INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

In Silico and Experimental Insights into Anticancer Potential of Herbal Phytoconstituents

Naveen Kumar B S*, B. Somasekhar, M. Rajeshwari, M. Mallikarjuna, Md. Faheem, Sneha Latha, Vinod Raja A

Togari Veeramallappa Memorial College of Pharmacy, Ballari, Karnataka

ARTICLE INFO

Published: 23 Feb 2026

Keywords:
Phytochemicals; Molecular docking; Anticancer; ADMET; Molecular dynamics; Natural products; Drug discovery; Herbal medicine

DOI:
10.5281/zenodo.18749372

ABSTRACT

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the continuous exploration of safer and more effective therapeutic strategies. Herbal phytoconstituents have emerged as promising sources of anticancer agents due to their structural diversity, multitarget potential, and relatively favorable safety profiles. In recent years, in silico approaches—including molecular docking, molecular dynamics (MD) simulations, network pharmacology, and ADMET prediction—have significantly accelerated the screening and mechanistic evaluation of plant-derived bioactive compounds. This review systematically analyzes recent in silico and experimental studies investigating major classes of phytochemicals, including alkaloids, flavonoids, saponins, coumarins, phenolics, tannins, and steroidal compounds such as diosgenin, for their anticancer potential. These compounds have been evaluated against key oncogenic targets such as estrogen receptor-α (ERα), topoisomerase II, cyclin-dependent kinases (CDKs), MDM2, TNF-α, Bcl-2 family proteins, epidermal growth factor receptor (EGFR), and Hippo signaling mediators. Several phytoconstituents demonstrated moderate to strong binding affinities, favorable pharmacokinetic predictions, and promising in vitro cytotoxic activity across breast, prostate, colorectal, hepatic, and osteosarcoma models. Despite encouraging computational and preliminary biological findings, critical methodological limitations persist. Many studies rely solely on docking scores without adequate validation through redocking protocols, binding free-energy calculations (MM-PBSA/MM-GBSA), long-duration MD simulations, or in vivo confirmation. Furthermore, translational gaps remain regarding pharmacokinetic optimization, toxicity profiling, and clinical applicability. Overall, herbal phytochemicals represent valuable scaffolds for multitarget anticancer drug development. However, integration of robust computational validation, mechanistic experimental studies, and translational pharmacological assessment is essential to advance these natural compounds from theoretical predictions

***Corresponding Author:** Naveen Kumar B S
Address: *Togari Veeramallappa Memorial College of Pharmacy, Ballari, Karnataka.*
Email ✉: naveentvmcp85@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

to clinically viable therapeutics.

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, representing a major public health burden. According to the Global Cancer Observatory (GLOBOCAN), cancer incidence and mortality rates continue to rise globally, driven by aging populations, environmental factors, and lifestyle changes [1]. Despite significant advances in surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy, major challenges persist, including systemic toxicity, multidrug resistance, tumor heterogeneity, high treatment cost, and limited selectivity toward malignant cells. These limitations underscore the urgent need for safer, more effective, and multitarget therapeutic strategies.

Natural products have historically played a pivotal role in anticancer drug discovery. Several clinically approved anticancer agents, including paclitaxel and camptothecin derivatives, originate from plant sources. The structural diversity and biological adaptability of phytochemicals enable them to interact with multiple molecular targets involved in tumor progression, apoptosis regulation, angiogenesis, and metastasis. Recent pharmacological studies have highlighted the therapeutic potential of various plant-derived compounds, including alkaloids [3–7], flavonoids [8–11], saponins [12–16], coumarins [17–19], phenolics [20–22], tannins [25], and steroidal phytoconstituents such as diosgenin [23,24].

In parallel with experimental pharmacology, computational approaches have emerged as powerful tools in modern drug discovery. In silico methodologies such as molecular docking, molecular dynamics (MD) simulations, network pharmacology, quantitative structure–activity relationship (QSAR) modeling, and ADMET prediction allow rapid screening of bioactive compounds, identification of molecular targets, and prediction of pharmacokinetic and toxicity profiles. Network-based pharmacological analyses have further enabled the systematic elucidation of multi-target mechanisms underlying phytochemical actions [21,24]. These approaches significantly reduce time, cost, and experimental burden while enhancing mechanistic understanding at the molecular level.

Recent studies have investigated phytochemicals against critical oncogenic targets, including estrogen receptor-α (ERα), topoisomerase II, cyclin-dependent kinases (CDKs), vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), Bcl-2 family proteins, MDM2, tumor necrosis factor-α (TNF-α), and key regulators of apoptosis and immune modulation [3–16,17–24]. Phenolic compounds and flavonoids have demonstrated multi-target interactions and promising pharmacokinetic characteristics in computational assessments [8–11,20–22], whereas saponins have shown membrane-modulating and apoptosis-inducing properties [12–16]. Similarly, diosgenin has been identified as a potential immunomodulatory and anticancer phytomedicine through integrated in silico and in vitro analyses [23,24].

Although numerous studies report favorable docking scores and preliminary cytotoxicity data, significant methodological limitations remain. Many investigations rely solely on docking results without rigorous validation through redocking protocols, binding free-energy calculations, long-term MD simulations, or comprehensive experimental confirmation. Furthermore, translational gaps persist regarding pharmacokinetic optimization, toxicity profiling, and clinical applicability.

Therefore, the present review aims to systematically analyze and critically evaluate recent in silico and experimental investigations on major classes of herbal phytoconstituents for cancer therapy. By integrating mechanistic insights, computational methodologies, and translational challenges, this review seeks to provide a comprehensive perspective on the current landscape and future directions of phytochemical-based anticancer drug discovery.

1. In Silico Methodologies In Anticancer Phytochemical Research

The integration of computational approaches into natural product–based drug discovery has significantly transformed the evaluation of herbal phytoconstituents for anticancer therapy. In silico methodologies provide mechanistic insights at the molecular level, reduce experimental burden, and accelerate the identification of promising lead compounds prior to laboratory validation. These techniques are particularly valuable in screening structurally diverse phytochemicals such as alkaloids [3–7], flavonoids [8–11], saponins [12–16], coumarins [17–19], phenolics [20–22], diosgenin [23,24], and tannins [25].

Molecular Docking

Molecular docking is the most widely employed computational technique in phytochemical anticancer research. It predicts the preferred binding orientation of a ligand within the active site of a target protein and estimates binding affinity through scoring functions. Numerous studies have utilized docking to evaluate interactions between plant-derived compounds and key oncogenic targets such as estrogen receptor-α (ERα), vascular endothelial growth factor (VEGF), cyclin-dependent kinases (CDKs), tumor necrosis factor-α (TNF-α), MDM2, aromatase (ARO), and epidermal growth factor receptor (EGFR) [3–11,13–15,17–19,23,24].

For example, alkaloid docking against ERα has been reported in Tacca integrifolia and Foeniculum vulgare investigations [3,4], while flavonoid interactions with VEGF and kinase domains have been evaluated computationally [8,9]. Coumarin derivatives have been modeled against ARO and EGFR targets [17–19], and saponins have been docked against TNF-α and MDM2 [14,15]. Diosgenin has also been subjected to docking analysis against MHC-I and oncogenic signaling proteins [23,24].

Docking analyses typically assess hydrogen bonding, hydrophobic interactions, π–π stacking, and electrostatic stabilization within catalytic or regulatory domains. However, while docking provides rapid screening capability, it represents a static model of protein–ligand interaction and requires further validation for dynamic stability and energetic reliability.

Molecular Dynamics (MD) Simulation

Molecular dynamics simulation complements docking by evaluating the stability and conformational behavior of ligand–protein complexes under physiological conditions over time. Parameters such as root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), and hydrogen bond occupancy are commonly analyzed to assess structural stability.

Several phytochemical studies have incorporated MD simulations to confirm stable binding interactions, particularly in saponin and diosgenin investigations [12,14,23,24]. TNF-α–saponin complexes were validated using MD simulations in Vietnamese ginseng research [14], while diosgenin–MHC-I and IGF1R complexes were

analyzed through extended (100 ns) MD simulations [23,24].

Despite these advancements, many phytochemical studies rely on short simulation durations or lack replicate runs, reducing predictive robustness.

Binding Free-Energy Calculations

Advanced computational approaches such as Molecular Mechanics Poisson–Boltzmann Surface Area (MM-PBSA) and Molecular Mechanics Generalized Born Surface Area (MM-GBSA) provide refined estimates of binding free energy beyond docking scores. These calculations improve accuracy by incorporating solvation effects and molecular mechanics energy terms.

Although selected saponin and diosgenin studies have integrated energetic validation approaches [14,23,24], many phytochemical investigations still depend solely on docking energies, highlighting a methodological gap that requires broader implementation across alkaloid, flavonoid, and coumarin research [3–11,17–19].

ADMET and Drug-Likeness Prediction

Pharmacokinetic profiling is essential for evaluating oral bioavailability, metabolic stability, and toxicity risk. In silico ADMET tools predict absorption, distribution, metabolism, excretion, and toxicity parameters based on molecular descriptors.

Flavonoid studies have frequently incorporated drug-likeness filters such as Lipinski, Ghose, Veber, Egan, and Muegge rules [8,11], while diosgenin investigations reported favorable ADMET characteristics supporting pharmacokinetic suitability [23,24]. Phenolic compounds have also been evaluated for drug-likeness and metabolic compatibility through integrated computational analyses [20–22].

However, pharmacokinetic predictions are often not supported by in vivo validation, and issues such as cytochrome P450 inhibition, poor solubility, or bioavailability limitations remain underexplored in several phytochemical classes [8–11,20–22].

Network Pharmacology and Systems Biology Approaches

Network pharmacology integrates bioinformatics, gene–compound interaction mapping, and pathway enrichment analysis to elucidate multi-target mechanisms of phytochemicals. This approach is particularly relevant for natural products, which frequently exert pleiotropic biological effects.

Phenolic compounds were ranked using weighted bipartite network modeling and PageRank-based algorithms targeting cancer stem cell (CSC) regulatory networks [21]. Similarly, systems pharmacology analysis of diosgenin identified hub proteins including IGF1R, MDM2, and SRC and mapped its modulation of PI3K–Akt, MAPK, Ras, and p53 signaling pathways [24].

Such integrative computational approaches provide a systems-level understanding of polypharmacological behavior, which is critical in oncology drug discovery.

Collectively, in silico methodologies serve as powerful preliminary tools for identifying and mechanistically characterizing anticancer phytochemicals. When combined with rigorous experimental validation, advanced energetic modeling, and systems pharmacology integration, these approaches can significantly accelerate the translation of herbal bioactive compounds into clinically viable therapeutic agents.

2. ALKALOIDS: Mechanistic Insights And Computational Evaluation In Cancer Therapy

Alkaloids constitute one of the most pharmacologically significant classes of plant-derived secondary metabolites. Structurally characterized by nitrogen-containing heterocyclic rings, alkaloids exhibit diverse biological activities, including pronounced anticancer effects. Historically, clinically approved chemotherapeutic agents such as vincristine and camptothecin derivatives have originated from alkaloid scaffolds, underscoring their therapeutic importance. Recent studies have increasingly incorporated in silico methodologies to evaluate alkaloid–target interactions and predict anticancer potential prior to experimental validation [3–7].

2.1 Targeting Estrogen Receptor-α (ERα)

Estrogen receptor-α (ERα) is a key regulator of hormone-dependent breast cancer progression. Computational screening of alkaloid-containing extracts has demonstrated moderate binding affinity toward ERα, suggesting potential endocrine-modulating effects. In silico docking analyses targeting ERα (PDB: 3ERT and mutant forms such as Y537S) were reported in investigations of *Tacca integrifolia* and *Foeniculum vulgare* phytoconstituents [3,4].

Docking results revealed hydrogen bonding and hydrophobic stabilization within the ligand-binding domain, supporting possible receptor modulation. However, several methodological limitations were noted, including absence of redocking validation against co-crystallized ligands, limited binding energy comparison with standard ER inhibitors, and insufficient dynamic simulation confirmation [3,4].

2.2 Topoisomerase II Inhibition

Topoisomerase II plays a critical role in DNA replication and cell division and is an established target in cancer chemotherapy. Alkaloid-rich fractions derived from medicinal plants have demonstrated cytotoxic effects in colorectal and breast cancer cell lines, accompanied by docking evidence suggesting interaction with Topoisomerase II catalytic domains [6].

Molecular docking analyses predicted hydrogen bonding and π–π interactions within ATP-binding and DNA-cleavage regions of the enzyme, indicating potential inhibitory activity. However, absence of molecular dynamics validation and limited biochemical enzyme inhibition assays restrict the strength of mechanistic conclusions [6].

2.3 Cytotoxic and In Vitro Validation Studies

Several alkaloid investigations have combined in silico docking with experimental cytotoxicity assays. For example, *Tacca integrifolia* rhizome extract and alkaloid-rich fractions from *Tiliacora acuminata* demonstrated cytotoxic effects against HT-29 and MCF-7 cancer cell lines [3,6].

Additionally, chemoinformatic analysis of *Cocculus hirsutus* methanolic extract evaluated physicochemical descriptors and drug-likeness parameters supporting anticancer potential [7].

2.4 Pharmacokinetics and Drug-Likeness Considerations

In silico ADMET prediction has been applied in selected alkaloid studies to assess oral bioavailability, solubility, and metabolic stability [7]. Many alkaloids demonstrate compliance with Lipinski's rule of five; however, certain glycosylated or high-molecular-weight derivatives may exhibit permeability challenges.

2.5 Critical Appraisal of Current Evidence

Although alkaloids demonstrate promising anticancer potential through ERα modulation, Topoisomerase II interaction, and cytotoxic activity, several recurring limitations are evident across studies [3–7]:

- Overreliance on docking scores without MM-PBSA/MM-GBSA rescoring
- Limited or absent molecular dynamics validation
- Insufficient statistical reporting and replicate runs
- Lack of robust in vivo tumor validation
- Moderate binding affinity compared to established inhibitors

To strengthen translational relevance, future alkaloid research should incorporate long-duration molecular dynamics simulations, binding free-energy calculations, target-specific biochemical assays, apoptosis pathway validation, and preclinical tumor models.

Alkaloids remain structurally versatile and mechanistically promising phytochemicals in anticancer drug discovery. Computational studies have highlighted potential interactions with ERα and Topoisomerase II, while preliminary cytotoxic assays support biological activity [3–7]. However, enhanced methodological rigor and comprehensive experimental validation are essential to advance alkaloid-based compounds from theoretical predictions to clinically relevant anticancer therapeutics.

3. FLAVONOIDS: Multi-Target Anticancer Mechanisms And Computational Evidence

Flavonoids represent one of the most extensively studied classes of plant-derived polyphenolic compounds and are widely recognized for their antioxidant, anti-inflammatory, and anticancer properties. Structurally characterized by a C6–C3–C6 backbone, flavonoids exhibit remarkable chemical diversity that enables interaction with multiple oncogenic signaling pathways. Increasingly, in silico methodologies have been employed to elucidate their molecular mechanisms and prioritize promising lead compounds for further experimental validation [8–11].

3.1 Targeting Angiogenesis and Tyrosine Kinases

Tumor angiogenesis plays a critical role in cancer progression and metastasis, making vascular endothelial growth factor (VEGF) and receptor tyrosine kinases important therapeutic targets. Docking studies of flavonoids derived from *Caesalpinia bonduc* and related plant sources demonstrated strong binding affinities toward VEGF and kinase domains, with interaction profiles comparable to certain standard inhibitors [8,9].

Molecular docking analyses revealed stable hydrogen bonding, hydrophobic contacts, and π–π interactions within catalytic sites, suggesting potential inhibition of angiogenic signaling cascades. However, in several investigations, docking results were not followed by molecular dynamics simulation or enzyme inhibition assays, limiting confirmation of binding stability and biological efficacy [8,9].

Additionally, comprehensive reviews of plant-derived bioactive compounds emphasize the importance of computational modeling in evaluating flavonoid-mediated anti-angiogenic mechanisms in breast cancer systems [10].

3.2 Cyclin-Dependent Kinase (CDK) Inhibition

Cyclin-dependent kinases (CDKs) regulate cell cycle progression and are frequently dysregulated in malignancies. Computational exploration of flavonoids targeting CDK8 has demonstrated favorable binding interactions within the ATP-binding pocket, supported by hydrogen bonding and hydrophobic stabilization [11].

Docking analyses identified potential inhibitory interactions with catalytic residues essential for CDK activity. ADMET predictions in these studies indicated acceptable drug-likeness profiles and favorable oral absorption characteristics [11]

3.3 Network Pharmacology and Multi-Target Mechanisms

A defining feature of flavonoids is their ability to modulate multiple signaling pathways simultaneously. Network pharmacology approaches have identified phenolic-flavonoid compounds such as resveratrol, quercetin, curcumin, epigallocatechin gallate, and genistein as high-ranking candidates targeting cancer stem cell (CSC) regulatory networks [21].

Weighted bipartite network modeling and PageRank-based algorithms revealed strong associations between flavonoids and pathways governing apoptosis, proliferation, immune modulation, and metastasis [21]. Such systems-level analyses reinforce the polypharmacological behavior of flavonoids and highlight their potential advantages over single-target therapeutic agents.

Moreover, computational and experimental investigations demonstrate that flavonoids influence oxidative stress regulation, kinase signaling cascades, and angiogenic pathways [8–11].

3.4 Pharmacokinetic and Toxicological Profiling

Drug-likeness evaluation using Lipinski, Ghose, Veber, Egan, and Muegge filters has been incorporated into several flavonoid studies [8,11]. ADMET profiling frequently predicts favorable intestinal absorption and acceptable toxicity parameters.

However, certain flavonoids exhibit cytochrome P450 inhibitory potential, which may increase the risk of drug–drug interactions [8–11]. Additionally, poor aqueous solubility and rapid metabolic degradation remain challenges limiting clinical translation.

Although computational toxicity assessments are encouraging, in vivo pharmacokinetic validation is often lacking.

3.5 Critical Evaluation of Current Evidence

While flavonoids exhibit strong theoretical potential as multi-target anticancer agents, several limitations are evident across studies [8–11,21]:

- Predominant reliance on docking without molecular dynamics validation
- Limited application of MM-PBSA/MM-GBSA binding free-energy calculations
- Incomplete in vivo tumor model validation
- Overinterpretation of moderate docking scores
- Insufficient pathway-specific biochemical assays

Despite these limitations, flavonoids remain promising due to:

- Structural diversity
- Multi-target capability

- Favorable drug-likeness profiles
- Systems-level pathway modulation

Flavonoids demonstrate significant potential in anticancer drug discovery through inhibition of angiogenesis, regulation of CDKs, and multi-target modulation of cancer-associated signaling networks [8–11,21]. Computational approaches have accelerated mechanistic understanding; however, enhanced methodological rigor—including extended MD simulations, energetic rescoring, and comprehensive experimental validation—is essential to advance flavonoid-based compounds toward translational and clinical applicability.

4. SAPONINS: Membrane Modulation, Apoptotic Signaling, And Computational Insights

Saponins are structurally diverse amphiphilic glycosides composed of a hydrophobic aglycone (sapogenin) linked to one or more hydrophilic sugar moieties. This dual structural nature enables strong interactions with biological membranes, cholesterol-rich domains, and intracellular signaling proteins. Increasing evidence highlights the anticancer potential of saponins through mechanisms involving membrane permeabilization, apoptosis induction, immune modulation, and inhibition of oncogenic signaling pathways [12–16].

4.1 Membrane Interaction and Cytotoxic Mechanisms

The amphiphilic properties of saponins allow them to interact with lipid bilayers and cholesterol molecules, leading to pore formation, membrane destabilization, and increased cellular permeability [12]. This interaction contributes to erythrocyte hemolysis and selective cytotoxicity in tumor cells.

Lorent et al. described the biophysical basis of saponin–membrane interaction, demonstrating their capacity to disrupt membrane integrity and alter lipid organization [12]. Such membrane-disruptive properties may enhance intracellular drug delivery and trigger mitochondrial dysfunction, ultimately activating intrinsic apoptotic pathways.

4.2 Modulation of Apoptosis and Oncogenic Pathways

Several saponins have been investigated for their ability to regulate apoptosis-related proteins such as Bcl-2, Bcl-xL, and caspases. Gymnema-derived saponins were evaluated through docking and experimental models targeting anti-apoptotic Bcl-2 family proteins [16]. These studies demonstrated modulation of apoptotic regulators and chemopreventive effects in prostate cancer models [16].

Steroidal saponins such as Paris saponin VII have been reported to activate the Hippo signaling pathway, promoting autophagy–apoptosis crosstalk in osteosarcoma systems [13]. Western blot analyses confirmed modulation of MST1/2, LATS1, YAP, LC3, and caspase-related proteins, supporting dual-mechanism anticancer activity [13].

4.3 Targeting TNF-α and Inflammatory Mediators

Inflammatory cytokines such as tumor necrosis factor-α (TNF-α) contribute to tumor progression and immune evasion. Docking and molecular dynamics simulation studies evaluating triterpene saponins from Vietnamese ginseng demonstrated

stable interaction with TNF-α, supported by RMSD and RMSF stability parameters [14].

Binding affinity values in the range of −7 to −9 kcal/mol were reported, suggesting potential inhibitory capacity [14].

4.4 MDM2 Inhibition and Apoptosis Reactivation

The p53–MDM2 axis plays a central role in tumor suppression. Computational docking studies have evaluated marine-derived saponins and related compounds for their potential to inhibit MDM2 and activate procaspase-3 [15].

Redocking validation and interaction analysis identified hydrogen bonding and hydrophobic stabilization within the MDM2 binding pocket [15].

4.5 In Vivo Chemopreventive Evidence

Some investigations integrate in silico docking with in vivo chemopreventive models. For example, gymnemic saponins have been evaluated against Bcl-2 and Bcl-xL through computational docking and short-duration molecular dynamics simulations, followed by testing in prostate cancer rat models [14-16].

Although apoptosis modulation was observed, limitations include short MD simulation duration (10 ns), small sample sizes, absence of tumor incidence analysis, and incomplete histopathological validation.

4.6 Critical Appraisal of Current Evidence

Although saponins exhibit multi-pathway anticancer activity, several recurring limitations are evident across studies [12–16]:

- Overreliance on docking without extended MD validation
- Limited binding free-energy calculations
- Insufficient pharmacokinetic confirmation
- Small sample sizes in in vivo studies
- Minimal clinical translation

Despite these limitations, saponins remain promising due to their:

- Membrane-modulating capability
- Apoptosis induction through intrinsic and extrinsic pathways
- Immune-modulatory potential
- Multi-target signaling regulation

Saponins demonstrate broad-spectrum anticancer activity through membrane interaction, apoptosis induction, inflammatory pathway modulation, and p53-axis regulation [12–16]. Computational analyses provide valuable mechanistic insights; however, enhanced methodological rigor—including extended molecular dynamics simulation, binding free-energy rescoring, pharmacokinetic optimization, and comprehensive in vivo validation—is essential for advancing saponin-based compounds toward clinical translation.

5. COUMARINS: Multitarget Inhibition And Structure–Activity Relationships In Cancer Therapy

Coumarins are benzopyrone derivatives widely distributed in medicinal plants and recognized for their diverse pharmacological properties, including anticoagulant, anti-inflammatory, antimicrobial, and anticancer activities. Structural

flexibility of the coumarin scaffold enables substitution at multiple positions, facilitating the rational design of multitarget anticancer agents. Recent investigations have integrated synthetic chemistry, in vitro cytotoxic evaluation, and in silico modeling to optimize coumarin-based therapeutics [17–19].

5.1 Aromatase and EGFR Inhibition in Breast Cancer

Hormone-dependent and triple-negative breast cancers frequently involve dysregulation of aromatase (ARO) and epidermal growth factor receptor (EGFR) signaling pathways. Rationally designed 4,7-disubstituted coumarin derivatives have demonstrated potent cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cell lines [17].

Molecular docking analyses revealed favorable binding interactions within the active sites of ARO and EGFR, characterized by hydrogen bonding, π–π stacking, and hydrophobic stabilization comparable to standard inhibitors [17]. Mechanistic investigations further confirmed apoptosis induction via caspase-9 activation, increased Bax/Bcl-2 ratio, and cell cycle arrest at G0/G1 and S phases [17].

These findings highlight the multitarget inhibitory capacity of coumarins in modulating hormone synthesis and receptor tyrosine kinase signaling simultaneously.

5.2 Structure–Activity Relationship (SAR) Insights

Structure–activity relationship (SAR) analyses have emphasized the importance of lipophilicity, electronic properties, and heterocyclic substitutions in enhancing anticancer potency. Comprehensive reviews of coumarin derivatives demonstrate that substitution at the C-4 and C-7 positions significantly influences binding affinity, target selectivity, and pharmacokinetic behavior [18].

Hybrid molecules incorporating triazole moieties, fused heterocyclic systems, and metal complexes have shown improved biological activity and potential to overcome drug resistance mechanisms [18]. Such structural optimization strategies aim to improve therapeutic efficacy while reducing off-target toxicity.

5.3 Mechanistic Landscape and Molecular Pathways

Beyond ARO and EGFR inhibition, coumarins have been reported to modulate multiple oncogenic pathways, including:

- Mitochondrial apoptosis signaling
- Cell cycle regulation
- Kinase inhibition
- Angiogenesis suppression
- Oxidative stress modulation

Recent mechanistic studies further underscore the role of coumarin derivatives in targeting breast cancer–associated molecular mediators and signaling cascades [19]. Molecular docking, ADMET prediction, and QSAR modeling were integrated to identify promising lead compounds with favorable pharmacological profiles [17–19].

5.4 Integration of In Silico and Experimental Validation

Among phytochemical classes discussed in this review, coumarins demonstrate relatively strong integration of computational and experimental methodologies.

Studies have combined:

- Molecular docking
- QSAR modeling
- ADMET prediction
- In vitro cytotoxicity assays

Docking analyses consistently report favorable binding energies and stable interactions within catalytic domains [17,19]. ADMET profiling suggests acceptable oral bioavailability and manageable toxicity risk [17].

However, despite encouraging findings, several limitations persist:

- Limited long-duration molecular dynamics validation
- Incomplete MM-PBSA/MM-GBSA binding free-energy calculations
- Insufficient in vivo tumor model confirmation
- Need for extended pharmacokinetic optimization

5.5 Critical Evaluation

Compared to alkaloids and saponins, coumarins exhibit stronger rational design strategies and clearer structure–activity relationships [17–19]. Nevertheless, certain methodological gaps remain:

- Overreliance on docking without extended dynamic validation
- Limited energetic rescoring
- Absence of large-scale in vivo validation
- Minimal clinical translation data

Despite these limitations, coumarins are among the most structurally optimized phytochemical classes in anticancer research, making them promising candidates for further translational development.

Coumarins represent versatile and chemically modifiable scaffolds with significant potential for multitarget anticancer therapy. Through rational structural optimization, integrated computational modeling, and in vitro validation, coumarin derivatives have demonstrated promising activity against breast and other cancer types [17–19]. Future investigations incorporating extended molecular dynamics simulations, comprehensive pharmacokinetic profiling, and in vivo tumor validation will be essential to advance coumarin-based compounds toward clinical applicability.

6. PHENOLICS: Network Pharmacology, Apoptosis Modulation, And Systems-Level Anticancer Insights

Phenolic compounds constitute a broad class of plant-derived secondary metabolites characterized by one or more hydroxyl groups attached to aromatic rings. These compounds exhibit potent antioxidant, anti-inflammatory, and anticancer activities. Owing to their structural diversity and redox-modulating properties, phenolics have been extensively investigated through integrated in silico, in vitro, and systems pharmacology approaches to elucidate their anticancer mechanisms [20–22].

6.1 Apoptosis Regulation and Molecular Docking Evidence

Apoptosis dysregulation is a hallmark of cancer progression. Several phenolic compounds have been evaluated for their ability to modulate apoptosis-related proteins. Docking studies of phenolic constituents from *Plectranthus*

amboinicus demonstrated favorable binding interactions with apoptosis-regulating proteins, supporting potential pro-apoptotic activity [20].

Complementary in vitro investigations using MTT assays confirmed dose-dependent cytotoxicity against hepatic cancer models, strengthening the biological relevance of computational findings [20]. Additionally, phenolic compounds isolated from *Moringa oleifera* exhibited anticancer potential supported by both docking analysis and experimental validation [22].

6.2 Hepatic Anticancer Potential and ADMET Profiling

Phytochemical screening of phenolic-rich plant extracts has identified compounds such as carvacrol, thymol, limonene, vanillin, cineole, and syringic acid with potential hepatic anticancer activity [20]. Drug-likeness evaluations using Lipinski, Ghose, Veber, Egan, and Muegge criteria indicated acceptable pharmacokinetic properties in selected phenolic compounds [20,22].

ADMET predictions further supported favorable absorption, metabolic compatibility, and manageable toxicity risk [22]. Molecular docking demonstrated moderate binding affinities toward apoptosis-related and oncogenic proteins, suggesting potential inhibitory interactions.

Additionally, in silico ranking and network modeling approaches have highlighted phenolic compounds as important modulators of cancer-associated pathways [21].

6.3 Cancer Stem Cell (CSC) Targeting and Network-Based Ranking

Cancer stem cells (CSCs) contribute to tumor initiation, metastasis, recurrence, and therapeutic resistance. Network pharmacology approaches have been applied to systematically rank phenolic compounds based on their regulatory influence over CSC-associated genes [21].

Using weighted bipartite network modeling and PageRank-based algorithms, phenolic compounds such as resveratrol, curcumin, quercetin, epigallocatechin gallate, and genistein were identified as top-ranking candidates targeting CSC regulatory networks [21]. Disease Specificity Index (DSI) and Disease Pleiotropy Index (DPI) analyses further supported their relevance across multiple malignancies.

This systems-level analysis underscores the polypharmacological nature of phenolics and their ability to simultaneously modulate apoptosis, proliferation, immune response, and metabolic pathways.

6.4 Integration of Experimental and Computational Findings

Phenolic research represents one of the more integrated phytochemical fields combining:

- GC–MS or chromatographic characterization
- In vitro cytotoxicity assays
- Molecular docking
- ADMET prediction
- Network pharmacology modeling

Studies on *Plectranthus amboinicus* and *Moringa oleifera* demonstrate combined computational and experimental validation pipelines [20,22], while systems-level CSC ranking provides broader mechanistic insights [21].

Although many phenolic compounds satisfy common drug-likeness criteria, bioavailability challenges remain due to:

- Rapid metabolism
- Low aqueous solubility
- First-pass hepatic clearance

While computational ADMET profiling suggests acceptable safety margins [20,22], clinical translation requires improved formulation strategies and pharmacokinetic optimization.

6.5 Critical Evaluation

Despite these advances, several limitations remain:

- Predominant reliance on docking without extended MD validation
- Limited MM-PBSA/MM-GBSA binding free-energy calculations
- Moderate binding energies compared to synthetic inhibitors
- Insufficient in vivo tumor model validation

Phenolic compounds demonstrate considerable anticancer potential through apoptosis modulation, oxidative stress regulation, and multi-target network interactions [20–22]. Systems pharmacology approaches highlight their relevance in cancer stem cell regulation and pathway modulation [21]. However, enhanced computational rigor, energetic rescoring, long-duration molecular dynamics validation, and comprehensive in vivo experimentation are essential to translate phenolic phytochemicals into clinically viable anticancer therapeutics.

7. DIOSGENIN: Immunomodulatory And Multi-Pathway Targeting Potential In Cancer Therapy

Diosgenin is a naturally occurring steroidal sapogenin widely distributed in medicinal plants, particularly *Dioscorea* species. Structurally characterized by a spirostane framework, diosgenin has attracted considerable attention due to its anti-inflammatory, immunomodulatory, and anticancer properties. Unlike broader phytochemical classes discussed earlier, diosgenin has been investigated as a defined lead compound through integrated computational, systems pharmacology, and experimental approaches [23,24].

7.1 Targeting MHC-I and Cancer Immunomodulation

Antigen presentation via major histocompatibility complex class I (MHC-I) plays a crucial role in tumor immune surveillance. In silico screening of phytochemicals targeting MHC-I (PDB: 3AM8) identified diosgenin as a top-ranked candidate with strong binding affinity (approximately −8.9 kcal/mol) [23].

Molecular docking analysis demonstrated stable hydrogen bonding and hydrophobic interactions within the antigen-binding cleft of MHC-I [23]. Subsequent molecular dynamics simulations (100 ns) confirmed the stability of the diosgenin–MHC-I complex, supported by favorable RMSD, RMSF, and radius of gyration parameters [23].

ADMET profiling further indicated compliance with Lipinski's rule of five, acceptable oral bioavailability, and minimal predicted toxicity [23].

These findings suggest that diosgenin may enhance antigen presentation or modulate immune recognition pathways, although direct immunological validation remains limited.

7.2 Systems Pharmacology and Multi-Target Mechanisms

Beyond immunomodulation, systems pharmacology analyses have elucidated the multi-target anticancer mechanisms of diosgenin in breast cancer models [24]. Network-based approaches identified key hub proteins including IGF1R, MDM2, SRC, and other regulators of proliferation and apoptosis resistance [24].

Pathway enrichment analysis revealed modulation of multiple oncogenic cascades, including:

- PI3K–Akt signaling
- MAPK pathway
- Ras signaling
- FoxO pathway
- p53 regulatory network

Molecular docking confirmed strong binding affinity of diosgenin toward IGF1R and additional oncogenic targets [24]. Molecular dynamics simulations further validated complex stability over extended simulation durations, strengthening confidence in predicted interactions [24].

7.3 In Vitro Validation and Functional Evidence

Importantly, diosgenin studies extend beyond computational modeling to include experimental validation. In vitro assays using breast cancer cell lines (e.g., MCF-7 and SKBR3) demonstrated significant cytotoxicity, inhibition of proliferation, and modulation of metabolic pathways associated with tumor growth [24].

Experimental findings corroborated computational predictions, supporting apoptosis induction and suppression of oncogenic signaling pathways. This integrated computational–experimental workflow distinguishes diosgenin research from many docking-only phytochemical investigations.

7.4 Pharmacokinetic and Drug-Likeness Profile

ADMET profiling of diosgenin indicates favorable pharmacokinetic properties, including acceptable lipophilicity, membrane permeability, and metabolic stability [23,24]. Compared to glycosylated saponins, diosgenin's relatively small steroidal structure enhances cellular uptake potential.

However, limited aqueous solubility remains a challenge, suggesting that formulation strategies such as nanoparticle encapsulation or structural modification may improve therapeutic applicability.

7.5 Critical Evaluation

Among the phytochemicals reviewed, diosgenin demonstrates one of the most comprehensive evaluation pipelines, integrating:

- Virtual screening
- Molecular docking
- 100-ns molecular dynamics simulation
- Systems pharmacology
- Pathway enrichment analysis
- In vitro cytotoxic validation

Despite these strengths, certain limitations persist [23,24]:

- Limited in vivo tumor xenograft validation
- Insufficient pharmacokinetic confirmation in animal models

- Need for functional immune assays to validate MHC-I modulation
- Absence of advanced clinical trial data

Nevertheless, diosgenin represents one of the most translationally promising phytochemicals discussed in this review.

Diosgenin exhibits multi-target anticancer potential supported by robust computational modeling and experimental validation [23,24]. Its ability to modulate immune pathways, apoptosis regulators, and major oncogenic signaling cascades positions it as a strong candidate for further preclinical development. Future research integrating in vivo tumor validation, pharmacokinetic optimization, and immunotherapeutic confirmation will be essential to advance diosgenin toward clinical application.

8. TANNINS: Polyphenolic Cytotoxic Agents And Apoptosis Induction In Cancer Therapy

Tannins are high-molecular-weight polyphenolic compounds broadly classified into hydrolyzable tannins and condensed tannins. Known for their strong protein-binding capacity and antioxidant properties, tannins have attracted attention for their potential anticancer activity. Their polyhydroxylated structure enables interaction with cellular proteins, enzymes, and signaling mediators, contributing to modulation of apoptosis, proliferation, and oxidative stress pathways in tumor cells [25].

8.1 Anti-Proliferative and Apoptotic Activity

Experimental investigations evaluating tannin-rich extracts have demonstrated significant anti-proliferative effects in cancer cell models. Tannins isolated from *Quercus infectoria* showed notable cytotoxic activity against oral cancer (KB) cell lines, accompanied by apoptosis induction [25].

Mechanistic studies reported activation of caspases, disruption of mitochondrial membrane potential, and modulation of apoptosis-related markers, indicating activation of intrinsic apoptotic pathways [25]. These findings suggest that tannins may function as pro-apoptotic agents capable of overcoming resistance mechanisms in malignant cells.

8.2 Molecular Interaction and Mechanistic Considerations

The polyphenolic nature of tannins allows formation of multiple hydrogen bonds with proteins involved in cell cycle regulation and apoptosis. The high density of hydroxyl groups facilitates strong binding interactions with enzymes and signaling proteins.

However, due to their large molecular size and structural complexity, tannins may experience reduced membrane permeability and limited intracellular accessibility. Comprehensive molecular docking and molecular dynamics investigations remain underexplored in tannin research, representing an important future direction for mechanistic validation [25].

8.3 Pharmacokinetic and Translational Challenges

Despite promising in vitro cytotoxicity, several pharmacological challenges limit tannin-based therapeutic development [25]:

- Poor oral bioavailability due to high molecular weight
- Limited membrane permeability
- Extensive gastrointestinal metabolism

- Non-specific protein binding
- Rapid systemic clearance

Few studies integrate ADMET prediction, pharmacokinetic modeling, or advanced computational simulations in tannin research. Compared to alkaloids, flavonoids, saponins, coumarins, phenolics, and diosgenin, tannins exhibit comparatively limited computational integration.

8.4 Critical Evaluation

Although tannins demonstrate clear anti-proliferative and pro-apoptotic effects in oral cancer models [25], several research gaps remain:

- Lack of target-specific docking validation
- Absence of molecular dynamics simulation
- Minimal energetic rescoring
- Limited in vivo tumor model confirmation
- Insufficient pharmacokinetic profiling

Nevertheless, tannins possess strong antioxidant and apoptosis-modulating properties, which may support their role as adjuvant or combination therapy agents in oncology.

Tannins demonstrate notable anticancer potential through apoptosis induction and anti-proliferative activity in oral cancer systems [25]. While experimental evidence supports biological efficacy, computational characterization and pharmacokinetic optimization remain limited. Future research integrating molecular docking, dynamic simulation, ADMET profiling, and in vivo tumor validation will be essential to fully elucidate the therapeutic potential of tannins in cancer treatment.

9. Comparative Analysis

The phytochemical classes discussed in this review—alkaloids, flavonoids, saponins, coumarins, phenolics, diosgenin, and tannins—demonstrate diverse anticancer mechanisms and varying degrees of computational and experimental validation. A comparative evaluation reveals differences in molecular targets, methodological robustness, pharmacokinetic suitability, and translational readiness [3–25].

Alkaloids primarily exhibit target-specific interactions, particularly against estrogen receptor-α (ERα) and Topoisomerase II, supported by docking and moderate cytotoxic validation [3–7]. However, most alkaloid studies lack extended molecular dynamics validation and energetic rescoring.

Flavonoids demonstrate broader multi-target modulation, including inhibition of VEGF, CDKs, and kinase pathways, supported by docking and ADMET profiling [8–11]. Network pharmacology analyses further highlight their systems-level regulatory influence on cancer stem cell (CSC) networks [21]. Despite strong theoretical potential, experimental validation remains limited in some investigations.

Saponins exhibit membrane-disruptive properties, apoptosis induction, and modulation of inflammatory and p53-related pathways [12–16]. Compared to alkaloids and flavonoids, saponin research more frequently integrates molecular dynamics simulations; however, pharmacokinetic limitations such as poor bioavailability and hemolytic potential restrict translational applicability.

Coumarins represent one of the more structurally optimized classes, with rational multitarget design strategies targeting aromatase (ARO) and EGFR in

breast cancer systems [17–19]. These studies demonstrate relatively strong integration of synthetic optimization, in vitro cytotoxicity, docking, and SAR modeling, suggesting improved translational readiness compared to several other phytochemical classes.

Phenolic compounds exhibit systems-level pathway modulation supported by docking, ADMET prediction, and network modeling approaches [20–22]. Cancer stem cell ranking and pathway enrichment analyses further reinforce their polypharmacological nature [21]. Nevertheless, moderate binding energies and limited in vivo validation remain challenges.

Diosgenin demonstrates one of the most comprehensive computational–experimental pipelines among all compounds reviewed. Studies integrate virtual screening, molecular docking, 100-ns molecular dynamics simulation, systems pharmacology, and in vitro cytotoxic validation [23,24]. Its ability to modulate immune pathways (MHC-I), IGF1R, PI3K–Akt, MAPK, and p53-related signaling pathways places diosgenin closer to translational applicability relative to other phytochemicals.

Tannins, while demonstrating strong anti-proliferative and pro-apoptotic activity in oral cancer models, remain predominantly experimentally characterized with minimal computational integration [25]. Pharmacokinetic limitations, including high molecular weight and poor bioavailability, further limit immediate translational potential.

Overall, comparative analysis indicates that:

- **Diosgenin** [23,24] **and rationally designed coumarins** [17–19] exhibit the most comprehensive computational–experimental integration.
- **Flavonoids and phenolics** [8–11,20–22] demonstrate strong multi-target and systems-level potential.
- **Saponins** [12–16] show potent biological activity but face pharmacokinetic challenges.
- **Alkaloids** [3–7] **and tannins** [25] remain at relatively earlier stages of mechanistic and translational development.

Comparative analysis reveals that while all phytochemical classes exhibit promising anticancer properties, significant variability exists in computational rigor, mechanistic depth, pharmacokinetic suitability, and translational readiness. Integrated computational–experimental workflows, advanced free-energy validation, pharmacokinetic optimization, and in vivo tumor models are essential to advance these natural compounds from theoretical promise to clinically viable anticancer therapeutics (Table.1).

Table 1: Comparative Overview of Phytochemical Classes in Anticancer Research

Phytochemical Class	Representative Phytochemical Constituents	Major Molecular Targets	Reported Binding Energy (kcal/mol)*	Computational Methods Used	Experimental Validation	Ref.
Alkaloids	Tiliacora alkaloids, Tacca integrifolia alkaloids, Foeniculum vulgare constituents	ERα, Topoisomerase II	−6.0 to −9.2	Molecular Docking	MTT assay, cytotoxic studies	[3–7]

Flavonoids	Quercetin, Kaempferol, Genistein, Flavonoids from Caesalpinia bonduc	VEGF, CDKs, kinase domains	−7.0 to −10.5	Docking, ADMET, Network pharmacology	Limited in vitro validation	[8–11,21]
Saponins	Paris saponin VII, Gymnemic saponins, Vietnamese ginseng saponins	Bcl-2, TNF-α, MDM2, Hippo pathway	−7.0 to −9.8	Docking, MD simulation (10–100 ns)	Apoptosis assays; limited in vivo	[12–16]
Coumarins	4,7-Disubstituted coumarins, Coumarin hybrids, Triazole–coumarin derivatives	Aromatase (ARO), EGFR	−8.0 to −11.2	Docking, QSAR, ADMET	Strong in vitro validation (MCF-7, MDA-MB-231)	[17–19]
Phenolics	Carvacrol, Thymol, Vanillin, Syringic acid, Phenolics from Moringa oleifera	Apoptosis mediators, CSC-associated genes	−4.8 to −8.5	Docking, ADMET, Network modeling	In vitro cytotoxic assays	[20–22]
Diosgenin	Diosgenin (steroidal sapogenin)	MHC-I, IGF1R, PI3K–Akt, MAPK	−8.5 to −10.0	Docking, 100-ns MD, Systems pharmacology	Strong in vitro validation	[23,24]
Tannins	Tannins from Quercus infectoria	Apoptosis-related proteins (general)	Not consistently reported	Minimal docking; limited MD	Strong anti-proliferative activity (KB cells)	[25]

10. Future Perspectives

The expanding application of in silico methodologies in phytochemical anticancer research has generated substantial preliminary evidence supporting the therapeutic potential of natural compounds. However, translating these computational findings into clinically viable therapeutics requires strategic integration of advanced technologies, experimental rigor, pharmacokinetic optimization, and translational frameworks [3–25].

10.1 Integration of Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) algorithms offer transformative opportunities in natural product drug discovery. Predictive modeling platforms can:

- Identify structure–activity relationships (SAR) more efficiently
- Predict target selectivity and off-target interactions
- Optimize pharmacokinetic properties
- Reduce false-positive docking predictions

Such approaches may significantly enhance lead identification among alkaloids [3–7], flavonoids

[8–11], saponins [12–16], coumarins [17–19], phenolics [20–22], and steroidal compounds such as diosgenin [23,24]. Integration of AI with molecular docking, molecular dynamics simulation, and network pharmacology could improve predictive accuracy and reproducibility across phytochemical classes.

10.2 Multi-Target and Polypharmacology-Based Drug Design

Cancer is a multifactorial disease characterized by dysregulation of interconnected signaling networks. Single-target inhibition often leads to resistance development. Phytochemicals inherently exhibit polypharmacological behavior, simultaneously modulating multiple pathways [21,24].

Future research should focus on:

- Designing hybrid molecules (e.g., coumarin-based conjugates) [17–19]
- Targeting central signaling hubs such as PI3K–Akt, MAPK, Ras, and p53 pathways [23,24]
- Combining phytochemicals with standard chemotherapeutics
- Evaluating synergistic interactions between natural compounds

Expansion of systems biology and network pharmacology approaches will be essential to identify optimal multi-target combinations and minimize resistance mechanisms [21,24].

10.3 Advanced Computational Validation Pipelines

To enhance reliability and translational value, future computational workflows should incorporate:

- Redocking validation with RMSD benchmarking
- Long-duration molecular dynamics simulations (>100 ns)
- MM-PBSA/MM-GBSA binding free-energy calculations
- Enhanced sampling techniques
- Replicate simulation runs for statistical robustness

Although molecular dynamics has been incorporated in selected saponin and diosgenin studies [14,23,24], many alkaloid, flavonoid, and coumarin investigations still rely predominantly on static docking predictions [3–11,17–19]. Standardization of docking parameters, reporting guidelines, and reproducibility metrics will improve cross-study comparability.

10.4 Pharmacokinetic Optimization and Drug Delivery Systems

Limited bioavailability remains a major barrier to clinical translation, particularly for large or highly glycosylated molecules such as saponins and tannins [12–16,25]. Even phenolic compounds and flavonoids may suffer from rapid metabolism and low systemic stability [20–22].

Innovative drug delivery strategies may overcome these challenges, including:

- Nanoparticle-based delivery systems
- Liposomal encapsulation
- Solid lipid nanoparticles

- Polymer-based controlled release formulations

Structural modification, prodrug design, and conjugation strategies may further enhance solubility, metabolic stability, and tissue targeting of phytochemicals [17–19,23,24].

10.5 Integration of Experimental and Clinical Validation

Computational predictions must be validated through rigorous experimental workflows, including:

- Enzyme inhibition assays
- Apoptosis and cell cycle analysis
- Gene expression profiling
- CRISPR-based target validation
- In vivo tumor xenograft and orthotopic models

Although diosgenin demonstrates integrated computational–experimental validation [23,24], most phytochemical classes lack comprehensive preclinical validation pipelines [3–25]. Pharmacokinetic and toxicity studies in animal models are essential prior to clinical evaluation.

Subsequent early-phase clinical trials will be necessary to assess safety, tolerability, and therapeutic efficacy of optimized phytochemical derivatives.

10.6 Personalized and Precision Oncology Approaches

Advances in genomics and molecular profiling enable personalized cancer treatment strategies. Future phytochemical research should explore:

- Matching compounds to tumor-specific mutations
- Biomarker-driven patient stratification
- Combination therapy tailored to molecular subtype

For example, ER-positive breast cancer may benefit from ER-modulating alkaloids or coumarins [3,4,17], while immune-responsive tumors may potentially benefit from immunomodulatory compounds such as diosgenin [23]. Systems pharmacology approaches can support precision-based selection of phytochemicals aligned with specific oncogenic signatures [21,24].

The future of phytochemical-based anticancer therapy lies in the convergence of artificial intelligence, advanced computational validation, rational structural optimization, innovative drug delivery systems, and rigorous experimental confirmation [3–25]. By adopting standardized, multidisciplinary research frameworks, herbal phytoconstituents may progress from promising computational candidates to clinically impactful anticancer therapeutics.

CONCLUSION

Herbal phytoconstituents represent a structurally diverse and biologically versatile reservoir of potential anticancer agents. The integration of in silico methodologies—including molecular docking, molecular dynamics simulations, ADMET prediction, and network pharmacology—has significantly accelerated the identification and mechanistic characterization of plant-derived bioactive compounds [3–25]. Across the phytochemical classes discussed in this review—alkaloids, flavonoids, saponins, coumarins, phenolics, diosgenin, and tannins—multiple

oncogenic targets have been explored, including ERα, Topoisomerase II, CDKs, VEGF, EGFR, Bcl-2 family proteins, MDM2, TNF-α, IGF1R, and key regulators of apoptosis and immune modulation [3–16,17–24].

Comparative evaluation indicates that flavonoids and phenolics demonstrate broad multi-target and systems-level modulation [8–11,20–22], while saponins exhibit membrane-disruptive and apoptosis-inducing properties supported by computational and experimental analyses [12–16]. Coumarins show promise through rational multitarget design and structure–activity optimization strategies [17–19]. Among all compounds reviewed, diosgenin presents one of the most comprehensive computational–experimental validation pipelines, integrating docking, extended molecular dynamics simulations, systems pharmacology, and in vitro cytotoxic confirmation [23,24]. In contrast, tannins, although demonstrating significant anti-proliferative activity, remain comparatively underexplored in computational modeling and pharmacokinetic optimization [25].

Despite encouraging docking scores and preliminary cytotoxic findings, several methodological limitations persist across studies. Overreliance on static docking predictions, limited application of binding free-energy calculations, insufficient long-duration molecular dynamics validation, inconsistent ADMET profiling, and lack of robust in vivo tumor confirmation restrict translational progression [3–25]. Furthermore, pharmacokinetic challenges such as poor bioavailability, metabolic instability, and potential toxicity must be addressed to enable clinical applicability.

In conclusion, herbal phytoconstituents offer substantial promise as multi-target anticancer agents. However, their successful transition from computational prediction to clinical implementation requires standardized computational workflows, rigorous experimental validation, pharmacokinetic optimization, and integration of systems-level and precision oncology approaches. Strengthened multidisciplinary collaboration across computational chemistry, molecular biology, pharmacology, and clinical oncology will determine whether these natural compounds evolve from promising bioactive scaffolds into effective and safe anticancer therapeutics.

REFERENCES

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: Cancer today. Lyon (FR): International Agency for Research on Cancer; 2020.
2. Zhao YZ, Zhang YY, Han H, Fan RP, Hu Y, Zhong L, et al. Advances in the antitumor activities and mechanisms of action of steroidal saponins. Chin J Nat Med. 2018;16(8):732–748.
3. Ahmed S, Paul A, Islam MA, et al. In vivo and in silico anticancer evaluation of Tacca integrifolia rhizome extract. Clin Phytosci. 2019;5(36):1-9.
4. Kaur B, Sharma M, Rani J, et al. In silico evaluation of Foeniculum vulgare phytoconstituents against ERα Y537S mutant: implications for breast cancer therapy. Comput Biol Chem. 2021;95:107585.
5. Jena S, Nayak S, Patel MP, et al. Cytotoxic and in silico evaluation of Piper trioicum essential oil. Pharmacogn Mag. 2020;16(69):124-130.
6. Rodrigues J, Pereira RTF, Oliveira MF, et al. Molecular docking and cytotoxic analysis of alkaloids from Tiliacora acuminata against

breast cancer targets. Phytother Res. 2021;35(4):2085-2096.
7. Salve NR, Patil MV, Shenoy RP. Chemoinformatic analysis of Cocculus hirsutus methanolic extract: Evaluation against cancer targets. J Pharm Bioallied Sci. 2020;12(3):131-139.
8. Iheagwam FN, Igoli JO, Igoli NP. Molecular docking and ADMET analysis of flavonoids from Caesalpinia bonduc. AIP Conf Proc. 2018;1954:030015.
9. Rajesh N, Karthikeyan C, Gopinath R, et al. Evaluation of selected flavonoids as anticancer agents using computational, in vitro cytotoxicity, and ADMET methods. Bioorg Chem. 2022;120:105535.
10. Shrihastini VK, Suchal K, Malik MR, et al. Plant-derived bioactive compounds and in silico approaches in breast cancer: A comprehensive review. Cancers (Basel). 2021;13(22):6222.
11. Rathod S, Patel P, Desai B, et al. Computational exploration of flavonoids against cyclin-dependent kinase 8. J Mol Model. 2022;28:57.
12. Lorent J, Quetin-Leclercq J, Mingeot-Leclercq MP. The amphiphilic nature of saponins and effects on biological membranes. RSC Adv. 2014;4:37840-37857.
13. Xiang YC, Meng XY, Li YG, et al. Paris saponin VII induces autophagy and apoptosis via Hippo pathway modulation in human osteosarcoma cells. Front Pharmacol. 2021;12:718151.
14. Kim OTP, Le MD, Trinh HX, Nong HV. Interaction of tumor necrosis factor-α with saponins from Vietnamese ginseng: docking and mechanistic insights. Int J Biol Macromol. 2016;86:123-132.
15. Yanuar A, Pratiwi I, Syahdi RR. Activity analysis of saponins against MDM2 inhibitor and procaspase-3 activator: A molecular docking study. J Young Pharm. 2018;10(2):204-209. doi:10.5530/jyp.2018.10.46
16. 1Pon Nivedha R, Ramasamy M, Siddique SI, et al. Chemopreventive effect of saponin on prostate cancer: In silico and in vivo evidence. BMC Complement Med Ther. 2017;17(1):204.
17. Takla FN, Bayoumi WA, ElMessery SM, Nasr MNA. Development of multitarget coumarin-based anti-breast cancer agents: Synthesis and evaluation. Sci Rep. 2023;13:13370. doi:10.1038/s41598-023-40313-6
18. Bhattarai N, Baral R, Aryal S, et al. Anticancer potential of coumarin derivatives: A mini review. Mini Rev Med Chem. 2021;21(16):2996-3029.
19. Hacholli VB, Alam M, Berisha A, et al. Coumarin derivatives as anticancer agents: Synthesis and structure–activity relationships. Molecules. 2025;30(3):4167.
20. Sindhu MS, Poonkothai M, Thirumalaisamy R. Phenolic compounds from Plectranthus amboinicus as hepatic anticancer agents. S Afr J Bot. 2022;149:420-432.
21. Mandal M, Ghosh S, Datta A, et al. In silico ranking of phenolics for cancer stem cells using network pharmacology. BMC Bioinformatics. 2020;21(Suppl 21):499.
22. Mumtaz MZ, Khan S, Qureshi R, et al. Anticancer activities of phenolic compounds extracted from Moringa oleifera. Beni-Suef Univ J Basic Appl Sci. 2022;11(1):96-109.
23. Jasrotia S, Sharma A, Bisht T, et al. In-silico identification of diosgenin targeting MHC-I for cancer therapy. J Mol Struct. 2022;1260:132791.
24. Khanal P, Patil VS. Systems and in vitro pharmacology profiling of diosgenin for breast cancer therapy. Front Pharmacol. 2023;14:1052849.

25. Ahmad F, Farooqui W, Rahman M, et al. Anti-proliferative activity of tannins from Quercus infectoria against oral cancer cells. J Appl Pharm Sci. 2024;14(06):184-199.

HOW TO CITE: Naveen Kumar B S, B. Somasekhar, M. Rajeshwari, M. Mallikarjuna, Md. Faheem, Sneha Latha, Vinod Raja A, In Silico and Experimental Insights into Anticancer Potential of Herbal Phytoconstituents, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 2, 3769-3791. https://doi.org/10.5281/zenodo.18749372