REVIEW ARTICLE

The Evolving Role of Phytochemicals in Cancer Therapy: Mechanistic Insights and Emerging Technologies

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Abstract

Cancer remains one of the leading causes of global morbidity and mortality, necessitating the search for novel, effective, and safer therapeutic strategies. Phytochemicals—bioactive compounds derived from medicinal plants—have demonstrated promising anticancer properties by targeting multiple oncogenic pathways, including apoptosis induction, angiogenesis inhibition, metastasis suppression, and immune modulation. Among the most studied phytochemicals, alkaloids (vincristine, camptothecin), flavonoids (quercetin, genistein), terpenoids (paclitaxel, artemisinin), and polyphenols (curcumin, resveratrol) exhibit potent anticancer effects through mechanisms such as DNA damage induction, inhibition of survival signaling pathways (NF-κB, MAPK, PI3K/Akt), and modulation of oxidative stress. Despite these promising therapeutic attributes, the clinical translation of phytochemicals remains limited due to poor bioavailability, rapid metabolism, and drug resistance. Recent advances in nanotechnology-based formulations, AI-driven phytochemical screening, and synergistic combinations with conventional cancer therapies have emerged as potential solutions to enhance their clinical efficacy. This review comprehensively explores the molecular mechanisms of key phytochemicals in cancer therapy, their synergistic effects with chemotherapy, radiotherapy, and immunotherapy, and the latest clinical trial updates. Additionally, we discuss bioavailability enhancement strategies, regulatory challenges, and the future of precision phytotherapy in personalized oncology. The integration of artificial intelligence in phytochemical research and the application of CRISPR-based gene editing for pathway-specific interventions represent emerging frontiers that could revolutionize the use of plant-derived compounds in cancer treatment. By addressing existing challenges and leveraging cutting-edge innovations, phytochemicals hold the potential to become integral components of next-generation anticancer therapeutics.

Keywords: Phytochemicals, Cancer Therapy, Natural Products, Apoptosis, Chemoprevention, Drug Resistance, Targeted Therapy.
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Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, with millions of new cases diagnosed annually . Despite advancements in conventional therapies such as chemotherapy, radiation, and surgery, challenges persist, including adverse side effects and the development of resistance. This has spurred interest in alternative and complementary therapeutic approaches.(1,2) .

Phytochemicals, naturally occurring bioactive compounds found in plants, have garnered attention for their potential anticancer properties(3). These compounds, encompassing categories like alkaloids, flavonoids, terpenoids, and polyphenols, exhibit potent anticancer properties by targeting multiple hallmarks of cancer . Unlike single-target synthetic drugs, phytochemicals often modulate multiple cellular pathways, enhancing their therapeutic efficacy while reducing adverse effects (4). Many plant-derived compounds, such as paclitaxel (Taxol), vincristine, camptothecin, and curcumin, have already been integrated into oncology (5). Phytochemicals combat cancer through multiple, interconnected mechanisms, including Apoptosis Induction – Activation of intrinsic and extrinsic pathways leading to cancer cell death (6). Inhibition of Angiogenesis – Suppression of VEGF and HIF-1α signaling, preventing tumor vascularization (7). Blocking Metastasis – Modulation of EMT (Epithelial-to-Mesenchymal Transition) and suppression of matrix metalloproteinases (MMPs) (8).Targeting Oxidative Stress and Inflammation – Reduction of ROS (Reactive Oxygen Species) and NF-κB-mediated chronic inflammation (9).These multimodal actions position phytochemicals as powerful candidates for chemoprevention and therapeutic intervention. Synergistic Potential and Clinical Relevance Emerging evidence suggests that combining phytochemicals with standard therapies enhances efficacy and reduces resistance ((10). For instance: Curcumin sensitizes cancer cells to chemotherapy and radiotherapy (11). Resveratrol enhances the efficacy of immune checkpoint inhibitors (12). Berberine and Quercetin suppress multidrug resistance (MDR) mechanisms, improving chemotherapy outcomes (13). Such combinations could redefine cancer treatment paradigms, making therapy more effective and less toxic.

While numerous studies have explored individual phytochemicals' effects on cancer cells, a comprehensive synthesis of their mechanisms, efficacy, and translational potential is essential. This review aims to collate current research findings, elucidate the molecular pathways influenced by these compounds, and assess their via bility as adjuncts or alternatives to traditional cancer therapies (14,15). This article delves into the anticancer mechanisms of key phytochemical classes, evaluates preclinical and clinical studies highlighting their therapeutic potential, and discusses challenges such as bioavailability and standardization. Additionally, it explores future directions for integrating phytochemicals into mainstream cancer treatment protocols.

Major Classes of Anticancer Phytochemicals

Molecular Targets and Therapeutic Potential Natural compounds derived from plants, known as phytochemicals, have demonstrated potent anticancer properties by targeting multiple hallmarks of cancer, including uncontrolled proliferation, angiogenesis, metastasis, and resistance to apoptosis (16). Among the vast array of bioactive plant-derived compounds, four major classes—alkaloids, flavonoids, terpenoids, and polyphenols have gained significant attention due to their ability to interfere with key oncogenic signalling pathways (17).

Alkaloids: Microtubule Disruptors and DNA Topoisomerase Inhibitors

Alkaloids are nitrogen-containing heterocyclic compounds known for their ability to interact with cellular microtubules and DNA, leading to cell cycle arrest, apoptosis, and inhibition of metastasis (18). Several alkaloid-derived drugs are currently used in chemotherapy.

Key Alkaloids and Their Mechanisms

Vincristine & Vinblastine (from Catharanthus roseus) Bind to β-tubulin, inhibiting microtubule polymerization and arresting mitosis at the M-phase, leading to apoptotic cell death (19).

Clinically used in Hodgkin's lymphoma, leukemia, and neuroblastoma. Camptothecin & Derivatives (from Camptotheca acuminata) Inhibit topoisomerase I, causing DNA breaks and triggering apoptosis (20). Semi-synthetic derivatives, Irinotecan and Topotecan, are FDA-approved for colorectal, ovarian, and small-cell lung cancer. Berberine (from Berberis species) Downregulates NF-κB, AMPK, and Akt signalling, reducing tumour cell proliferation and enhancing chemosensitivity (21). Investigated for breast, prostate, and gastric cancer therapy (21). These alkaloids and their mechanisms are details in Table 1.

Vincristine & Vinblastine (from Catharanthus roseus)

Vincristine and vinblastine, members of the vinca alkaloid class, exert their anticancer effects by targeting microtubules, essential cytoskeletal components that regulate mitotic spindle formation and chromosome segregation during cell division (22,23).

Mechanism of Action

β-Tubulin Binding and Microtubule Destabilization

These alkaloids selectively bind to the β-tubulin subunit of microtubules, disrupting the tubulin polymerization dynamics necessary for mitotic spindle assembly (24). This leads to the inhibition of microtubule extension and stabilization, preventing proper spindle fiber formation required for chromosomal alignment and segregation during mitosis Bind to β-tubulin, inhibiting microtubule polymerization, causing mitotic arrest at M-phase. Leads to disruption of chromosome segregation and apoptotic cell death (25).

Mitotic Arrest and Apoptosis Induction in Vinca Alkaloid-Treated Cells

Vinca alkaloids induce mitotic arrest by disrupting microtubule dynamics, preventing chromosome alignment and activating the spindle assembly checkpoint (SAC) (26,27). Prolonged SAC activation leads to mitotic catastrophe, triggering p53-dependent apoptosis(28). Microtubule destabilization alters Bcl-2/Bax balance, promoting mitochondrial outer membrane permeabilization (MOMP), cytochrome c release, and caspase-9 activation, culminating in caspase-3/7-mediated apoptosis(29). This mechanism underlies their anticancer efficacy, enforcing both cell cycle arrest and apoptotic signaling (30). The transition from normal metaphase to mitotic blockade induced by vinca alkaloids is illustrated in Figure 1.

Clinical Significance

Vincristine: Used in Hodgkin's lymphoma, leukemia, and neuroblastoma. Vinblastine: Approved for testicular cancer, non-small cell lung cancer, and lymphomas. Neurotoxicity and dose-limiting side effects. Development of resistance due to P-glycoprotein (P-gp) efflux pumps(31).

Camptothecin & Derivatives (from Camptotheca acuminata)

Camptothecin, derived from Camptotheca acuminata, exerts anticancer activity by inhibiting topoisomerase I, an enzyme essential for DNA replication. It stabilizes the topoisomerase I-DNA complex, preventing DNA strand re-ligation, leading to single-strand breaks. During replication, these breaks convert into double-strand breaks, triggering cell cycle arrest (S-phase) and apoptosis (32,33).

Clinical Significance

Semisynthetic derivatives irinotecan and topotecan are FDA-approved: Irinotecan: Used in colorectal cancer (FOLFIRI regimen). Topotecan: Approved for Berberine: A Multifunctional Alkaloid in Cancer Therapy ovarian, small-cell lung, and cervical cancer (34).

Berberine (from Berberis species)

Berberine, a naturally occurring isoquinoline alkaloid derived from Berberis species, exhibits potent anticancer properties by targeting multiple cellular pathways. Its therapeutic effects include tumor growth inhibition, metastasis suppression, and enhancement of chemosensitivity (35).

Mechanism of Action

Regulation of Cell Signalling

Berberine downregulates NF-κB, AMPK, and Akt signaling, inducing cell cycle arrest and apoptosis in cancer cells (36,37). Inhibition of Metastasis: It suppresses matrix metalloproteinases (MMPs), reducing tumor invasion and metastatic spread (38).

Clinical Applications

Investigated in multiple cancers, including breast, prostate, gastric, and colorectal malignancies (39). Enhances chemosensitivity to cisplatin, doxorubicin, and paclitaxel, improving treatment outcomes in drug-resistant cancers (40). Nanoparticle-based delivery, liposomes, and micelles are being developed to enhance stability and therapeutic efficacy (41).

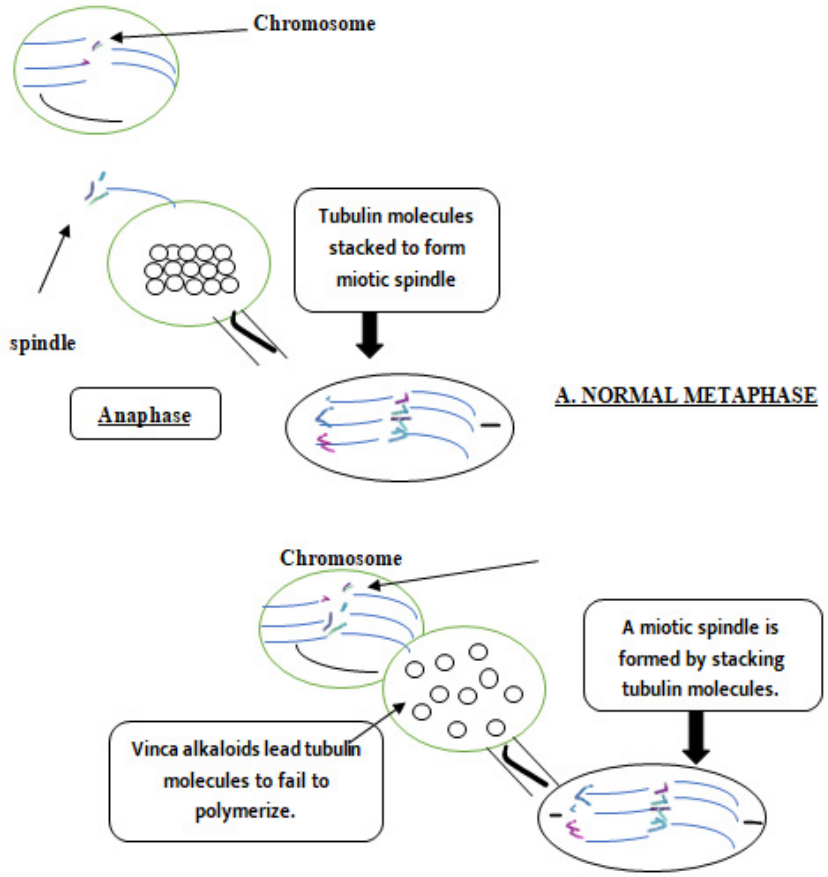

Fig. 1: Mechanism of Action of Vinca Alkaloids: Inhibition of Microtubule Polymerization and Mitotic Arrest

Table 1: Alkaloids and Their Anticancer Activities

Alkaloid	*Source*	*Anticancer Activity*	*Reference*
Vincristine	Catharanthus roseus	Binds to β-tubulin, inhibits microtubule polymerization, induces mitotic arrest	(19)
Vinblastine	Catharanthus roseus	Prevents mitotic spindle formation, triggers apoptosis in rapidly dividing cells	(22)
Camptothecin	Camptotheca acuminata	Inhibits topoisomerase I, leading to DNA breaks and apoptosis	(24)
Irinotecan	Camptothecin derivative	FDA-approved for colorectal cancer; inhibits topoisomerase I	(32)
Topotecan	Camptothecin derivative	Used for ovarian, small-cell lung, and cervical cancers; induces S-phase arrest	(34)
Berberine	Berberis species	Downregulates NF-κB, suppresses metastasis, enhances chemosensitivity	(35)

Key Flavonoids and Their Mechanisms

Flavonoids are multifunctional polyphenols that exert anticancer effects through various mechanisms, including apoptosis induction, angiogenesis inhibition, immune modulation, and suppression of metastasis(42). Their ability to interact with multiple molecular targets makes them promising candidates for cancer therapy(43). The key flavonoids, along with their botanical sources and specific anticancer mechanisms, are comprehensively summarized in Table 2, titled "Biological Activities of Flavonoids in Cancer Treatment"

Quercetin (from onions, apples, and tea)

Suppresses PI3K/Akt/mTOR signalling, leading to cell cycle arrest and apoptosis (44).Enhances chemosensitivity in breast and lung cancer cells. Genistein (from soybeans and legumes). Inhibits tyrosine kinases and estrogen receptors (ER-α), reducing hormone-driven cancers (45). Being tested in prostate cancer prevention trials. Apigenin (from parsley, celery, and chamomile) Downregulates VEGF and MMPs, suppressing angiogenesis and metastasis (46). Potential for colorectal and cervical cancer chemoprevention.

Genistein (from soybeans, legumes, and chickpeas)

- *Mechanisms of Action*

Inhibits tyrosine kinases and estrogen receptors (ER-α), blocking hormone-dependent cancer growth (47). Suppresses VEGF and HIF-1α, inhibiting tumor angiogenesis (48). Reduces STAT3 phosphorylation, impairing cancer stem cell survival (49).

- *Clinical Significance*

Studied in prostate, breast, and ovarian cancer prevention trials (50). Combination therapy with docetaxel shows increased efficacy in hormone-refractory prostate cancer (51).

Apigenin (from parsley, celery, chamomile, and citrus fruits)

- *Mechanisms of Action*

Downregulates VEGF and MMPs, suppressing angiogenesis and metastasis (52) .Inhibits Wnt/β-catenin signalling, impairing tumour cell proliferation (53). Induces cell cycle arrest at G0/G1 phase, reducing tumour progression (54).

- *Clinical Significance*

Shows potential for colorectal, cervical, and lung cancer chemoprevention (55).Being tested as an adjuvant agent in chemoresistant tumors (56).

Epigallocatechin Gallate (EGCG) (from green tea)

Mechanisms of Action

Inhibits EGFR and HER2 signalling(57), reducing tumour cell survival in breast cancer (58). Suppresses NF-κB and COX-2, decreasing inflammation-mediated tumour progression (59). Induces autophagy in hepatocellular carcinoma by activating AMPK/mTOR pathway (60).

Clinical Significance

Studied for prostate, lung, and pancreatic cancer prevention (61). Shows potential in immune checkpoint blockade therapy (62).

Luteolin (from green pepper, broccoli, thyme, and carrots)

Mechanisms of Action

Suppresses MAPK and JAK/STAT3 pathways, reducing tumor proliferation (63). Induces ROS-mediated apoptosis, selectively targeting cancer cells while sparing normal cells (64). Inhibits glucose metabolism (Warburg effect), impairing tumor energy supply (65).

Clinical Significance

Investigated in hepatocellular carcinoma, colorectal, and lung cancers (66). Enhances chemotherapy efficacy by reducing multidrug resistance proteins (MDR1, MRP1) (64).

Naringenin (from citrus fruits, tomatoes, and cherries)

Mechanisms of Action

Suppresses Akt and NF-κB, reducing inflammation-induced tumor progression(67) .Downregulates Bcl-2 while upregulating Bax, promoting apoptosis (68). Enhances DNA

Table 2: Biological Activities of Flavonoids in Cancer Treatment

Flavonoid	*Source*	*Anticancer Activity*	*Reference*
Quercetin	Onions, Apples, Tea	Suppresses PI3K/Akt/mTOR signaling, induces apoptosis, enhances chemosensitivity	(44)
Genistein	Soybeans, Legumes	Inhibits tyrosine kinases and estrogen receptors, reduces hormone-driven cancers	(45)
Apigenin	Parsley, Celery, Chamomile	Downregulates VEGF and MMPs, inhibits angiogenesis and metastasis	(46)
Epigallocatechin Gallate (EGCG)	Green Tea	Inhibits VEGF, COX-2, and MMPs, suppresses angiogenesis and metastasis	(57)
Luteolin	Green Pepper, Broccoli, Thyme	Suppresses MAPK and JAK/STAT3 pathways, induces ROS-mediated apoptosis	(63)
Naringenin	Citrus Fruits, Tomatoes, Cherries	Suppresses Akt and NF-κB, promotes apoptosis, enhances radiotherapy sensitivity	(67)

Table 3: Terpenoids and Their Anticancer Activities

Terpenoid	*Source*	*Anticancer Activity*	*Reference*
Paclitaxel	Taxus brevifolia (Pacific yew tree)	Promotes microtubule polymerization, induces mitotic arrest, triggers apoptosis	(75)
Artemisinin	Artemisia annua (Sweet wormwood)	Generates reactive oxygen species (ROS), selectively induces apoptosis in cancer cells	(76)
Limonene	Citrus fruits	Acts as an antioxidant, reduces DNA damage, inhibits Wnt/β-catenin signaling	(77)
Carotenoids (β-Carotene, Lycopene)	Carrots, Tomatoes	Inhibits oxidative stress, suppresses inflammation, reduces cancer risk	(78)
Farnesol	Essential oils (lemongrass, chamomile)	Inhibits Ras-dependent tumor growth, induces apoptosis via mitochondrial pathway	(79)
Geraniol	Rose, Citronella, Lemongrass	Suppresses tumor proliferation, inhibits HMG-CoA reductase, induces cell cycle arrest	(80)

Table 4: Polyphenols and Their Anticancer Activities

Polyphenol	*Source*	*Anticancer Activity*	*Reference*
Epigallocatechin-3-gallate (EGCG)	Green Tea	Inhibits DNMTs, reactivates tumor suppressor genes, modulates histone acetylation	(85)
Genistein	Soy Products	Inhibits HDACs and DNMTs, enhances immune responses by modulating cytokines	(86)
Curcumin	Turmeric	Inhibits DNMTs and HDACs, modulates immune response by affecting cytokines	(87)
Resveratrol	Grapes, Berries	Modulates sirtuin activity, influences histone acetylation and gene expression	(88)
Fisetin	Strawberries, Apples	Induces apoptosis, inhibits NF-κB signaling, reduces cancer cell proliferation	(89)
Kaempferol	Broccoli, Spinach	Suppresses angiogenesis, inhibits PI3K/Akt signaling, promotes apoptosis	(90)

damage response, leading to increased cancer cell sensitivity to radiotherapy (69).

Clinical Significance

Studied for breast, cervical, and liver cancers.Potential use in targeted therapy for chemoresistant tumours(70).

Terpenoids: Modulators of Apoptosis, Cell Cycle, and Angiogenesis

Terpenoids, also known as isoprenoids, are a diverse group of plant-derived compounds that exert cytotoxic effects by regulating apoptosis, modulating immune responses, and mitigating oxidative stress (71). Several terpenoids have demonstrated synergistic effects when combined with standard chemotherapeutic agents. The key terpenoids such as paclitaxel (from Taxus brevifolia, the Pacific yew tree), artemisinin (from Artemisia annua, sweet wormwood), and carotenoids (including ß-carotene and lycopene)-along with their natural sources and specific anticancer mechanisms, are systematically presented in Table 3, titled "Terpenoids and Their Anticancer Activities" (72, 73, 74).

Polyphenols: Epigenetic Regulators and Immunomodulators in Cancer Therapy

Polyphenols, a diverse group of natural antioxidants, are renowned for their potent anti-inflammatory, anti-proliferative, and DNA-repair enhancing properties. In addition to these effects, polyphenols have been shown to modulate various epigenetic mechanisms and immune responses, which makes them highly promising candidates for both cancer prevention and therapeutic intervention (81). The biological activities of key polyphenols, their mechanisms of action, and their natural sources are comprehensively summarized in Table 4, titled "Polyphenols and Their Anticancer Activities".

Major Polyphenols and Their Mechanisms

- *Resveratrol (from grapes, berries, and peanuts)*

Activates sirtuins (SIRT1), AMPK, and inhibits NF-κB, leading to tumor suppression (82). Potentially beneficial in colorectal and breast cancer therapy.Curcumin (from turmeric, Curcuma longa)

Modulates multiple signaling pathways (p53, STAT3, Wnt/β-catenin) and enhances the efficacy of chemotherapy (83). Studied in clinical trials for pancreatic and colorectal cancers. Epigallocatechin Gallate (EGCG) (from green tea) Inhibits VEGF, COX-2, and MMPs, suppressing angiogenesis and metastasis (84). Shows potential in lung, prostate, and breast cancer prevention.

Bioavailability Challenges and Formulation Strategies

Phytochemicals exhibit promising anticancer activity, but their poor aqueous solubility, instability, and rapid metabolism pose significant barriers to clinical translation (91). Their low water solubility limits absorption in the

gastrointestinal tract, while first-pass metabolism in the liver rapidly degrades many phytochemicals before reaching systemic circulation(92). Strategies to Enhance Bioavailability: Nanoparticles (PLGA, chitosan, lipid-based): Improve solubility and targeted delivery (93). Liposomes & Phytosomes: Enhance cellular uptake and prevent enzymatic degradation. Solid Lipid Nanoparticles (SLNs): Provide controlled drug release and improve absorption(94)

Self-Emulsifying Drug Delivery Systems (SEDDS)

Create nanoemulsions to enhance solubility (95).

Recent studies report that nano-formulated curcumin has up to 200-fold higher bioavailability than free curcumin, demonstrating the potential of advanced drug delivery techniques(94) .

AI-Driven Phytochemical Screening and Drug Discovery

AI and computational tools are revolutionizing phytochemical-based cancer drug discovery, significantly reducing the time and cost of identifying bioactive compounds (96). AI-driven models allow virtual screening molecular docking, and deep learning-based predictions to assess the anticancer potential of plant-derived molecules.(97)

AI Tools Used in Phytochemical Drug Discovery

AutoDock & Molecular Docking

Predicts binding affinity of phytochemicals to cancer targets (98).

DeepChem & Virtual Screening

Identifies potential anticancer compounds from large chemical libraries (99).

AlphaFold & Protein Structure Prediction

Helps in structural-based drug design (100). Recent research using machine learning models has identified novel flavonoid derivatives with high anticancer potential, highlighting AI's growing role in oncology research (101).

Synergistic Effects with Conventional Cancer Therapies

Phytochemicals have emerged as effective adjuvants in cancer therapy due to their ability to enhance the efficacy of conventional treatments such as chemotherapy, radiotherapy, and immunotherapy. These natural compounds exhibit synergistic effects by promoting apoptosis, sensitizing tumor cells to cytotoxic agents, reversing multidrug resistance (MDR), and modulating immune responses. Notably, combinations of phytochemicals with standard anticancer drugs have demonstrated reduced toxicity and improved therapeutic outcomes in preclinical and clinical studies. Representative examples of such synergistic interactions are summarized in Table 5, titled "Synergistic Effects of Phytochemicals with Conventional Cancer Therapies" (102-106).

Safety Considerations

Hepatotoxicity

Berberine shows liver toxicity at high doses(113).

Drug Interactions

Curcumin alters CYP enzyme activity, affecting chemotherapy drugs (114)

Quality Control

Standardization remains a significant challenge (115).

Challenges and Future Directions

Bioavailability and Pharmacokinetic Limitations

One of the biggest challenges in phytochemical-based cancer therapy is poor bioavailability due to low solubility, rapid metabolism, and inefficient absorption (116). Many phytochemicals, such as curcumin and resveratrol, undergo extensive first-pass metabolism, reducing their therapeutic efficacy (117). Strategies such as liposomal formulations, polymeric nanoparticles, and phytosomes have shown promise in enhancing systemic bioavailability (118). Recent advances in self-emulsifying drug delivery systems (SEDDS) and solid lipid nanoparticles (SLNs) have improved solubility and absorption, making these phytochemicals more clinically viable (119,120).

Tumor Heterogeneity and Drug Resistance

Cancer is a highly heterogeneous disease, and tumor heterogeneity poses a significant barrier to the efficacy of phytochemicals (121). Tumors adapt and develop resistance via mechanisms such as epigenetic modifications, efflux

Table 5: Synergistic Effects of Phytochemicals with Conventional Cancer Therapies

Phytochemical	*Conventional Therapy*	*Mechanism of Synergy*	*Reference*
Curcumin	Cisplatin	Enhances DNA damage & apoptosis	(102)
Resveratrol	PD-1 Inhibitors	Boosts immune response	(103)
Genistein	Radiotherapy	Sensitizes tumors to radiation-induced DNA damage	(104)
Quercetin	Doxorubicin	Reverses multidrug resistance (MDR)	(105)
Berberine	Paclitaxel	Suppresses cancer cell proliferation	(106)

Table 6: Clinical Translation and Ongoing Human Trials

Phytochemical	*Cancer Type*	*Trial Phase*	*Outcome*
Curcumin	Colorectal Cancer	Phase II	Tumor reduction & enhanced chemotherapy response (107)
Berberine	Breast Cancer	Phase II	Suppresses metastasis & MDR reversal (108)
Quercetin	Lung Cancer	Phase I	Safe profile, induces apoptosis(109)

Table 7: Regulatory and Safety Aspects of Phytochemical-Based Cancer Therapy

Regulatory Body	*Region*	*Guidelines*	*Reference*
FDA	USA	Requires clinical validation for therapeutic claims	(110)
EMA	Europe	Approves under Traditional Herbal Medicinal Products Directive	(111)
AYUSH	India	Regulates phytochemicals under Ayurvedic Pharmacopoeia	(112)

transporters (P-glycoprotein), and enhanced DNA repair pathways (122). For example, quercetin and berberine have shown the ability to reverse multidrug resistance (MDR), but their full clinical potential remains underexplored (123). Combining phytochemicals with standard therapies, such as immune checkpoint inhibitors (ICIs), can enhance cancer immunotherapy responses (124).

Regulatory and Safety Considerations

The regulatory framework for phytochemical-based therapies varies globally, with different standards for quality, efficacy, and safety. In the United States, the FDA mandates rigorous clinical validation before approval of phytochemicals as therapeutic agents. The European Medicines Agency (EMA) evaluates these compounds under the Traditional Herbal Medicinal Products Directive. In India, the Ministry of AYUSH governs the regulation and standardization of phytochemicals within traditional medicine systems. These regulatory guidelines are summarized in Table 7, titled "Regulatory and Safety Aspects of Phytochemical-Based Cancer Therapy" (110–112).

AI-Driven Phytochemical Drug Discovery

Artificial Intelligence (AI) has revolutionized phytochemical screening and drug discovery by predicting molecular interactions, binding affinity, and toxicity profiles (125). AI-based platforms such as AutoDock, DeepChem, and Alpha Fold are accelerating molecular docking and virtual screening (126). Additionally, machine learning models are identifying novel bioactive phytochemicals with high anticancer potential (127). Future research should integrate AI with high-throughput screening (HTS) and multi-omics data to optimize phytochemical-based precision therapy (128).

Precision Oncology and Personalized Phytotherapy

Unlike conventional cancer therapies, phytochemicals offer a multi-targeted approach that can be integrated into precision oncology (129). Biomarker-based screening could identify patients most likely to benefit from specific phytochemicals (130). For example, resveratrol and genistein modulate epigenetic markers, suggesting their role in personalized cancer therapy (131). Advances in phytochemical-gene interaction studies may allow for individualized treatment strategies, reducing toxicity and side effects (132).

Regulatory and Clinical Translation Barriers

Regulatory hurdles remain a major bottleneck for phytochemical-based therapeutics. Unlike synthetic drugs, herbal compounds lack standardization and clinical validation (133). The FDA, EMA, and AYUSH regulatory frameworks for herbal medicines differ, complicating global approvals . Future strategies should focus on randomized controlled trials (RCTs), Good Manufacturing Practices (GMP), and global standardization guidelines to facilitate clinical translation(134).

Conclusion

Phytochemicals are emerging as promising anticancer agents due to their ability to target multiple oncogenic pathways, including apoptosis induction, angiogenesis inhibition, and metastasis suppression. Key phytoconstituents such as alkaloids, flavonoids, terpenoids, and polyphenols have demonstrated significant potential in preclinical and clinical studies, often enhancing the efficacy of conventional therapies while reducing toxicity. However, challenges such as poor bioavailability, rapid metabolism, and tumor resistance hinder their clinical application. Advanced drug delivery strategies, including nanoparticles, phytosomes, and self-emulsifying systems, offer solutions to improve their pharmacokinetic profiles. Additionally, AI-driven drug discovery and precision oncology approaches are revolutionizing phytochemical research, enabling the identification of novel bioactive compounds with enhanced therapeutic efficacy. Despite regulatory and translational challenges, integrating phytochemicals into personalized cancer therapies holds great potential. Future research should focus on optimizing their formulation, conducting large-scale clinical trials, and standardizing regulatory frameworks. With

continued advancements, phytochemicals could serve as effective, targeted, and safer alternatives or adjuncts to existing cancer treatments, contributing to the development of more sustainable and innovative oncological therapies.

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