Biocompounds

www.bic.reapress.com

Biocompd. Vol. 3, No. 1 (2026) 1–12.

Paper Type: Original Article

Plant-Derived Bioactive Compounds in Cancer Therapy: Mechanisms, Clinical Advances, and Future Perspectives

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Citation:

Received: 07 August 2025 *Revised: 25 October 2025* *Accepted: 16 December 2025*	Edalatpanah, S. A. (2026). Plant-derived bioactive compounds in cancer therapy: Mechanisms, clinical advances, and future perspectives. *Biocompounds, 3*(1), 1-12.

Abstract

Cancer remains a leading cause of morbidity and mortality worldwide, necessitating innovative therapeutic strategies with improved selectivity and reduced toxicity. Plant-derived bioactive compounds, encompassing secondary metabolites such as alkaloids, terpenoids, phenolics, saponins, and organosulfur compounds, have emerged as a rich and sustainable source of novel anticancer agents. Clinically established drugs, including paclitaxel, vinca alkaloids, and camptothecin derivatives, exemplify the successful translation of phytochemicals into frontline oncology therapies, primarily through mechanisms involving microtubule disruption, topoisomerase inhibition, apoptosis induction, cell cycle arrest, angiogenesis suppression, and modulation of key signaling pathways (e.g., NF-κB, PI3K/Akt, MAPK, Wnt/β-catenin, and p53). This review comprehensively examines the major classes of plant-derived bioactive compounds with documented anticancer potential, highlights notable examples (paclitaxel, vincristine, curcumin, resveratrol, EGCG, and others), and synthesizes preclinical (in vitro and in vivo) and clinical evidence supporting their efficacy, often in combination regimens or as chemosensitizers. Despite promising multi-target actions and favorable selectivity profiles, significant challenges persist, including poor bioavailability, pharmacokinetic variability, dose-limiting toxicities, Multidrug Resistance (MDR), standardization issues, and regulatory hurdles. Addressing these limitations through advanced formulation technologies (e.g., nano-delivery systems), metabolic engineering, semi-synthetic optimization, and interdisciplinary approaches holds substantial promise for enhancing translational success. As global cancer incidence continues to rise, plant-derived phytochemicals offer a bridge between traditional ethnopharmacology and modern precision oncology, potentially delivering more effective, accessible, and sustainable anticancer therapies in the future.

Keywords: Phytochemicals, Anticancer agents, Secondary metabolites, Apoptosis, Bioavailability, Precision Oncology.

1 | Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with an estimated 19.3 million new cases and nearly 10 million deaths reported in 2020, projections indicating a rise to over 28 million cases by 2040 due to aging populations and lifestyle factors [1]. Despite significant advancements in therapeutic

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https://doi.org/10.48313/bic.v3i1.57

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modalities such as surgery, radiation, chemotherapy, immunotherapy, and targeted therapies, the efficacy of conventional anticancer drugs is often hampered by severe side effects, including cardiotoxicity, neurotoxicity, and immunosuppression, as well as the emergence of Multidrug Resistance (MDR) in tumor cells. These limitations underscore the urgent need for novel anticancer agents that exhibit high selectivity, reduced toxicity, and enhanced efficacy against resistant cancers [1].

Natural products have historically served as a cornerstone in drug discovery, particularly in oncology, where approximately 60% of approved anticancer agents are derived from or inspired by natural sources. Among these, plant-derived bioactive compounds stand out due to their structural diversity, evolutionary optimization for biological interactions, and multifaceted pharmacological activities. Plants synthesize a vast array of secondary metabolites such as alkaloids, flavonoids, terpenoids, polyphenols, saponins, and glycosides as defense mechanisms against environmental stressors, many of which possess potent anticancer properties. These compounds exert their effects through multiple mechanisms, including induction of apoptosis, cell cycle arrest, inhibition of angiogenesis, modulation of signaling pathways (e.g., MAPK/ERK, PI3K/Akt, NF-κB), and suppression of metastasis [2–4].

Iconic examples of plant-derived anticancer agents include vinca alkaloids (vincristine and vinblastine) from Catharanthus roseus, which disrupt microtubule assembly and are used in treating lymphomas and leukemias; paclitaxel (Taxol) from Taxus brevifolia, a microtubule stabilizer effective against breast, ovarian, and lung cancers; and camptothecin derivatives (e.g., irinotecan) from Camptotheca acuminata, which inhibit topoisomerase I and are employed in colorectal cancer therapy. More recent investigations have highlighted compounds like curcumin from Curcuma longa, resveratrol from grapes, betulinic acid from birch trees, and quercetin from various fruits and vegetables, which demonstrate antiproliferative, antioxidant, and anti-inflammatory effects in preclinical models. These bioactive agents often target Cancer Stem Cells (CSCs), overcome MDR by sensitizing tumors to conventional drugs, and exhibit chemopreventive potential by enhancing immune responses and reducing oxidative stress [5].

The biodiversity of medicinal plants, particularly from tropical rainforests and ethnopharmacological traditions, offers an untapped reservoir for novel drug leads. Advances in high-throughput screening, metabolic engineering, and bioinformatics have accelerated the identification and optimization of these compounds, enabling Structure-Activity Relationship (SAR) studies to enhance potency and bioavailability. For instance, synthetic analogs of plant alkaloids have shown improved pharmacokinetics while retaining anticancer efficacy. Moreover, combinatorial approaches integrating plant extracts with synthetic drugs could mitigate toxicities and synergize therapeutic outcomes.

2 | Major Classes of Plant-Derived Bioactive Compounds with Anticancer Potential

Plant-derived bioactive compounds, widely known as phytochemicals or secondary metabolites, constitute a structurally diverse library of molecules evolved by plants for protection against pathogens, herbivores, and environmental stresses. These compounds are biosynthesized through distinct pathways (e.g., shikimate for phenolics, mevalonate/MEP for terpenoids, and amino acid-derived for alkaloids) and are classified into several major chemical families based on their carbon skeletons and functional groups. The principal classes with documented anticancer activity include alkaloids, terpenoids (isoprenoids), phenolic compounds (including polyphenols, flavonoids, and stilbenes), saponins, and organosulfur compounds. These classes often exhibit pleiotropic effects, targeting multiple hallmarks of cancer such as sustained proliferation, evasion of apoptosis, angiogenesis, metastasis, and immune evasion, while displaying favorable selectivity toward malignant cells compared to normal tissues *(Table 1)* [6–10].

2.1 | Alkaloids

Alkaloids are nitrogen-containing heterocyclic compounds primarily derived from amino acids (e.g., tryptophan, tyrosine, ornithine). They represent one of the most clinically successful classes, with several

FDA-approved anticancer drugs. Vinca alkaloids (vincristine, vinblastine) from Catharanthus roseus inhibit tubulin polymerization, causing mitotic spindle disruption and G2/M arrest. Camptothecin derivatives (irinotecan, topotecan) from Camptotheca acuminata stabilize topoisomerase I–DNA cleavage complexes, inducing DNA strand breaks. Berberine (from Berberis vulgaris and related species) modulates NF-ϰB, PI3K/Akt/mTOR, and AMPK pathways, promoting apoptosis and inhibiting metastasis. Homoharringtonine from Cephalotaxus harringtonia inhibits protein synthesis and is approved for chronic myeloid leukemia [11].

2.2 | Terpenoids (Isoprenoids)

Terpenoids, the largest phytochemical class, are synthesized via the mevalonate or 2-C-methyl-D-erythritol-4-phosphate (MEP) pathways and classified by isoprene unit number (monoterpenes, sesquiterpenes, diterpenes, triterpenes). Paclitaxel (Taxol®) and docetaxel, diterpenoids from Taxus species, stabilize microtubules, leading to mitotic arrest and apoptosis in breast, ovarian, and lung cancers. Artemisinin (sesquiterpene lactone) from Artemisia annua generates ROS via endoperoxide bridge cleavage, inducing ferroptosis and apoptosis. Betulinic acid and ursolic acid (pentacyclic triterpenoids) from birch bark and various fruits trigger mitochondrial outer membrane permeabilization, caspase activation, and VEGF downregulation for anti-angiogenic effects [9].

2.3 | Phenolic Compounds

Phenolic compounds encompass aromatic molecules with hydroxyl groups, derived from the shikimate/phenylpropanoid pathway. Subclasses include phenolic acids, flavonoids (flavonols, flavones, flavanols, isoflavones, anthocyanins), stilbenes, and lignans. Curcumin from Curcuma longa suppresses NF-ϰB, STAT3, Wnt/β-catenin, and PI3K/Akt signaling, induces p53-dependent apoptosis, and sensitizes cells to chemotherapy. Resveratrol (stilbene) from Vitis vinifera activates sirtuins (SIRT1), p53, and AMPK while inhibiting mTOR and angiogenesis. Flavonoids such as quercetin (widely distributed in onions, apples), Epigallocatechin Gallate (EGCG) from Camellia sinensis (green tea), and genistein from soybean inhibit CDK-cyclin complexes for G1/S arrest, downregulate MMPs to block invasion, and exert strong antioxidant/anti-inflammatory effects via Nrf2 activation [6], [8].

2.4 | Saponins

Saponins are glycosylated triterpenoids or steroids with amphiphilic properties. Ginsenosides from Panax ginseng induce apoptosis via caspase-3/8/9 activation, reverse MDR by inhibiting P-glycoprotein, and suppress NF-ϰB-mediated inflammation. Other saponins (e.g., from Dioscorea species) disrupt membrane integrity and modulate immune responses [9].

2.5 | Organosulfur Compounds

Organosulfur compounds (e.g., isothiocyanates, thiosulfinates) from Allium and cruciferous vegetables activate Phase II detoxification enzymes via Nrf2, induce apoptosis, and inhibit HDAC activity. Sulforaphane from broccoli is a potent HDAC inhibitor and Nrf2 activator. These classes provide structurally optimized, multi-target scaffolds that address key limitations of conventional chemotherapeutics, including resistance and toxicity. Their diversity supports ongoing high-throughput screening, semi-synthesis, and nanoformulation efforts to enhance bioavailability and clinical translation [10].

Table 1. Overview of key phytochemical classes and their anticancer properties.

Targeted Cancer Types	Key Anticancer Mechanisms	Primary Plant Source(s)	Key Compound Examples	Major Subclasses	Chemical Class
Leukemia, Lymphoma, Colorectal, Breast, Ovarian, Chronic myeloid leukemia	Microtubule disruption, Topoisomerase I inhibition, NF-κB/PI3K/Akt/mTOR inhibition, Protein synthesis inhibition	Catharanthus roseus, Camptotheca acuminata, Berberis spp., Cephalotaxus harringtonia	Vincristine, Vinblastine, Irinotecan, Topotecan, Berberine, Homoharringtonine	Vinca alkaloids, Camptothecins, Isoquinoline alkaloids	Alkaloids
Breast, Ovarian, Lung, Leukemia, Melanoma, Prostate	Microtubule stabilization, ROS generation and ferroptosis, Mitochondrial apoptosis, VEGF downregulation and anti-angiogenesis	Taxus spp., Artemisia annua, Birch bark (Betula spp.), Various fruits and herbs	Paclitaxel, Docetaxel, Artemisinin, Betulinic acid, Ursolic acid	Diterpenoids, Sesquiterpenes, Triterpenoids	Terpenoids (Isoprenoids)
Colorectal, Breast, Prostate, Lung, Multiple cancers	NF-κB/STAT3/Wnt/β-catenin/PI3K/Akt inhibition, p53-dependent apoptosis, G1/S cell cycle arrest, MMP downregulation and anti-metastasis, Nrf2 activation	Curcuma longa, Vitis vinifera (grapes), Onions/apples, Camellia sinensis (green tea), Soybean	Curcumin, Resveratrol, Quercetin, EGCG, Genistein	Flavonoids (flavonols, flavanols, isoflavones), Stilbenes, Phenolic acids	Phenolic Compounds/Polyphenols
Breast, Lung, Prostate, Liver, Colon	Caspase-3/8/9 activation and apoptosis, P-glycoprotein inhibition and MDR reversal, NF-κB suppression, Immune modulation	Panax ginseng, Dioscorea spp.	Ginsenosides (Rg3, Rh2), Diosgenin derivatives	Triterpenoid saponins, Steroidal saponins	Saponins
Prostate, Breast, Colon, Bladder	Nrf2 activation and phase II enzyme induction, HDAC inhibition, Apoptosis induction	Cruciferous vegetables (e.g., broccoli), Allium spp. (garlic, onion)	Sulforaphane, Allicin	Isothiocyanates, Thiosulfinates	Organosulfur Compounds

3 | Notable Examples of Plant-Derived Anticancer Agents

Building upon the classification of major phytochemical classes outlined in the previous section, this part focuses on selected representative compounds that have achieved significant milestones in anticancer research and clinical application. These agents exemplify the transition from traditional ethnopharmacological use to modern oncology, highlighting both approved therapeutics and promising investigational leads. The compounds discussed here, primarily paclitaxel (and taxanes), vinca alkaloids (vincristine and vinblastine), camptothecin derivatives, curcumin, resveratrol, and EGCG have been extensively studied in preclinical models, clinical trials, and routine clinical practice *(Table 2)*. Their inclusion underscores the structural diversity, mechanistic versatility, and translational success of plant-derived molecules in addressing the hallmarks of cancer [10–12].

3.1 | Paclitaxel and Taxane Derivatives

Paclitaxel (Taxol), a complex diterpenoid originally isolated from the bark of the Pacific yew tree (Taxus brevifolia), represents one of the most impactful plant-derived anticancer agents in modern medicine. Approved by the FDA in 1992, paclitaxel exerts its primary cytotoxic effect by binding to β-tubulin subunits,

promoting microtubule polymerization and stabilization. This hyperstabilization disrupts the dynamic equilibrium required for mitotic spindle assembly, resulting in prolonged mitotic arrest at the G2/M phase, activation of the spindle assembly checkpoint, and ultimately apoptosis via caspase-dependent pathways. Docetaxel, a semi-synthetic analog with improved water solubility and potency, shares a similar mechanism but exhibits enhanced tubulin affinity and broader spectrum activity [8–10].

Clinically, paclitaxel and docetaxel are integral to standard regimens for breast, ovarian, non-small cell lung, and head and neck cancers, often in combination with platinum agents or anthracyclines. Despite their efficacy, limitations include peripheral neuropathy, myelosuppression, and hypersensitivity reactions (attributable to the Cremophor EL vehicle in conventional formulations). Nanoparticle albumin-bound paclitaxel (nab-paclitaxel, Abraxane) addresses some of these issues by improving bioavailability and reducing toxicity, leading to superior outcomes in metastatic breast cancer and pancreatic adenocarcinoma. Ongoing research explores taxane combinations with targeted therapies (e.g., PARP inhibitors, immune checkpoint inhibitors) to overcome resistance mediated by efflux transporters (e.g., P-glycoprotein) or tubulin mutations [11].

3.2 | Vinca Alkaloids (Vincristine and Vinblastine)

The vinca alkaloids, isolated from the Madagascar periwinkle (Catharanthus roseus), were among the earliest plant-derived anticancer drugs introduced into clinical practice (vincristine in 1963, vinblastine in 1965). These dimeric indole alkaloids bind to tubulin at a distinct site from taxanes, inhibiting microtubule assembly and causing depolymerization. The resulting disruption of mitotic spindles leads to metaphase arrest and apoptotic cell death, preferentially in rapidly proliferating cells. Vincristine remains a cornerstone in pediatric Acute Lymphoblastic Leukemia (ALL), Hodgkin and non-Hodgkin lymphomas, and Wilms tumor protocols (e.g., within COG and SIOP regimens). Vinblastine is frequently incorporated into regimens for testicular cancer, Kaposi sarcoma, and advanced Hodgkin lymphoma. Neurotoxicity (peripheral and autonomic) constitutes the principal dose-limiting toxicity, prompting investigations into liposomal vincristine formulations (e.g., Marqibo) that improve pharmacokinetics and reduce cumulative neuropathy. Recent studies also explore vinca analogs and conjugates to enhance tumor selectivity and circumvent MDR [11].

3.3 | Camptothecin Derivatives (Irinotecan and Topotecan)

Camptothecin, a quinoline alkaloid from Camptotheca acuminata, inspired the development of topoisomerase I inhibitors. The parent compound exhibited promising activity but poor solubility and toxicity; semi-synthetic derivatives irinotecan (approved 1996) and topotecan (approved 1996) overcame these barriers. These agents stabilize the topoisomerase I–DNA cleavable complex, preventing religation and generating persistent single-strand breaks that convert to lethal double-strand breaks during S-phase replication. Irinotecan is a key component of FOLFIRI regimens for metastatic colorectal cancer and is active in small-cell lung cancer and cervical cancer. Topotecan is indicated for relapsed ovarian cancer, small-cell lung cancer, and cervical cancer. Irinotecan metabolism via carboxylesterases and UGT1A1 influences efficacy and toxicity, guiding pharmacogenomic dosing strategies [13].

3.4 | Curcumin

Curcumin, the principal curcuminoid from turmeric (Curcuma longa), is a pleiotropic polyphenol with extensive preclinical evidence of anticancer activity. It modulates multiple signaling cascades including NF-ϰB, STAT3, PI3K/Akt/mTOR, Wnt/β-catenin, and MAPK, leading to downregulation of pro-survival genes, induction of p53-dependent apoptosis, cell cycle arrest (primarily G1/S or G2/M), suppression of angiogenesis (via VEGF inhibition), and inhibition of invasion/metastasis (via MMP-2/9 downregulation). Curcumin also sensitizes cancer cells to conventional chemotherapeutics and radiotherapy while exhibiting chemopreventive properties through Nrf2 activation and antioxidant effects. Despite promising in vitro and in vivo data across breast, colorectal, pancreatic, prostate, and glioblastoma models, clinical translation is hampered by poor bioavailability (rapid metabolism and low aqueous solubility). Strategies such as

nanoparticle formulations (e.g., liposomal, polymeric, or phospholipid complexes), structural analogs (e.g., EF24, FLLL32), and combination therapies have advanced curcumin into phase II/III trials for colorectal adenoma prevention, pancreatic cancer, and multiple myeloma. Ongoing studies evaluate its role as an adjunct to standard care [11–13].

3.5 | Resveratrol

Resveratrol, a stilbene phytoalexin abundant in grape skins (Vitis vinifera), peanuts, and berries, activates sirtuins (particularly SIRT1), p53, and AMPK while inhibiting mTOR, NF-ϰB, and STAT3 pathways. These actions promote apoptosis, cell cycle arrest (G1 phase), autophagy, and anti-angiogenic effects, with additional benefits in overcoming MDR and targeting CSCs. Preclinical efficacy spans breast, prostate, colorectal, and leukemia models. Clinical trials have explored resveratrol in colorectal cancer prevention (reduced proliferation markers), prostate cancer (PSA modulation), and as a radiosensitizer. Low bioavailability remains a challenge, addressed through micronized or methylated derivatives and nano formulations [14].

3.6 | Epigallocatechin Gallate

EGCG, the major catechin in green tea (Camellia sinensis), inhibits multiple targets, including EGFR, VEGF, NF-ϰB, and PI3K/Akt, inducing apoptosis, cell cycle arrest, and anti-metastatic effects. It shows promise in prostate, breast, colorectal, and lung cancers. Clinical studies indicate chemopreventive potential (e.g., reduced prostate cancer progression in high-grade PIN) and synergy with conventional agents [15]. A schematic representation of the chemical structures and primary plant sources of these notable agents is presented in *Fig. 1*, laying the foundation for the subsequent discussion of preclinical and clinical evidence.

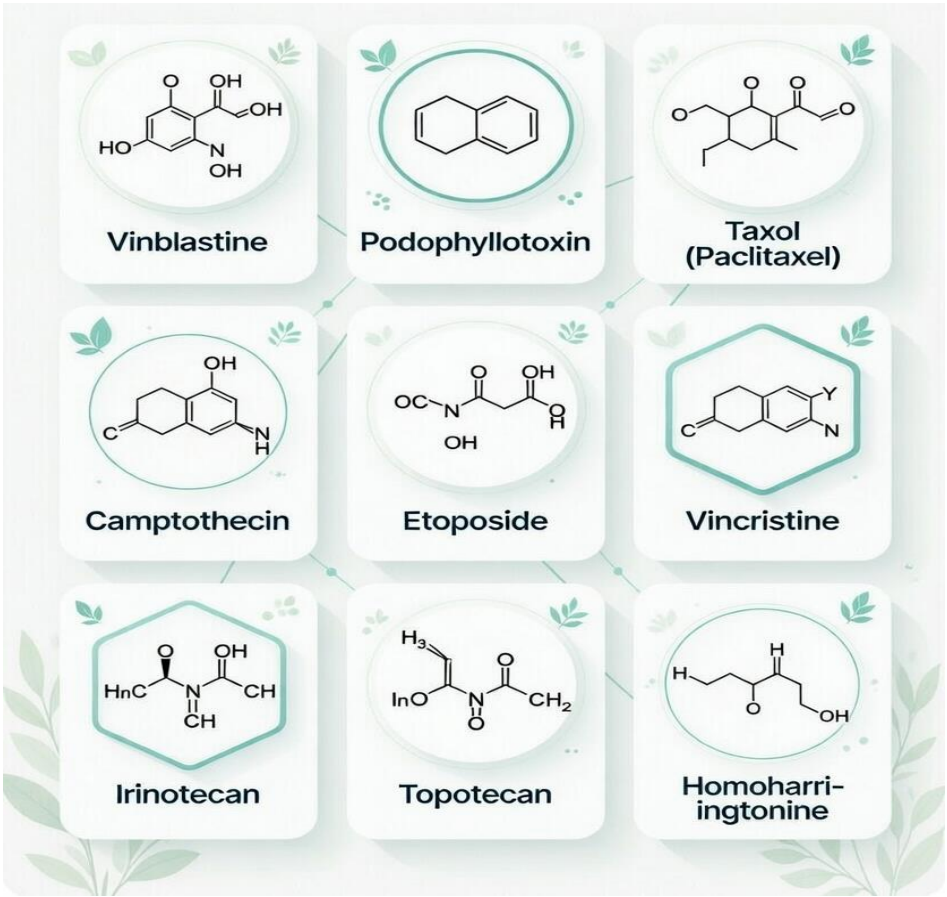

Fig. 1. Schematic overview of notable plant-derived anticancer agents, illustrating their key chemical structures and primary plant sources.

Table 2. Notable examples of plant-derived anticancer agents: key compounds, sources, mechanisms, and clinical applications.

Compound	Chemical Class	Primary Plant Source	Key Mechanism of Action	Main Targeted Cancers/Clinical Use	Status (FDA/Approved or Stage)
Paclitaxel (Taxol)	Diterpenoid (Taxane)	Taxus brevifolia (Pacific yew bark)	Stabilizes microtubules → mitotic arrest (G2/M phase), apoptosis	Breast, ovarian, non-small cell lung, head and neck, pancreatic (nab-paclitaxel)	FDA-approved (1992)
Docetaxel	Diterpenoid (Taxane, semi-synthetic)	Semi-synthetic from Taxus precursors	Similar to paclitaxel: microtubule stabilization, enhanced potency	Breast, prostate, lung, gastric, head and neck	FDA-approved (1996)
Vincristine	Vinca alkaloid	Catharanthus roseus (Madagascar periwinkle)	Inhibits tubulin polymerization → mitotic spindle disruption, G2/M arrest	ALL, lymphomas, Wilms tumor	FDA-approved (1963)
Vinblastine	Vinca alkaloid	Catharanthus roseus	Similar to vincristine: microtubule depolymerization	Hodgkin lymphoma, testicular cancer, Kaposi sarcoma	FDA-approved (1965)
Irinotecan	Camptothecin derivative	Semi-synthetic from Camptotheca acuminata	Topoisomerase I inhibition → DNA strand breaks, S-phase lethality	Metastatic colorectal (FOLFIRI), small-cell lung, cervical	FDA-approved (1996)
Topotecan	Camptothecin derivative	Semi-synthetic from Camptotheca acuminata	Topoisomerase I inhibition	Relapsed ovarian, small-cell lung, cervical	FDA-approved (1996)
Curcumin	Polyphenol (Curcuminoid)	Curcuma longa (Turmeric rhizome)	Pleiotropic: NF-κB, STAT3, PI3K/Akt, Wnt inhibition; p53-dependent apoptosis; anti-angiogenic	Colorectal, pancreatic, breast, prostate (preclinical/adjunct)	Investigational (Phase II/III trials), poor bioavailability addressed by formulations
Resveratrol	Stilbene (Polyphenol)	Vitis vinifera (Grapes), berries	SIRT1 activation, p53/AMPK upregulation, mTOR/NF-κB inhibition; anti-angiogenic, CSC targeting	Colorectal prevention, prostate, breast (preclinical/radiosensitizer)	Investigational (Phase I/II trials)
EGCG	Catechin (Flavonoid)	Camellia sinensis (Green tea)	EGFR/VEGF/PI3K/Akt/NF-κB inhibition; apoptosis, cell cycle arrest	Prostate (chemoprevention), breast, colorectal, lung	Investigational (Phase II trials, green tea extracts)
Artemisinin/ Artesunate	Sesquiterpene lactone	Artemisia annua	ROS generation via endoperoxide bridge → ferroptosis, apoptosis	Leukemia, breast, colorectal (preclinical/repurposed)	Investigational (Phase I/II, malaria drug repurposed)
Betulinic acid	Pentacyclic triterpenoid	Birch bark (Betula spp.)	Mitochondrial apoptosis, caspase activation, anti-angiogenic (VEGF↓)	Melanoma, neuroblastoma, leukemia (preclinical)	Investigational (early trials)

4 | Preclinical and Clinical Evidence

The anticancer potential of plant-derived bioactive compounds has been rigorously evaluated through a continuum of experimental models, progressing from in vitro assays and in vivo animal studies to human clinical trials. Preclinical investigations provide mechanistic insights, dose-response relationships, and proof-of-concept efficacy, while clinical evidence establishes translational relevance, safety profiles, and therapeutic impact in patients. This section synthesizes recent findings (primarily from 2020–2026 literature) on key compounds discussed earlier, highlighting both established agents (e.g., paclitaxel, vinca alkaloids) and emerging phytochemicals (e.g., curcumin, resveratrol, EGCG), as well as broader trends in plant secondary metabolites [15].

4.1 | Preclinical Evidence (in Vitro and in Vivo Models)

In vitro studies using human cancer cell lines consistently demonstrate that plant-derived compounds target multiple hallmarks of cancer. For instance, paclitaxel and docetaxel induce profound G2/M arrest and apoptosis in breast, ovarian, and lung cancer lines via microtubule stabilization, with IC_{50} values often in the nanomolar range. Vinca alkaloids (vincristine, vinblastine) similarly disrupt microtubule dynamics, leading to mitotic catastrophe in leukemia and lymphoma models.

Curcumin exhibits pleiotropic effects across diverse cell lines (e.g., colorectal HCT116, pancreatic MIA PaCa-2, breast MCF-7), suppressing NF-κB, STAT3, PI3K/Akt/mTOR, and Wnt/β-catenin pathways, downregulating anti-apoptotic proteins (Bcl-2, survivin), upregulating pro-apoptotic Bax and caspases, and inhibiting invasion/metastasis via MMP-2/9 downregulation. Recent reviews (2024–2026) emphasize curcumin's ability to induce ferroptosis, autophagy, and epigenetic modulation (e.g., HDAC inhibition). Resveratrol activates SIRT1/AMPK, inhibits mTOR/NF-κB, and targets CSCs in breast, prostate, and colorectal models, often synergizing with chemotherapy to reverse MDR via P-glycoprotein inhibition. EGCG from green tea modulates EGFR, VEGF, and PI3K/Akt signaling, inducing apoptosis and cell cycle arrest (G1/S) in prostate, breast, and lung cancer cells, with strong antioxidant effects via Nrf2 activation [11–15].

Terpenoids such as artemisinin derivatives generate ROS and induce ferroptosis in leukemia and breast cancer lines, while betulinic acid triggers mitochondrial apoptosis and anti-angiogenic effects (VEGF suppression) in melanoma and neuroblastoma models. Organosulfur compounds like sulforaphane activate Nrf2-mediated phase II detoxification and inhibit HDAC, exerting chemopreventive activity in prostate and colon models. In vivo xenograft and orthotopic models in mice/rats corroborate these findings. Paclitaxel/docetaxel significantly reduces tumor volume in breast and ovarian xenografts. Curcumin formulations (e.g., liposomal, nanoparticle) inhibit tumor growth in pancreatic and colorectal models, often enhancing gemcitabine or 5-FU efficacy. Resveratrol and EGCG reduce metastasis in orthotopic breast cancer models and improve survival in prostate cancer xenografts. Recent studies (2024–2025) highlight synergistic effects of combinations (e.g., curcumin + resveratrol, EGCG + chemotherapy) in overcoming resistance and targeting tumor microenvironment inflammation. Overall, preclinical data from 2023–2026 reviews confirm multi-target mechanisms (apoptosis induction, cell cycle arrest, anti-angiogenesis, anti-metastasis, pathway modulation including MAPK/ERK, PI3K/Akt, NF-κB, Wnt/β-catenin, and p53 activation), with many compounds showing selectivity for malignant cells and low toxicity to normal tissues [14].

4.2 | Clinical Evidence and Trials

Several plant-derived agents have advanced to clinical use or ongoing evaluation. Paclitaxel and docetaxel remain standard-of-care in multiple regimens (e.g., breast, ovarian, lung, pancreatic), with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) demonstrating superior efficacy and tolerability in metastatic settings (e.g., pancreatic adenocarcinoma). Vinca alkaloids continue in pediatric ALL, lymphoma, and testicular cancer protocols, with liposomal formulations mitigating neurotoxicity. Curcumin has progressed to Phase II/III trials as an adjunct. Examples include trials in advanced pancreatic cancer (combined with

gemcitabine), colorectal adenoma prevention, and multiple myeloma, showing improved response rates, reduced inflammation markers (e.g., IL-6, CRP), and enhanced chemotherapy tolerance. Nanoformulations and bioenhancers (e.g., piperine) address bioavailability issues, with promising pharmacokinetics in recent studies. Resveratrol has been evaluated in Phase I/II trials for colorectal cancer prevention (reduced proliferation markers), prostate cancer (PSA modulation), and as a radiosensitizer, with evidence of safety and biological activity (e.g., SIRT1 activation). EGCG (as Polyphenon E or green tea extracts) shows chemopreventive potential in high-grade prostatic intraepithelial neoplasia (reduced progression) and synergy in breast/colorectal trials.

Other compounds in active or recent trials (2024–2026 updates) include:

I. Artemisinin derivatives (artesunate) in Phase I/II for breast/colorectal (repurposed from malaria, inducing ferroptosis).

II. Sulforaphane/broccoli sprout extracts in prostate/breast prevention trials (Nrf2 activation, HDAC inhibition).

III. Berberine, genistein, and thymoquinone in early-phase studies for various solid tumors.

Challenges in clinical translation include variable bioavailability (especially polyphenols), inter-individual pharmacokinetic differences, and need for standardized extracts/formulations. However, combinatorial approaches (phytochemical + conventional therapy) frequently yield synergistic outcomes, reduced toxicity, and improved quality of life [16].

5 | Challenges and Limitations in the Development and Application of Plant-Derived Anticancer Agents

Despite the impressive track record and promising potential of plant-derived bioactive compounds in anticancer therapy, several significant challenges continue to hinder their widespread clinical adoption, optimization, and translation from bench to bedside. These limitations span pharmacokinetic, pharmacodynamic, toxicological, regulatory, and practical domains and must be systematically addressed to fully realize the therapeutic value of these natural products [11].

5.1 | Poor Bioavailability and Pharmacokinetics

One of the most frequently cited barriers is the generally low oral bioavailability of many promising phytochemicals, particularly polyphenols (e.g., curcumin, resveratrol, EGCG) and certain terpenoids. Rapid Phase II metabolism (glucuronidation, sulfation), extensive first-pass effect, low aqueous solubility, limited intestinal permeability, and active efflux by transporters such as P-glycoprotein and BCRP result in sub-therapeutic plasma concentrations even at high oral doses. For example, curcumin exhibits bioavailability <1% in humans, while resveratrol typically reaches peak plasma concentrations in the low nanomolar range. These pharmacokinetic shortcomings severely restrict the achievement of pharmacologically active concentrations at tumor sites, especially in solid tumors with poor vascularization [10].

5.2 | Dose-Limiting Toxicities and Off-Target Effects

Although many plant compounds show favorable selectivity in preclinical models, clinical use often reveals unexpected toxicities. Vinca alkaloids and taxanes are notorious for dose-limiting peripheral neuropathy, myelosuppression, and hypersensitivity reactions. Camptothecin derivatives frequently cause severe diarrhea (irinotecan) or neutropenia (topotecan). Even "safer" polyphenols can induce gastrointestinal upset, hepatotoxicity, or pro-oxidant effects at high doses. Additionally, some compounds exhibit hormesis beneficial effects at low doses but cytotoxicity or genotoxicity at higher concentrations, complicating dose selection [2–5].

5.3 | Drug Resistance and Tumor Heterogeneity

MDR mediated by efflux pumps, altered drug targets (e.g., tubulin mutations), enhanced DNA repair, and activation of survival pathways remains a major obstacle. While some phytochemicals (e.g., curcumin, resveratrol, ginsenosides) can sensitize resistant cells or inhibit P-gp, many tumors rapidly adapt through genetic and epigenetic heterogeneity. CSC populations, which are often resistant to conventional therapies, are only partially targeted by most plant compounds, limiting long-term disease control [11].

5.4 | Standardization, Quality Control, and Batch-to-Batch Variability

Plant extracts and even purified natural products suffer from significant variability in active compound content due to differences in plant genotype, geographic origin, harvest time, drying method, storage conditions, and extraction procedures. This variability poses serious challenges for reproducible preclinical and clinical studies and for regulatory approval. The lack of Good Manufacturing Practice (GMP)-grade material for many promising leads further delays clinical development [17].

5.5 | Regulatory and Intellectual Property Hurdles

Natural products face unique regulatory challenges. The U.S. FDA and EMA classify many phytochemicals as dietary supplements rather than drugs, limiting rigorous clinical development pathways. Demonstrating "substantial equivalence" to existing therapies is difficult, and large-scale, adequately powered Phase III trials are resource-intensive. Intellectual property protection is also problematic; pure natural compounds are generally not patentable unless significantly modified (e.g., semi-synthetic derivatives like docetaxel or irinotecan). This reduces commercial incentive for pharmaceutical investment despite strong scientific rationale [10].

5.6 | High Cost and Scalability Issues

Sustainable sourcing of rare or slow-growing plants (e.g., Taxus brevifolia for paclitaxel) raises ecological and supply chain concerns. Total chemical synthesis of complex structures like paclitaxel is possible but extremely costly. Biotechnological production (plant cell culture, microbial engineering) is advancing but not yet fully scaled for clinical-grade material [9].

6 | Conclusion

Plant-derived bioactive compounds have long served as a cornerstone in anticancer drug discovery, providing structurally diverse scaffolds with multi-target mechanisms that often surpass the limitations of single-target synthetic therapies. From clinically established agents such as paclitaxel, vinca alkaloids, and camptothecin derivatives to promising investigational leads like curcumin, resveratrol, EGCG, and artemisinin analogs, these phytochemicals demonstrate potent effects on key cancer hallmarks including apoptosis induction, cell cycle arrest, angiogenesis inhibition, metastasis suppression, and modulation of critical signaling pathways (e.g., NF-κB, PI3K/Akt, MAPK, Wnt/β-catenin, and p53). Preclinical and clinical evidence collectively supports their efficacy, selectivity toward malignant cells, and potential in overcoming MDR and targeting CSCs. Nevertheless, persistent challenges including poor bioavailability, pharmacokinetic variability, dose-limiting toxicities, tumor heterogeneity, standardization issues, and regulatory hurdles, continue to impede broader clinical integration and full therapeutic exploitation.

Advances in nanotechnology, metabolic engineering, semi-synthesis, combination regimens, and pharmacogenomic-guided approaches offer realistic pathways to mitigate these limitations and enhance translational success. As global cancer burden escalates, particularly in aging populations and resource-limited settings, harnessing the biodiversity of medicinal plants through rigorous, interdisciplinary research remains a sustainable and promising strategy. Ultimately, plant-derived bioactive compounds not only bridge traditional ethnopharmacology with modern precision oncology but also hold immense potential to deliver safer, more accessible, and effective anticancer therapies in the coming decades.

Authors' Contributions

All aspects of the research and manuscript preparation were carried out by the author. The author has read and approved the final version of the manuscript.

Funding

This study did not receive any specific funding from public, commercial, or non-profit funding agencies.

Data Availability

All data are included in the text.

Conflict of Interest

The author declares that he does not have any conflict of interest.

Consent for Publication

The author has given consent for the publication of this manuscript.

Ethics Approval and Consent to Participate

This study does not involve any research conducted on human participants or animals.

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