Biologics: Targets and Therapy

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REVIEW

Herbal Therapies for Cancer Treatment: A Review of Phytotherapeutic Efficacy

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Abstract: Natural products have proven to be promising anti-cancer agents due to their diverse chemical structures and bioactivity. This review examines their central role in cancer treatment, focusing on their mechanisms of action and therapeutic benefits. Medicinal plants contain bioactive compounds, such as flavonoids, alkaloids, terpenoids and polyphenols, which exhibit various anticancer properties. These compounds induce apoptosis, inhibit cell proliferation and cell cycle progression, interfere with microtubule formation, act on topoisomerase targets, inhibit angiogenesis, modulate key signaling pathways, improve the tumor microenvironment, reverse drug resistance and activate immune cells. Herbal anti-cancer drugs offer therapeutic advantages, particularly selective toxicity against cancer cells, reducing the adverse side effects associated with conventional chemotherapy. Recent studies and clinical trials highlight the benefits of herbal medicines in alleviating side effects, improving tolerance to chemotherapy and the occurrence of synergistic effects with conventional treatments. For example, the herbal medicine SH003 was found to be safe and potentially effective in the treatment of solid cancers, while Fucoidan showed anti-inflammatory properties that are beneficial for patients with advanced cancer. The current research landscape on herbal anticancer agents is extensive. Numerous studies and clinical trials are investigating their efficacy, safety and mechanisms of action in various cancers such as lung, prostate, breast and hepatocellular carcinoma. Promising developments include the polypharmacological approach, combination therapies, immunomodulation and the improvement of quality of life. However, there are still challenges in the development and use of natural products as anti-cancer drugs, such as the need for further research into their mechanisms of action, possible drug interactions and optimal dosage. Standardizing herbal extracts, improving bioavailability and delivery, and overcoming regulatory and acceptance hurdles are critical issues that need to be addressed. Nonetheless, the promising anticancer effects and therapeutic benefits of natural products warrant further investigation and development. Multidisciplinary collaboration is essential to advance herbal cancer therapy and integrate these agents into mainstream cancer treatment.

Keywords: herbal, anti-cancer, chemotherapy, cancer therapy, drug resistance

Introduction

Cancer is a serious metabolic disease and remains a major cause of mortality despite advances in diagnostic tools, treatment and preventive measures.[1–8] Cancer is one of the leading causes of death and disease worldwide, with the number of cases steadily increasing and expected to reach 21 million by 2030.[9,10] Cancer research has always been a challenge due to its complexity. Different types of cancer can vary significantly in terms of genetic alterations, organs affected, prognosis and treatment approaches.[11] Although there are numerous treatment options, their success depends on the type and stage of the disease. Common treatments include surgical removal of malignant tissue or tumors,

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radiotherapy, chemotherapy and immunotherapy. Surgery and radiotherapy have a local effect, while chemotherapy and targeted therapy have a systemic effect. The type and stage of the cancer determine whether these therapies are used individually or in combination with others, such as the combination of radiotherapy and chemotherapy.[12] Targeted therapy with small molecules and chemotherapy are two methods of treating cancer with chemical compounds. Chemotherapeutic agents usually act as cytotoxic agents that disrupt different stages of the cell cycle. The reason for their use is that cancer cells usually divide faster than normal cells, which makes them more susceptible to chemotherapeutic agents.[13] In general, these drugs can be divided into five categories based on their biochemical properties: Alkylating agents (such as cisplatin), antimetabolites (such as 5-fluorouracil), antitumor antibiotics (such as doxorubicin), topoisomerase inhibitors (such as topotecan), and tubulin-binding drugs (such as paclitaxel).[14] Although chemotherapeutic agents are effective, they can also cause adverse effects in normal cells such as nausea, vomiting, mucositis, alopecia, neuropathy and myelosuppression. In addition, these drugs are associated with multidrug resistance (MDR), a problem responsible for more than 90% of cancer patient deaths during chemotherapy.[15] Small molecule targeted therapy (SMTT) differs from chemotherapy in that it uses chemicals that specifically target molecular structures in cancer cells. These target structures are typically genetically altered in cancer and play a crucial role in tumor growth and survival. They are often involved in signaling pathways that are dysregulated during cancer development.[16] Targeted agents used in the clinic include tyrosine kinase inhibitors, proteasome inhibitors and poly-ADP-ribose polymerase inhibitors such as imatinib, carfilzomib and ribociclib. These SMTT drugs are designed to be more specific and may have less toxic effects on healthy cells. However, side effects such as skin rash, diarrhea and high blood pressure have been reported. In addition, these treatments can trigger mechanisms that lead to drug resistance. Despite their effectiveness in treating various types of cancer, these therapies have their limitations. These include cancer recurrence and lack of patient compliance due to severe side effects such as fatigue, pain, nausea, anemia, vomiting and hair loss. It is important to note that many synthetic chemotherapeutic agents that have been developed to date do not meet the standards of clinical trials despite high development costs. Therefore, ongoing efforts are focused on finding better alternatives that balance efficacy and toxicity while preventing drug resistance.[17] In recent years, there has been renewed interest in the use of medicinal plants in developing countries, as herbal medicines are considered safe and have few or no adverse effects, especially when compared to synthetic drugs.[18] Herbal medicine has been extensively studied as a potential source of anticancer drugs due to the large number of bioactive compounds contained in plants. Numerous plant compounds have shown promising anticancer properties based on various mechanisms, such as inducing apoptosis (programmed cell death) in cancer cells, inhibiting angiogenesis (formation of new blood vessels supplying the tumor), and interfering with important signaling pathways involved in cancer progression and metastasis.[19–21] The anti-cancer properties of ten herbs commonly used by cancer patients in the Middle East include Olea europaea (olive), Nigella sativa (black cumin), Crocus sativus (saffron), Punica granatum (pomegranate), Urtica dioica (stinging nettle), Allium sativum L.(garlic), Allium cepa (onion), Curcuma longa (curcumin), Arum palaestinum (Palestinian arum) and Vitis vinifera (grapes).[22] One of the earliest and most successful examples of herbal anticancer agents are the vinca alkaloids vinblastine and vincristine, which are extracted from the Madagascar periwinkle plant (Catharanthus roseus). Introduced in the 1960s, these compounds are widely used to treat various cancers, including breast cancer, Hodgkin's lymphoma, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, and Wilms' tumor.[22–24] Other important herbal anticancer agents include paclitaxel (Taxol®), which is extracted from the Pacific yew (Taxus brevifolia) and is used to treat breast, ovarian, lung and other cancers.[25] Camptothecin, which is extracted from the Chinese tree Camptotheca acuminata, led to the development of topotecan and irinotecan, which are used to treat ovarian, lung and colorectal cancer.[26] Etoposide and teniposide, semisynthetic derivatives of epipodophyllotoxin from the corn plant (Podophyllum peltatum), were approved for the treatment of testicular cancer, small cell lung cancer, lymphomas and leukemias.[27–30] Building on these early successes, more recent research has focused on the anticancer potential of bioactive compounds in traditional herbal medicines. Examples include curcumin from turmeric, resveratrol from grapes and epigallocatechin gallate (EGCG) from green tea. These compounds have shown promising results in preclinical studies demonstrating anti-cancer activity through mechanisms such as antioxidant activity, induction of apoptosis and inhibition of angiogenesis and metastasis.[31,32] Herbal medicine has been used for centuries to treat various ailments, including cancer. Many traditional systems of medicine, such as Traditional Chinese Medicine (TCM) and Ayurveda,

have relied on herbal remedies to treat cancer. These ancient practices have laid the foundation for modern research into the anticancer potential of herbal compounds.[33] With the advances in industrial development and industrial medicine, the use of herbs was neglected for some time.[34] With the advent of new technologies, the challenges associated with natural compounds have diminished, leading to a renewed interest in incorporating these natural ingredients into the pharmaceutical industry.[35,36] The World Health Organization estimates that 80% of the world's population is dependent on traditional treatments.[37] Modern biomolecular science, which identifies important properties such as anti-cancer, anti-inflammatory and anti-viral effects, has improved the understanding of the effects of herbs on various targets. With this growing knowledge, the effect of herbal medicines against various types of cancer was also recognized. For example, hepatocellular carcinoma (HCC), now considered the fifth most common malignancy worldwide, has seen an increase in incidence.[38,39] Numerous studies have investigated the use of herbal medicines in the treatment and prevention of HCC. These studies have shown that herbal ingredients can affect all phases of HCC, including initiation, promotion and progression.[40,41] Innovative delivery systems, such as nanoparticles, have been extensively developed to improve the bioavailability, targeted delivery, and therapeutic efficacy of herbal anti-cancer agents. These advanced delivery systems have been developed to overcome the major limitations often associated with herbal agents, such as poor aqueous solubility, low bioavailability and non-specific distribution.[42–45] Despite the promising anticancer potential of herbal compounds, there are challenges associated with their use in modern cancer treatment. These challenges include the variability in the quality and concentration of bioactive compounds in medicinal plants, the need for standardization of herbal extracts, and the potential for drug interactions. Additionally, the precise mechanisms of action for many herbal compounds are not yet fully understood, necessitating further research to elucidate their pathways and interactions.[46,47] In summary, cancer remains a major global health burden, and conventional treatments often have limitations, such as severe side effects and the development of drug resistance. Herbal medicine has shown promising potential as a source of anticancer agents, with numerous bioactive compounds demonstrating various mechanisms of action against cancer cells. However, challenges associated with the use of herbal compounds in modern cancer treatment need to be addressed. This review aims to explore the central role of natural products in the fight against cancer, focusing on their mechanisms of action, therapeutic benefits, and the current research landscape, while also discussing the challenges and future.

Obtaining Information and Data

The information and data used in this review were obtained from reputable scientific databases, including Google Scholar, PubMed, SpringerLink, Medline, ScienceDirect and Mendeley. From these databases, 270 references were found for this review.

Natural Products (NPs) Against Cancer

The central role of natural products (NPs) in the fight against cancer. Due to their diverse chemical structures and bioactivity, natural products have always been an important source of inspiration for drug discovery, especially for cancer treatment.[45–48] These naturally occurring compounds offer several advantages, including structural complexity, diverse scaffolds, and evolutionary optimization for biological functions, making them invaluable sources for the development of new and effective cancer therapies.[45,47] The structural complexity and rigidity of natural products can be an advantage when it comes to addressing difficult protein-protein interactions that play a role in carcinogenesis.[49] In addition, natural products are often rich in "bioactive" compounds that cover a broader chemical spectrum than typical synthetic small molecule libraries, increasing the chances of discovering effective anticancer agents.[50] In the past, natural products have played a crucial role in the treatment of human diseases. Many successful anticancer drugs have been derived from plant, microbial and marine sources.[51]

Bioactive Substances in Medicinal Plants

Medicinal plants are rich in bioactive compounds that have a variety of pharmacological effects, including anti-cancer properties. These compounds can be categorized into several main groups, such as flavonoids, alkaloids, terpenoids and polyphenols. Flavonoids, for instance, are a diverse group of phytonutrients found in almost all fruits and vegetables. They are known for their antioxidant properties, which help in protecting cells from damage caused by free radicals.

Some flavonoids have been shown to inhibit the growth of cancer cells and reduce inflammation, making them promising candidates for cancer prevention and treatment. Alkaloids are another significant group of bioactive compounds found in medicinal plants. They are characterized by their nitrogen-containing structures and exhibit a wide range of pharmacological activities, including analgesic, anti-malarial, and anti-cancer effects. Some well-known alkaloids, such as vincristine and vinblastine derived from the Madagascar periwinkle, are already used in clinical settings for their potent anti-cancer properties. Terpenoids, also known as isoprenoids, are the largest and most diverse class of plant secondary metabolites. They play crucial roles in plant growth and development and have various medicinal properties. Terpenoids such as taxol, extracted from the bark of the Pacific yew tree, have been widely used in cancer chemotherapy due to their ability to disrupt cell division in cancer cells. Polyphenols are a group of compounds characterized by the presence of multiple phenol groups. They are known for their antioxidant and anti-inflammatory properties. Polyphenols such as resveratrol, found in grapes and red wine, have been studied for their potential to prevent and treat cancer by modulating various signaling pathways involved in cell growth and apoptosis. In summary, the bioactive compounds in medicinal plants, including flavonoids, alkaloids, terpenoids, and polyphenols, offer a wide range of pharmacological effects that can be harnessed for cancer treatment and prevention. Ongoing research continues to uncover the full potential of these compounds, paving the way for the development of new and effective therapeutic agents.[52]

Flavonoids

Flavonoids are a type of polyphenolic compound commonly found in plants. They have a basic structure consisting of two aromatic rings connected by a three-carbon bridge. Flavonoids can be further subdivided into subgroups such as flavonols, flavones, flavanones, isoflavones and anthocyanidins.[53] Flavonoids are found in a variety of fruits, vegetables, grains, nuts and beverages such as tea and wine. Notable sources include citrus fruits, berries, onions, soybeans and green tea.[54,55] Flavonoids have shown anti-cancer effects via several mechanisms, including inducing apoptosis, inhibiting cell proliferation, suppressing angiogenesis and modulating signaling pathways associated with cancer progression.[56–58] For instance, quercetin has been demonstrated to induce apoptosis and inhibit cell growth in a variety of cancer cell lines.[59]

Alkaloids

Alkaloids are a diverse group of nitrogen-containing compounds characterized by a heterocyclic ring structure. They are known for their potent biological activities and are frequently used as therapeutic agents.[60,61] Alkaloids are found in various plant families, such as Solanaceae (eg tobacco, tomato), Papaveraceae (eg opium poppy) and Ranunculaceae (eg buttercup).[62] Numerous alkaloids have shown promising anticancer effects by inhibiting topoisomerase enzymes, inducing apoptosis and disrupting microtubule dynamics. For example, camptothecin, which is extracted from the Chinese tree Camptotheca acuminata, and its derivatives are potent topoisomerase I inhibitors used in cancer therapy. This action prevents cancer cells from repairing DNA, thus halting their proliferation. Similarly, vinca alkaloids and taxanes disrupt microtubule dynamics, essential for cell division, leading to apoptosis or programmed cell death in cancer cells. Beyond oncology, alkaloids like morphine serve as powerful analgesics, while quinine has been pivotal in antimalarial treatments. The therapeutic application of alkaloids, however, must be carefully managed due to their potential toxicity; the line between a therapeutic and a toxic dose can be quite narrow, necessitating precise dosage control. The complexity of their structures often leads to the development of semi-synthetic derivatives to optimize their pharmacological benefits while minimizing adverse effects. Research into alkaloids continues to uncover new compounds and refine existing ones, enhancing their efficacy in treating diseases, particularly cancer, where novel mechanisms of action are crucial for overcoming resistance and improving patient outcomes.[63–66]

Terpenoids

Terpenoids, also known as isoprenoids, are a large and diverse group of natural compounds consisting of isoprene units with five carbon atoms. They can be categorized according to the number of isoprene units, eg monoterpenes, sesquiterpenes and triterpenes.[67,68] Terpenoids are found in various plant sources, including essential oils, resins and latex. Examples include limonene from citrus fruits, artemisinin from Artemisia annua, and paclitaxel from Pacific yew.[69–73] Terpenoids have shown anticancer properties by inducing apoptosis, inhibiting cell proliferation, suppressing

angiogenesis and modulating signaling pathways. For example, paclitaxel, a diterpenoid, is a chemotherapeutic agent that disrupts microtubule dynamics, leading to cell cycle arrest and apoptosis. The therapeutic potential of terpenoids in cancer treatment is immense, with paclitaxel being a prime example, used widely in chemotherapy for various cancers due to its microtubule-stabilizing effect. However, the clinical use of terpenoids involves challenges such as ensuring adequate bioavailability, managing potential toxicity, and overcoming the complexities associated with their natural synthesis or extraction. Research continues to explore these compounds for new drug development, focusing on structural modifications to enhance efficacy, reduce toxicity, and improve delivery methods, thereby broadening their application in oncology and other therapeutic areas.[74–76]

Polyphenols

Polyphenols are a diverse group of compounds characterized by the presence of multiple phenolic rings. They can be classified into subgroups such as phenolic acids, stilbenes, and lignans.[77] Polyphenols are abundant in plants, particularly in fruits, vegetables, grains, and beverages like tea and wine. Significant sources include grapes, berries, nuts, and green tea.[78,79] These compounds have demonstrated anticancer properties through various mechanisms, such as antioxidant activity, modulation of signaling pathways, induction of apoptosis, and inhibition of angiogenesis. For example, resveratrol, a stilbene found in grapes, has been shown to inhibit cell proliferation and induce apoptosis in several cancer cell lines. The bioactive compounds derived from medicinal plants exhibit a wide range of chemical structures and mechanisms of action, making them promising candidates for the development of novel anticancer agents. However, further research is necessary to fully understand their potential and optimize their therapeutic applications.[80–84]

Figure 1 show the mechanisms of natural products in cancer prevention.

Mechanisms of Action

Natural products have demonstrated various mechanisms of action in exhibiting anticancer effects (Table 1 and Figure 2).

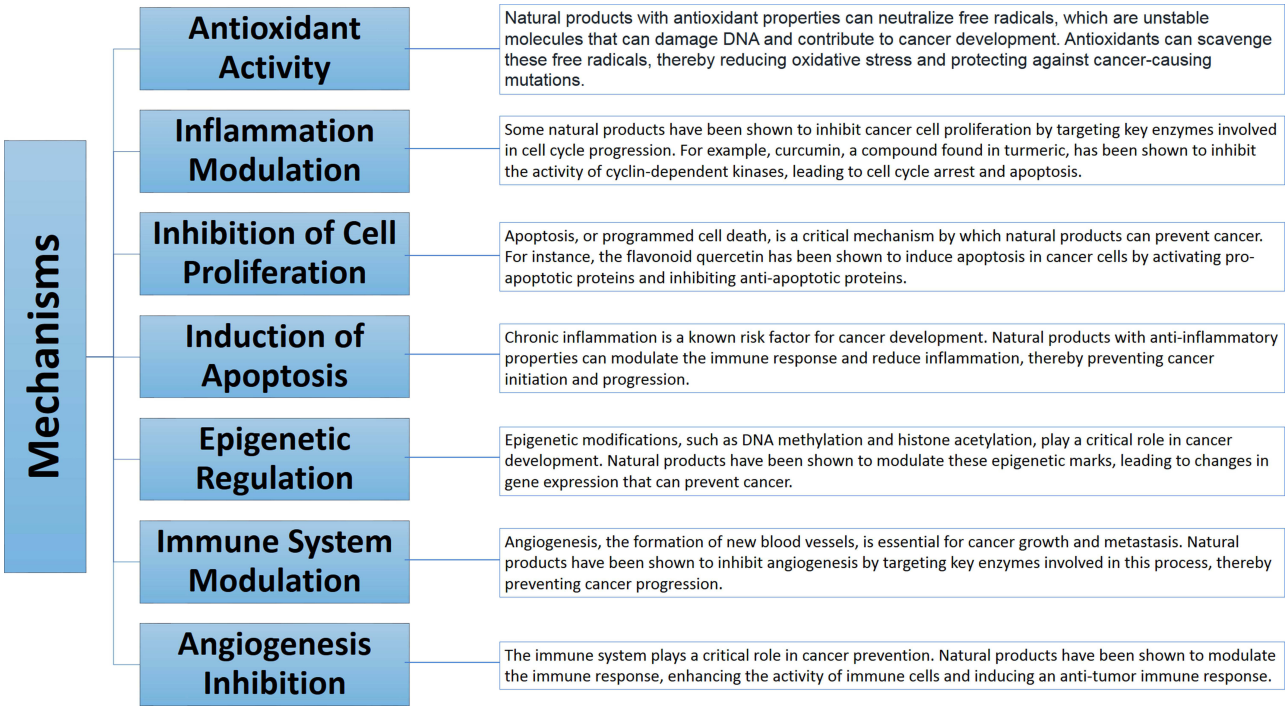

Figure 1 Mechanisms of natural products in cancer prevention.

Table 1 Natural Products (NPs) Have Demonstrated Various Mechanisms of Action in Exhibiting Anticancer Effects

Mechanism of Action	Natural Product	Cancer Type(s)	Details	References
Inducing Apoptosis	Curcumin	Breast, colon, prostate, lung, glioblastoma	Regulates Bcl-2 family proteins, activates caspases, targets NF-κB, PI3K/Akt, MAPK pathways, enhances chemotherapeutic agents, triggers intrinsic and extrinsic apoptotic pathways.	[85–92]
	Resveratrol	Breast, prostate, leukemia	Alters Bcl-2 family proteins, initiates caspases, impairs mitochondrial function, increases chemotherapy sensitivity.	[83,93–97]
	Artesunate	Glioblastoma, breast, colorectal	Causes oxidative DNA damage, triggers DNA damage response, initiates apoptosis via caspase-dependent and independent mechanisms.	[98–101]
	EGCG	Colon, prostate, breast, lung	Activates intrinsic and extrinsic apoptotic pathways, influences Bcl-2 family proteins, initiates caspase activation, disrupts mitochondrial membrane potential.	[102–109]
	Genistein	Breast, prostate, leukemia	Causes cell cycle arrest, alters cell cycle regulators, triggers caspase cascade, reduces anti-apoptotic proteins, inhibits NF-κB signaling, enhances chemotherapeutic sensitivity.	[110–113]
	Quercetin	Colon, breast, lung	Alters Bcl-2 family proteins, activates caspases, induces cytochrome c release, disrupts mitochondrial membrane potential, regulates cell cycle proteins, inhibits NF-κB signaling.	[59,114–118]
Inhibiting Cell Proliferation and Cell Cycle Progression	Ellagic acid	Breast, colon, melanoma, liver, ovarian, gastric, cervical	Induces G0/G1 arrest, modulates TGF-β1/Smad3 pathway, affects cyclin B1 and cdc2 kinase, inhibits cell proliferation.	[119–129]
	Quercetin	Breast, hepatocellular carcinoma	Causes G2/M phase arrest, modulates cyclin B1, cdc2, PI3K/Akt, MAPK, NF-κB pathways, inhibits cell proliferation.	[130–138]
Interfering with Microtubule Formation	Vinca alkaloids	Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, non-small cell lung cancer, Kaposi sarcoma	Interfere with microtubule functions, inhibit cell division, bind to β-tubulin, prevent polymerization.	[139–148]
	Taxanes	Breast, ovarian, prostate, head and neck, non-small cell lung	Stabilize microtubules, prevent disassembly, effective against solid tumors, used in combination with other agents.	[149–154]
Acting on Topoisomerase Targets and Preventing DNA Replication	Camptothecin	Breast, ovarian, lung, colorectal	Inhibits topoisomerase I, prevents DNA replication, induces apoptosis, used with other anticancer agents.	[155–160]
	Thymoquinone	Breast, lung, colon	Inhibits topoisomerase II, increases DNA cleavage.	[161,162]

(*Continued*)

Table 1 (Continued).

Mechanism of Action	Natural Product	Cancer Type(s)	Details	References
	Berberine	Breast, lung, colon	Inhibits topoisomerase II, increases DNA cleavage.	[163–165]
	Coptisine	Breast, lung, colon	Inhibits topoisomerase I, causes DNA double-strand breaks.	[163,166–168]
	Curcumin	Breast, lung, colon	Inhibits topoisomerase II, increases DNA cleavage.	[169,170]
	Myricetin	Breast, lung, colon	Inhibits topoisomerase I and II, causes DNA double-strand breaks.	[171–173]
	Fisetin	Breast, lung, colon	Inhibits topoisomerase I and II, induces DNA double-strand breaks.	[174–177]
	EGCG	Breast, lung, colon	Inhibits topoisomerase II, increases DNA cleavage.	[178–181]
Inhibiting Angiogenesis	Polyphenols	Skin, breast, lung, liver, colon, prostate, ovary	Target VEGF/VEGFR2, PI3K/Akt, MAPK, ERK, calcineurin/NFAT, HIF-1α pathways.	[182–185]
	Polysaccharides	Esophagus, breast, lung, liver, colon, prostate, ovary	Display anti-angiogenic effects, alter tumor microenvironment, modulate immune responses.	[186–190]
	Alkaloids	Esophagus, breast, lung, liver, colon, prostate, ovary	Induce apoptosis in endothelial cells, reduce expression of angiogenic factors.	[191–194]
	Saponins	Esophagus, breast, lung, liver, colon, prostate, ovary	Target endothelial cell proliferation, migration, and tube formation.	[195–198]
	Curcumin, EGCG	Esophagus, breast, lung, liver, colon, prostate, stomach	Inhibit aminopeptidase-N (CD13), involved in angiogenesis.	[85,179,199–207]
	Genistein	Breast, prostate, colon, liver, ovarian, bladder, gastric, brain, neuroblastoma	Inhibits EGF effects on uPA, promoting angiogenesis.	[207–210]
	Nutrition	Various cancers	High intake of vegetables and fruits linked to decreased cancer incidence.	[211]
Modulating Key Signaling Pathways	Curcumin	Various cancers	Modulates NF-κB, PI3K/Akt, MAPK, JAK/STAT pathways, downregulates genes involved in cell proliferation, antiapoptosis, metastasis.	[212,213]
	Resveratrol	Various cancers	Modulates SIRT1-dependent AMPK activation, suppresses STAT3 signaling, inhibits PI3K/Akt/mTOR pathway, upregulates tumor suppressor miRNAs.	[212,214]
	EGCG	Various cancers	Regulates NF-κB, MAPK, PI3K/Akt, JAK/STAT pathways.	[185,212,213,215–217]

(*Continued*)

Table 1 (Continued).

Mechanism of Action	Natural Product	Cancer Type(s)	Details	References
Improving the Tumor Microenvironment	Curcumin	Prostate	Reduces invasive properties of cancer-associated fibroblasts by inhibiting mTOR/HIF-1α signaling, accumulates in CAFs.	[218]
	Resveratrol	Gastric	Induces ER stress response, autophagy, apoptosis, modulates immune cells and factors.	[219]
	Melatonin	Various cancers	Modulates ER stress, autophagy, RAS/RAF/ERK pathway.	[219–221]
	Silibinin	Lung, liver, prostate, breast, skin, colorectal	Inhibits invasion and metastasis by modulating CAFs, fibronectin, integrins, focal adhesion kinase (FAK).	[218,222]
	Polysaccharides	Various cancers	Show anti-angiogenic effects by influencing tumor microenvironment, modulating immune responses.	[218,219]
Reversing Multidrug Resistance	Flavonoids	Various cancers	Counteract MDR by inhibiting efflux proteins, inducing apoptosis, regulating cell cycle, modulating signaling pathways.	[56,223–226]
	Alkaloids	Various cancers	Inhibit drug efflux transporters, modulate apoptosis pathways. Examples: berberine, evodiamine, matrine.	[227–231]
	Terpenoids	Various cancers	Inhibit drug efflux transporters, modulate apoptosis pathways. Examples: celastrol, oridonin.	[232–236]
	Polyphenols	Various cancers	Inhibit drug efflux transporters, modulate apoptosis pathways. Examples: curcumin, resveratrol.	[237–240]
	Coumarins	Various cancers	Inhibit drug efflux transporters, modulate apoptosis pathways. Example: osthole.	[241–243]
Activating Immune Cells and Regulating Immune Function	Polyphenols	Various cancers	Modulate immune cells, inhibit immune checkpoints, induce immunogenic cell death, deactivate key signaling pathways. Examples: curcumin, resveratrol.	[244–247]
	Terpenoids	Various cancers	Enhance cancer immunotherapy by modulating immune cells, regulating immune function. Examples: paclitaxel, artemisinin.	[245,248]
	Polysaccharides	Various cancers	Enhance anti-tumor immune responses by targeting cells in the TME. Example: lentinan.	[219]
	Cardiotonic steroids	Various cancers	Enhance cancer immunotherapy. Examples: digoxin, bufalin.	[245,248]

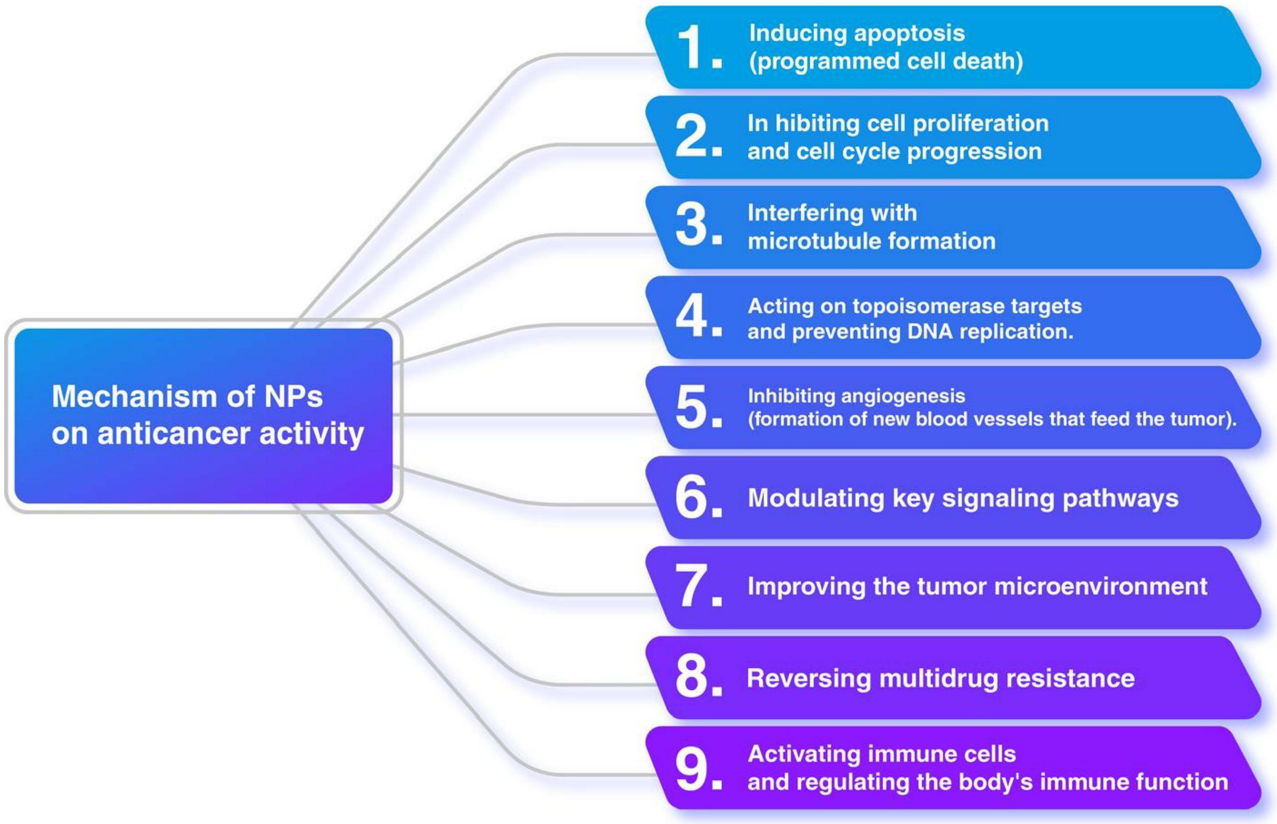

Figure 2 Natural products (NPs) have demonstrated various mechanisms of action in exhibiting anticancer effects.

Inducing Apoptosis (Programmed Cell Death)

The pursuit of effective anticancer strategies has led researchers to explore the potential of natural compounds in inducing apoptosis, or programmed cell death, in cancer cells. This approach involves regulating key apoptotic protein expression, thereby modulating apoptotic pathways and proteins.[249,250] Several natural compounds have demonstrated significant promise in this regard.

Curcumin, for instance, has exhibited anticancer effects across multiple cancer types, including breast, colon, prostate, lung, and glioblastoma.[85–87] Its mechanism of action involves modulating the expression of Bcl-2 family proteins, activating caspases, and targeting various signaling pathways such as NF-κB, PI3K/Akt, and MAPK.[88–90] Curcumin has been studied in combination with chemotherapeutic agents, like paclitaxel, to enhance efficacy by promoting apoptosis and overcoming drug resistance.[91] This compound initiates both the intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways in cancer cells.[92] Resveratrol, a stilbene found in grapes and other plants, also shows pro-apoptotic effects in various cancer cell lines, including breast, prostate, and leukemia.[83,93,94] It induces apoptosis by modulating the levels of Bcl-2 family proteins, activating caspases, and disrupting mitochondrial function.[95,96] Resveratrol can sensitize cancer cells to chemotherapy by enhancing their susceptibility to undergo apoptosis.[97] Artesunate, a derivative of artemisinin from Artemisia annua, has been shown to induce apoptosis in various cancer cell lines, such as glioblastoma, breast, and colorectal cancers.[98–100] It causes oxidative DNA damage, leading to DNA double-strand breaks and triggering the DNA damage response.[100] Artesunate initiates apoptosis via both caspase-dependent and caspase-independent mechanisms.[101] EGCG (Epigallocatechin gallate) induces apoptosis in a variety of cancer cell lines, including those derived from colon, prostate, breast, and lung cancers.[102–105] It activates both the intrinsic (mitochondrial) and extrinsic (death receptor) pathways of apoptosis.[106] EGCG modulates the expression of Bcl-2 family proteins by increasing the levels of pro-apoptotic Bax and Bak and decreasing the levels of anti-apoptotic Bcl-2 and Bcl-xL.[107] It can initiate caspase activation, cause cytochrome c release, and disrupt mitochondrial membrane potential to induce apoptosis.[108,109] Genistein, an isoflavone derived from soybeans, exhibits pro-apoptotic effects

in various cancer cell lines, including those from breast, prostate, and leukemia.[110] It induces cell cycle arrest and apoptosis by modulating cell cycle regulators and activating the caspase cascade.[111] Genistein can promote apoptosis by reducing the levels of anti-apoptotic proteins like Bcl-2 and inhibiting NF-κB signaling.[112] It enhances the sensitivity of cancer cells to chemotherapeutic agents by increasing their apoptotic potential.[113] Quercetin, a flavonol present in various plants, induces apoptosis in several cancer cell lines, such as colon, breast, and lung cancers.[59,114,115] It modulates the expression of Bcl-2 family proteins by increasing pro-apoptotic Bax and decreasing anti-apoptotic Bcl-2.[116,117] Quercetin can initiate apoptosis by activating caspases, inducing cytochrome c release, and disrupting mitochondrial membrane potential.[118] It can also regulate cell cycle proteins and inhibit NF-κB signaling to enhance apoptosis.[116] These natural compounds can influence the expression of critical apoptotic proteins, including Bcl-2 family members, caspases, and inhibitors of apoptosis proteins (IAPs), thereby triggering apoptosis in cancer cells. It is crucial to acknowledge that the specific mechanisms and pathways involved may vary depending on the type of cancer and the particular compound being examined.[114–118] This diversity underscores the complexity of cancer biology and the need for tailored therapeutic approaches.

Inhibiting Cell Proliferation and Cell Cycle Progression

The inhibition of cell proliferation and cell cycle progression is a critical strategy in the arsenal against cancer. This approach involves disrupting the delicate balance of cell cycle kinetics and influencing key signaling pathways that drive cancer progression. Numerous polyphenolic compounds have been identified for their potent anticancer effects through these mechanisms. Among these, ellagic acid and quercetin stand out as prominent examples of polyphenols with strong antiproliferative and cell cycle inhibitory activities. Ellagic acid (EA), a polyphenolic compound abundant in various fruits and nuts, has shown the capacity to inhibit cell proliferation and induce cell cycle arrest across a spectrum of cancer cell lines, including those of breast, colon, melanoma, liver, ovarian, gastric, and cervical origin.[119–128] In colon cancer cells (HCT-116), EA induces a G0/G1 arrest by engaging the TGF-β1/Smad3 pathway and altering the expression of key cell cycle-related genes such as cyclin D1, p21, and p27.[121] Furthermore, EA can induce a G2/M phase arrest in cancer cells by targeting the expression and activity of cyclin B1 and cdc2 kinase.[129] Quercetin, a flavonol widely distributed in fruits and vegetables, exhibits robust antiproliferative and cell cycle inhibitory effects in a variety of cancer cell lines, notably including breast and hepatocellular carcinoma.[130,131] It can induce a G2/M phase arrest by modulating the expression of cyclin B1, cdc2, and other pivotal mitotic regulators.[132] Quercetin's influence extends to several signaling pathways central to cell cycle regulation, such as the PI3K/Akt, MAPK, and NF-κB pathways, resulting in the suppression of cell proliferation and the induction of cell cycle arrest.[133,134] Other notable polyphenols, including curcumin, resveratrol, and EGCG, also demonstrate antiproliferative and cell cycle inhibitory effects by targeting signaling pathways like PI3K/Akt and NF-κB.[80,135–138] The ability of ellagic acid and quercetin to disrupt cell cycle kinetics and modulate key signaling pathways involved in cancer progression underscores their potent anticancer activities. This makes them compelling candidates for further research and potential therapeutic applications.[130–138] In summary, the modulation of cell proliferation and cell cycle progression through the action of natural polyphenols represents a promising avenue in cancer therapy. By understanding and harnessing these mechanisms, researchers aim to develop more effective and targeted treatments that can disrupt the relentless growth of cancer cells, ultimately improving patient outcomes.

Acting on Topoisomerase Targets and Preventing DNA Replication

The strategic targeting of topoisomerases, crucial enzymes involved in DNA replication and repair, represents a significant approach in cancer therapy. By inhibiting these enzymes, natural compounds and their derivatives can prevent DNA replication in tumor cells, thereby disrupting the growth and survival of cancerous cells. Camptothecin and its derivatives, such as irinotecan and topotecan, are well-known for their effectiveness against a range of cancers, including breast, ovarian, lung, and colorectal cancers. These compounds function by inhibiting topoisomerase I (TOP1), an essential enzyme for DNA replication and repair. By binding to the TOP1-DNA complex, camptothecin traps the enzyme in a covalent complex with DNA, preventing its release and thus halting DNA replication.[66,157] These derivatives offer improved efficacy and reduced side effects compared to the original compound.[65] However, tumor cells can develop resistance to these agents through various mechanisms, necessitating careful combination with other anticancer agents to enhance efficacy and mitigate resistance.[158–160] Thymoquinone, a compound derived from black

cumin seed, has been shown to inhibit topoisomerase II activity and increase DNA cleavage in various cancers, including breast, lung, and colon cancer. By interfering with the enzyme's function, thymoquinone causes the accumulation of DNA strand breaks, which are potentially lethal to cancer cells. This mechanism is akin to that of certain chemotherapy drugs, suggesting broad-spectrum anticancer activity.[161,162] Berberine, a natural alkaloid from plants like Berberis vulgaris and Coptis chinensis, also inhibits topoisomerase II activity and increases DNA cleavage in breast, lung, and colon cancer. This action induces DNA strand breaks, promoting apoptosis in cancer cells.[163–165] Coptisine, another natural compound, inhibits topoisomerase I activity and causes DNA double-strand breaks in multiple cancers, such as breast, lung, and colon cancer. This leads to significant DNA damage and disruption of cellular processes critical for cancer cell survival.[163,166–168] Curcumin, myricetin, fisetin, and epigallocatechin gallate (EGCG) are additional compounds that have been found to inhibit topoisomerase activities and induce DNA damage in various cancers. Curcumin and EGCG inhibit topoisomerase II, while myricetin and fisetin target both topoisomerase I and II, leading to DNA double-strand breaks and increased DNA cleavage in breast, lung, and colon cancer cells.[169–181] In summary, the targeting of topoisomerases by natural compounds and their derivatives is a promising strategy in cancer therapy. By preventing DNA replication and inducing DNA damage, these agents can disrupt the growth and survival of cancer cells, offering potential for improved therapeutic outcomes. Further research and development in this area are crucial for harnessing the full anticancer potential of these compounds.

Inhibiting Angiogenesis (Formation of New Blood Vessels That Feed the Tumor)

Inhibiting angiogenesis, the process of forming new blood vessels that feed tumors, is a critical strategy in cancer therapy. Natural products, including various compounds and nutrients, have demonstrated promising potential in this area by targeting key signaling pathways and transcription factors involved in angiogenesis. Polyphenols, such as ellagic acid, chlorogenic acid, quercetin, catechin, baicalin, and delphinidin, have been shown to inhibit angiogenesis by targeting crucial signaling pathways and transcription factors involved in the process. These include VEGF/VEGFR2, PI3K/Akt, MAPK, ERK, calcineurin/NFAT, and HIF-1α.[183–185] Polyphenols have been effective against a wide range of cancers, including those of the skin, breast, lung, liver, colon, prostate, and ovary.[182] Polysaccharides, derived from natural sources, also display anti-angiogenic effects by altering the tumor microenvironment and modulating immune responses.[189,190] They have been shown to inhibit cancers of the esophagus, breast, lung, liver, colon, prostate, and ovary.[186–188] Alkaloids, such as berberine and camptothecin, exhibit anticancer effects on various cancers and have been found to inhibit angiogenesis by inducing apoptosis in endothelial cells and reducing the expression of angiogenic factors.[192–194] These alkaloids are effective against cancers of the esophagus, breast, lung, liver, colon, prostate, and ovary.[191] Saponins, another class of natural substances, are capable of targeting various stages of the angiogenesis process, including endothelial cell proliferation, migration, and tube formation.[198] They exhibit anticancer effects on various cancers, including those of the esophagus, breast, lung, liver, colon, prostate, and ovary.[195–197] Curcumin from turmeric and epigallocatechin-3 gallate (EGCG) from green tea are known for their anticancer effects on multiple types of cancer, including those of the esophagus, breast, lung, liver, colon, prostate, and stomach.[85,179,199–204] These compounds can inhibit aminopeptidase-N (CD13), a member of the matrix metalloproteinase family that plays a role in the angiogenic switch process.[205–207] Genistein, an isoflavone derived from soy, demonstrates both in vitro and in vivo anticancer effects on a variety of cancers, including breast, prostate, colon, liver, ovarian, bladder, gastric, brain cancers, and neuroblastoma.[208] It can inhibit the effects of epidermal growth factor (EGF) on the expression of urokinase-type plasminogen activator (uPA), which can promote angiogenesis.[207,209,210] Epidemiological studies have indicated a decrease in cancer incidence with a high intake of vegetables and fruits, suggesting that natural products may have the potential to inhibit tumor angiogenesis.[211] In summary, the inhibition of angiogenesis by natural products represents a promising avenue in cancer therapy. By targeting key signaling pathways and transcription factors involved in angiogenesis, these compounds can disrupt the growth and survival of tumors, offering potential for improved therapeutic outcomes. Further research and development in this area are essential to fully harness the anticancer potential of these natural agents.

Modulating Key Signaling Pathways

Modulating key signaling pathways involved in cancer progression is a critical strategy in cancer therapy. Natural compounds such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) have demonstrated the ability to influence these pathways, thereby inhibiting cell proliferation, inducing apoptosis, and suppressing metastasis. Curcumin, a polyphenol derived from turmeric, modulates the NF-κB signaling pathway both directly and indirectly by regulating key factors. It downregulates the expression of genes involved in cell proliferation, antiapoptosis, and metastasis, and inhibits the PI3K/Akt pathway in high glucose-exposed HepG2 cells. Additionally, curcumin downregulates the EphA2/PI3K/MMP pathway in a lung cancer model.[212] It modulates various cellular pathways, including NF-κB, MAPK, PI3K/Akt, and JAK/STAT.[213] Resveratrol, a polyphenol found in grapes and other plants, modulates tumor cell proliferation and protein translation through SIRT1-dependent AMPK activation and suppresses the STAT3 signaling pathway in HepG2 cells.[212] It inhibits the PI3K/Akt/mTOR pathway, effectively reducing cellular growth and invasiveness in breast cancer. Resveratrol also efficiently upregulates various tumor suppressor miRNAs while suppressing oncogenic miRNAs across different cancer types.[214] EGCG, a major component of green tea, regulates multiple cellular pathways, including NF-κB, MAPK, PI3K/Akt, and JAK/STAT.[213] These polyphenols can target several signaling pathways involved in cancer progression, such as NF-κB, PI3K/Akt, MAPK, JAK/STAT, and mTOR. By regulating these pathways, they can inhibit cell proliferation, induce apoptosis, and suppress metastasis in various types of cancer.[185,215–217] However, it is important to acknowledge that these compounds exhibit non-specific actions and can interact with a wide array of molecular targets, resulting in divergent opinions in the literature regarding their true contribution to anticancer therapy. Further research is necessary to fully comprehend their mechanisms of action and potential clinical applications.[212] In summary, the modulation of key signaling pathways by natural compounds like curcumin, resveratrol, and EGCG represents a promising approach in cancer therapy. By targeting these pathways, these compounds can disrupt the growth and survival of cancer cells, offering potential for improved therapeutic outcomes. Continued research and development in this area are crucial to harness the full anticancer potential of these natural agents.

Improving the Tumor Microenvironment

Improving the tumor microenvironment is a strategic approach in cancer therapy that aims to inhibit cancer cell invasion, adhesion, and metastasis. Certain natural products have demonstrated the ability to modify the tumor microenvironment, enhancing their anticancer effects. Curcumin, a polyphenol derived from turmeric, can reduce the invasive properties of prostate-derived cancer-associated fibroblasts (CAFs) by inhibiting the mTOR/HIF-1α signaling pathway. Curcumin-loaded lipid nanoparticles exhibit a greater ability to cross tumor barriers and accumulate in CAFs compared to cancer cells, enhancing their efficacy.[218] Resveratrol, a polyphenol found in grapes and other plants, induces endoplasmic reticulum (ER) stress response, cellular autophagy, and apoptosis in gastric cancer cells in a dose-dependent manner. It also modulates immune cells and immune factors, reshaping the tumor microenvironment and promoting cancer cell death.[219] Melatonin, a hormone produced by the pineal gland, has demonstrated potential anticancer effects against various types of cancer, including breast, prostate, liver, skin, lung, hepatic, renal cell, non-small cell lung, colon, oral, neck, and head cancers. Melatonin may inhibit cancer survival by modulating ER stress, autophagy, and the RAS/RAF/ERK signaling pathway.[219–221] Silibinin, a flavonoid derived from milk thistle, has demonstrated potential anticancer effects against various types of cancer, including lung, liver, prostate, breast, skin, and colorectal cancers. Silibinin inhibits the invasion and metastasis of prostate cancer cells by modulating cancer-associated fibroblasts (CAFs). It also reduces the motility and proliferation of prostate cancer cells by blocking fibronectin and downregulating integrins and focal adhesion kinase (FAK).[218] Polysaccharides from natural sources can show anti-angiogenic effects by influencing the tumor microenvironment and modulating immune responses.[219] These natural products can modulate various signaling pathways within the tumor microenvironment, including immune responses, cell metabolism, epigenetics, angiogenesis, and the extracellular matrix (ECM). Targeting specific cells and molecules in the tumor microenvironment can inhibit cancer cell invasion, adhesion, and metastasis. Using nanoparticles as carriers for these natural products can improve their delivery to the tumor stroma and cancer-associated fibroblasts (CAFs), which are critical barriers to drug penetration in solid tumors. This approach can enhance the anti-tumor effectiveness of natural products against cancer cells.[218] In summary, the modulation of the tumor microenvironment by natural products represents a promising strategy

in cancer therapy. By targeting specific cells and molecules within the tumor microenvironment, these compounds can inhibit cancer cell invasion, adhesion, and metastasis, offering potential for improved therapeutic outcomes. Further research and development in this area are crucial to harness the full anticancer potential of these natural agents.

Reversing Multidrug Resistance

Reversing multidrug resistance (MDR) is a significant challenge in cancer therapy, as it allows tumor cells to evade the effects of multiple chemotherapy agents. Certain natural products have demonstrated the ability to overcome MDR in tumor cells through various mechanisms, enhancing the efficacy of cancer treatments. Flavonoids, such as quercetin, baicalein, and chrysin, exhibit promise in both preventing and treating various forms of cancer.[223] These compounds can counteract MDR by inhibiting efflux proteins, inducing apoptosis, regulating the cell cycle, and modulating signaling pathways.[56,224,225] Flavonoids can enhance the MDR-reversal effect of statins.[226] Alkaloids, including berberine, evodiamine, and matrine, have demonstrated the ability to reverse MDR in various cancer cell lines by inhibiting drug efflux transporters like P-glycoprotein (P-gp) and modulating apoptosis pathways.[227–231] Amaryllidaceae alkaloids were studied for their MDR reversal effects in human colon cancer cells, with certain compounds found to be more potent inhibitors than verapamil.[227] Terpenoids such as celastrol and oridonin have been shown to reverse MDR in various cancer cell lines by inhibiting drug efflux transporters like P-gp and modulating apoptosis pathways.[232–236] Polyphenols, including curcumin and resveratrol, have demonstrated the ability to reverse MDR in various cancer cell lines by inhibiting drug efflux transporters like P-gp and modulating apoptosis pathways.[237–240] Coumarins, such as osthole, have been shown to reverse MDR in various cancer cell lines by inhibiting drug efflux transporters like P-gp and modulating apoptosis pathways.[241–243] These natural substances can counteract MDR through different mechanisms, including the inhibition of drug efflux pumps (like P-gp and MRP1), modulation of apoptosis pathways, induction of DNA damage and cell cycle arrest, and regulation of signaling pathways associated with MDR development.[223–243] In summary, the ability of natural products to reverse multidrug resistance represents a promising avenue in cancer therapy. By targeting the mechanisms underlying MDR, these compounds can enhance the susceptibility of cancer cells to chemotherapy, potentially improving treatment outcomes. Further research and development in this area are crucial to harness the full potential of these natural agents in cancer treatment.

Activating Immune Cells and Regulating the Body's Immune Function

Activating immune cells and regulating the body's immune function is a critical strategy in cancer therapy. Natural products have demonstrated significant potential in combating cancer by modulating the immune system, thereby enhancing anti-tumor immune responses. Remodeling the tumor microenvironment (TME) is a key mechanism through which natural products can influence cancer progression. These compounds can modulate and regulate immune cells like T cells, macrophages, mast cells, and inflammatory cytokines within the TME. By targeting key cell populations in the TME, including fibroblasts, inflammatory factors, and macrophages, natural products enhance anti-tumor immune responses.[219] Modulating T cell function is another important aspect. Curcumin, for example, can transform immunosuppressive regulatory T cells (Tregs) into anti-tumor Th1 cells in colorectal and lung cancers. Berberine suppresses Treg activation, reduces myeloid-derived suppressor cells (MDSCs), and boosts tumor-infiltrating T cell immunity. Resveratrol enhances Th1 immune responses and CD8+ T cell activity in lung tumors by reducing PD-1 expression.[244,245] Inhibiting immune checkpoints is a strategy that natural products can employ to enhance the effectiveness of immunotherapy. Curcumin, for instance, lowers PD-L1 expression, increases CD8+ T cells, and reduces Tregs and MDSCs in oral cancers.[246,247] Natural products can influence immune checkpoint-related signaling molecules through various pathways in the TME, boosting the effectiveness of immunotherapy and decreasing resistance.[219] Inducing immunogenic cell death is another mechanism by which certain natural products can stimulate anti-tumor immunity. These compounds trigger immunogenic apoptosis in tumor cells, releasing tumor antigens and danger signals that stimulate anti-tumor immunity.[245,251] Regulating key signaling pathways is also crucial. Natural products can deactivate pathways such as NF-κB, PI3K/Akt, MAPK, and JAK/STAT, which are essential for tumor immune evasion.[245] Examples of natural products with immune-modulating effects include polyphenols (curcumin, resveratrol), terpenoids (paclitaxel, artemisinin), polysaccharides (lentinan), and cardiotonic steroids (digoxin, bufalin). While these natural products have potential

to enhance cancer immunotherapy, challenges persist in fully understanding their targets and mechanisms, as well as in broadening their clinical efficacy and applications.[245,248] Combining natural products with conventional therapies could offer safer and more effective cancer treatment strategies by utilizing their immunomodulatory properties.[219,245] In summary, the modulation of the immune system by natural products represents a promising approach in cancer therapy. By activating immune cells and regulating the body's immune function, these compounds can enhance anti-tumor immune responses, potentially improving treatment outcomes. Further research and development in this area are crucial to harness the full potential of these natural agents in cancer treatment.

Therapeutic Benefits and Selective Toxicity

The therapeutic benefits of herbal anticancer agents are significant, particularly due to their selective toxicity towards cancer cells, which minimizes the adverse side effects associated with conventional chemotherapy. Recent studies and clinical trials have underscored these advantages:

Selective Toxicity and Reduced Side Effects: Herbal medicines have been shown to alleviate the side effects of anticancer drugs, enabling patients to complete their treatment regimens. For example, herbal medicine was effective in mitigating the side effects of Tamoxifen in a metastatic breast cancer patient, allowing the continuation of treatment.[252]

Enhancing Treatment Tolerance: Research indicates that herbal medicines can enhance patients' tolerance to chemotherapy. A double-blind placebo-controlled study demonstrated that traditional Chinese herbal medicine significantly reduced chemotherapy-induced nausea.[253]

Synergistic Effects with Conventional Treatments: Herbal medicines have the potential to synergistically enhance the effects of conventional treatments. The herbal medicine SH003, which includes Astragalus membranaceus, Angelica gigas, and Trichosanthes kirilowii, was found to be safe and potentially effective for treating solid cancers.[254]

Clinical Benefits and Improved Quality of Life: Herbal medicines such as Fucoidan have exhibited anti-inflammatory properties that are beneficial for patients with advanced cancer, helping to maintain their quality of life by stabilizing inflammatory markers.[255]

Potential for Reducing Cancer Growth: In some cases, herbal medicines have contributed to controlling cancer growth. A report highlighted instances where combining herbal medicines with anticancer drugs helped regain control of cancer growth when drug resistance was observed.[256]

In summary, the therapeutic benefits of herbal anticancer agents, including their selective toxicity and reduced side effects, make them promising adjuncts to conventional cancer treatments. By enhancing treatment tolerance, demonstrating synergistic effects, improving quality of life, and potentially reducing cancer growth, these herbal medicines offer a multifaceted approach to cancer therapy. Further research and clinical trials are essential to fully understand their efficacy and safety in various cancer contexts.

Clinical Applications and Current Research

The current research landscape on herbal anti-cancer agents is extensive and continually expanding, with numerous studies and clinical trials examining their efficacy, safety, and mechanisms of action. This section reviews recent studies and clinical trials, highlighting the types of cancers being targeted, observed outcomes, and promising advancements in the field.

Targeted Cancers and Outcomes

Lung Cancer

Studies suggest that lung cancer patients are interested in using herbal remedies for symptom management, though well-designed clinical trials are still needed. Herbal remedies, with their long history of use in traditional medicine systems, offer a potentially gentler and more natural approach to symptom management. They are often sought after by patients who may be seeking alternatives or complements to conventional treatments that can have harsh side effects. The willingness of nearly half of the lung cancer patients surveyed to participate in herbal clinical trials is a clear indication

that there is a desire for more research in this area. Research involving lung cancer patients revealed that nearly half were willing to participate in herbal clinical trials, indicating a promising area for future research.[257]

Prostate Cancer

The herbal supplement PC-SPES, which includes a blend of eight herbs, has demonstrated efficacy in androgen-independent prostate cancer (AIPC). A randomized Phase II study showed that PC-SPES led to significant declines in prostate-specific antigen (PSA) levels and median time to progression compared to diethylstilbestrol (DES), although contamination with synthetic estrogens was an issue.[258]

Breast Cancer

Herbal therapy combining yunzhi and danshen has been shown to enhance the quality of life in breast cancer patients by reducing fatigue, improving sleep, appetite, and emotional stability.[259] Additionally, the cardioprotective effects of Platycodon grandiflorum granules are being evaluated in patients receiving anthracycline-based chemotherapy.[260]

Hepatocellular Carcinoma

Icaritin, derived from Epimedii herba, has shown promising results in enhancing overall survival in patients with advanced hepatocellular carcinoma with poor conditions. A Phase III trial indicated that Icaritin improved median overall survival compared to a commonly used traditional Chinese medicine formula.[261]

Promising Developments

Polypharmacology Approach

Herbal compounds often target multiple pathways simultaneously, increasing efficacy and reducing the chance of cancer cells developing resistance. This approach is illustrated by curcumin, which modulates several signaling pathways involved in cancer progression. By adopting a multi-targeted approach, these compounds can offer a more robust strategy against cancer, potentially reducing resistance and enhancing the effectiveness of conventional treatments. However, translating these findings into clinical practice requires overcoming challenges like bioavailability and conducting rigorous clinical trials to establish safety and efficacy profiles.[262]

Combination Therapies

Using herbal medicines in combination with conventional treatments has shown potential to improve outcomes and reduce side effects. For example, combining traditional Chinese herbal medicine with chemotherapy has significantly reduced chemotherapy-induced nausea. Traditional Chinese herbal medicine encompasses a vast array of herbal formulations that have been used for centuries to treat various ailments, including cancer. These herbal remedies are believed to work in harmony with the body's natural healing processes, supporting the immune system and helping to restore balance. When combined with chemotherapy, Traditional Chinese herbal medicine can provide a complementary approach that targets both the cancer and the side effects of treatment. The reduction in chemotherapy-induced nausea achieved through the combination of Traditional Chinese herbal medicine and chemotherapy is attributed to the anti-emetic properties of certain herbs. For instance, herbs like ginger and zedoary have been traditionally used to alleviate nausea and vomiting. Scientific studies have confirmed these effects, showing that these herbs can modulate the neurotransmitters and receptors involved in nausea and vomiting, thereby reducing the severity of these symptoms. Moreover, Traditional Chinese herbal medicine can also help mitigate other common side effects of chemotherapy, such as fatigue, loss of appetite, and immune suppression. By supporting the body's overall health and vitality, Traditional Chinese herbal medicine can enable patients to better tolerate the rigors of chemotherapy, potentially leading to improved treatment adherence and outcomes. It is important to note that while the use of herbal medicines in combination with conventional treatments shows promise, it should be approached with caution and under the guidance of healthcare professionals. Herbal medicines can interact with chemotherapy drugs, and their efficacy and safety profiles can vary. Therefore, a personalized approach to integrative cancer care, which takes into account the individual patient's condition and treatment regimen, is essential.[253]

Immunomodulation

Some herbal compounds have immunomodulatory effects, which can be advantageous in cancer treatment. Active hemicellulose compound (AHCC) has demonstrated potential activity against castration-resistant prostate cancer through its immunomodulatory properties. AHCC is a proprietary extract derived from hybridized mushrooms, particularly shiitake mushrooms. It has gained attention for its immunomodulatory effects, which can be advantageous in various health contexts, including cancer treatment. AHCC has been studied for its potential activity against castration-resistant prostate cancer (CRPC), a challenging form of prostate cancer that no longer responds to hormonal treatment. The immunomodulatory properties of AHCC are believed to enhance the body's natural defenses against cancer. It does this by stimulating the activity of immune cells such as dendritic cells, natural killer (NK) cells, and cytokines. These immune cells play a crucial role in recognizing and eliminating cancer cells. By boosting the immune system, AHCC may help in controlling the growth and spread of cancer cells, including those that are resistant to conventional therapies like androgen deprivation therapy (ADT). AHCC can increase the number and activity of NK cells, which are key players in the immune response against cancer. Additionally, AHCC has been found to enhance the function of dendritic cells, which are responsible for presenting antigens to T cells, thereby activating the adaptive immune response. This enhanced immune response can potentially lead to better control of cancer progression and improved patient outcomes. Furthermore, AHCC has been investigated for its safety and tolerability in clinical trials, with results suggesting that it is well-tolerated and does not cause significant adverse effects. This makes it a promising complementary therapy for cancer patients, especially those with castration-resistant prostate cancer, where treatment options are limited and the disease is often fatal.[263]

Quality of Life Improvements

Herbal therapies have demonstrated significant potential in enhancing the quality of life for cancer patients by effectively alleviating various treatment-related side effects and psychological distress. These natural remedies can significantly improve physical function, reduce fatigue, and enhance emotional stability, offering a complementary approach to conventional cancer treatments. For instance, herbs such as ginger are known to alleviate chemotherapy-induced nausea and vomiting, while aloe vera and chamomile can soothe oral mucositis, a common and painful side effect of cancer therapies. Additionally, energy-boosting herbs like ginseng and ashwagandha have been studied for their ability to combat cancer-related fatigue, a pervasive issue among patients. Psychologically, herbal supplements such as St. John's Wort and kava can help mitigate anxiety and depression, common emotional burdens for cancer patients. Furthermore, herbs like valerian root and passionflower can improve sleep quality, which is often compromised due to stress and treatment side effects, thereby contributing to better emotional stability. Digestive health is another area where herbal therapies can provide relief, with herbs such as peppermint and fennel aiding in digestion and reducing gastrointestinal issues. Some herbs, including echinacea and astragalus, are believed to support immune function, which can be weakened by both cancer and its treatments. It is crucial, however, that herbal therapies are used judiciously and under the guidance of healthcare professionals, given the potential for interactions with chemotherapy or radiation therapies. Ongoing clinical trials and research are essential to fully understand the role of herbal therapies in cancer care, ensuring that they are safely and effectively integrated into standard treatment protocols to maximize their benefits for patients.[259]

Challenges and Future Directions

Despite the promising potential of herbal anti-cancer agents, several challenges need to be addressed to fully incorporate these therapies into mainstream cancer treatment. A significant obstacle is the variability in the quality and concentration of bioactive compounds in medicinal plants, which can impact the consistency and effectiveness of herbal treatments. Standardizing herbal extracts is essential to ensure uniform therapeutic outcomes. Additionally, although phytochemicals' selective targeting of cancer cells helps minimize side effects, the precise mechanisms of action for many herbal compounds are not yet fully understood, necessitating further research to elucidate their pathways and interactions.[252,262,264,265]

Another major challenge involves the bioavailability and delivery of these compounds. Many herbal bioactive substances have poor aqueous solubility and low bioavailability, limiting their effectiveness when administered traditionally. To address these issues, innovative drug delivery systems, such as nanoparticles, have been extensively developed. These systems improve the bioavailability, targeted delivery, and therapeutic efficacy of herbal compounds, tackling problems related to non-specific distribution and systemic toxicity. However, developing and optimizing these advanced delivery systems require substantial investment and rigorous testing to ensure safety and effectiveness.[254,266,267]

Moreover, integrating herbal anti-cancer agents into clinical practice faces regulatory and acceptance barriers. Herbal medicines often exist in a gray area between conventional pharmaceuticals and dietary supplements, leading to regulatory challenges that can hinder their clinical adoption. Rigorous clinical trials are necessary to validate the efficacy and safety of these agents, yet funding and conducting such trials can be complex and resource-intensive. Additionally, the medical community's acceptance of herbal treatments requires a shift in perspective, supported by robust scientific evidence and clear clinical guidelines.[268–270]

Looking ahead, multidisciplinary collaboration will be essential to address these challenges and advance the field of herbal anti-cancer therapy. Researchers, clinicians, and regulatory bodies must work together to standardize herbal extracts, develop innovative delivery systems, and conduct comprehensive clinical trials. The future of cancer treatment could be significantly enhanced by integrating herbal anti-cancer agents, offering a more holistic, effective, and patient-friendly approach. However, achieving this potential will depend on overcoming current obstacles through continued research, innovation, and collaboration.

Novel Herbal Agents and Innovative Treatments

In addition to the well-established herbal anticancer agents, recent research has identified several novel bioactive compounds with promising anticancer potential. For example, withaferin A, a steroidal lactone isolated from Withania somnifera (Ashwagandha), has been shown to induce apoptosis and inhibit angiogenesis in various cancer cell lines.[48–50] In a study, withaferin A demonstrated potent anticancer effects in breast cancer cells by inducing reactive oxygen species (ROS) generation, leading to apoptosis and inhibition of cell proliferation.[48] Another study by Suman et al revealed that withaferin A could sensitize ovarian cancer cells to cisplatin treatment, suggesting its potential as an adjuvant therapy.[49] Another novel compound, triptolide, derived from Tripterygium wilfordii (Thunder God Vine), has demonstrated potent anticancer effects by inducing apoptosis and inhibiting cell proliferation.[51–53] Triptolide has been shown to induce apoptosis in various cancer cell lines, including pancreatic, breast, and prostate cancer cells, through the modulation of multiple signaling pathways such as NF-κB, MAPK, and PI3K/Akt.[51,52] In a study by Wang et al, triptolide exhibited potent anticancer activity in a mouse model of pancreatic cancer, reducing tumor growth and metastasis.[53] In addition to these novel compounds, innovative herbal formulations and delivery systems have been developed to enhance the efficacy and specificity of herbal agents. Nanoparticle-based delivery systems, such as liposomes and polymeric nanoparticles, have been employed to improve the bioavailability and targeted delivery of herbal compounds.[54–56] For instance, curcumin-loaded nanoparticles have shown enhanced cellular uptake and increased anticancer activity compared to free curcumin.[57,58] In a study, curcumin-loaded magnetic nanoparticles demonstrated enhanced anticancer effects in prostate cancer cells, inducing apoptosis and inhibiting cell proliferation.[57] Another study by Ganta et al developed a novel nanoparticle formulation of EGCG, which showed improved stability and enhanced anticancer activity in breast cancer cells.[58] Furthermore, novel herbal formulations combining multiple bioactive compounds have been developed to achieve synergistic anticancer effects. For example, a study by Wang et al investigated the anticancer potential of a traditional Chinese medicine formula, Huang-Lian-Jie-Du-Tang (HLJDT), which contains four herbs: Coptis chinensis, Scutellaria baicalensis, Phellodendron amurense, and Gardenia jasminoides.[59] The study found that HLJDT exhibited potent anticancer effects in colorectal cancer cells by inducing apoptosis and inhibiting cell proliferation, suggesting its potential as a novel herbal formulation for cancer treatment.[59] Another innovative approach is the development of herbal-based combination therapies, which aim to enhance the efficacy of conventional cancer treatments while reducing their adverse effects. For instance, a study by Jiang et al investigated the combination of curcumin with 5-fluorouracil (5-FU) in the treatment of colorectal cancer.[60] The study found that curcumin enhanced the anticancer

effects of 5-FU and reduced its toxic side effects, suggesting the potential of herbal-based combination therapies.[60] These novel approaches aim to overcome the limitations associated with traditional herbal preparations and optimize their therapeutic potential. By identifying new bioactive compounds, developing innovative delivery systems, and exploring synergistic combinations, researchers are paving the way for the development of more effective and targeted herbal anticancer agents. However, further research, including preclinical and clinical studies, is necessary to fully understand the mechanisms of action, safety profiles, and clinical efficacy of these novel herbal agents and innovative treatments.

Conclusion

This review underscores the immense potential of herbal medicines in the fight against cancer, highlighting novel herbal agents and innovative approaches that have emerged in recent years. The bioactive compounds found in medicinal plants, such as flavonoids, alkaloids, terpenoids, and polyphenols, have demonstrated a wide range of anticancer mechanisms, including the induction of apoptosis, inhibition of angiogenesis, prevention of metastasis, and modulation of the immune response. Beyond well-known compounds, this review explores recent discoveries, such as withaferin A from Withania somnifera (Ashwagandha) and triptolide from Tripterygium wilfordii (Thunder God Vine). These novel herbal agents have shown potent anticancer effects in preclinical studies, inducing apoptosis, inhibiting cell proliferation, and sensitizing cancer cells to conventional treatments. Moreover, the review emphasizes the innovative aspects of herbal medicine research, particularly the development of nanoparticle-based delivery systems and novel herbal formulations. These cutting-edge approaches aim to enhance the efficacy, specificity, and bioavailability of herbal compounds, addressing the limitations associated with traditional herbal preparations. The discussion of herbal-based combination therapies further highlights the potential for synergistic effects and reduced toxicity when combining herbal agents with conventional cancer treatments. However, the review acknowledges that further research is necessary to fully realize the potential of herbal medicines in cancer treatment. Preclinical and clinical studies are needed to validate the efficacy and safety of novel herbal agents and innovative treatments. Elucidating the detailed mechanisms of action and potential drug interactions of herbal compounds is crucial for their successful integration into cancer therapy. Additionally, efforts should be directed towards standardizing herbal preparations to ensure consistent quality and potency. Future research should focus on identifying new bioactive compounds from medicinal plants, exploring their anticancer potential, developing herbal-based combination therapies, and optimizing delivery systems. By addressing these challenges and advancing research in these areas, herbal medicines can become valuable tools in the fight against cancer, complementing conventional therapies and improving patient outcomes. In conclusion, this review contributes to the current understanding of herbal medicines in cancer treatment by presenting novel herbal agents, innovative approaches, and future research directions. The findings discussed herein underscore the importance of continued research and development in this field, with the ultimate goal of providing safe, effective, and accessible cancer therapies derived from nature's bounty. As the scientific community continues to unravel the mysteries of medicinal plants and their bioactive compounds, the future of cancer treatment holds great promise, offering hope to millions of patients worldwide.

Disclosure

The authors report no conflicts of interest in this work.

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