campanulata*. Experimental evidence suggests that its phytochemicals interfere with several hallmarks of cancer by inducing apoptosis, suppressing tumour cell proliferation, inhibiting angiogenesis, modulating oxidative stress, and regulating intracellular signalling pathways such as PI3K/Akt, MAPK, NF-κB, and p53 [26]. These multi-target actions make *S. campanulata* an attractive candidate for the development of novel phytopharmaceuticals against ovarian cancer and other malignancies.

Collectively, the botanical characteristics, ethnomedicinal importance, phytochemical diversity, and broad spectrum of pharmacological activities establish *S. campanulata* as a promising medicinal plant for further investigation in anticancer drug discovery [27]. A comprehensive understanding of its phytoconstituents and molecular mechanisms is therefore essential for developing effective plant-derived therapeutics targeting ovarian cancer.

Taxonomic Rank	**Classification**
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Lamiales
Family	Bignoniaceae
Genus	*Spathodea*
Species	*Spathodea campanulata* P. Beauv.
Common name	African tulip tree
Native origin	Tropical Africa
Distribution	Tropical and subtropical regions worldwide

Table 2. Botanical classification of *Spathodea campanulata* P. Beauv.

Plant Part	**Traditional Uses**	**Reported Pharmacological Activities**
Bark	Malaria, dysentery, infections	Antimicrobial, anti-inflammatory
Leaves	Wound healing, diabetes	Antioxidant, antidiabetic
Flowers	Skin disorders	Antioxidant, antimicrobial
Stem bark	Pain and inflammation	Analgesic, anti-inflammatory
Whole plant	General folk medicine	Cytotoxic and pharmacological potential

Table 3. Ethnomedicinal uses and pharmacological activities of different parts of *Spathodea campanulata*.

Figure 4. Botanical characteristics of *Spathodea campanulata* showing the whole tree, leaves, flowers, bark, fruits, and seeds

IV. Phytochemical Constituents of Spathodea campanulate

The therapeutic potential of *Spathodea campanulata* is primarily attributed to its rich diversity of secondary metabolites, which collectively contribute to its pharmacological activities. Phytochemical investigations have demonstrated that different parts of the plant, including the leaves, bark, flowers, stem bark, and roots, contain numerous bioactive compounds such as flavonoids, phenolic compounds, triterpenoids, phytosterols, iridoids, alkaloids, tannins, saponins, glycosides, and polysaccharides [28]. These phytoconstituents possess antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, and anticancer properties, making *S. campanulata* a valuable source of natural therapeutic agents.

The anticancer activity of *S. campanulata* arises from the synergistic interaction of multiple phytochemicals rather than the action of a single constituent. These compounds target several hallmarks of cancer by regulating apoptosis, cell cycle progression, oxidative stress, angiogenesis, metastasis, and intracellular signalling pathways. Among the identified phytochemicals, flavonoids, triterpenoids, phenolic compounds, and phytosterols have received the greatest scientific attention because of their potent biological activities [29,30].

A. Flavonoids

Flavonoids constitute one of the most abundant classes of phytochemicals present in *S. campanulata*. Quercetin and kaempferol are the principal flavonoids responsible for many of the plant's anticancer effects. Quercetin exhibits strong antioxidant activity while simultaneously inducing oxidative stress selectively in cancer cells [31]. It promotes mitochondrial dysfunction, activates caspase-dependent apoptosis, suppresses anti-apoptotic proteins such as Bcl-2, and increases the expression of pro-apoptotic proteins including Bax. Furthermore, quercetin inhibits PI3K/Akt, MAPK, and NF-κB signalling pathways, thereby reducing tumour cell proliferation, migration, and invasion [32].

Kaempferol is another important flavonoid that demonstrates significant anticancer activity through multiple molecular mechanisms. It induces G2/M and G1/S cell cycle arrest, promotes reactive oxygen species (ROS)-mediated apoptosis, suppresses angiogenesis by downregulating VEGF expression, and activates p53-dependent signalling pathways. In addition, kaempferol inhibits epithelial-mesenchymal transition (EMT), thereby reducing metastatic potential in various human cancers [33].

B. Phenolic Compounds

Phenolic compounds represent another major group of phytoconstituents in *S. campanulata*. These compounds exhibit remarkable antioxidant properties by scavenging free radicals and protecting cellular components from oxidative damage. In cancer cells, however, phenolics may induce excessive ROS accumulation, leading to mitochondrial dysfunction and apoptosis. Several studies have demonstrated that

phenolic compounds suppress inflammatory mediators including cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and NF-κB signalling, thereby reducing tumour-promoting inflammation and cellular proliferation [34,35].

C. Triterpenoids

Triterpenoids are naturally occurring pentacyclic compounds that contribute substantially to the pharmacological properties of *S. campanulata*. Ursolic acid and oleanolic acid are among the most extensively investigated triterpenoids due to their broad-spectrum anticancer activity. These compounds inhibit tumour cell growth by inducing mitochondrial-mediated apoptosis, suppressing inflammatory cytokines, regulating oxidative stress, and inhibiting matrix metalloproteinases involved in tumour invasion and metastasis [36]. Moreover, triterpenoids interfere with multiple signalling pathways, including PI3K/Akt, MAPK, STAT3, and mTOR, thereby limiting tumour progression and improving therapeutic responsiveness.

D. Phytosterols

β-Sitosterol is the predominant phytosterol identified in *S. campanulata* and has been widely investigated for its anticancer properties. This compound integrates into cellular membranes, alters membrane fluidity, and activates intrinsic apoptotic pathways through mitochondrial cytochrome c release and caspase activation. β-Sitosterol has also been shown to suppress tumour angiogenesis by reducing VEGF expression, inhibit cell proliferation through cell cycle arrest, and decrease metastatic potential by regulating epithelial-mesenchymal transition [37]. Additionally, β-sitosterol exhibits anti-inflammatory and immunomodulatory activities that may further contribute to its anticancer effects.

E. Synergistic Anticancer Potential of Phytochemicals

Unlike conventional chemotherapeutic agents that frequently target a single molecular pathway, the phytochemicals present in *S. campanulata* exhibit a multi-target mode of action. The combined activity of flavonoids, phenolics, triterpenoids, and phytosterols enables simultaneous regulation of apoptosis, oxidative stress, angiogenesis, inflammation, metastasis, and intracellular signalling pathways [38]. Such synergistic interactions may improve therapeutic efficacy, minimise drug resistance, and reduce adverse effects associated with conventional chemotherapy. Consequently, the phytochemical complexity of *S. campanulata* provides a strong scientific basis for its development as a potential phytopharmaceutical against ovarian cancer.

Overall, the phytochemical profile of *S. campanulata* demonstrates that the plant is not merely a source of individual bioactive molecules but rather a reservoir of structurally diverse compounds capable of collectively targeting multiple hallmarks of cancer [39]. This multi-component nature forms the foundation for the anticancer mechanisms discussed in the subsequent sections of this review.

Phytochemical	Chemical Class	Major Biological Activity	Principal Molecular Targets
Quercetin	Flavonoid	Antioxidant, apoptosis induction	PI3K/Akt, MAPK, NF-κB, Bax/Bcl-2
Kaempferol	Flavonoid	Cell cycle arrest, anti-angiogenic	p53, VEGF, Cyclins
β-Sitosterol	Phytosterol	Apoptosis, anti-proliferative	Caspases, VEGF, Bcl-2
Ursolic acid	Triterpenoid	Anti-inflammatory, apoptosis	STAT3, PI3K/Akt, mTOR
Oleanolic acid	Triterpenoid	Anti-metastatic	MAPK, NF-κB
Phenolic compounds	Polyphenols	Antioxidant	ROS, COX-2, iNOS

Table 4. Major phytochemical constituents identified in *Spathodea campanulata* and their reported anticancer mechanisms

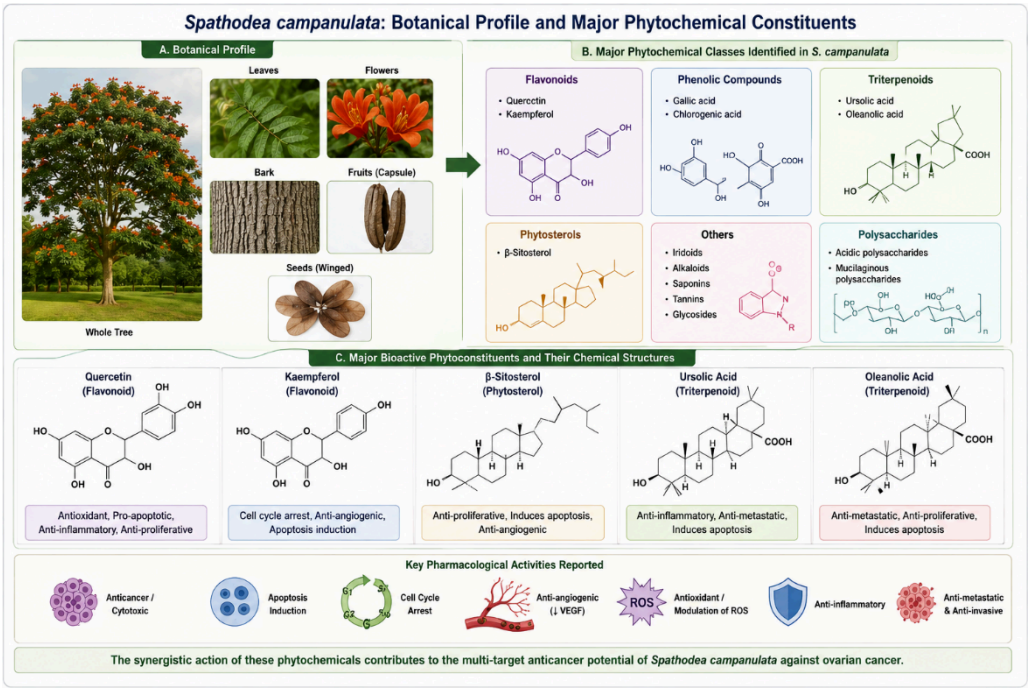

Figure 5. Botanical profile, major phytochemical constituents, and pharmacological activities of *Spathodea campanulate*

Plant Part	Major Constituents	Pharmacological Importance
Leaves	Flavonoids, phenolics	Antioxidant, anticancer
Bark	Triterpenoids, tannins	Anti-inflammatory, antimicrobial
Flowers	Flavonoids, glycosides	Antioxidant
Stem bark	Sterols, triterpenoids	Cytotoxic activity
Roots	Phenolics, alkaloids	Antimicrobial and antioxidant

Table 5. Distribution of important phytochemicals in different parts of *Spathodea campanulata*

V. Multi-target Anticancer Mechanisms of Spathodea campanulata

The development and progression of ovarian cancer involve the dysregulation of multiple molecular pathways that regulate cell proliferation, apoptosis, angiogenesis, oxidative stress, metastasis, and immune responses. Unlike conventional chemotherapeutic agents that frequently target a single pathway, phytochemicals present in *Spathodea campanulata* exhibit multi-target pharmacological activities capable of simultaneously modulating several hallmarks of cancer [40]. Such pleiotropic effects are particularly advantageous in overcoming tumour heterogeneity and chemoresistance, which remain major challenges in ovarian cancer therapy.

The principal bioactive constituents of *S. campanulata*, including quercetin, kaempferol, β-sitosterol, ursolic acid, and oleanolic acid, influence numerous intracellular signalling cascades associated with tumour development [41]. These phytochemicals regulate programmed cell death, inhibit tumour proliferation, suppress angiogenesis, reduce oxidative stress, interfere with metastatic dissemination, and modulate oncogenic signalling pathways. The major anticancer mechanisms are discussed below.

A. Induction of Apoptosis

Apoptosis is a tightly regulated physiological process that eliminates damaged or abnormal cells without inducing inflammation. One of the defining characteristics of malignant cells is their ability to evade apoptosis, thereby promoting uncontrolled tumour growth. Restoration of apoptotic signalling is therefore considered an important therapeutic strategy in ovarian cancer treatment [42].

Experimental studies have demonstrated that phytochemicals present in *S. campanulata* activate both intrinsic (mitochondrial) and extrinsic apoptotic pathways. Quercetin promotes mitochondrial membrane depolarization, increases the Bax/Bcl-2 ratio, releases cytochrome c into the cytoplasm, and activates caspase-9 and caspase-3, ultimately leading to apoptotic cell death. Kaempferol and β-sitosterol similarly enhance caspase activation while suppressing anti-apoptotic proteins such as Bcl-2 and surviving [43]. Ursolic acid and oleanolic acid further contribute to apoptosis by increasing intracellular reactive oxygen species (ROS), disrupting mitochondrial integrity, and activating p53-dependent signalling pathways. The coordinated activation of these mechanisms facilitates selective elimination of malignant cells while minimizing damage to normal tissues [44].

B. Cell Cycle Arrest

Uncontrolled cell division is one of the fundamental characteristics of cancer. Progression through the cell cycle is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumour suppressor proteins. Dysregulation of these regulatory molecules enables continuous proliferation of ovarian cancer cells [45].
Several phytochemicals identified in *S. campanulata* interfere with cell cycle progression by modulating cyclin-CDK complexes. Quercetin has been reported to induce G1/S phase arrest, whereas kaempferol predominantly causes G2/M phase arrest through downregulation of Cyclin D1, Cyclin B1, CDK2, and CDK4. Activation of p21 and p27 further inhibits cell cycle progression, thereby preventing DNA replication and tumour growth.

C. Modulation of Oxidative Stress

Reactive oxygen species (ROS) play a dual role in cancer biology. Moderate ROS levels promote tumour survival and proliferation, whereas excessive ROS accumulation induces oxidative damage leading to apoptosis [46].
The flavonoids and phenolic compounds present in *S. campanulata* exhibit potent antioxidant properties by scavenging free radicals and enhancing endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Interestingly, these compounds can also elevate ROS selectively within cancer cells, resulting in mitochondrial dysfunction, DNA damage, and activation of apoptotic signalling pathways [47]. This selective modulation of oxidative stress contributes significantly to the anticancer potential of the plant.

D. Inhibition of Angiogenesis

Tumour angiogenesis is essential for providing rapidly proliferating cancer cells with oxygen and nutrients. Vascular endothelial growth factor (VEGF) is considered the principal regulator of angiogenesis in ovarian cancer.
Quercetin, kaempferol, β-sitosterol, ursolic acid, and oleanolic acid have been reported to suppress VEGF expression and inhibit endothelial cell proliferation. Inhibition of VEGF-mediated signalling limits neovascularization, thereby reducing tumour growth and metastatic dissemination. Downregulation of hypoxia-inducible factor-1 alpha (HIF-1α) further enhances the anti-angiogenic activity of these phytochemicals [48,49].

E. Suppression of Tumor Invasion and Metastasis

Metastatic dissemination represents the primary cause of mortality among ovarian cancer patients. Tumour invasion involves degradation of the extracellular matrix by matrix metalloproteinases (MMP-2 and MMP-9), epithelial-mesenchymal transition (EMT), and enhanced cell migration [50].
Bioactive compounds isolated from *S. campanulata* suppress metastatic progression by inhibiting MMP expression, reducing EMT, increasing E-cadherin expression, and suppressing N-cadherin and vimentin. These molecular changes decrease cellular motility and impair tumour invasion into surrounding tissues.

F. Regulation of Cell Signaling Pathways

The anticancer activity of *S. campanulata* is largely mediated through modulation of several intracellular signalling pathways.

The PI3K/Akt pathway is inhibited by quercetin, ursolic acid, and β-sitosterol, resulting in reduced cellular proliferation and enhanced apoptosis. Kaempferol suppresses MAPK signalling, thereby limiting tumour growth and migration. Several phytochemicals inhibit NF-κB activation, reducing inflammatory cytokine production and tumour-promoting inflammation. Activation of p53 promotes DNA repair and apoptosis, whereas inhibition of mTOR suppresses protein synthesis and tumour metabolism. Furthermore, downregulation of VEGF signalling inhibits angiogenesis, collectively producing a comprehensive anticancer response [51,52].

G. Synergistic Multi-target Anticancer Effects

The anticancer potential of *S. campanulata* arises from the synergistic interaction of multiple phytochemicals rather than the activity of any individual compound. Flavonoids, triterpenoids, phenolics, and phytosterols collectively target numerous molecular pathways involved in tumour progression, thereby producing complementary therapeutic effects [53]. Such multi-target activity is particularly advantageous in ovarian cancer, where activation of compensatory signalling pathways frequently contributes to treatment failure and chemoresistance.

Collectively, current evidence indicates that *S. campanulata* phytoconstituents possess considerable potential as multi-target therapeutic agents capable of regulating apoptosis, cell cycle progression, oxidative stress, angiogenesis, metastasis, and intracellular signalling pathways [54]. Nevertheless, additional mechanistic studies, standardized extract characterization, and clinical investigations are required to facilitate their translation into effective phytopharmaceutical interventions for ovarian cancer [55].

Table 6. Major molecular targets modulated by the principal phytochemicals of *Spathodea campanulata*

Phytochemical	Major Molecular Targets	Biological Effect
Quercetin	PI3K/Akt, NF-κB, Bax/Bcl-2	Apoptosis, antioxidant, anti-proliferative
Kaempferol	MAPK, p53, VEGF	Cell cycle arrest, anti-angiogenic
β-Sitosterol	Caspase-3, Caspase-9, VEGF	Apoptosis, anti-metastatic
Ursolic acid	STAT3, PI3K/Akt, mTOR	Anti-inflammatory, apoptosis
Oleanolic acid	MAPK, NF-κB	Anti-metastatic, anti-proliferative

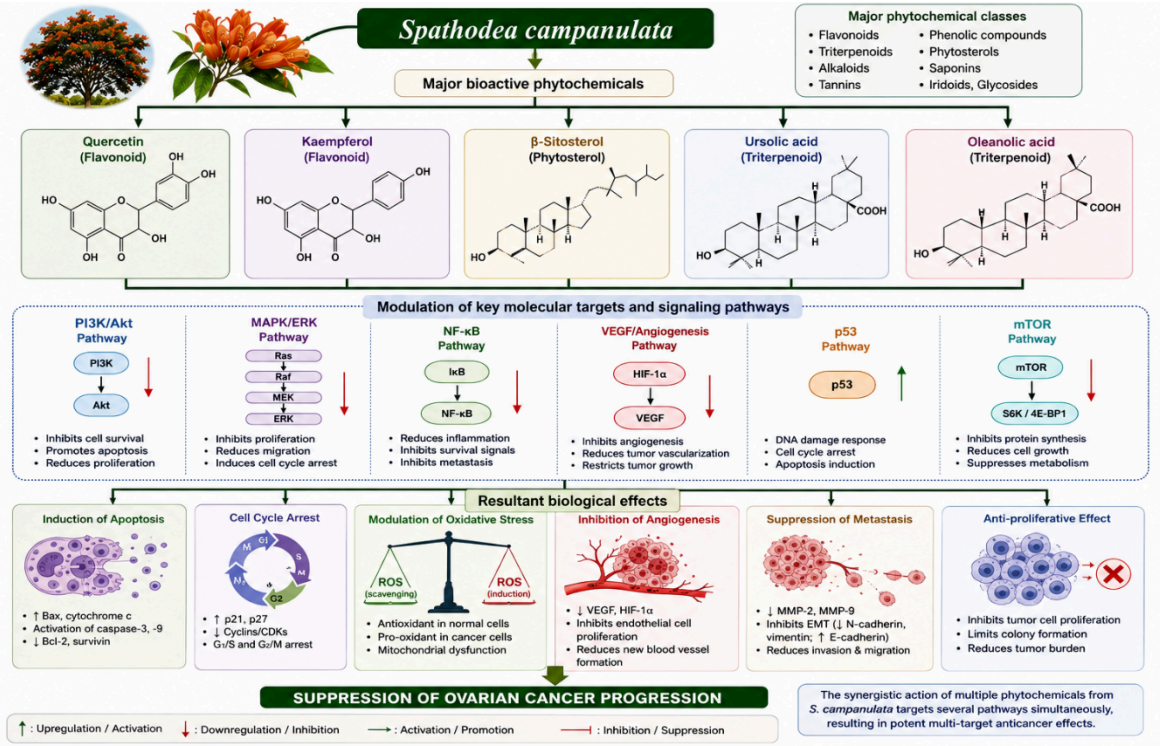

Figure 6. Proposed multi-target anticancer mechanisms of *Spathodea campanulata* phytoconstituents against ovarian cancer.

VI. In Vitro Evidence of the Anticancer Potential of Spathodea campanulate

Experimental *in vitro* studies provide essential evidence for evaluating the cytotoxic and antiproliferative activities of medicinal plants before progressing to animal experiments and clinical investigations. Cell culture-based assays enable researchers to investigate the effects of plant extracts and isolated phytochemicals on cancer cell viability, apoptosis, oxidative stress, cell cycle regulation, migration, and molecular signalling pathways under controlled laboratory conditions [56]. Consequently, *in vitro* studies represent a crucial step in validating the therapeutic potential of *Spathodea campanulata* against ovarian cancer.

Several investigations have demonstrated that extracts of *S. campanulata*, particularly methanolic, ethanolic, and aqueous extracts of the leaves, bark, and flowers, possess significant cytotoxic activity against a variety of human cancer cell lines [57]. The observed biological effects are largely attributed to the presence of flavonoids, phenolic compounds, triterpenoids, and phytosterols, which collectively interfere with multiple oncogenic pathways [58].

Among the available cytotoxicity assays, the **3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay** is one of the most widely employed methods for assessing cell viability. The assay measures mitochondrial metabolic activity, where viable cells reduce the yellow tetrazolium salt (MTT) into insoluble purple formazan crystals through the action of mitochondrial dehydrogenase enzymes. The quantity of formazan produced is directly proportional to the number of viable cells and is quantified spectrophotometrically following solubilization [59]. A reduction in absorbance indicates decreased cell viability and increased cytotoxic activity of the tested compound.

In ovarian cancer research, the **A2780** human ovarian carcinoma cell line is extensively used because of its well-characterized genetic background and reproducible response to anticancer agents. This cell line serves as an excellent experimental model for evaluating the cytotoxic efficacy of natural products and for investigating mechanisms associated with apoptosis, oxidative stress, and chemoresistance [60]. Additional ovarian cancer cell lines, including **SKOV3**, **OVCAR-3**, and **CAOV3**, are frequently employed to assess the broad-spectrum anticancer activity of phytochemicals and to compare their therapeutic responses across different molecular subtypes.

Several phytochemicals reported in *S. campanulata* have individually demonstrated potent anticancer activity in *in vitro* studies. Quercetin significantly decreases the viability of ovarian cancer cells by inducing mitochondrial-mediated apoptosis, activating caspase-3 and caspase-9, increasing the Bax/Bcl-2 ratio, and suppressing PI3K/Akt signalling. Kaempferol inhibits cellular proliferation by inducing G2/M phase arrest, promoting reactive oxygen species (ROS)-mediated apoptosis, and suppressing angiogenic signalling pathways such as VEGF. Similarly, β-sitosterol has been reported to inhibit tumour growth by activating intrinsic apoptotic pathways and reducing metastatic behaviour through modulation of epithelial–mesenchymal transition (EMT) markers [61].

In addition to cytotoxicity, *in vitro* investigations have demonstrated that phytochemicals derived from *S. campanulata* possess strong antioxidant and anti-inflammatory properties. These compounds reduce the expression of inflammatory mediators including nuclear factor-kappa B (NF-κB), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), thereby limiting the inflammatory microenvironment that supports tumour progression. Furthermore, suppression of matrix metalloproteinases (MMP-2 and MMP-9) reduces cancer cell migration and invasion, indicating the potential of these phytochemicals to inhibit metastatic dissemination [62].

Although encouraging results have been obtained from *in vitro* studies, several limitations should be considered. Variations in extraction methods, solvent systems, phytochemical composition, treatment concentrations, and exposure durations can influence biological outcomes. Moreover, isolated cell culture models do not fully replicate the complexity of the tumour microenvironment observed in living organisms.

Therefore, standardized extract characterization, dose optimization, mechanistic investigations, and validation through *in vivo* studies remain essential before clinical application [63].

Overall, current *in vitro* evidence strongly supports the anticancer potential of *Spathodea campanulata*. Its phytochemicals exhibit significant cytotoxic, antiproliferative, pro-apoptotic, antioxidant, and anti-metastatic activities through modulation of multiple molecular targets. These findings provide a robust experimental foundation for further *in vivo* investigations and support the continued development of *S. campanulata*-derived phytoconstituents as promising candidates for ovarian cancer therapy.

Phytochemical	Cell Line	Experimental Assay	Major Findings
Quercetin	A2780	MTT assay	Reduced cell viability; apoptosis induction
Kaempferol	SKOV3	Cell cycle analysis	G2/M arrest and anti-proliferative activity
β-Sitosterol	OVCAR-3	Apoptosis assay	Caspase activation; inhibition of migration
Ursolic acid	A2780	ROS assay	Increased oxidative stress and apoptosis
Oleanolic acid	CAOV3	Migration assay	Reduced invasion and metastatic potential

Table 7. Representative *in vitro* studies demonstrating the anticancer activities of major phytochemicals associated with *Spathodea campanulata*

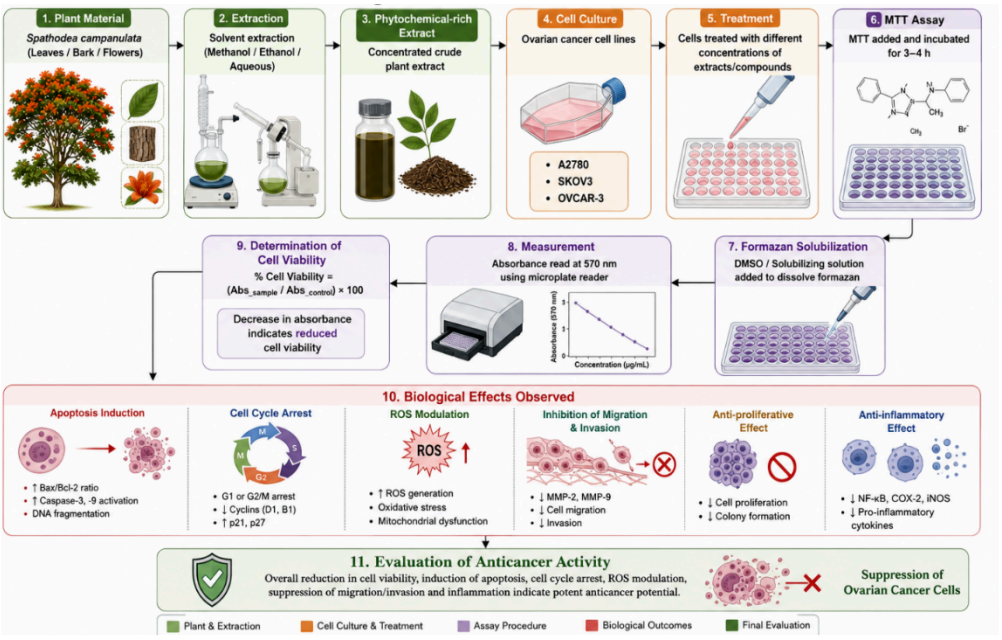

Figure 7. Experimental workflow for evaluating the *in vitro* anticancer activity of *Spathodea campanulata* extracts and phytoconstituents against ovarian cancer cell lines.

VII. In Silico Evidence and Molecular Docking Studies

Advances in computational biology have transformed the process of drug discovery by enabling rapid identification and evaluation of bioactive compounds before experimental validation. *In silico* techniques, particularly molecular docking, molecular dynamics (MD) simulations, quantitative structure–activity relationship (QSAR) analysis, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction, have become indispensable tools in natural product research [64]. These computational approaches facilitate the prediction of ligand–protein interactions, binding affinity,

pharmacokinetic properties, and potential toxicity, thereby reducing the time, cost, and resources required for conventional drug discovery.

Molecular docking is one of the most widely employed *in silico* techniques for predicting the interaction between a small bioactive molecule (ligand) and a target protein (receptor).

The primary objective of docking is to determine the preferred binding orientation and estimate the binding affinity of phytochemicals towards proteins associated with disease progression. Strong binding interactions indicate a greater likelihood of biological activity and provide valuable insights for selecting compounds for further experimental investigation [65].

In ovarian cancer research, molecular docking is extensively applied to identify phytochemicals capable of interacting with key proteins involved in tumour growth, apoptosis, angiogenesis, metastasis, and chemoresistance. Common therapeutic targets include phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), tumour suppressor protein p53, B-cell lymphoma 2 (Bcl-2), caspase-3, matrix metalloproteinases (MMP-2 and MMP-9), mammalian target of rapamycin (mTOR), and nuclear factor-kappa B (NF-κB). These proteins regulate essential cellular processes such as proliferation, survival, apoptosis, angiogenesis, and invasion, making them attractive targets for computational screening [66].

The major phytochemicals identified in *Spathodea campanulata*, including quercetin, kaempferol, β-sitosterol, ursolic acid, and oleanolic acid, have demonstrated favourable docking interactions with several cancer-associated proteins in independent computational studies. Quercetin exhibits strong binding affinity towards PI3K, Akt, EGFR, and Bcl-2 through multiple hydrogen bonds and hydrophobic interactions, suggesting its ability to suppress tumour cell survival pathways. Kaempferol has shown stable interactions with VEGFR, p53, and MAPK-associated proteins, supporting its anti-angiogenic and pro-apoptotic properties [67]. Likewise, β-sitosterol, ursolic acid, and oleanolic acid have demonstrated promising binding affinities for proteins involved in apoptosis, inflammation, and metastatic progression.

Docking studies generally involve several sequential steps. Initially, the three-dimensional structure of the target protein is retrieved from the Protein Data Bank (PDB), while ligand structures are obtained from public chemical databases such as PubChem. The protein and ligand structures undergo preparation through energy minimization, removal of water molecules, addition of hydrogen atoms, and assignment of atomic charges. Subsequently, docking simulations are performed using specialized software such as AutoDock Vina, AutoDock 4.2, Schrödinger Glide, MOE, or Discovery Studio Visualizer. The resulting binding poses are ranked according to their binding energies, hydrogen bonding interactions, hydrophobic contacts, and conformational stability [68].

Although molecular docking provides valuable preliminary evidence regarding ligand–protein interactions, it has inherent limitations. Docking algorithms often consider proteins as relatively rigid structures and may not fully capture conformational flexibility under physiological conditions. Furthermore, favourable docking scores do not necessarily guarantee biological activity, as pharmacokinetic behaviour, metabolism, cellular uptake, and target accessibility also influence therapeutic efficacy [69]. Consequently, docking studies should always be complemented by *in vitro*, *in vivo*, and molecular dynamics investigations before drawing definitive conclusions.

Recent advances in molecular dynamics simulations have further strengthened computational drug discovery by enabling the assessment of protein–ligand complex stability over time under near-physiological conditions. Parameters such as root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), hydrogen bond occupancy, and binding free energy calculations provide additional evidence supporting the stability and reliability of docking results. Furthermore, ADMET prediction tools facilitate early evaluation of pharmacokinetic properties and toxicity

profiles, thereby assisting in the identification of promising lead compounds suitable for further drug development [70].

Overall, *in silico* studies provide a robust computational platform for prioritizing phytochemicals with potential anticancer activity before laboratory validation. The integration of molecular docking, molecular dynamics simulations, and ADMET analysis with *in vitro* cytotoxicity studies offers a comprehensive strategy for accelerating the discovery of plant-derived therapeutics. Considering the favourable biological activities of *Spathodea campanulata* phytochemicals, computational approaches continue to play an essential role in elucidating their molecular mechanisms and identifying promising candidates for the development of novel anti-ovarian cancer agents.

Target Protein	Biological Function	Therapeutic Significance in Ovarian Cancer
PI3K	Cell survival and proliferation	Inhibition reduces tumour growth
Akt	Cell survival signalling	Promotes apoptosis when inhibited
EGFR	Cell proliferation	Target for anticancer therapy
VEGFR	Angiogenesis	Suppresses tumour blood vessel formation
Bcl-2	Anti-apoptotic protein	Promotes programmed cell death when inhibited
Caspase-3	Execution of apoptosis	Marker of apoptotic activation
MMP-2	Extracellular matrix degradation	Inhibits tumour invasion
MMP-9	Metastasis	Prevents cancer dissemination
mTOR	Protein synthesis and growth	Reduces tumour metabolism
NF-κB	Inflammation and survival	Suppresses tumour-promoting inflammation

Table 8. Major molecular targets frequently employed in *in silico* docking studies for ovarian cancer.

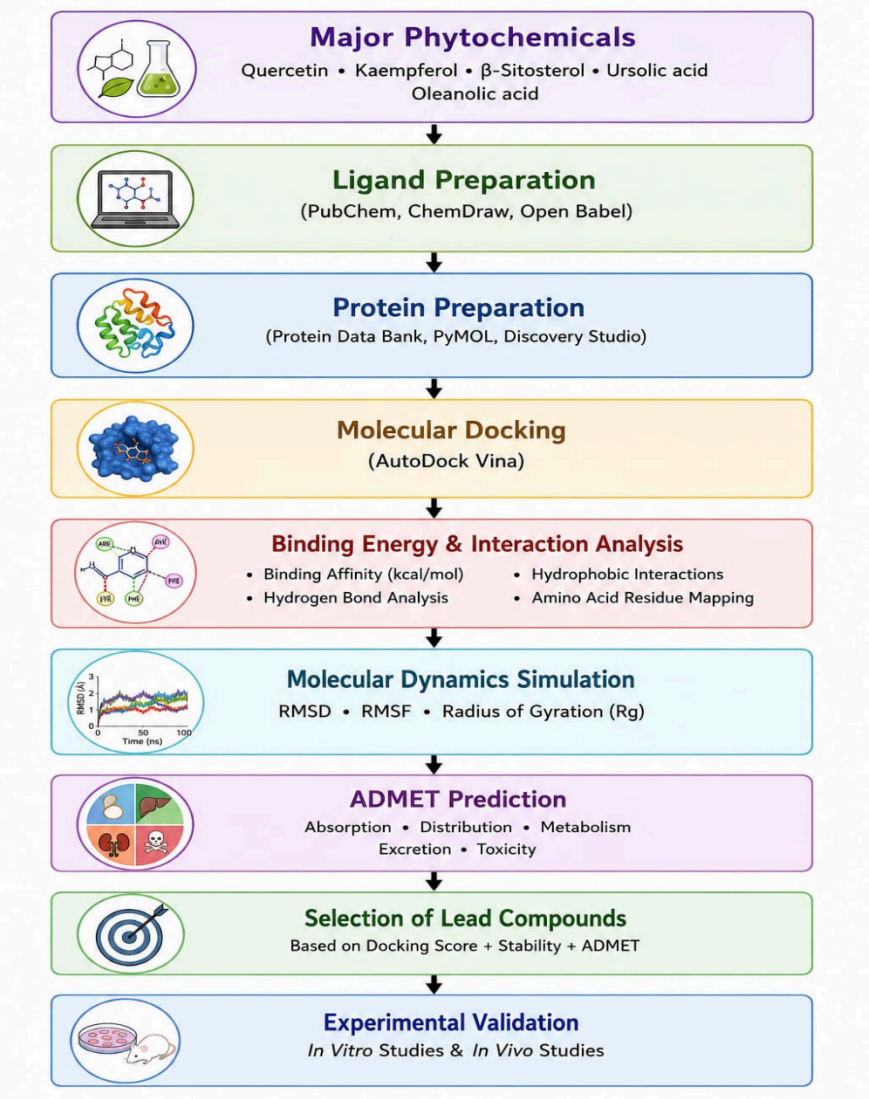

Figure 8. Workflow of *in silico* drug discovery illustrating molecular docking, molecular dynamics simulation, ADMET prediction, and experimental validation of *Spathodea campanulata* phytoconstituents against ovarian cancer targets.

VIII. Challenges, Future Perspectives, and Clinical Translation

Despite the growing body of evidence supporting the anticancer potential of *Spathodea campanulata*, several scientific and translational challenges remain before its phytoconstituents can be developed into clinically approved therapeutic agents [71]. Although numerous studies have demonstrated promising antioxidant, anti-inflammatory, antiproliferative, and pro-apoptotic activities, the majority of available evidence is derived from *in vitro* experiments and computational investigations. Consequently, additional *in vivo* studies and well-designed clinical trials are required to establish the safety, efficacy, pharmacokinetic behaviour, and therapeutic applicability of *S. campanulata* in ovarian cancer management[72].

One of the major limitations in medicinal plant research is the lack of standardized extraction procedures. The phytochemical composition of *S. campanulata* varies depending on geographical origin, climatic conditions, harvesting season, plant age, and extraction solvent. Such variability can significantly influence biological activity and reduce the reproducibility of experimental findings. Therefore, future studies should focus on developing standardized extraction protocols, quality control parameters, and phytochemical fingerprinting methods to ensure batch-to-batch consistency and reproducibility.

Another important challenge is the relatively poor bioavailability of many naturally occurring phytochemicals. Compounds such as quercetin, kaempferol, ursolic acid, and oleanolic acid exhibit limited aqueous solubility, poor intestinal absorption, rapid metabolism, and low systemic availability following oral administration. These pharmacokinetic limitations may reduce their therapeutic effectiveness despite demonstrating excellent biological activity under laboratory conditions. Consequently, innovative drug delivery systems are required to improve their stability, bioavailability, and tumour-specific distribution.

Recent advances in nanotechnology provide promising opportunities to overcome these limitations. Nanoparticle-based drug delivery systems, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanoemulsions, dendrimers, and phytosomes, have been extensively investigated for enhancing the delivery of plant-derived phytochemicals. Nanoformulations can improve drug solubility, prolong circulation time, enhance tumour targeting through the enhanced permeability and retention (EPR) effect, reduce systemic toxicity, and provide controlled drug release. The incorporation of *S. campanulata* phytoconstituents into nanocarrier systems therefore represents an attractive strategy for improving therapeutic efficacy against ovarian cancer [73].

Future investigations should also explore synergistic therapeutic approaches involving *S. campanulata* phytochemicals in combination with conventional chemotherapeutic agents such as cisplatin, carboplatin, and paclitaxel. Combination therapy may reduce the required dose of cytotoxic drugs, minimize adverse effects, overcome multidrug resistance, and enhance overall treatment efficacy through simultaneous modulation of multiple molecular pathways.

Although molecular docking studies have identified favourable interactions between *S. campanulata* phytochemicals and several ovarian cancer-associated proteins, computational predictions require experimental validation. Future studies integrating molecular docking, molecular dynamics simulations, transcriptomic analysis, proteomics, metabolomics, and systems biology approaches will provide deeper insights into the complex molecular mechanisms underlying the anticancer activity of the plant.

Another promising direction is the isolation and structural characterization of novel bioactive compounds from *S. campanulata*. Advanced analytical techniques such as high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC-MS/MS), gas chromatography–mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy can facilitate the identification of previously unexplored phytoconstituents with potential anticancer activity. These compounds may serve as lead molecules for the development of new phytopharmaceuticals targeting ovarian cancer [74].

Furthermore, increasing attention should be directed toward personalized medicine and biomarker-guided therapy. Understanding the molecular profile of individual ovarian tumours may enable the selection of specific phytochemicals that target dysregulated signalling pathways, thereby improving treatment efficacy while minimizing toxicity. Integration of artificial intelligence, machine learning, and computational drug discovery platforms may further accelerate the identification and optimization of plant-derived anticancer agents.

Overall, the available evidence suggests that *Spathodea campanulata* possesses significant therapeutic potential for ovarian cancer management. However, successful clinical translation will require multidisciplinary collaboration involving pharmacognosy, molecular biology, pharmacology, nanotechnology, medicinal chemistry, bioinformatics, and clinical oncology. Continued research integrating standardized phytochemical characterization, mechanistic investigations, advanced drug delivery systems, and rigorous clinical evaluation will be essential for transforming *S. campanulata* from a promising medicinal plant into a clinically useful anticancer phytopharmaceutical [75].

Table 9. Major challenges limiting the clinical translation of *Spathodea campanulata* and proposed future research strategies.

Current Challenge	Impact	Future Strategy
Lack of standardized extracts	Variable experimental outcomes	Develop standardized extraction and quality control protocols
Poor bioavailability	Reduced therapeutic efficacy	Nanoformulations, liposomes, phytosomes, polymeric nanoparticles
Limited *in vivo* evidence	Uncertain translational potential	Conduct animal efficacy and toxicity studies
Absence of clinical trials	No clinical validation	Design Phase I–III clinical studies
Computational predictions require validation	Unconfirmed biological relevance	Combine docking with molecular dynamics and laboratory validation
Limited molecular characterization	Unknown active constituents	Employ HPLC, LC-MS/MS, GC-MS, and NMR for phytochemical profiling

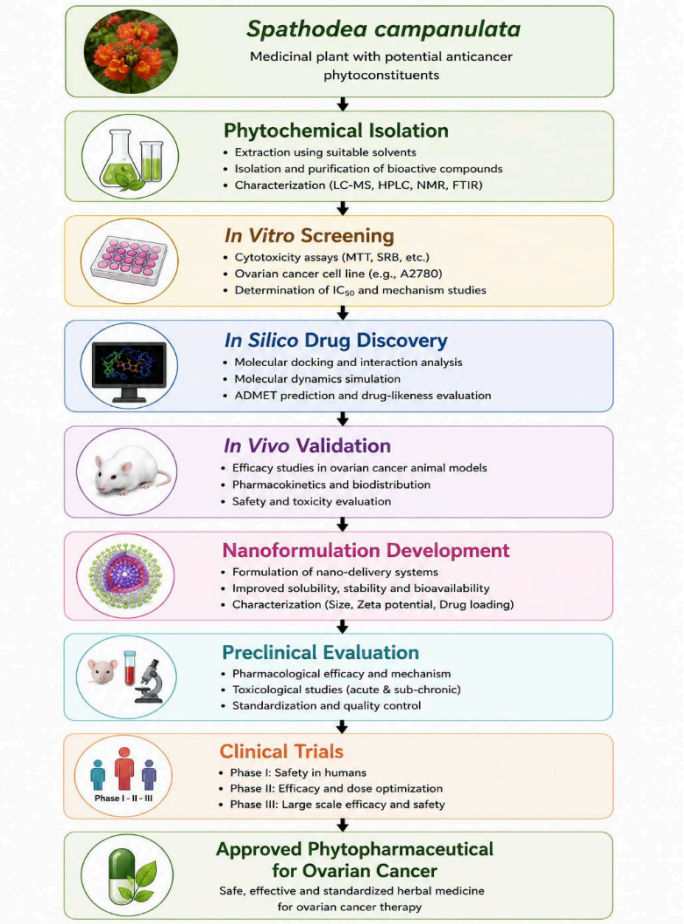

Figure 9. Translational roadmap illustrating the progression of *Spathodea campanulata* from phytochemical discovery to the potential development of clinically approved phytopharmaceuticals for ovarian cancer

IX. Conclusion

Ovarian cancer remains one of the most aggressive gynecological malignancies worldwide, with high mortality rates largely attributed to late-stage diagnosis, extensive metastatic spread, and the development of chemoresistance. Although significant advances have been achieved through cytoreductive surgery, platinum-based chemotherapy, targeted therapy, and immunotherapy, treatment outcomes remain suboptimal for many patients. These limitations underscore the urgent need for safer, more effective, and multi-target therapeutic strategies capable of overcoming the biological complexity of ovarian cancer.

Natural products continue to represent an invaluable source of novel bioactive compounds for anticancer drug discovery. Among them, *Spathodea campanulata* has emerged as a promising medicinal plant owing to its rich phytochemical diversity and broad spectrum of pharmacological activities. The plant contains numerous biologically active constituents, including quercetin, kaempferol, β-sitosterol, ursolic acid, oleanolic acid, phenolic compounds, and other secondary metabolites that collectively contribute to its therapeutic potential. These phytochemicals exhibit antioxidant, anti-inflammatory, antiproliferative, anti-angiogenic, and pro-apoptotic properties through simultaneous modulation of multiple molecular pathways associated with ovarian cancer progression.

The available scientific evidence demonstrates that *S. campanulata* phytoconstituents regulate several hallmarks of cancer by inducing apoptosis, promoting cell cycle arrest, modulating oxidative stress, suppressing angiogenesis, inhibiting tumour invasion and metastasis, and regulating key signalling pathways such as PI3K/Akt, MAPK, NF-κB, VEGF, p53, and mTOR. The ability of these phytochemicals to influence multiple molecular targets simultaneously provides a significant advantage over single-target therapeutic approaches and may contribute to overcoming drug resistance frequently observed in ovarian cancer.

Furthermore, both *in vitro* investigations and *in silico* molecular docking studies provide encouraging evidence supporting the anticancer potential of *S. campanulata*. Cell-based experiments have demonstrated significant cytotoxic and antiproliferative effects against ovarian cancer models, while computational analyses have revealed favourable interactions between major phytochemicals and several cancer-associated molecular targets. The integration of computational drug discovery with experimental validation represents a rational and efficient strategy for identifying promising lead compounds for future therapeutic development.

Despite these encouraging findings, the clinical application of *S. campanulata* remains limited by several challenges, including the lack of standardized extracts, variability in phytochemical composition, poor bioavailability of certain bioactive compounds, and insufficient *in vivo* and clinical evidence. Addressing these limitations through standardized phytochemical characterization, advanced drug delivery systems, nanotechnology-based formulations, molecular pharmacology, and well-designed preclinical and clinical investigations will be essential for translating laboratory findings into clinically useful therapies.

Overall, the collective evidence reviewed in this article highlights *Spathodea campanulata* as a promising source of multi-target phytochemicals with considerable potential for ovarian cancer management. Continued interdisciplinary research integrating pharmacognosy, molecular biology, computational drug discovery, nanotechnology, and clinical oncology may facilitate the development of novel phytopharmaceuticals capable of improving treatment outcomes while minimizing toxicity. Future investigations should focus on validating these findings through rigorous mechanistic studies, standardized extract development, animal models, and clinical trials to fully establish the therapeutic value of *S. campanulata* in ovarian cancer prevention and treatment.

Abbreviations

Abbreviation	Full Form
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
Akt	Protein Kinase B
ATP	Adenosine Triphosphate
Bax	Bcl-2-associated X protein
Bcl-2	B-cell Lymphoma 2
CAT	Catalase
CDK	Cyclin-Dependent Kinase
COX-2	Cyclooxygenase-2
EMT	Epithelial–Mesenchymal Transition
EGFR	Epidermal Growth Factor Receptor
GC-MS	Gas Chromatography–Mass Spectrometry
GPx	Glutathione Peroxidase
HGSOC	High-Grade Serous Ovarian Carcinoma
HIF-1α	Hypoxia-Inducible Factor-1 Alpha
HPLC	High-Performance Liquid Chromatography
iNOS	Inducible Nitric Oxide Synthase
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry
MAPK	Mitogen-Activated Protein Kinase
MD	Molecular Dynamics
MMP	Matrix Metalloproteinase
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
mTOR	Mammalian Target of Rapamycin
NF-κB	Nuclear Factor-Kappa B
NMR	Nuclear Magnetic Resonance
PDB	Protein Data Bank
PI3K	Phosphatidylinositol 3-Kinase
QSAR	Quantitative Structure–Activity Relationship
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

References

[1] Sung, J. Ferlay, R. L. Siegel, et al., "Global Cancer Statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA Cancer J. Clin.*, vol. 74, no. 3, pp. 229–263, 2024.

[2] R. L. Siegel, K. D. Miller, H. E. Fuchs, and A. Jemal, "Cancer statistics, 2025," *CA Cancer J. Clin.*, vol. 75, no. 1, pp. 5–38, 2025.

[3] National Comprehensive Cancer Network, *Ovarian Cancer Clinical Practice Guidelines in Oncology*, Version 2025.

[4] World Health Organization, *Classification of Female Genital Tumours*, 5th ed. Lyon: IARC Press, 2020.
[5] [5] International Agency for Research on Cancer, *World Cancer Report: Cancer Research for Cancer Prevention*. Lyon: IARC, 2020.
[6] Douglas Hanahan, "Hallmarks of cancer: New dimensions," *Cancer Discov.*, vol. 12, no. 1, pp. 31–46, 2022.
[7] Douglas Hanahan and Robert A. Weinberg, "Hallmarks of cancer: The next generation," *Cell*, vol. 144, no. 5, pp. 646–674, 2011.
[8] National Cancer Institute, *Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®)–Health Professional Version*, 2025.
[9] European Society for Medical Oncology, "Ovarian cancer: ESMO Clinical Practice Guidelines," *Ann. Oncol.*, 2023.
[10] Robert C. Bast Jr., B. Hennessy, G. B. Mills, and D. M. Bast, "The biology of ovarian cancer: New opportunities for translation," *Nat. Rev. Cancer*, vol. 9, pp. 415–428, 2009.
[11] Judah Folkman, "Role of angiogenesis in tumor growth and metastasis," *Semin. Oncol.*, vol. 29, pp. 15–18, 2002.
[12] William G. Kaelin Jr. and Peter J. Ratcliffe, "The HIF pathway in cancer and oxygen sensing," *Cell*, vol. 184, pp. 405–421, 2021.
[13] Timothy A. Yap, "Targeting DNA repair in ovarian cancer," *Nat. Rev. Clin. Oncol.*, vol. 16, pp. 681–700, 2019.
[14] American Cancer Society, *Cancer Facts & Figures 2025*. Atlanta, GA: American Cancer Society, 2025.
[15] Krzysztof Książek, "Molecular mechanisms involved in ovarian cancer progression and therapeutic targets," *Int. J. Mol. Sci.*, vol. 24, 2023.
[16] The Plant List, *The Plant List: A Working List of All Plant Species*. Version 1.1. Royal Botanic Gardens, Kew and Missouri Botanical Garden, 2013.
[17] Plants of the World Online, *Spathodea campanulata P. Beauv.* Royal Botanic Gardens, Kew, 2025.
[18] J. O. Kokwaro, *Medicinal Plants of East Africa*, 3rd ed. Nairobi: University of Nairobi Press, 2009.
[19] Trease and Evans' Pharmacognosy, 17th ed. London: Elsevier, 2024.
[20] K. R. Kirtikar and B. D. Basu, *Indian Medicinal Plants*, Vol. 3. Dehradun: International Book Distributors.
[21] A. Elusiyan, S. O. Popoola, and T. O. Olajide, "Phytochemical screening and antimicrobial activities of *Spathodea campanulata* extracts," *African Journal of Traditional, Complementary and Alternative Medicines*, vol. 8, no. 1, pp. 66–71, 2011.
[22] M. J. O. Ofori-Kwakye, E. K. Ayim, and P. G. Appiah, "Ethnomedicinal uses and pharmacological activities of *Spathodea campanulata*: A review," *Journal of Ethnopharmacology*, vol. 250, 2020.
[23] S. K. Pandey and A. K. Tripathi, "Chemistry and biological activities of flavonoids," *Natural Product Research*, vol. 36, no. 8, pp. 1950–1972, 2022.
[24] Harborne J. B., *Phytochemical Methods: A Guide to Modern Techniques of Plant Analysis*, 3rd ed. London: Chapman & Hall.
[25] W. C. Evans, *Trease and Evans Pharmacognosy*, 16th ed. Elsevier, 2009.
[26] D. Procházková, I. Boušová, and N. Wilhelmová, "Antioxidant and prooxidant properties of flavonoids," *Fitoterapia*, vol. 82, no. 4, pp. 513–523, 2011.
[27] G. R. Beecher, "Overview of dietary flavonoids: Nomenclature, occurrence and intake," *Journal of Nutrition*, vol. 133, pp. 3248S–3254S, 2003.
[28] B. Salehi, A. Fokou, W. N. Sharifi-Rad, et al., "The therapeutic potential of quercetin: A comprehensive review," *Phytotherapy Research*, vol. 33, pp. 1–33, 2019.
[29] M. Imran, M. Salehi, J. Sharifi-Rad, et al., "Kaempferol: A key emphasis to its anticancer potential," *Molecules*, vol. 24, no. 12, 2019.

[30] M. B. Gupta and R. K. Sharma, "Phytochemical constituents and pharmacological properties of medicinal plants containing triterpenoids and phytosterols," *Journal of Herbal Medicine*, vol. 29, 2021.
[31] D. Bishayee, G. Sethi, A. Thoppil, H. Darvesh, and A. K. Youns, "Ursolic acid in cancer prevention and therapy: Molecular targets, pharmacokinetics and clinical studies," *Pharmacol. Res.*, vol. 146, p. 104332, 2019.
[32] M. Shanmugam, G. Sethi, K. Siveen, A. Arfuso, and A. P. Kumar, "Oleanolic acid and its synthetic derivatives for the prevention and therapy of cancer: Preclinical and clinical evidence," *Cancer Lett.*, vol. 346, no. 2, pp. 206–216, 2014.
[33] B. Awad, C. Fink, and C. Williams, "β-Sitosterol as a potential anticancer agent: Current evidence and mechanisms of action," *Phytomedicine*, vol. 79, p. 153329, 2021.
[34] M. Imran, M. Salehi, J. Sharifi-Rad, et al., "Kaempferol: A key emphasis to its anticancer potential," *Molecules*, vol. 24, no. 12, p. 2277, 2019.
[35] B. Salehi, J. Sharifi-Rad, A. Fokou, et al., "Therapeutic potential of quercetin in cancer treatment," *Phytother. Res.*, vol. 33, no. 4, pp. 1013–1031, 2019.
[36] D. Hanahan, "Hallmarks of cancer: New dimensions," *Cancer Discov.*, vol. 12, no. 1, pp. 31–46, 2022.
[37] J. Luo, B. D. Manning, and L. C. Cantley, "Targeting the PI3K-Akt pathway in human cancer," *Cancer Cell*, vol. 4, no. 4, pp. 257–262, 2003.
[38] A. R. Pearson, K. Robinson, T. B. Gibson, et al., "Mitogen-activated protein (MAP) kinase pathways: Regulation and physiological functions," *Endocr. Rev.*, vol. 22, no. 2, pp. 153–183, 2001.
[39] M. Karin, "NF-κB as a critical link between inflammation and cancer," *Cold Spring Harb. Perspect. Biol.*, vol. 1, no. 5, p. a000141, 2009.
[40] D. G. Hardie, "AMPK and mTOR signalling in cancer and metabolism," *Nat. Rev. Mol. Cell Biol.*, vol. 13, no. 4, pp. 251–262, 2012.
[41] G. L. Semenza, "Hypoxia-inducible factors in physiology and medicine," *Cell*, vol. 148, no. 3, pp. 399–408, 2012.
[42] N. Ferrara, "VEGF and the regulation of angiogenesis," *Nat. Med.*, vol. 9, no. 6, pp. 669–676, 2003.
[43] B. Vogelstein, D. Lane, and A. J. Levine, "Surfing the p53 network," *Nature*, vol. 408, pp. 307–310, 2000.
[44] B. Halliwell and J. M. C. Gutteridge, *Free Radicals in Biology and Medicine*, 5th ed. Oxford: Oxford University Press, 2015.
[45] D. Trachootham, J. Alexandre, and P. Huang, "Targeting cancer cells by ROS-mediated mechanisms: A radical therapeutic approach?" *Nat. Rev. Drug Discov.*, vol. 8, no. 7, pp. 579–591, 2009.
[46] Tim Mosmann, "Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays," *J. Immunol. Methods*, vol. 65, no. 1–2, pp. 55–63, 1983.
[47] C. Carmichael, J. DeGraff, A. F. Gazdar, et al., "Evaluation of a tetrazolium-based semiautomated colorimetric assay: Assessment of chemosensitivity testing," *Cancer Res.*, vol. 47, no. 4, pp. 936–942, 1987.
[48] Oleg Trott and Arthur J. Olson, "AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading," *J. Comput. Chem.*, vol. 31, no. 2, pp. 455–461, 2010.
[49] David S. Goodsell, G. M. Morris, and A. J. Olson, "Automated docking using AutoDock," *J. Mol. Recognit.*, vol. 9, no. 1, pp. 1–5, 1996.
[50] Protein Data Bank, "Protein Data Bank: The single global archive for 3D macromolecular structure data," *Nucleic Acids Res.*, vol. 47, pp. D520–D528, 2019.
[51] PubChem, "PubChem in 2023: New data content and improved web interfaces," *Nucleic Acids Res.*, vol. 51, pp. D1373–D1380, 2023.
[52] David E. Shaw, "Molecular dynamics simulations in drug discovery," *Science*, vol. 330, no. 6002, pp. 341–346, 2010.

[53] D. E. Vanommeslaeghe and A. D. MacKerell Jr., "Molecular dynamics simulations in drug discovery: Current status and future prospects," *Curr. Opin. Struct. Biol.*, vol. 35, pp. 31–40, 2015.
[54] A. Daina, O. Michielin, and V. Zoete, "SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *Sci. Rep.*, vol. 7, p. 42717, 2017.
[55] W. Yang, M. Wang, and H. Chen, "ADMET prediction in drug discovery: Current status and future perspectives," *Acta Pharm. Sin. B*, vol. 13, no. 2, pp. 684–699, 2023.
[56] V. Torchilin, "Multifunctional nanocarriers for drug delivery," *Nat. Rev. Drug Discov.*, vol. 13, no. 11, pp. 813–827, 2014.
[57] S. Mitragotri, P. A. Burke, and R. Langer, "Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies," *Nat. Rev. Drug Discov.*, vol. 13, no. 9, pp. 655–672, 2014.
[58] M. Ferrari, "Cancer nanotechnology: Opportunities and challenges," *Nat. Rev. Cancer*, vol. 5, no. 3, pp. 161–171, 2005.
[59] Y. Patra, G. Das, A. Fraceto, et al., "Nano based drug delivery systems: Recent developments and future prospects," *J. Nanobiotechnol.*, vol. 16, p. 71, 2018.
[60] P. Agostinis, K. Berg, K. A. Cengel, et al., "Photodynamic therapy of cancer: An update," *CA Cancer J. Clin.*, vol. 61, no. 4, pp. 250–281, 2011.
[61] G. K. Padhy, S. K. Behera, and P. K. Panda, "*Spathodea campanulata* P. Beauv.—A review of its traditional uses, phytochemistry, pharmacology and toxicology," *J. Appl. Pharm. Sci.*, vol. 11, no. 8, pp. 1–15, 2021.
[62] D. Duryat, R. I. Ghozali, R. Rodiani, and I. Ismanto, "Phytochemical screening of an ethanolic extract of *Spathodea campanulata* leaf using GC-MS and LC-MS technology," *J. Multidiscip. Appl. Nat. Sci.*, vol. 5, no. 3, pp. 983–997, 2025.
[63] A. Daina, O. Michielin, and V. Zoete, "SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *Sci. Rep.*, vol. 7, p. 42717, 2017.
[64] C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," *Adv. Drug Deliv. Rev.*, vol. 46, no. 1–3, pp. 3–26, 2001.
[65] W. L. DeLano, *PyMOL Molecular Graphics System*. San Carlos, CA: DeLano Scientific, 2002.
[66] BIOVIA Discovery Studio, *Discovery Studio Visualizer User Guide*. San Diego, CA: Dassault Systèmes BIOVIA.
[67] M. J. Abraham, T. Murtola, R. Schulz, et al., "GROMACS: High performance molecular simulations through multi-level parallelism," *SoftwareX*, vol. 1–2, pp. 19–25, 2015.
[68] D. E. Shaw, R. O. Dror, J. K. Salmon, et al., "Millisecond-scale molecular dynamics simulations on Anton," *SC09: Proc. ACM/IEEE Conf. High Performance Computing*, pp. 1–11, 2009.
[69] B. K. Mize, A. M. Reed, and coauthors, "Discovery and development of botanical natural products for ovarian cancer," *Cancers*, vol. 15, 2023.
[70] K. Bhattacharya, B. C. Nath, E. Ahmed, et al., "Integration of network pharmacology, molecular docking, and molecular dynamics simulations to evaluate phytochemicals against cancer," *RSC Adv.*, vol. 14, pp. 4188–4200, 2024.
[71] [71] M. Hu, Y. Zhang, and coauthors, "Network pharmacology combined with molecular docking to elucidate anticancer mechanisms of natural products," *Front. Pharmacol.*, 2025.
[72] A. D. Ananto, T. Oktriawan, K. Gurning, et al., "A promising computational study of ovarian cancer treatment using molecular docking, molecular dynamics and ADMET prediction," *J. Herbmed Pharmacol.*, vol. 15, no. 1, pp. 122–134, 2026.
[73] V. Torchilin, "Multifunctional nanocarriers for drug delivery of anticancer agents," *Nat. Rev. Drug Discov.*, vol. 13, no. 11, pp. 813–827, 2014.
[74] Y. Patra, G. Das, A. Fraceto, et al., "Nano based drug delivery systems: Recent developments and future prospects," *J. Nanobiotechnol.*, vol. 16, p. 71, 2018.
[75] S. Mitragotri and R. Langer, "Current status and future prospects of drug delivery technologies," *Nat. Rev. Drug Discov.*, vol. 20, pp. 101–124, 2021.