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Review

Plant-Derived Bioactive Compounds in Cancer Therapy: Molecular Mechanisms, Preclinical Evidence, and Translational Perspectives

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Abstract

Cancer remains one of the leading causes of death and is driven by complex interactions among oxidative stress, inflammation, and dysregulated cellular signaling. Over the past few years, plant-derived antioxidants have shown exciting anticancer potential in preclinical trials. However, translating these findings into effective clinical therapies remains a challenge. Moreover, their safety profile depends on the individual compound, dosage, formulation, and duration of exposure. This review provides a comprehensive overview of plant-derived antioxidants and their therapeutic potential in cancer prevention and treatment, with particular emphasis on their molecular mechanisms, biological activities, and translational relevance. Plant-derived compounds exhibit significant anticancer potential through the regulation of signaling pathways such as NF-κB, PI3K/Akt, MAPK, and Nrf2, thereby influencing cell proliferation, apoptosis, angiogenesis, inflammation, and metastasis. Despite this promising therapeutic potential, their clinical application remains challenging. Recent advances in drug delivery systems have shown their considerable promise in overcoming these limitations and enhancing their therapeutic efficacy. Consequently, natural antioxidants may represent a multi-targeted and biologically relevant strategy for cancer management. However, further mechanistic studies and well-designed clinical trials are needed to validate their therapeutic potential and support their integration into modern oncology, ultimately contributing to the development of safer and more effective anticancer therapies.

Keywords: natural products; antioxidants; cancer therapy; oxidative stress; phytochemicals; bioavailability

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1. Introduction

Natural products have emerged as promising anticancer therapeutic agents because of their ability to modulate oxidative stress, regulate signaling pathways, and influence several key processes implicated in cancer initiation, progression, and metastasis [1]. Natural products are compounds that are derived from plants, animals, and other living organisms and have contributed to the development of several anticancer drugs. In addition, many cancer patients use natural products as part of a complementary and integrated approach to treatment [2]. Their ability to act on multiple targets has continued to attract interest in their use as complementary agents, although their safety and potential benefits need

to be evaluated more thoroughly [3]. Natural products can affect the tumor microenvironment through immunomodulatory and antioxidant effects. While antioxidants may protect healthy cells from chronic oxidative stress linked with carcinogenesis, some natural compounds can act as pro-oxidants within cancer cells, promoting apoptosis and cell cycle arrest. Overall, these compounds can modulate pathways involved in oxidative homeostasis, inflammation, and DNA repair and thus trigger cancer cells to undergo apoptosis or cell cycle arrest [1]. The principal molecular mechanisms through which plant-derived natural products exert anticancer effects are summarized in Figure 1. Among plant-derived bioactive compounds, flavonoids and phenolic acids have attracted considerable attention because of their broad-spectrum anticancer activities.

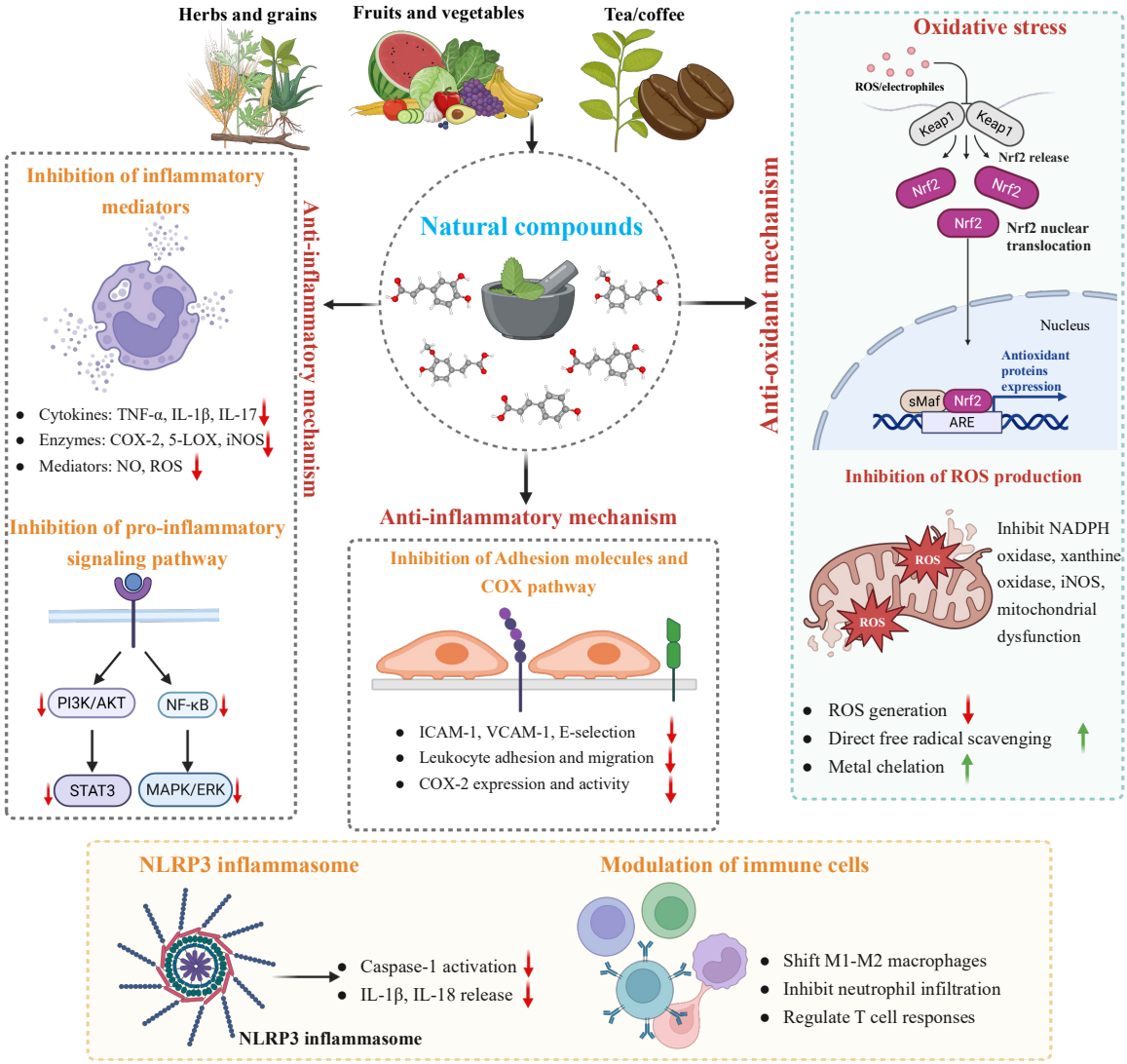


Figure 1. Natural compounds derived from fruits and vegetables exert anti-inflammatory and antioxidant effects through multiple molecular mechanisms. Anti-inflammatory activities include inhibition of inflammatory mediators and suppression of pro-inflammatory signaling pathways, reduced expression of adhesion molecules, leukocyte adhesion and migration, and COX-2 activity. These compounds also modulate the NLRP3 inflammasome, reducing caspase-1 activation and IL-1β and IL-18 release, while regulating immune cell responses. The antioxidant mechanisms involve activation of the Keap1/Nrf2/ARE signaling pathway, promoting antioxidant protein expression, inhibiting ROS production, and enhancing free-radical scavenging. Collectively, these mechanisms contribute to the attenuation of oxidative stress and inflammation. Created in BioRender. Rahmani, A.H. (2026) https://BioRender.com/0awy6qz (accessed on 25 October 2026).

These compounds have been reported to inhibit tumor growth and progression in experimental and preclinical models by targeting multiple pathways involved in proliferation, angiogenesis, invasion, and metastasis [Figure 1]. Flavonoids can regulate key factors such as VEGF, MMPs, and EGFR, thereby limiting angiogenesis and tumor progression [4]. They can also promote apoptosis and inhibit pro-survival signaling in cancer cells. Chrysin and kaempferol have also shown anticancer activity in preclinical studies, including effects on cancer-cell survival and responses to conventional anticancer agents [5]. However, the clinical relevance of these findings remains to be established.

Apoptosis is one of the major mechanisms underlying the anticancer effects of natural products. Plant-derived natural products, particularly flavonoids and phenolic acids, have received considerable attention for their potential role in cancer prevention and treatment. Compounds such as apigenin, quercetin, baicalein, gallic acid, and rosmarinic acid have been investigated in different cancer models, providing a basis for further research into their biological activities [6–26]. These compounds represent diverse chemical groups, and their effects may differ according to their chemical structure, concentration, and the biological environment in which they act. Although experimental findings have highlighted their potential to influence processes associated with cancer development and progression, the strength and relevance of the available evidence vary among compounds and cancer types. Therefore, promising findings from cell-based and animal studies should be interpreted cautiously, as they do not necessarily predict clinical benefits.

Their multi-targeted biological activities have sustained interest in their investigation as potential complementary agents; however, their safety and suitability for clinical use depend on the specific compound, dose, formulation, exposure, and concomitant medications.

Despite their strong anticancer potential, natural products face important challenges, including poor bioavailability, low solubility, and rapid metabolism, which can limit their therapeutic efficacy. Further, their antioxidant or pro-oxidant effects may vary depending on the compound, concentration, and cellular context, making their biological effects complex [27]. So, a better understanding of their molecular mechanisms, pharmacokinetics, and delivery modes is needed to improve their therapeutic potential. This review provides an overview of plant-derived bioactive compounds and evaluates their potential as anticancer agents, with particular emphasis on their molecular mechanisms, pharmacokinetic challenges, and possible therapeutic application.

Although several reviews have discussed the anticancer properties of polyphenols, important questions remain regarding their bioavailability, safety, interactions with anticancer drugs, and potential for clinical application. This review focuses on flavonoids and phenolic acids, examining their anticancer mechanisms alongside the limitations that may affect their therapeutic use. Particular attention is given to achievable concentrations in the body, dose-dependent effects, potential drug interactions, and strategies to improve delivery. By considering both promising findings and existing limitations, this review aims to provide a clearer understanding of the therapeutic potential of polyphenols and the challenges that must be addressed before their wider application in cancer treatment.

2. Search Methodology

This narrative review was prepared following a literature search using PubMed, Scopus, Web of Science, and Google Scholar. Manuscript preparation commenced on 1 January 2026, and the final literature search was completed on 25 June 2026. Publications from 2010 to 25 June 2026 were considered. The search focused on plant-derived polyphenols, particularly flavonoids and phenolic acids, their anticancer activities, molecular mechanisms, pharmacokinetics, safety, and potential applications in combination with conventional anticancer therapies.

The literature search used combinations of relevant keywords and Boolean operators (AND and OR). Representative search terms included ("plant-derived polyphenols" OR phytochemicals OR flavonoids OR "phenolic acids" OR quercetin OR apigenin OR "gallic acid" OR "rosmarinic acid") AND (cancer OR neoplasm OR tumor OR anticancer) AND ("molecular mechanisms" OR apoptosis OR "cell cycle arrest" OR "signalling pathways" OR pharmacokinetics OR bioavailability OR toxicity OR "combination therapy"). Search terms were adapted according to the requirements of individual databases.

Search results were assessed for relevance to the review. Priority was given to original peer-reviewed research providing relevant mechanistic evidence and quantitative pharmacokinetic or combination-treatment findings. Preclinical and human clinical studies were considered separately to distinguish laboratory findings from evidence in humans. Studies outside the scope of the review, non-English publications, and those lacking sufficient supporting data were excluded.

3. Plant-Based Bioactive Compounds in Cancer Therapy: Mechanisms and Perspectives

Despite advances in cancer therapy, including surgery, chemotherapy, and radiation therapy, treatment efficacy is often limited by toxicity, resistance, and the immunosuppressive tumor microenvironment. Chemotherapy-induced adverse effects can further restrict optimal dosing, highlighting the need for safer, more effective, and targeted therapeutic strategies [28]. Although some naturally occurring phytochemicals have demonstrated favorable safety profiles [29] in experimental and clinical studies, their toxicity and safety vary depending on the compound, dosage, bioavailability, and duration of exposure. Therefore, their safety for human consumption requires evaluation on a compound-specific basis. However, some compounds may produce adverse or organ-specific effects at higher exposures. Many phytochemicals have also shown promising anticancer activity, although their effects and underlying mechanisms vary across compounds and cancer models.

3.1. Therapeutic Potential of Plant Flavonoids in the Treatment of Cancer

Flavonoids represent a diverse group of plant-derived compounds that have attracted considerable interest for their potential anticancer properties across different cancer models. Their biological effects vary among individual compounds, as summarized in Table 1 and are discussed in the following sections [30]. Flavonoids can influence several molecular pathways involved in cancer development and progression. They may inhibit receptor-mediated oncogenic signaling, thereby reducing cell survival, proliferation, and the expression of pro-survival genes. They can also promote mitochondrial apoptosis by increasing pro-apoptotic proteins and reducing anti-apoptotic proteins. In addition, flavonoids may induce cell-cycle arrest by modulating cell-cycle regulatory proteins. Their effects on invasion and metastasis are associated with the regulation of matrix metalloproteinases and angiogenic pathways (Figure 2).

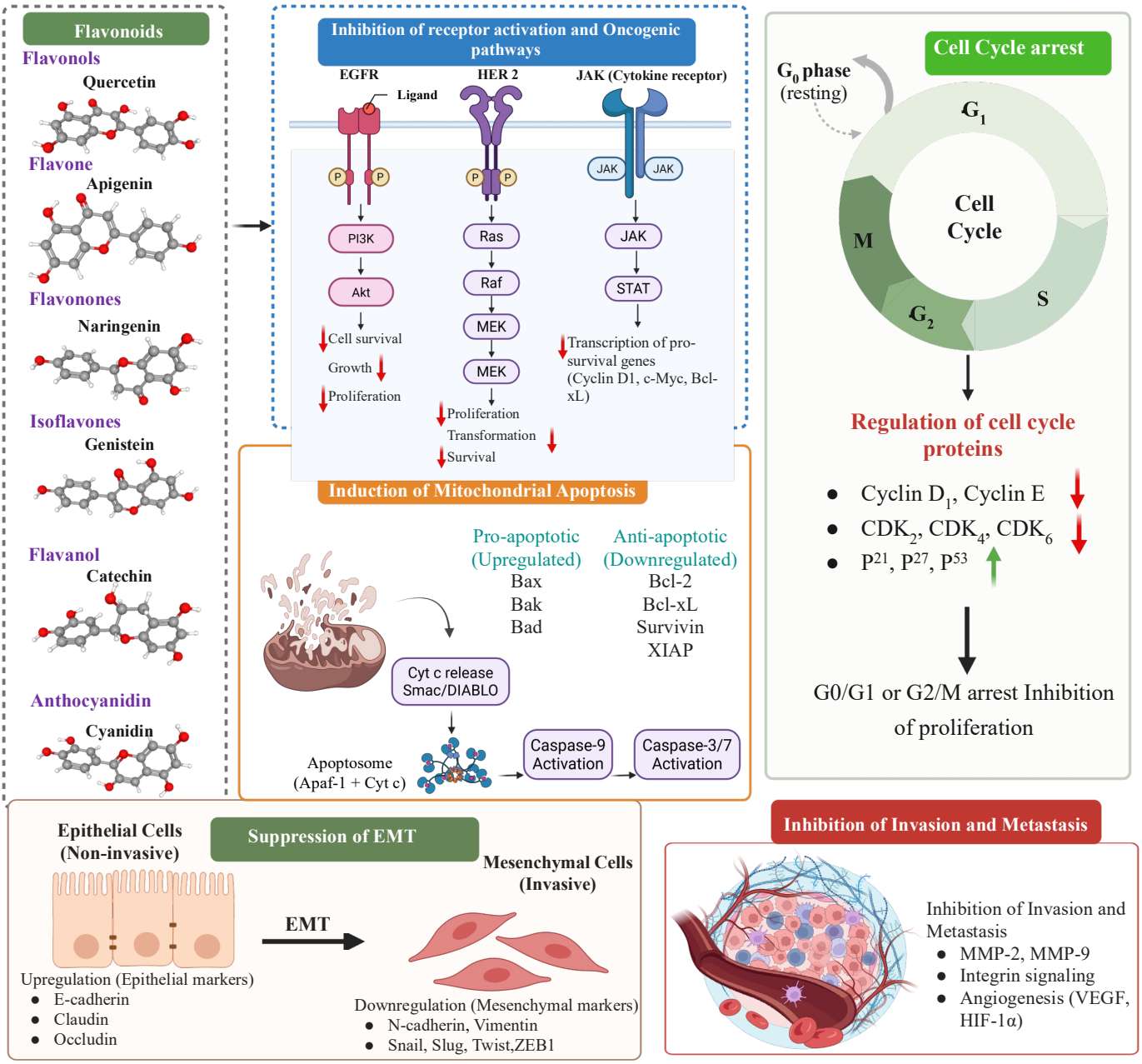


Figure 2. Anticancer effects of dietary flavonoids. Flavonoids exert anticancer effects through multiple molecular mechanisms. These mechanisms include inhibition of receptor activation and oncogenic signaling pathways, leading to reduced cell survival, proliferation, transformation, and expression of pro-survival genes. Flavonoids also induce apoptosis by promoting the expression of pro-apoptotic proteins and downregulating anti-apoptotic proteins. Furthermore, they regulate cell-cycle proteins while increasing the cell-cycle inhibitors, thereby promoting G0/G1 or G2/M cell-cycle arrest and inhibiting proliferation. Flavonoids also suppress epithelial–mesenchymal transition (EMT) by maintaining epithelial markers and reducing mesenchymal markers. Additionally, they inhibit cancer invasion and metastasis by modulating MMP-2 and MMP-9, integrin signaling, and angiogenesis-associated factors. Created in BioRender. Rahmani, A.H. (2026) https://BioRender.com/0awy6qz (accessed on 25 October 2026).

Table 1. Anticancer Effects and Molecular Targets of Flavonoids in Preclinical Cancer Models.

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Apigenin	Breast cancer	Suppresses tumor progression and angiogenesis while alleviating oxidative stress	↑ SOD, GPx, CAT; ↓ TBARS; ↓ VEGF-mediated angiogenesis	In vivo/preclinical	[31]
Apigenin	Hepatocellular carcinoma	Attenuates oxidative stress, inflammation, fibrosis, and angiogenesis, thereby reducing conditions that favor hepatocarcinogenesis	↑ CAT, ↑ GSH, ↓ MDA, ↓ IL-1β, ↓ IL-6, ↓ TNF-α, ↓ VEGF, ↓ CD34, improved liver function (AST, ALT, TB)	Preclinical	[32]
Apigenin	Non-small cell lung cancer (NSCLC)	Inhibits angiogenesis and tumor growth by suppressing endothelial cell migration and reducing pericyte coverage	↓ HIF-1α, ↓ VEGF-A/VEGFR2 signaling, ↓ PDGF-BB/PDGFRβ signaling, reduced microvessel density and pericyte coverage	In vitro + in vivo/preclinical	[33]
Apigenin	Oral cancer (DMBA-induced buccal pouch carcinoma)	Prevents tumor formation and reduces tumor burden by enhancing antioxidant defenses and detoxification pathways	Decreases lipid peroxidation; restores antioxidant status; modulates phase I and phase II detoxification enzymes, promoting elimination of DMBA metabolites	In vivo/preclinical	[34]
Apigenin	Head and neck Squamous cell carcinoma (HNSCC)	Inhibits cell proliferation, induces G2/M cell cycle arrest and apoptosis, enhances chemosensitivity to 5-FU and cisplatin	Increases intracellular ROS, depletes GSH, activates TNF-R-, TRAIL-R-, and Bcl-2-mediated caspase-dependent apoptosis, inhibits lipid peroxidation, and exhibits antioxidant activity in normal cells	In vitro/preclinical	[35]
Apigenin	Gastric cancer	Suppresses gastric cancer progression; reduces inflammation and Helicobacter pylori colonization	Anti-inflammatory and anti-H. pylori pathways; inhibition of gastritis-associated tumor progression	In vivo/preclinical	[36]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Apigenin	Colorectal cancer	Suppresses tumor growth and potentiates ABT-263-induced apoptosis.	Inhibits Mcl-1, Akt, and ERK signaling; upregulates Bim and activates Bax-dependent apoptosis.	In vitro	[37]
Chrysin	Hepatocellular carcinoma (HCC)	Suppresses tumor growth, inhibits glycolysis, and induces apoptosis	Downregulates HK-2 expression, reduces glucose uptake and lactate production, disrupts HK-2/VDAC-1 interaction, promotes Bax translocation, activates apoptosis	In vitro + In vivo/preclinical	[38]
Chrysin	Lung cancer	Prevents lung tumor development, reduces oxidative stress, and suppresses inflammation and cell proliferation	Decreases lipid peroxidation and carcinoembryonic antigen (CEA); restores SOD, CAT, GPx, GR, GSH, vitamin C, and vitamin E levels; downregulates PCNA, COX-2, and NF-κB expression	In vivo/preclinical	[39]
Chrysin	Gastric cancer	Inhibits cancer cell growth; regulates tumor-suppressive and oncogenic miRNAs	Modulation of miRNA expression (↑ let-7a, miR-9, miR-22, miR-34a, miR-126; ↓ miR-18a, miR-21, miR-221)	In vitro	[40]
Chrysin	Oral squamous cell carcinoma (OSCC)	Enhances cisplatin sensitivity, inhibits cell proliferation, and promotes apoptosis through oxidative DNA damage	Increases ROS generation and γ-H2AX expression, elevates 8-OXO-dG levels, downregulates antioxidant enzymes, activates caspase-8-mediated apoptosis, and potentiates cisplatin-induced cytotoxicity	In vitro	[41]
Chrysin	Head and neck squamous cell carcinoma (HNSCC)	Inhibits cell proliferation, migration, and invasion while promoting apoptosis	Suppresses malignant phenotype by reducing proliferative and metastatic potential and inducing early apoptotic cell death	In vitro	[42]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Chrysin (quinoline–chrysin hybrids)	Head and neck squamous cell carcinoma (HNSCC)	Inhibits cancer cell viability and exhibits antioxidant activity with improved potency over native chrysin	C7 quinoline modification improves anticancer potency; limited effects on TP53/BAX/BCL2 expression, indicating possible alternative apoptotic pathways	In vitro/preclinical	[43]
Chrysin	Colorectal Cancer	Inhibits colon and rectal cancer cell proliferation and viability.	Activates AhR/CYP1A1 signaling and induces p21-dependent cell cycle arrest	In vitro	[44]
Baicalin	Hepatocellular carcinoma (HCC)	Inhibits cancer cell proliferation and tumor growth while inducing apoptosis	S-phase cell cycle arrest by downregulating Cyclin A, CDK2, and Cyclin D1 and promoting mitochondrial apoptosis through ↑ Bax, ↓ Bcl-2, and activation of Caspase-9, Caspase-3, and PARP cleavage	In vitro and In vivo	[45]
Baicalein	Gastric cancer	Induces pyroptosis; inhibits tumor cell survival	NF-κB/NLRP3 signaling activation; pyroptosis-related pathways	In vitro	[46]
Baicalein	Lung cancer	Inhibits cell proliferation, migration, inflammation, and tumor growth while inducing apoptosis	Upregulates SOCS1, leading to inhibition of the NF-κB/STAT3 signaling pathway, thereby suppressing inflammation and lung cancer progression	In vitro + In vivo/preclinical	[47]
Baicalein	Oral squamous cell carcinoma (OSCC)	Inhibits cell proliferation, induces apoptosis, and drives G0/G1 cell cycle arrest	↓ Sp1, ↓ NF-κB (p65/p50), G0/G1 cell cycle arrest, ↑ apoptosis	In vitro + In vivo	[48]
Baicalin	Head and neck squamous cell carcinoma (HNSCC)	Reverses cisplatin resistance and enhances chemotherapy efficacy	Targets GSTP1 (Cys47), ↑ intracellular cisplatin accumulation, ↑ JNK activation, restores cisplatin sensitivity	in vitro and in vivo	[49]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Hesperidin	Hepatocellular carcinoma	Induced apoptosis and inhibited cell proliferation	Caspase activation, Bax/Bak upregulation, Bcl-xL downregulation, mitochondrial and death receptor pathways	In vitro	[50]
Hesperidin	Lung cancer	Inhibited cell proliferation, migration, and invasion; promoted cellular senescence; suppressed tumor progression	Upregulation of PinX1 tumor suppressor signaling	In vitro and In vivo	[51]
Hesperidin	Oral squamous cell carcinoma (OSCC)	Inhibited cell viability, proliferation, migration, and invasion	Downregulated PD-L1 expression via STAT1/STAT3 inhibition	In vitro	[52]
Hesperidin	Breast cancer	Inhibited tumor growth and enhanced doxorubicin efficacy	Suppressed angiogenesis (VEGF/VEGFR2), proliferation (Ki-67), metastasis (MMP-2/MMP-9), and inflammation (COX-2); increased E-cadherin and IFN-γ	In vivo/preclinical	[53]
Hesperidin	Ehrlich ascites carcinoma	Enhanced cisplatin antitumor efficacy and reduced hepatotoxicity	Decreased MDA, increased GSH and CAT activity; reduced Ki-67 expression and enhanced caspase-3-mediated apoptosis; attenuated cisplatin-induced hepatotoxicity	In vivo/preclinical	[54]
Hesperidin	Gastric cancer	Induces apoptosis; inhibits cell growth and viability	PI3K inhibition; Bax/Bcl-2 regulation; apoptosis-related pathways	In vitro	[55]
Hesperetin	Human oral cancer	Hesperetin induces cell death through multiple mechanisms	Induced apoptotic and necrotic cell death, as well as substantial oxidative DNA damage	In vitro	[56]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Quercetin	Liver cancer (Hepatocellular carcinoma)	Enhances doxorubicin-induced cytotoxicity and apoptosis, suppresses tumor growth, and protects normal liver tissue from chemotherapy-induced damage.	Sensitizes cancer cells to doxorubicin through p53-dependent apoptosis and downregulation of Bcl-xL, leading to caspase-mediated cell death.	In vitro + in vivo/preclinical	[57]
Quercetin	Lung cancer	Inhibits proliferation of A549 and H69 lung cancer cells, induces apoptosis, and alleviates cyclophosphamide-induced lung toxicity.	Modulates Bax/Bcl-2 signaling, activates caspase-3, and enhances antioxidant defenses by reducing oxidative stress.	In vitro + In vivo/preclinical	[58]
Quercetin	Pancreatic cancer	Inhibits pancreatic cancer cell growth, suppresses tumor progression in vivo, and promotes apoptosis in orthotopic pancreatic tumor models.	Induces apoptosis and reduces tumor cell proliferation, resulting in significant inhibition of pancreatic tumor growth.	In vitro + In vivo/preclinical	[59]
Quercetin	Breast cancer	Inhibits breast cancer cell proliferation, migration, and tumor growth; induces apoptosis and suppresses metastasis.	Inhibits Akt/mTOR signaling, activates AMPK, suppresses p70S6K and 4EBP1 phosphorylation, and induces G2/M cell cycle arrest.	In vitro + in vivo/preclinical	[60]
Quercetin	Colorectal cancer	Enhances radiosensitivity, suppresses colon cancer stem-like cells (CSCs), and inhibits tumor growth both in vitro and in vivo.	Inhibits Notch-1 signaling and γ-secretase complex proteins, reduces CSC markers, and potentiates radiation-induced anticancer effects.	In vitro	[61]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Quercetin	Gastric cancer	Enhances irinotecan/SN-38 efficacy; induces apoptosis; inhibits EMT and angiogenesis	β-catenin, COX-2, VEGF/VEGFR2 inhibition; downregulation of EMT markers (Twist1, ITGβ6)	In vitro + in vivo/preclinical	[62]
Kaempferol	Breast cancer	Inhibits estrogen- and triclosan-induced breast cancer cell proliferation and suppresses tumor growth in xenograft models.	Inhibits ERα/IGF-1R-Akt/ERK signaling, induces cell cycle arrest, and promotes apoptosis.	In vitro + in vivo/preclinical	[63]
Kaempferol	Hepatocellular carcinoma (HCC)	Inhibits proliferation and motility of Hep3B liver cancer cells, promotes apoptosis and autophagy	Downregulates the expression of Bcl-2 and upregulates Bax and Bid, Caspase-3, Beclin-1, and LC3. KP showed a better binding affinity with Nrf2, PERK, and IRE1α	In vitro	[64]
Kaempferol	Lung cancer	Inhibits tumor growth in xenograft lung cancer models and suppresses LLC cell proliferation.	Enhances antitumor immunity by activating cytotoxic T cells and NK cells, while modulating gut microbiota through enrichment of beneficial bacterial species including Lactobacillus and Bacteroides.	In vivo/preclinical	[65]
Kaempferol	Oral squamous cell carcinoma (OSCC)	Inhibits OSCC cell proliferation and migration, reduces cell viability, and promotes apoptosis through ferroptosis induction.	Promotes CA9-mediated ferroptosis and regulates p53/FoxO/cellular senescence signaling pathways.	In vitro + in vivo/preclinical	[66]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Kaempferol	Colon cancer (main), also breast, lung, liver	Enhances cisplatin effect; promotes cancer cell death; slows cell growth; causes cell cycle arrest	Increases pro-apoptotic signals (Bax, caspases), reduces anti-apoptotic proteins (Bcl-2); mainly involves mitochondrial apoptosis and PI3K/Akt-related pathways	In vitro	[67]
Kaempferol	Head and neck cancer	Reduces energy production; inhibits cell growth and migration; promotes apoptosis; enhances cisplatin sensitivity	Mitochondrial dysfunction (↓ oxygen consumption, ↓ ATP), loss of membrane potential; activation of apoptotic signaling pathways; possible involvement of intrinsic apoptosis pathways	In vitro	[68]
Kaempferol	Gastric cancer	Inhibits proliferation; induces apoptosis and G2/M cell cycle arrest; suppresses tumor growth	Akt/ERK/COX-2 inhibition; Bax/Bcl-2 modulation; activation of caspase-3/-9 and PARP cleavage	In vitro + in vivo/preclinical	[69]
Myricetin	Hepatocellular carcinoma (liver cancer stem cells)	Inhibits proliferation; induces apoptosis; triggers cell cycle arrest; suppresses stemness and metastasis traits; enhances effect with autophagy inhibition	PI3K/Akt/mTOR inhibition; activation of intrinsic and extrinsic apoptosis; suppression of STAT3; downregulation of EMT and stemness markers (Sox2, Oct4, Nanog, ALDH1A1).	In vitro	[70]
Myricetin derivative (S4-2-2)	Non-small cell lung cancer (NSCLC, A549 cells)	Strong inhibition of tumor growth; reduces migration and invasion; induces apoptosis (without major cell cycle arrest)	Regulation of endoplasmic reticulum (ER) stress-related protein processing; activation of apoptosis-related proteins	In vitro + in vivo/preclinical	[71]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Myricetin	Triple-negative breast cancer (TNBC)	Induces apoptosis; inhibits proliferation, invasion, and angiogenesis; modulates tumor aggressiveness	PI3K/Akt/mTOR and MAPK inhibition; regulation of NF-κB, STAT3, Hippo, GSK-3β, Nrf2/HO-1, and related signaling pathways	In vitro	[72]
Myricetin	Pancreatic cancer	Induces apoptosis; reduces tumor growth and metastasis; promotes tumor regression with limited toxicity	Inhibition of PI3 kinase (PI3K) signaling; activation of apoptotic pathways	In vitro + in vivo/preclinical	[73]
Myricetin	Gastric cancer	Inhibits proliferation; induces apoptosis and autophagy; suppresses tumor growth	PI3K/Akt/mTOR pathway inhibition	In vitro + in vivo/preclinical	[74]
Myricetin	Colon cancer	Inhibits cell growth; induces apoptosis and autophagy; enhances cancer cell death (especially when autophagy is blocked)	Suppression of PI3K/Akt/mTOR signaling pathway; regulation of apoptosis- and autophagy-related proteins	In vitro	[75]
Fisetin	Pancreatic cancer	Inhibits tumor growth (dose-dependent); suppresses cancer progression in vitro and in vivo	Inhibition of PI3K/Akt/mTOR signaling pathway	In vitro + In vivo/preclinical	[76]
Fisetin	Liver cancer	Inhibits proliferation, migration, and invasion; induces apoptosis; suppresses EMT; reduces tumor growth and improves survival	Dopamine receptor D2 (DRD2) activation; caspase-3 activation; inhibition of TGF-β1, VEGFR1, and MAPK signaling (p-ERK1/2, p38, p-JNK)	In vivo	[77]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Fisetin	Non-small cell lung cancer (NSCLC, A549 cells)	Acts synergistically with paclitaxel; reduces proliferation, migration, and invasion; disrupts cytoskeleton; modulates metastasis-related gene expression	Regulation of actin and vimentin cytoskeleton remodeling; modulation of metastasis-associated genes; enhancement of paclitaxel response pathways	In vitro	[78]
Fisetin	Oral squamous cell carcinoma (OSCC)	Induces apoptosis; inhibits cell survival; enhances cancer cell death when autophagy is blocked	Autophagy regulation (pro-survival autophagy inhibition); apoptosis-related signaling pathways	In vitro	[79]
Fisetin	Gastric cancer	Inhibits cell proliferation; induces apoptosis	ERK1/2 signaling inhibition	In vitro	[80]
Fisetin	Head and neck squamous cell carcinoma (HNSCC)	Induces apoptosis and G2/M cell cycle arrest; causes DNA damage; inhibits tumor growth; autophagy inhibition enhances cell death	EGFR/Akt/ERK1/2/STAT3 inhibition; JNK/c-Jun and caspase activation; regulation of p53, p21, p27, CDK1, and cyclin B1	In vitro + In vivo/preclinical	[81]
Luteolin	Head and neck squamous cell carcinoma (HNSCC)	Inhibits tumor growth, migration, and cell cycle progression	p300 inhibition; reduced histone acetylation; modulation of tumor-suppressive miRNAs	In vivo/preclinical	[82]
Luteolin	Oral squamous cell carcinoma (OSCC)	Induces apoptosis; inhibits cell growth; enhances paclitaxel efficacy	Downregulation of CDKs, cyclins, and p-Rb; activation of caspase-9/-3 and PARP cleavage	In vitro + in vivo/preclinical	[83]
Luteolin	Lung cancer	Induces apoptosis; causes G1 cell cycle arrest; inhibits tumor growth	LIMK1 inhibition; suppression of p-LIMK/p-cofilin signaling; downregulation of cyclin D1 and activation of caspase-3	In vitro + in vivo/preclinical	[84]

Table 1. *Cont.*

Flavonoid	Cancer Type	Key Anticancer Role	Principal Target	Study Type	Reference
Luteolin	Liver cancer	Suppresses tumor development; reduces oxidative stress and inflammation; improves antioxidant defense	Antioxidant and anti-inflammatory pathways; modulation of AFP, SOD, CAT, AST, ALT, IL-2, and IFN-γ levels	In vivo/preclinical	[85]
Luteolin	Gastric cancer	Inhibits proliferation and invasion; induces apoptosis; suppresses tumor growth	cMet/Akt/ERK pathway inhibition; downregulation of MMP9; activation of caspase-3 and PARP	In vitro + in vivo/preclinical	[86]

3.1.1. Apigenin

Apigenin has gained considerable attention due to its selective effects on normal and cancer cells. Its anti-inflammatory and antioxidant properties, together with its ability to modulate multiple cellular signaling pathways, contribute to its anticancer potential. Apigenin modulates pathways involved in cancer suppression, angiogenesis, apoptosis, and cell cycle control, including PI3K/Akt, NF-κB, MAPK/ERK, STAT3 [87], Wnt/β-catenin pathways [88], and oncogenic non-coding RNA networks [89]. It also affects angiogenesis, epithelial–mesenchymal transition (EMT), cancer stem cell maintenance, and cell cycle progression, ultimately promoting cancer cell death [89].

Apigenin has demonstrated anticancer effects in various cancer types. In resistant breast cancer, it inhibits cell proliferation and induces apoptosis by targeting PI3K/AKT, HER2, and caspase signaling [90–93]. It has also shown potential against cervical cancer, including HPV-related cases [94]. Apigenin inhibits angiogenesis by suppressing HIF-1α and VEGF-A/VEGFR2 and PDGF signaling, especially in lung squamous cell carcinoma [33].

In liver cancer, apigenin promotes apoptosis through increased oxidative stress and activation of caspase/Bax and improves immune responses (↑ *Th*1 and ↓ *Th*2), while modulating inflammatory signals including TNF-α and ILs [95]. Apigenin reduces cell growth, blocks cell cycle progression, and induces apoptosis. Also, apigenin suppresses inflammation-driven pathways by blocking TNF- and IL-1β-induced NF-kB and c-Jun N-terminal kinases (JNK) signaling [96]. Following apigenin treatment, NF-κB p105/p50 expression and Akt phosphorylation significantly decreased, inflammation was reduced, and cell cycle progression was arrested [97].

3.1.2. Chrysin

Chrysin is a natural flavonoid found in honey and many plants. It shows diverse anticancer activities. Its effects are mediated through several mechanisms, including induction of mitochondrial apoptosis, inhibition of cell-survival signaling, modulation of oxidative stress, and regulation of autophagy and inflammation. It promotes cytochrome c release and caspase-3 activation while suppressing anti-apoptotic proteins such as XIAP and Bcl-2 family members. It also reduces AKT phosphorylation and inhibits the PI3K/Akt pathway, thereby promoting cancer cell death [98,99]. The anticancer effects of chrysin appear to vary depending on the type of cancer and the cellular context. It acts through several important signaling pathways, including PI3K/Akt/mTOR, Nrf2, MAPK/ERK, p38, and AMPK, which together help control cancer cell growth, survival, apoptosis, and autophagy. Chrysin also affects key molecules such as TLR-4, Notch-1, and SLUG, which are involved in tumor progression and cancer cell behavior [100]. Cancers of the breast, gastrointestinal tract, liver and hepatocytes, bladder, male and female reproductive systems, choroid, respiratory tract, thyroid, skin, eye, brain, blood cells, leukemia, osteoblast, and lymph could all be alleviated by chrysin [7].

3.1.3. Baicalein and Baicalin

Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one) is obtained from the dried root of Scutellaria baicalensis Georgi, and it shows strong anticancer effects on inflammation, angiogenesis, and metastasis without endangering healthy cells. Baicalein has shown anticancer effects in experimental models, including the inhibition of cell proliferation, angiogenesis, invasion, and metastasis, as well as the induction of apoptosis and modulation of autophagy, cellular metabolism, the tumor immune microenvironment, and cancer stem cells. However, further studies are needed to establish its safety and potential adverse effects in humans. Baiclein induces apoptosis in multiple cancers such as breast, renal, glioma, cervical, epidermoid, and bladder cancers by suppressing the PI3K/Akt sig-

naling pathway [8]. This inhibition promotes cancer cell death, as seen in breast cancer cell lines like MCF-7 and MDA-MB-231 [101]. Baicalin may prevent prostate cancer cells from proliferating. Different cell lines responded differently to baicalin, with LNCaP cells being the most resistant and DU145 cells being the most vulnerable. Following a brief exposure to baicalin, the suppression of prostate cancer cell proliferation was linked to apoptosis induction [102]. Tumor formation is significantly influenced by the Akt pathway [103].

By lowering p-Akt, p-mTOR, NF-κB, and p-IκB concentrations and raising IκB expression, baicalein treatment can mitigate these effects [101]. Additionally, research has demonstrated that Baicalein increases the pro-apoptotic protein Bax's activity, which depletes the anti-apoptotic protein Bcl-2 [9]. Programmed cell death is significantly influenced by caspase cascades, especially when death protease (caspase 3) activity is stimulated [104]. In a number of malignancies, including bladder carcinoma, lymphoma, osteosarcoma, and pancreatic cancer, baicalein has been demonstrated to increase caspase-3 activation [105].

Baicalein reduced the protein quantity of survivin, a member of the anti-apoptotic gene group, and elevated p38-MAPK phosphorylation in lung, bladder, and breast malignant tissues [106]. Both Baicalein and Baicalin increased apoptosis by activating caspase-3 and caspase-9, inhibiting Bcl-2, and increasing Bax or p53 with the aid of the ERK/p38 and MAPK axis [10].

Baicalein upregulates lncRNA PAX8-AS1, which interacts with miR-17-5p and causes apoptosis in vitro in breast cancer cell lines [107]. Baicalein reduced the expression of anti-apoptotic genes, including BCL2, Bcl-xL, XIAP, and survivin, leading to decreased cell viability and increased apoptosis in T24 and 253J bladder cancer cells [108]. By downregulating ezrin expression, baicalein activates miR-183 and induces apoptosis in specific osteosarcoma cell types (MG-63 and Saos-2) [109]. Baicalein may also target the Wnt/-catenin signaling cascade in HeLa cells (cervical cancer cell line) to cause apoptosis by reducing Wnt activity and catenin nuclear translocation, most likely via CCND1 [11].

Human prostate cancer cells [102] and human cervical cancer cells [110] have been shown to undergo apoptosis when exposed to baicalin. HeLa cells treated with baicalin showed upregulated expression of Bax, Fas, FasL, and Caspase-8 and downregulated expression of Bcl-2 [110]. It showed that baicalin activated the extrinsic apoptotic pathway, which in turn caused apoptosis. According to reports, baicalin slows the spread of cancer by preventing cancer cells from migrating, invading, and metastasizing. By reducing the production of MMP-2, MMP-9, uPA, and uPAR and modifying the p38MAPK signaling pathway, baicalin inhibited the tumorigenicity of MDA-MB-231 cells [111].

3.1.4. Hesperidin

Hesperidin is a flavonoid that is found in many citrus species. Because of its anti-inflammatory, anticancer, and antioxidant qualities, as well as its capacity to prevent other forms of pathogenesis, hesperidin has been linked to health management. Through the management of inflammation, cell cycle arrest, apoptosis, angiogenesis, and cell signaling pathways, hesperidin's anticancer potential has been established [12]. By deactivating the STAT1 and STAT3 signaling pathways, hesperidin inhibited the production of programmed cell death ligand 1 (PD-L1) in oral cancer cells [52]. Another study found that after hesperidin was administered, STAT3, STAT2, and STAT1 genes were significantly downregulated. It was anticipated that hesperidin would inhibit STAT3 activation, slowing the development of endometrial cancer cells [112]. A study showed that hesperidin treatment efficiently preserved the integrity of the liver tissues against the development of hepatocellular carcinoma and reduced the level of Akt, PI3K, and cyclin-dependent kinase-2 (CDK-2) protein expression caused by DEN [113]. A study on renal carcinogenesis indicated that hesperidin reduced PGE2 levels and downregulated the production of

COX-2 and vascular endothelial growth factor [114]. By preventing p53 and MDMX from interacting, hesperidin can prevent lung cancer. Additionally, hesperidin and carboplatin together can increase the anticancer impact of carboplatin by inhibiting lung cancer cell line motility and invasion through p53 overexpression [115]. Hesperidin inhibited Bcl-2 and increased Bax expression at the protein level to cause cellular death in MCF-7 breast cancer cells. However, hesperidin did not activate the Bax/Bcl-2 pathway; instead, it induced apoptosis in the MDA-MB-231 breast cancer cell line. In the MCF-7 and MDA-MB-231 cell lines, hesperidin also caused cell cycle arrest at the S phase [13]. Hesperidin was shown to significantly increase p-ERK1/2 protein levels while significantly lowering total ERK1/2 protein levels, indicating that hesperidin causes paraptosis via activating ERK1/2 [116]. Hesperidin dramatically reduced the TPA-induced MMP-9 mRNA level. Hesperidin inhibited the action of Activator protein 1 (AP-1) and nuclear factor-kappaB (NF-kappaB) to reduce MMP-9 transcription. Hesperidin inhibited TPA-induced AP-1 activity through the inhibitory phosphorylation of p38 kinase and c-Jun N-terminal kinase (JNK) signaling pathways, as well as TPA-stimulated NF-κB translocation into the nucleus through IκB inhibitory signaling routes [117].

3.1.5. Quercetin

Quercetin is a natural flavonoid with strong anticancer effects. It works by reducing tumor growth, invasion, and metastasis by regulating multiple signaling pathways like p53, NF-kB, MAPK, JAK/STAT, PI3K/Akt, and Wnt/β-catenin, and apoptosis. It also controls tumor-related ncRNAs, helping to slow cancer progression [14]. Both in vitro and in vivo studies confirm its antioxidant activity and its ability to inhibit angiogenesis, to arrest the cell cycle, to inhibit proliferation, and to prevent metastasis [15]. Quercetin strongly induces apoptosis by increasing p53, Bax, and caspases and by reducing anti-apoptotic signals. It also controls the cell cycle by activating p21 and decreasing cyclin/CDK activity [118]. Additionally, it suppresses cancer growth by targeting the EGFR-ERK/MAPK signaling pathway and downregulating PTGS2 expression [119].

In NSCLC cells, it reduces cell growth, migration, and invasion by increasing caspase-3 activity, disrupting mitochondrial function, and downregulating membrane potential. Quercetin also shows dose-dependent cytotoxicity and reduces cell invasion by downregulating genes like GJB2, showing dose-dependent cytotoxic effects [120]. Quercetin shows strong anti-proliferative effects in cancer cell lines, including colon, breast, ovarian, lymphoma, and prostate cancers [121–128]. Its main mechanism is cell cycle arrest (G1 phase) by downregulation of cyclin B1 and CDK1 and regulation of pRb phosphorylation, which slows down cancer cell growth and proliferation. The anticancer ability of quercetin is also linked to its potential to induce apoptosis and autophagy in various cancer cells and models. Quercetin increases apoptotic markers like caspase-3.9 activation, nuclear fragmentation, and sub-G1 phase cells while reducing mitochondrial membrane potential. Mechanistically, quercetin induces apoptosis by targeting JNK activation and p53 signaling and can also induce protective autophagy, which further influences cancer cell survival and death [16]. Quercetin suppresses the downstream regulatory component Akt in prostate and breast cancers and targets the VEGFR-2-mediated angiogenesis pathways to reduce tumor growth [129]. By preventing c-Met phosphorylation, decreasing its homodimerization, and eventually blocking the HGF/c-Met signaling pathway, quercetin demonstrated anti-metastatic efficacy in melanoma [130].

3.1.6. Kaempferol

Kaempferol is a widely studied flavonoid with anti-inflammatory, antidiabetic, antioxidant, and anticancer properties. It inhibits cancer cell growth, induces G2/M cell-cycle

arrest, and promotes apoptosis by regulating PI3K/Akt/mTOR, MAPK/ERK1/2, and VEGF signaling. It also suppresses epithelial–mesenchymal transition (EMT) and invasion by modulating N-cadherin, E-cadherin, Snail, Slug, and MMP-2, while activating apoptotic proteins such as caspases-3, -7, -9, and PARP [131,132].

Its effects have been demonstrated in various cancer cell lines and animal models, with relatively limited toxicity toward normal cells observed under specific experimental conditions [133]. However, the extent to which this selectivity translates to pharmacological exposure in humans remains uncertain. Kaempferol has shown activity against breast, prostate, bladder, cervical, colon, liver, lung, and ovarian cancers, leukemia, and other malignancies, mainly by inhibiting cell growth, migration, and invasion while promoting apoptosis [134]. Kaempferol also exerts protective effects by increasing PPARα expression and regulating redox balance through the Nrf2 pathway. By modulating the Nrf2-Keap1 system, it promotes antioxidant and anti-inflammatory responses and helps maintain mitochondrial function [135]. In HT-29 cells, Kaempferol induces apoptosis through both death-receptor and mitochondrial pathways, increasing cytochrome c release, caspase-3, -7, -8, and -9 activation, and PARP cleavage, while altering Bik, Bcl-xL, Bad, Akt, Fas ligand, and Bid levels [136]. In triple-negative breast cancer (TNBC), Kaempferol reduces migration and invasion by modulating RhoA/Rac1 and ER-dependent signaling and suppressing EMT and metastasis through the MAPK/ERK/MEK1/ELK1 pathway [131,137–141]. In glioblastoma, it inhibits cell growth and migration while promoting apoptosis, ROS generation, mitochondrial dysfunction, and inhibition of ERK and Akt signaling [142,143]. In hepatocellular carcinoma (HCC), Kmp inhibits proliferation, induces apoptosis and G2/M arrest, and promotes ROS-mediated mitochondrial damage and caspase-3 activation while suppressing the PI3K/Akt/mTOR pathway [144,145].

3.1.7. Myricetin

Myricetin is a widely distributed flavonoid found in fruits, vegetables, berries, nuts, herbs, beverages, and medicinal plants. Its potential in cancer prevention and treatment has received considerable attention. Myricetin affects several processes involved in cancer development, including angiogenesis, cell-cycle progression, inflammation, and apoptosis. It also lowers inflammatory mediators such as inducible nitric oxide synthase (iNOS) and COX-2 and may improve the effects of conventional anticancer drugs by acting on multiple signaling pathways [146].

Myricetin has been reported to inhibit the growth of several cancers, including skin, lung, liver, and rectal cancers, while also influencing intracellular processes, lipid metabolism, inflammation, and microbial growth [147]. Its anticancer effects are partly linked to the regulation of oncogenic proteins such as Akt, Fyn, MEK1, and JAK1–STAT3, which can limit neoplastic transformation. In liver cancer, myricetin also suppresses CDK1, leading to antimitotic effects, and promotes programmed cell death through mitochondrial dysfunction [148]. In A431 skin cancer cells, myricetin promotes apoptosis by altering Bax and Bcl-2 expression and also reduces cell motility, invasion, and cell-cycle progression [149]. In bladder cancer, it induces G2/M arrest and apoptosis through changes in cyclin B1, cdc2, Bcl-2, and caspase-3. It also inhibits Akt, activates p38 MAPK, lowers MMP-9 levels, and reduces cell migration and tumor growth in animal models [150]. Myricetin has also shown activity against gastrointestinal cancers. In AGS gastric cancer cells, it reduces cell viability by inhibiting the PI3K/Akt/mTOR pathway, leading to apoptosis and autophagy, with similar tumor-suppressive effects observed in vivo [74]. In colon cancer cells, inhibition of the same pathway reduces proliferation and promotes cell death [75]. In JAR and JEG-3 choriocarcinoma cells, myricetin promotes apoptosis, affects cell-cycle progression, and reduces invasion and angiogenesis through MAPK and PI3K/akt signaling. It also induces

apoptosis in triple-negative breast cancer cells by inhibiting PI3K/Akt/mTOR signaling and reducing cancer cell survival [72].

3.1.8. Naringenin and Naringin

Naringin and naringenin are naturally occurring flavonoids predominantly found in citrus fruits and have received considerable attention for their anticancer potential. They target key signaling pathways involved in inflammation and cancer progression, including GSK3β, NF-kB, COX-2, and JAK2/STAT3. They also regulate intracellular adhesion molecule-1 (ICAM-1), upregulate Notch1 expression, and activate p38/MAPK and caspase-3, contributing to apoptosis [17]. Naringenin can induce apoptosis and cause cell cycle arrest in several cancer cell lines, including MDA-MB-231 breast tumor cells [151], HepG2 human hepatocellular carcinoma cells [152], E0771 mammary tumor cells [153], and PC3 and LNCaP prostate cancer cells [154]. Naringenin also has antioxidant and anti-inflammatory properties. It can induce cell cycle arrest, downregulate growth factors, inhibit cytokine production, and modulate signaling pathways [19]. By affecting pro-inflammatory cytokines and growth factors like IFN-γ, TNF, IL-1α/β, IL-6, and growth factors like VEGF, naringin and naringenin may limit processes linked to inflammation, proliferation, apoptosis, autophagy, angiogenesis, invasion and metastasis; these compounds demonstrate a potential capability to interfere with tumor development and progression [18]. In hepatocellular carcinoma, naringin and naringenin promote human hepatocellular carcinoma cells through both extrinsic and intrinsic apoptotic pathways, involving caspase 9 and caspase 8 activation [50]. In HepG2 cells, naringenin arrests the cell cycle at G0/G1 and G2/M phases, possibly through increased p53. It promotes apoptosis by increasing the Bax/Bcl-2 ratio, cytochrome C release, and activating caspase-3 [155]. Naringenin has also demonstrated strong anticancer activity in lung cancer cell lines (H1299 and A459), where it reduces cell viability, induces cell cycle arrest, and promotes autophagy through ROS-mediated AMPK activation. Animal studies have further confirmed inhibition of tumor growth and increased apoptosis [156]. Naringin also inhibits NEU3 and suppresses EGFR signaling through GM3 ganglioside accumulation, thereby limiting cancer cell proliferation [157]. Naringenin may also limit metastasis. In TSGH-8301 bladder cancer cells, it blocks the nuclear translocation of nuclear factor κ-light-chain-enhancer of activated B cells and inhibits Akt activity, reducing migration of bladder cancer cells via Akt and MMP-2 pathways [158]. More recently, naringin combined with cisplatin showed stronger anticancer effects than either treatment alone. This combination more effectively suppressed proliferation and promoted apoptosis, as shown by increased caspase 3/7 activity. These studies suggest that naringin may improve the therapeutic efficacy of cisplatin, and it could serve as a promising adjunct strategy in the treatment of bladder cancer [159].

3.1.9. Tangeretin

The peels of citrus fruits, particularly oranges and tangerines, contain the flavonoid tangeretin (5,6,7,8,4′-pentamethoxyflavone), which has pharmacological characteristics including antiproliferative, anti-invasive, and anti-metastatic effects, as well as the ability to induce apoptosis in some types of cancer. Tangeretin has antiproliferative, anti-invasive, and anti-metastatic pharmacological qualities. It can also cause apoptosis in certain types of cancer [160]. The capacity of TAN to cause oxidative stress as the principal anticancer mechanism has been the main focus of prior research on its application in cancer treatment. Furthermore, some research indicates that TAN may have additional anticancer effects, including upregulating tumor suppressor proteins, triggering apoptosis, and lowering the percentage of cancer stem cells (CSCs) [161]. Tangeretin has shown a protective effect against cisplatin-induced liver injury in rats by reducing histopathological damage and by

modulating inflammatory responses. Its anti-inflammatory mechanism is associated with suppression of tumor necrosis factor-alpha (TNF-α) and increased interleukin-10 (IL-10) levels, highlighting its potential to alleviate severe side effects of cisplatin treatment [162]. When colorectal carcinoma cells were treated with tangeretin, the expression of cell division-retarding tumor suppressor proteins, such as p21, p53, and p27, increased. This promoted the inhibition of cell growth by blocking enzymes that regulate cell cycle progression and cyclin-dependent kinases (CDK2 and CDK4) [163]. Treatment with tangeretin dramatically reduces Ishikawa cell viability and proliferation. Furthermore, it increases the production of ROS, inhibits cell motility, and causes Ishikawa cells to undergo apoptosis. Tangeretin therefore has anticancer effects on endometrial cancer cells by increasing apoptosis and preventing migration and proliferation [164]. TAN induces apoptosis and regulates autophagy in cancer cells. TAN also induces cell cycle arrest in cancer cells via the regulation of the expression of cyclin family proteins and retinoblastoma (Rb) proteins, which play important roles in the regulation of the cell cycle. TAN inhibits angiogenesis through the inhibition of the expression of proteins such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1 (HIF-1) [161].

3.1.10. Fisetin

A naturally occurring flavonoid found in a variety of fruits, vegetables, nuts, and wines is fisetin (3,7,3′,4′-tetrahydroxyflavone). Studies conducted both in vitro and in vivo have shown the therapeutic potential of fisetin in a variety of disorders [165]. Fisetin has a variety of biological effects on cancer, including blocking cell migration, decreasing the development of new blood vessels, inducing programmed cell death, and preventing oxidative stress. Furthermore, fisetin has the potential to improve chemotherapeutic efficacy. Numerous chemicals and signaling pathways, such as vascular endothelial growth factor (VEGF), mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), PI3K/Akt/mTOR, and Nrf2/HO-1, are responsible for fisetin's anticancer activities. Fisetin is therefore a promising therapeutic drug for the treatment of cancer [166]. The strong anticancer effect of fisetin was linked to the regulation of the PI3K/Akt/mTOR pathway. In vivo experiments showed that fisetin suppressed the growth of 4T1 cell-derived orthotopic breast tumors and enhanced tumor cell apoptosis, and the assessed levels of alanine amino transferase and aspartate amino transferase in the serum of tumor-bearing mice suggested that fisetin may have adverse effects on liver biochemical function [149]. Fisetin has anticancer properties through ROS generation, most likely via MRC complex I, which causes apoptosis in human gastric carcinoma cells. The mechanisms by which fisetin inhibits the development and survival of human gastric cancer AGS and SNU-1 cells were examined. Fisetin (25–100 μM) decreased G1 phase cyclins and CDKs while increasing p53 and its S15 phosphorylation in gastric cancer cells [167]. Fisetin causes cell cycle arrest, caspase-dependent apoptosis, and enhanced cytotoxicity of chemotherapy drugs in triple-negative breast cancer cells. Fisetin inhibited the growth of estrogen receptor-bearing MCF-7 breast cancer cells and human epidermal growth factor receptor 2-overexpressing SK-BR-3 breast cancer cells. This potential was linked to mitochondrial membrane permeability, caspase-9 and caspase-8 activation, and poly (ADP-ribose) polymerase-1 cleavage [168].

3.1.11. Luteolin

Luteolin (3′,4′,5,7-tetrahydroxy flavone) is abundant in many fruits and vegetables, such as celery, carrots, onion leaves, and chrysanthemum flowers. This specific phenolic phytochemical, which is a member of the flavone class of flavonoids, has been used to treat cancer by inducing apoptosis and cell cycle arrest, as well as reducing angiogenesis, metastasis, and cell proliferation [169]. Luteolin has been shown to decrease angiogenesis,

invasion, metastasis, mTOR/PI3K/Akt, STAT3, Wnt/β-catenin, cell-cycle arrest, and apoptosis. Additionally, research indicates that this substance is essential for the upregulation or downregulation of microRNAs (miRNAs) in cancer treatment [170].

By triggering caspases and impairing mitochondria, luteolin causes malignant cells to undergo apoptosis. By preventing cell cycle progression and decreasing DNA synthesis and repair, it also prevents cell proliferation. Additionally, by preventing the epithelial-to-mesenchymal transition (EMT) and decreasing the production of mesenchymal markers like vimentin and N-cadherin, it inhibits metastasis. Additionally, luteolin suppresses pro-angiogenic expressions, including VEGF, to prevent angiogenesis. It affects several elements of malignant cell survival and metastasis, such as the PI3K/Akt and NF-κB signaling pathways [171].

By upregulating BAX, caspase-3, and p21 and downregulating Akt, PLK-1, cyclin-B1, cyclin-A, CDC-2, CDK-2, Bcl-2, and Bcl-xL, luteolin induces cell death. Additionally, it has been shown to reduce STAT3 activation and increase STAT3 protein degradation in a variety of cancer cells, hence inhibiting STAT3 signaling. MMPs, pro-inflammatory cytokines like TNF-α, IL-6, IL-1, NF-κB, and endothelial migration are all inhibited by luteolin. Luteolin also inhibits the EGFR-signaling pathway, which lowers cell invasion and metastasis. Additionally, luteolin regulates key pathways like PI3K/AKT/mTOR, ERK, and p38, leading to reduced proliferation, migration, and invasion. It also modulates miRNA expression by increasing tumor-suppressive miRNA and reducing oncogenic miRNA expression, which can be both increased and decreased by luteolin [172]. By encouraging the breakdown of Tyr705- and Ser727-phosphorylated STAT3, luteolin can cause cancer cells to undergo apoptosis [173]. By influencing the IL-6/STAT3 pathway, luteolin reduced the proliferation, migration, and invasion capability of SW620 and SW480 colon cancer cells brought on by M1 polarization [174].

Lastly, Yao et al. (2019) [175] investigated the roles of microRNAs (miRNAs) in treating colorectal cancer (CRC) cells with luteolin. They discovered that luteolin inhibits the migration and invasion of CRC cells by regulating the miR-384/pleiotrophin axis, indicating that miR-384 and pleiotrophin may be significant targets for treating CRC [175]. Lutein reduces the expression of stemness-related transcriptional factors, ATP-binding cassette transporter G2 (ABCG2), CD44, aldehyde dehydrogenase 1 activity, and the sphere-forming capabilities of breast CSCs. Additionally, luteolin inhibited the protein expressions of Nrf2, heme oxygenase 1 (HO-1), and Cripto-1, all of which have been shown to play a crucial role in CSC characteristics [176]. Lung cancer cells are encouraged to undergo apoptosis by luteolin. By upregulating the expression of JNK and p53, causing ROS accumulation, activating caspase-3 and caspase-9, causing the release of Cyt c, raising Bax expression, and lowering Bcl-2 expression, luteolin can induce apoptosis [177].

3.2. Therapeutic Potential of Plant Phenolic Acids in the Treatment of Cancer

Phenolic acids, particularly benzoic and cinnamic acid derivatives, are naturally occurring plant phenolics recognized for their broad spectrum of biological activities in both in vitro and in vivo models. Their anticancer potential is largely attributed to their ability to induce apoptosis, suppress uncontrolled cellular proliferation, and inhibit angiogenesis, thereby interfering with multiple stages of tumor development [Figure 3]. These bioactivities are closely associated with their structural characteristics, including the aromatic backbone, hydroxyl group configuration, and highly unsaturated side chains, which influence their biochemical reactivity and therapeutic potential [178]. Table 2 summarizes the anticancer activities and underlying molecular mechanisms of various phenolic acids across different types of cancer as reported in preclinical studies.

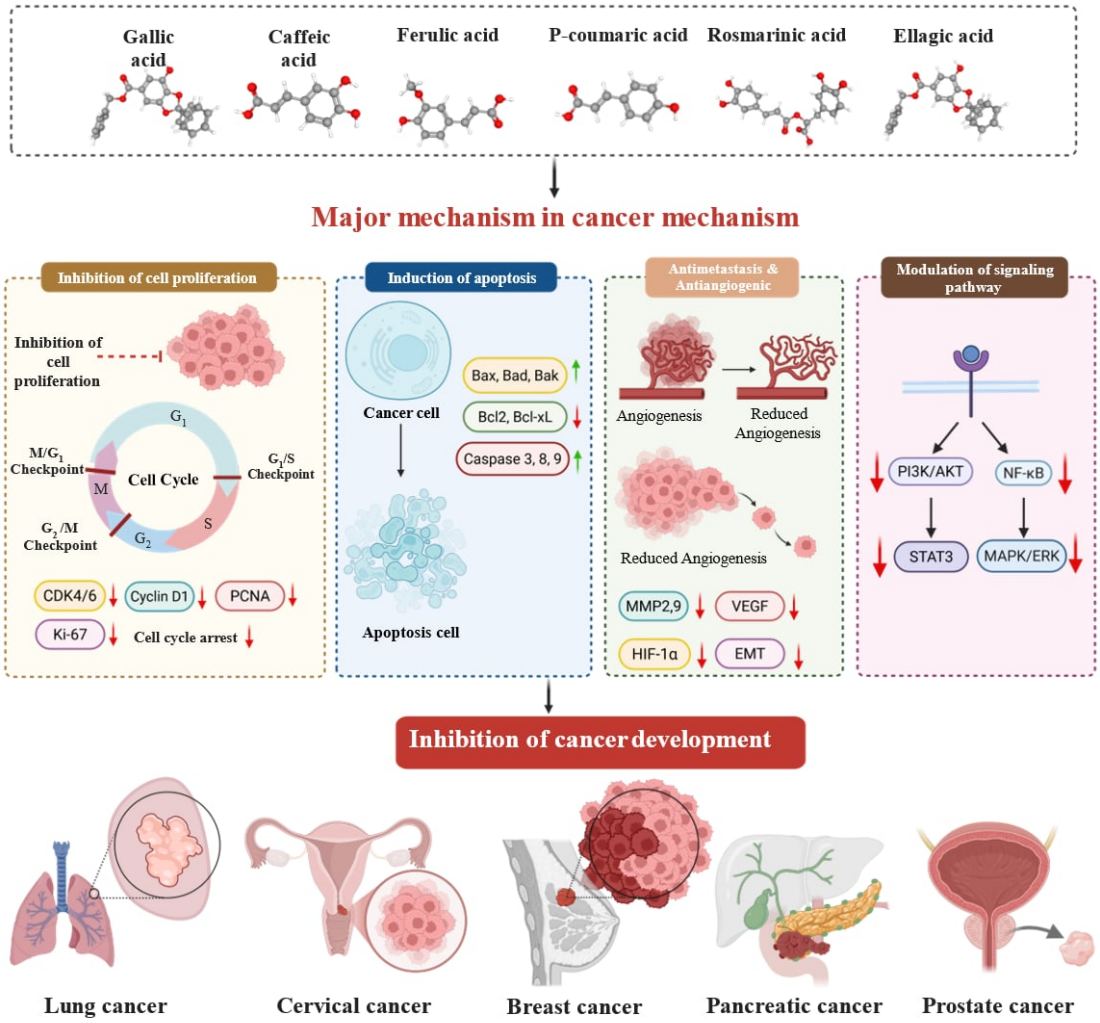


Figure 3. Anticancer mechanisms of phenolic acids. Phenolic acids exhibit anticancer activities through multiple molecular mechanisms. These compounds inhibit cancer cell proliferation by regulating cell-cycle progression and reducing the expression of proliferation-associated markers, thereby promoting cell-cycle arrest. They induce apoptosis by upregulating pro-apoptotic proteins, downregulating anti-apoptotic proteins, and activating caspases. Furthermore, phenolic acids exhibit antiangiogenic and antimetastatic effects by suppressing MMP-2 and MMP-9, VEGF, HIF-1α, and epithelial–mesenchymal transition (EMT), thereby limiting angiogenesis, invasion, and metastatic progression. Collectively, these mechanisms may suppress cancer development and progression across several cancer types. Created in BioRender. Rahmani, A.H. (2026) https://BioRender.com/0awy6qz (accessed on 25 October 2026).

Table 2. Anticancer Effects and Molecular Mechanisms of Phenolic Acids in Preclinical Cancer Models.

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
Gallic acid	Gastric precancerous lesions (GPL)/Gastric cancer	Inhibits proliferation; induces G0/G1 arrest; suppresses EMT and malignant transformation	Wnt/β-catenin pathway inhibition; downregulation of EMT markers (N-cadherin, Vimentin) and upregulation of E-cadherin	In vitro and in vivo study	[179]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
Gallic acid	Hepatocellular carcinoma (HCC)	Induces apoptosis; suppresses tumor growth; reduces inflammation and oxidative stress	STAT3 pathway inhibition; SOCS3 activation; downregulation of AFP, GPC3, GGT, and HSP gp96	In vivo/ preclinical	[20]
Gallic acid	Non-small cell lung cancer (NSCLC)	Induces apoptosis; inhibits proliferation; enhances cisplatin sensitivity	JAK/STAT3 inhibition; Bax upregulation and Bcl-2 downregulation	In vitro	[180]
Gallic acid	Colon cancer	Inhibits proliferation; induces apoptosis; causes cell cycle arrest	ROS-mediated mitochondrial apoptosis; loss of mitochondrial membrane potential; Sub-G1 cell cycle arrest	In vitro	[181]
Gallic acid	Oral squamous cell carcinoma (OSCC)	Inhibits cell growth; induces apoptosis	PI3K/Akt/mTOR inhibition; PTEN upregulation; Bax and caspase-3/7 activation	In vitro	[182]
Gallic acid	Breast cancer	Induces apoptosis; inhibits proliferation, migration, and invasion; suppresses tumor growth	Ahr activation; induction of CYP1A1 and miR-212/132, miR-335; downregulation of BCL-2, COX-2, and SOX4; upregulation of p53	In vitro and In vivo/ preclinical	[183]
o-Coumaric acid (OCA)	Non-small cell lung cancer (NSCLC)	Inhibits cell growth and migration; induces cancer cell death	EGFR targeting/inhibition; apoptosis-related pathways	In vitro and in silico study	[184]
p-Coumaric acid (PCA)	Liver cancer (HepG2 cells)	Reduces oxidative stress and DNA damage; modulates apoptosis	Ras/Raf/MEK pathway inhibition; PRDX-1 upregulation; regulation of Bax, Bcl-2, and caspase-3	In vitro	[185]
p-Coumaric acid derivative	Breast cancer (MCF-7)	Inhibits cancer cell proliferation; selective cytotoxicity toward tumor cells	Antiproliferative pathways	In vitro	[186]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
p-Coumaric acid (PCA)	Colon cancer (HT-29)	Induces apoptosis and autophagy; inhibits cell growth	PI3K/Akt/mTOR and AMPK/mTOR modulation; regulation of Bax, Bad, Bcl-2, Beclin-1, LC3, Atg5, and p53	In vitro	[187]
p-Coumaric acid + Naringin	Skin cancer (A431 epidermoid carcinoma)	Induces apoptosis; causes S-phase cell cycle arrest; increases ROS; reduces cell viability	ROS-mediated mitochondrial apoptosis; disruption of mitochondrial membrane potential; cell cycle regulation	In vitro	[188]
Ferulic acid	Esophageal squamous cell carcinoma (ESCC)	Induces ferroptosis and apoptosis; inhibits proliferation, migration, invasion, and angiogenesis	Ferroptosis pathway activation (↑ ACSL4, HO-1; ↓ SLC7A11, GPX4); ROS and iron accumulation	In vitro	[22]
Ferulic acid	Lung cancer	Inhibits proliferation and migration; induces apoptosis	β-catenin degradation; Bax upregulation; survivin downregulation; inhibition of MMP-2 and MMP-9	In vitro	[189]
Ferulic acid	Breast cancer	Induces apoptosis; inhibits proliferation and metastasis	Reversal of EMT (epithelial–mesenchymal transition); apoptosis-related pathways	In vitro + In vivo/ preclinical	[190]
Ferulic acid–ZnO nanoparticle conjugate (ZnONPs-FAC)	Hepatocellular carcinoma (HCC)	Induces apoptosis; inhibits tumor growth; promotes oxidative DNA damage and cell cycle disruption	ROS generation; mitochondrial dysfunction; DNA damage (γ-H2AX, 8-OHdG); Ki67 suppression	In vitro + In vivo/ preclinical	[191]
Ferulic acid	Colon cancer	Inhibits proliferation and migration; induces cell cycle arrest and apoptosis	ATM/Chk2 and ATR/Chk1 activation; p53/p21 upregulation; downregulation of CDK2/Cyclin A2 and CDK4/6-Cyclin D1/E1 complexes	In vitro	[192]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
Ferulic acid	Oral cancer (buccal pouch carcinoma/ OSCC model)	Suppresses tumor formation; inhibits inflammation and angiogenesis	Downregulation of COX-2, NF-κB, and VEGF signaling	In vivo/ preclinical	[193]
Ellagic acid	Oral squamous cell carcinoma (OSCC)	Inhibits cell growth; reduces invasiveness and metastatic potential	Downregulation of MMP-2 and MMP-9; upregulation of TIMP-2	In vitro	[194]
Ellagic acid	Hepatocellular carcinoma (HCC)	Induces apoptosis; suppresses cancer stem cells; modulates tumor microenviron-ment	Downregulation of TGF-α, TGF-β, and VEGF; p53 restoration; caspase-3 activation; CD44 suppression	In vivo/ preclinical	[23]
Ellagic acid	Lung cancer	Inhibits proliferation; disrupts mitochondrial metabolism; induces energy stress and tumor suppression	AMPK activation; HIF-1α suppression; mitochondrial dysfunction (↓ ATP, ↓ oxygen consumption, ↓ mitochondrial membrane potential)	In vitro + in vivo/ preclinical	[195]
Ellagic acid	Colorectal cancer (CRC)	Induces apoptosis and autophagy; inhibits cancer cell growth	AMPK activation; mTOR inhibition; AMPK/mTOR signaling pathway modulation	In vitro	[196]
Ellagic acid (EA)	Breast cancer	Inhibits cell proliferation and colony formation; induces apoptosis	CDK6 inhibition; downregulation of CDK6 expression; cell cycle regulation	In vitro + In silico	[197]
Vanillic acid	Benign prostatic hyperplasia (BPH); TP-treated RWPE-1 cells	Reduces prostate enlargement and epithelial proliferation; improves histology	Suppression of DHT, 5α-reductase, androgen receptor, estrogen receptor α, and steroid receptor coactivator 1	In vitro + in vivo/ preclinical	[198]
Vanillic acid	Colon cancer (HCT116)	Inhibits proliferation and angiogenesis; induces G1 cell cycle arrest; suppresses tumor growth	HIF-1α inhibition; suppression of mTOR/p70S6K/4E-BP1 and Raf/MEK/ERK pathways; downregulation of VEGF and EPO	In vitro	[199]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
Vanillic acid	Hepatocellular carcinoma (HCC)	Suppresses tumor initiation; inhibits proliferation; induces apoptosis	Nrf2/GSTA-5 activation; Cyclin D1 downregulation; Caspase-3 and Bad upregulation; Bcl-2 downregulation	In vivo/ preclinical	[25]
Vanillic acid	Lung cancer	Suppresses tumor development; reduces oxidative stress; enhances antioxidant defense	↑ SOD, CAT, GR, GPx, GSH); reduction in tumor markers CEA and NSE; ROS scavenging	In vivo/preclinic	[200]
Vanillic acid	Oral cancer (buccal pouch carcinoma)	Prevents tumor formation; enhances detoxification and chemopre-vention	Modulation of Phase I and Phase II detoxification enzymes; carcinogen detoxification pathways	In vivo/ preclinical	[201]
Vanillic acid	Gastrointestinal cancers	Inhibits proliferation; induces apoptosis; exhibits antioxidant activity	mTOR downregulation; apoptosis-related pathways; antioxidant/ROS modulation	In vitro	[202]
Syringic Acid	Oral Squamous Cell Carcinoma (OSCC)	Inhibited cell proliferation, induced cytotoxicity and apoptosis, promoted mitochondrial-mediated cell death, and suppressed OSCC cell growth.	↑ Bax, cytochrome c, caspase-9, caspase-3; ↓ Bcl-2; activation of intrinsic/mitochon-drial apoptotic pathway	In vitro	[203]
Syringic Acid	Colorectal cancer	Inhibited cell proliferation, induced apoptosis, and reduced tumor volume and incidence in vivo	↑ ROS generation; ↑ DNA damage; modulation of antioxidant enzymes; ↓ proliferative genes; activation of apoptosis pathways	In vitro + in vivo/ preclinical	[204]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
vitexin + syringic acid as key actives)	Breast Cancer	Inhibited breast cancer cell growth via synergistic vitexin–syringic acid action and disruption of lipid membrane synthesis.	↓ GRP78 → inhibition of SREBP-1 → ↓ SCD1; suppression of SFA → MUFA conversion; inhibition of membrane lipid synthesis	In vitro	[205]
Syringic Acid	Hepatocellular carcinoma	Induced cytotoxicity, oxidative stress–mediated mitochondrial apoptosis, morphological apoptotic changes (membrane blebbing), and reduced cell viability in HepG2 cells	↑ ROS generation; ↑ caspase-3, caspase-9, cytochrome c, Apaf-1, Bax, p53; ↓ Bcl-2	In vitro	[206]
Syringic Acid	Gastric cancer	Induced apoptosis, suppressed proliferation and inflammation, and reduced cell viability via oxidative stress–mediated mitochondrial dysfunction	↑ ROS; ↓ mitochondrial membrane potential; activation of caspase-3, caspase-9, PARP cleavage; ↓ Bcl-2; modulation of oxidative stress enzymes (↓ SOD, CAT, GSH-Px; ↑ TBARS); inhibition of mTOR/Akt signaling	In vitro	[26]
Caffeic Acid	Gastric cancer	Increased intracellular Ca^{2+} signaling, reduced cell viability, and induced apoptosis	PLC-dependent ER Ca^{2+} release; activation of store-operated Ca^{2+} entry (SOCE); modulation of cytosolic Ca^{2+} signaling; Ca^{2+}-independent apoptosis	In vitro	[207]
Caffeic Acid	Breast cancer	Reduced cell viability (IC50 ~159 µg/mL), induced apoptosis and morphological changes	Modulation of apoptotic genes (↑ p53, ↑ p21, ↓ Mcl-1); interaction with estrogen receptor α; activation of intrinsic apoptosis pathway	In vitro + In silico	[208]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
Caffeic Acid	Non-small-cell lung cancer (H1299)	Enhanced paclitaxel cytotoxicity; inhibited tumor cell proliferation; increased apoptosis; tumor suppression in vivo; no toxicity in normal lung cells	↑ Bax, Bid, cleaved PARP; ↑ caspase-3/9 activation; MAPK activation (↑ ERK1/2, JNK1/2); caspase-dependent apoptosis induction.	In vitro + In vivo/ preclinical	[209]
Caffeic acid derivatives	Colorectal cancer (CRC)	↓ Proliferation; G0/G1 arrest; ↑ apoptosis; ↓ tumor growth	Modulation of PI3K/Akt, AMPK, mTOR pathways; apoptosis induction	In vitro + In vivo/ preclinical	[210]
Caffeic acid phenethyl ester	Oral squamous cell carcinoma (TW2.6)	↓ Proliferation and colony formation; cell cycle arrest (↑ G2/M); ↑ apoptosis; additive effect with 5-FU	↓ Akt1/2/3, p-Akt; ↓ NF-κB, GSK3β, FOXO, cyclin D1, Skp2; ↑ p27Kip; modulation of cell cycle and survival pathways	In vitro	[211]
Cinnamic acid	Triple-negative breast cancer (MDA-MB-231)	↓ Cell viability; ↑ DNA damage; ↑ apoptosis; selective cytotoxicity	TNFα–TNFR1-mediated extrinsic apoptosis; ↑ caspase-8/-3 activation; DNA damage induction	In vitro	[212]
Cinnamic acid	Hepatocellular carcinoma (Hep3B)	↓ Proliferation and migration; ↑ apoptosis; dose-dependent cytotoxicity	Multi-target inhibition of PI3K/Akt pathway (↓ PI3K, p-Akt); ↓ Bcl-2; ↑ Bax, Caspase-3/8; network pharmacology-validated multi-target action	In vitro + in silico	[213]
Cinnamic acid (cis/trans)	Lung adenocarcinoma (A549)	↓ Invasion and metastasis; ↓ MMP-2/9 activity	Inhibition of MMP-2/9 via ↑ TIMP-1 and PAI-2; suppression of uPA system; inhibition of AP-1, NF-κB and MAPK signaling pathways	In vitro	[214]
Cinnamic acid	Colorectal cancer (HT-29)	↓ Cell viability; ↓ cancer stem-like cells; ↓SP/CD44/CD133 population; ↓ CSC marker expression	Downregulation of OCT4, NANOG, ABCB1, ALDH1A; targeting cancer stem cell–associated pathways	In vitro	[215]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
Cinnamic acid	Nasopharyngeal carcinoma (CNE2)	↓ Proliferation; ↑ apoptosis; cytotoxicity	↑ Bax, p53, Fas-L, caspase-3, KLF6; ↓ Bcl-2, cyclin D1; activation of apoptotic signaling pathways	In vitro	[216]
ZnO–cinnamic acid NPs	Oral epidermoid carcinoma (KB cells)	Anticancer activity; antimicrobial and strong antioxidant activity; ↓ cell viability	↑ BAX, BCL-2, P53 expression; nanoparticle-mediated oxidative stress and apoptosis induction	In vitro	[217]
Rosmarinic Acid	Gastric carcinoma	Suppressed Warburg effect; inhibited tumor growth via anti-inflammatory metabolic reprogramming	↓ glucose uptake; ↓ lactate production; ↓ HIF-1α; inhibition of IL-6/STAT3 pathway; ↓ miR-155-mediated signaling	In vitro	[218]
Rosmarinic Acid	Oral squamous cell carcinoma (OSCC)	Reduced cell mass and metabolic activity; inhibited invasion; induced autophagy; suppressed tumor spheroids; modulated EMT and extracellular matrix remodeling	↓ MMP-2/9; EMT reversal (↓ VIM, SNAIL1, SOX9; ↑ CADM1); ↑ BNIP3, BECN1; ↓ BIRC5; ↓ mitochondrial membrane potential; oxidative/redox modulation	In vitro + in silico	[219]
Rosmarinic Acid	Colitis-associated colorectal cancer	Reduced inflammation, tumor incidence, and adenoma formation; suppressed tumor progression	Inhibits TLR4 signaling; ↓ NF-κB and STAT3 activation; ↓ anti-apoptotic factors; blocks TLR4–MD2 interaction; anti-inflammatory tumor microenvironment modulation	In vitro + in vivo + in silico	[24]

Table 2. *Cont.*

Phenolic Acid	Cancer Type	Key Anticancer Role	Principal Target	Evidence Type	Reference
Rosmarinic Acid	Hepatocellular carcinoma	Inhibited proliferation and invasion; induced G1 arrest and apoptosis; suppressed tumor growth in vivo	Inhibition of PI3K/Akt/mTOR signaling; modulation of EMT; IGF-1 rescue confirmed pathway involvement	In vitro + in vivo/ preclinical	[220]
Rosmarinic Acid	Non-small cell lung cancer (NSCLC)	Inhibited proliferation and colony formation; induced G1 arrest and apoptosis; reversed cisplatin resistance	↓ MDR1 and P-gp expression; activation of MAPK pathway; ↑ p53 and p21; enhanced chemosensitivity to cisplatin	In vitro + in vivo/ preclinical	[221]
Rosmarinic Acid	Head and neck squamous cell carcinoma (HNSCC)	Inhibited cell viability, migration, and ROS production; suppressed EGF-driven tumor growth signals	↓ EGFR phosphorylation; inhibition of PI3K/Akt and MAPK/ERK signaling; blockade of EGF-stimulated pathways	In vitro	[222]

3.2.1. Gallic Acid

Gallic acid is a natural phenolic acid and is found in many dietary substances and herbs. It has antibacterial, antiviral, antioxidant, and anti-inflammatory qualities. There have been numerous reports of GA's in vitro and in vivo tests against different cancer cell lines. According to earlier research, depending on the type of cancer being studied, GA's anticancer activity is linked to the induction of apoptosis through a variety of mechanisms, including the production of reactive oxygen species (ROS), the regulation of apoptotic and anti-apoptotic proteins, the suppression and promotion of oncogenes, the inhibition of matrix metalloproteinases (MMPs), and cell cycle arrest. Prostate cancer, melanoma, leukemia, oral cancer, colon cancer, lymphoma, and breast cancer cells have all been shown to be susceptible to the anticancer effects of gallic acid and its derivatives [223]. Gallic acid works by targeting molecular pathways like the PI3K/Akt pathway, which is involved in cancer progression [224]. Gallic acid and Gallic Chinensis were shown to induce apoptosis in human gastric cancer cells. Gallic acid increased the levels of cell death-related proteins like Fas, FasL, and DR5. Tumor suppressor protein p53 also plays an important role in cell death in AGS cells. In simple terms, gallic acid may be used to treat gastric cancer [225]. Gallic acid suppresses PI3K/Akt/NF-κB signaling and mitochondrial dysfunction to inhibit bladder cancer T24 cell progression [226]. Gallic acid showed anticancer activity against HCT-15 colon cancer cells by reducing their growth and inducing apoptosis in these cells. Gallic acid treatment stopped the cell cycle progression at the sub-G1 phase. SEM and photomicrograph pictures showed morphological alterations in the Gallic acid-treated cells, such as membrane blebbing and shrinkage. Gallic acid caused time-dependent apoptosis in

HCT-15 cells via the ROS-mitochondrial pathway [181]. Gallic acid and cisplatin worked in concert to modulate the activity of molecules linked to apoptosis and induce these pro-apoptotic mediators. However, the cell death brought on by cisplatin with Gallic acid was reversed when N-acetyl-l-cysteine (NAC), a particular ROS inhibitor, inhibited the production of ROS. Thus, gallic acid had an anticancer effect on human SCLC H446 cells and improved cisplatin's antitumor activities through the ROS-dependent mitochondrial apoptotic pathway [227]. Gallic acid caused the inhibition of the proliferation of both HepG2 and SMMC-7721 cells by triggering apoptosis, especially in SMMC-7721 cells. Gallic acid works by increasing ROS levels, activating caspase-3 and caspase-9, boosting pro-apoptotic proteins like Bcl-2-like protein 4 and mitochondrial membrane potential in SMMC-7721 cells. Gallic acid demonstrated more toxicity toward HCC cells than normal cells [228].

3.2.2. p-Coumaric Acid

p-coumaric acid (p-CouA) is a derivative of cinnamic acid and is found in many fruits, vegetables, and plants. p-Coumaric acid has been shown to exert anticancer activity through targeting oxidative stress and inflammation, promoting apoptosis, disrupting the cell cycle, modulating cellular proliferation pathways, and increasing chemotherapeutic sensitivity [229]. In a study, p-Coumaric acid was reported to induce apoptosis in gastric cancer (SNU-16) cells by regulating key apoptotic proteins. Gene expression analysis showed that p-CouA affects multiple biological processes, including inflammation, apoptosis, cell cycle control, and immune responses. p-Coumaric acid was reported to target important cancer-related pathways like PI3K-Akt signaling pathways [230]. A study explored the antitumor activity of the p-coumaric acid derivative (4-ACGC) against lung cancer. 4-ACGC showed strong anti-proliferative effects in various lung cancer cell lines. Further, it inhibited tumor growth in animal cell models (in vivo). 4-ACGC was supposed to induce mitochondria-mediated apoptosis by increasing pro-apoptotic proteins like caspase-3, caspase-9, Bad, and Bax and by decreasing antiapoptotic proteins like Bcl-2 [231].

3.2.3. Ferulic Acid

Ferulic acid is a plant-derived polyphenolic compound with notable anticancer potential. It regulates key proteins implicated in cell cycle control and apoptosis by enhancing tumor-suppressive and pro-apoptotic factors such as p53, p21, Bax and caspases, while reducing proliferative proteins like cyclin D1 and cyclin E. It also suppresses Bcl-2, MMP-9, and NF-kB signaling, leading to decreased VEGF levels and cell cycle arrest at the G0/G1 phase [232]. Moreover, ferulic acid targets many molecular pathways such as PI3K/Akt, p38/MAPK/ERK, Akt/mTOR, and NF-κB signaling pathways, thereby suppressing cancer cell growth, invasion, migration and angiogenesis. Hence, ferulic acid demonstrated promising anticancer activity through underlying mechanisms such as induction of oxidative stress, cytotoxic effect, cell cycle arrest, apoptotic effect, suppression of antiproliferative effect, autophagy, and genotoxic and mutagenic effects [233]. In HeLa and CaSki cells, ferulic acid can dramatically reduce cell invasion and proliferation. By preventing autophagy and causing cell cycle arrest in human cervical carcinoma cells, it may have anticancer properties [234].

In the breast cancer cell line MDA-MB-231, ferulic acid therapy led to lower viability, increased apoptosis, and reduced metastatic potential. Additionally, it was shown that the reversal of the epithelial–mesenchymal transition (EMT) controlled ferulic acid's anticancer effect and its function in inhibiting metastasis. Ferulic acid's anticancer efficacy was confirmed in an MDA-MB-231 xenograft mouse model, which showed markedly reduced tumor volume, weight, and enhanced apoptosis, in line with in vitro findings [190]. Using the Matrigel invasion chamber, wound healing, and colony formation assay, ferulic acid in

TT cells inhibited invasion, migration, and colony formation, respectively. In conclusion, it is believed that by influencing cell cycle arrest, apoptosis, invasion, migration, and colony formation in TT cells, ferulic acid demonstrates anticarcinogenic action [235]. Ferulic acid decreased apoptotic nuclei, necrotic nodules, and the formation of vacuolated cytoplasm brought on by HCC. Lastly, ferulic acid reduced the expression of cyclin D1, HIF-1α, NFκB, TNF-α, mTOR, STAT3, and cMyc. Ferulic acid is thought to have anticancer effects by preventing hypoxia brought on by HCC by suppressing the production of HIF-1α. Moreover, it slows down the growth of tumors by lowering the expression of mTOR, STAT3, cMyc, and cyclin D1. Finally, ferulic acid decreased hepatic tissue inflammation by suppressing TNF-α and NF-Kb [236]. Ferulic acid inhibited the invasion of LNCaP and PC-3 cells. It also inhibited the establishment of colonies. It has been noted that FA may result in apoptosis in LNCaP cells and cell cycle arrest in PC-3 cells [237]. The effects of ferulic acid on invasion and colony formation were observed in the MIA PaCa-2 cells. Ferulic acid acts as an anticancer agent by influencing MIA PaCa-2 cells' cell cycle, apoptosis, invasion, and colony formation behaviors [238].

3.2.4. Ellagic Acid

Many berries, pomegranates, and dried fruits contain large amounts of ellagic acid (EA), a naturally occurring polyphenolic molecule with potent antioxidant and anticancer activities. EA's direct antiproliferative and apoptotic actions have been primarily responsible for its anticancer efficacy. Additionally, EA can prevent angiogenesis, extracellular matrix invasion, and tumor cell migration. Furthermore, EA may make tumors more susceptible to radiation and chemotherapy. Vascular endothelial growth factor-A (VEGF-A) is implicated in bladder cancer. EA inhibited cell proliferation, tumor invasion and chemotaxis in response to VEGF-A and enhanced the antitumor activity of mitomycin C [239]. When EA was administered to PANC-1 xenografted mice, tumor growth was significantly inhibited. This was linked to the induction of PARP cleavage, suppression of cell proliferation, and caspase-3 activation. EA increased the expression of Bax and decreased the expression of Bcl-2, cyclin D1, CDK2, and CDK6, inhibiting angiogenesis and metastasis biomarkers [240]. When human prostate carcinoma (PC3) cells were treated with EA, their growth and viability were inhibited. As demonstrated by the cleavage of poly (ADP-ribose) polymerase (PARP) and morphological alterations, EA-induced suppression of cell growth promoted apoptosis. EA upregulated Bax and suppressed Bcl-2, altering the Bax:Bcl-2 ratio in favor of apoptosis. It was also shown that treating PC3 cells with EA significantly activated caspases [241]. In T24 and 5637 cells, EA demonstrated a strong anticancer effect. The expression of PTEN/p-Akt and the inverse relationship suggested a change in the PTEN/Akt pathway, and EA therapy in bladder cancer may be beneficial in such circumstances [242]. EA's apoptotic, antiangiogenic, and antiproliferative properties may have a helpful chemopreventive function against hepatocarcinogenesis in rat models [243]. EA inhibits the PI3K/Akt signaling pathway in human NSCLC A549 cells, suppressing cell growth, arresting the cell cycle, and causing apoptosis [244].

3.2.5. Vanillic Acid

Vanillic acid is a naturally occurring phenolic compound found in Angelica sinensis and green tea, and it has attracted attention for its broad anticancer potential. Studies have shown that it can interfere with several stages of cancer progression by suppressing tumor cell proliferation, inducing apoptosis, and limiting invasion, migration, and angiogenesis. These effects have been reported in multiple cancers, including lung, liver, endometrial, and colorectal cancers. In addition, VA may improve the effectiveness of chemotherapeutic drugs while helping reduce their adverse effects. At the molecular level, VA induces

apoptosis through regulation of Bcl-2, reactive oxygen species (ROS), and proliferating cell nuclear antigen (PCNA). It also disrupts cancer cell cycle progression, particularly by arresting cells at the G1 phase. Furthermore, VA inhibits several major oncogenic signaling pathways, including JAK/STAT, NF-κB, and PI3K/Akt/mTOR, while enhancing antioxidant defense by increasing superoxide dismutase (SOD) activity. Its ability to reduce VEGF, MMP-2, and MMP-9 expression further contributes to the inhibition of tumor invasion and metastasis [245].

In colorectal cancer HCT116 cells, VA suppressed angiogenesis and cell proliferation by reducing HIF-1α protein synthesis through inhibition of the mTOR/p70S6K/4E-BP1 and Raf/MEK/ERK pathways [200]. Moreover, its antioxidant and free radical scavenging properties have also been linked to chemoprotective effects, including protection against benzo(a)pyrene-induced lung carcinogenesis [199]. Vanillic acid suppresses the growth of intestinal cancer cells by inhibiting mTOR signaling and promoting apoptosis. Its anticancer activity is believed to be associated with modulation of the mTOR pathway, a key regulator of cell proliferation and tumor progression, although its direct apoptotic effects appear to be relatively moderate [202].

Further, vanillic acid has demonstrated notable chemoprotective benefits against hepatocarcinogenesis in rats produced by 1,2-dimethylhydrazine (DMH) and diethylnitrosamine (DEN). The activation of the Nrf-2 signaling pathway, which results in the induction of the detoxifying enzyme GST, is linked to its anticancer effect during the early stages of liver carcinogenesis. Additionally, it promotes apoptosis by upregulating Bad and Caspase-3 expression and downregulating Bcl-2 expression while suppressing cell proliferation by downregulating Cyclin D1 expression [25].

3.2.6. Syringic Acid

Syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid) is a naturally occurring phenolic acid found in cereal grains, grapes, olives, mushrooms, spices, and several medicinal plants. Numerous cancer types, including colorectal cancer, lung cancer, oral squamous cell carcinoma, gastric cancer, and ovarian teratocarcinoma, have shown that SA has anticancer potential [246]. It has been reported to modulate various proteins, transcription factors, growth factors, and signaling molecules involved in cancer progression. In gastric cancer cells (AGS), syringic acid was shown to suppress cell growth, inflammation, and apoptosis through modulation of the AKT/mTOR signaling pathway [26]. Syringic acid's anticancer properties were assessed in rats with colorectal cancer induced by DMH. When compared to the control group, oral syringic acid therapy (50 mg/kg) for 15 weeks dramatically decreased tumor incidence and tumor volume. Mechanistically, syringic acid demonstrated potential anticancer action against colorectal cancer by inhibiting cellular proliferation, promoting apoptosis through enhanced ROS production and DNA damage, and downregulating important proliferative genes [204].

With an emphasis on cytotoxicity, induction of apoptosis, inhibition of cell migration, modulation of molecular signaling pathways, possible synergistic interactions with chemotherapeutic agents, and regulation of intracellular inflammatory and antioxidant systems, a study sought to examine the anticancer potential of syringic acid on human endometrioid adenocarcinoma RL95-2 cells as well as its effects on normal human endometrial stromal cells (HESCs). While syringic acid offers cytoprotective advantages in HESC normal cells, it has complex anticancer effects in RL95-2 EC cells. Through the synergistic control of apoptosis, cell cycle arrest, migratory inhibition, inflammation, and oxidative stress, Syringic acid and Dox improve anticancer activity [246].

In PA-1 ovarian cancer cells, syringic acid demonstrated potent anticancer effects by inhibiting cell growth and migration, promoting apoptosis through caspase activation and

Bax upregulation, reducing Bcl-2 expression, and suppressing major cancer-related signaling pathways such as STAT3, JNK, NF-κB, and AKT [247]. Syringic acid primarily inhibits the Nox/PTP-κ/EGFR axis to have strong chemopreventive effects on skin carcinogenesis [248].

3.2.7. Caffeic Acid

Caffeic acid is a naturally occurring polyphenolic compound widely found in vegetables, fruits, coffee beans, olives, potatoes, carrots, and propolis and is considered one of the major hydroxycinnamic acids in the human diet. Its anticancer activity is largely linked to its antioxidant and pro-oxidant properties, which are influenced by structural features such as free phenolic hydroxyl groups, the catechol moiety, and the double bond present in its carbon chain [21].

In HT-1080 human fibrosarcoma cells, caffeic acid demonstrated potent anticancer activity by reducing cancer cell proliferation through oxidative stress–mediated mechanisms. Treatment with CA increased intracellular ROS production and lipid peroxidation, disrupted mitochondrial membrane integrity, and promoted oxidative DNA damage, ultimately leading to apoptotic cell death. These findings indicate that caffeic acid interferes with cancer cell survival by triggering ROS-dependent mitochondrial dysfunction and apoptosis [249].

In human cervical cancer cells, caffeic acid induces apoptosis through the mitochondrial pathway by suppressing Bcl-2 activity, promoting cytochrome c release, and activating caspase-3, ultimately leading to programmed cancer cell death [250]. It showed remarkable anticancer effects against HCT116 colorectal cancer cells by slowing cell growth, promoting apoptosis, and reducing invasive behavior. It influenced the expression of key genes and microRNAs involved in apoptosis, cell cycle regulation, and metastasis, while also lowering oxidative stress and GST enzyme activity [251].

Caffeic acid therapy suppresses the growth of prostate cancer cells (PC-3 and LNCaP) and causes reactive oxygen species (ROS), cell cycle arrest, and apoptosis. Additionally, in PC-3 cells, caffeic acid administration reduces the expression of phosphorylated forms of MAPK families, such as extracellular signal-regulated kinase 1 (ERK1), c-Jun N-terminal kinase (JNK), and p38. Prostate cancer metastasis and migration are caused by proliferation and antiapoptosis, which are regulated by IL-6-mediated JAK/STAT3 expressions. Consequently, reducing IL-6/JAK/STAT-3 expression is thought to be a crucial target for prostate cancer treatment [252]. In human breast cancer, caffeine and caffeic acid inhibit growth and alter the levels of insulin-like growth factor I and estrogen receptors [253]. Caffeic acid reduces the tumorigenicity of triple-negative breast cancer cells via the FOXO1/FIS pathway [254].

3.2.8. Gentisic Acid

Gentisic acid (2,5-dihydroxybenzoic acid, GeA) is a catabolic tyrosine byproduct found in citrus fruits, grapes, artichokes, sesame, and olives. It is used to treat cardiovascular problems and has anti-inflammatory and antioxidant properties. GeA has strong antioxidant properties that can be either direct—it scavenges free radicals—or indirect—it acts as an agonist of NRF2, which controls the production of antioxidant molecules [255]. Crucially, in vitro C6 glioma development, DNA synthesis, and colony formation were blocked when GeA was administered at therapeutically feasible levels. GeA improved the survival of Ehrlich breast ascites carcinoma-bearing mice in an in vivo model. GeA slowed the growth of Ehrlich solid tumors (EST) that were impacted by either sodium selenite or GeA alone. GeA did not alter the antineoplastic effects of selenium that initially slowed EST growth. But later on, GeA caused the selenite's tumor stimulation to be blocked. Finally, GeA reduced doxorubicin side effects, including myofibrillary and endothelial damage and hyalinization necrosis [256].

Furthermore, GeA indirectly controls brain glioblastoma by blocking the solute carrier-22A8 and OAT3, which are involved in the brain efflux of anticancer medicines. This causes chemotherapeutic medications to accumulate in the brain, which slows the growth of the tumor. Furthermore, by inhibiting CDK1 enzymatic activity, GeA and its isomers control the advancement of the cell cycle [257]. In addition to improving survival rates and pathological alterations in a dose-dependent manner, GeA showed a therapeutic effect on CRC metastasis. As a GPR81 inhibitor, GeA successfully inhibited EMT and mTOR signaling in lactate-induced colorectal cancer (CRC) both in vivo and in vitro. Mechanistically, GeA prevented DEPDC5 from being degraded by lactate by preventing the activation of chaperone-mediated autophagy (CMA) [258].

A study assessed GeA's ability to protect Swiss albino mice from the hepatotoxicity and genotoxicity caused by cyclophosphamide (CP). The administration of CP in mice increased the malondialdehyde level, depleted the glutathione content and antioxidant enzymes, and induced DNA strand breaks and micronuclei induction. Oral pretreatment with GeA caused a significant reduction in malondialdehyde and increased glutathione levels, restoration of antioxidant enzyme activity, reduction in micronuclei formation, and DNA fragmentation [259].

3.2.9. Cinnamic Acid

Cinnamic acid, also called 3-phenyl-2-propenoic acid, is a naturally occurring aromatic fatty acid that is frequently found in cinnamon, grapes, tea, cocoa, spinach, and celery. Studies have shown that cinnamic acid has anti-proliferative action on glioblastoma, melanoma, prostate, and lung carcinoma cells. The aim of the study was to look into the molecular mechanism behind CA's cytotoxic effect in MDA-MB-231 triple-negative breast cancer cells. Through the extrinsic apoptotic pathway regulated by TNFα-TNFR1, CA induces apoptosis in breast cancer cells [212].

A study examined the cytotoxic and genotoxic effects of cinnamic acid in human melanocyte and human melanoma cell lines (HT-144). Cinnamic acid demonstrated both genotoxic effects and potent antiproliferative activity. Thus, melanoma cell proliferation was successfully inhibited by cinnamic acid [260]. Berberine and cinnamic acid have demonstrated promising antitumor and antioxidant agents, largely attributed to their proapoptotic properties. These compounds modulate the expression of proapoptotic and antiapoptotic genes, thereby promoting apoptosis in cancer cells. In addition, they have been reported to enhance the anticancer efficacy of cisplatin [261].

By modifying PTEN and ATG5 expression, cinnamic acid increases vinorelbine-induced cytotoxicity in MDA-MB-231 cells. By encouraging PTEN-mediated apoptotic signaling and autophagy-related gene 5-associated autophagy, vinorelbine and cinnamic acid appear to work in concert to increase cancer cell death [262]. The pharmacological actions of cinnamic acid may immediately materialize through a multi-target and multi-pathway approach for decreasing ovarian cancer, and it can effectively exert antineoplastic effects against ovarian cancer [263].

3.2.10. Rosmarinic Acid

Rosmarinic acid (RA) is primarily found in herbs of the Lamiaceae family, which includes rosemary (Rosmarinus officinalis), basil (Ocimum basilicum), sage (Salvia officinalis), thyme (Thymus vulgaris), and mints. RA has demonstrated significant anticancer promise in multiple preclinical investigations, with evidence supporting its ability to induce apoptosis, decrease proliferation, and modify inflammation and metastasis across a wide range of cancer types. In vitro, in vivo, and in silico models have all shown that RA has anticancer characteristics, mainly via activating apoptotic pathways and inhibiting critical

enzymes implicated in cancer metastasis, such as MMP-2 and MMP-9. One of the most promising factors of RA is its capacity to regulate both oxidative stress and inflammation, which are important contributors to cancer formation, particularly in inflammation-related malignancies such as colorectal cancer. RA has the ability to prevent cancer progression by inhibiting pro-inflammatory pathways such as NF-κB and STAT3, while also reducing oxidative damage through antioxidant actions [264].

By inhibiting DJ-1 through regulation of the PTEN-PI3K-Akt signaling pathway, RA demonstrated anticancer effects in osteosarcoma cells [265]. A study evaluated the anticancer activity of RA in 2D and 3D models of OSCC cells, and the findings showed that RA dramatically reduced cell mass and metabolic activity in highly invasive OSCC, while preserving normal mucosa at therapeutic levels. RA triggered autophagy, upregulating BNIP3 and BCNL1 and downregulating BIRC5. The upregulation of CADM1 and downregulation of VIM, CADM2, SNAIL1, and SOX9 highlighted the modulation of epithelial–mesenchymal transition and the remodeling of the extracellular matrix by the downregulation of MMP-2 and MMP-9 [219].

In MKN45 gastric cancer cells, RA suppressed pro-inflammatory cytokines and deactivated the inflammatory pathway. RA sensitized TNF-α-induced apoptosis in leukemia U937 cells via inhibiting NF-κB and reactive oxygen species [266]. Through the receptor activator of NF-κB ligand (RANKL)/RANK osteoprotegerin pathway, RA mostly prevented MDA-MB-231BO bone-homing breast cancer cells from migrating [267]. In AGS gastric cancer cells, the combination activity of anti-MUC1 and rosmarinic acid has an anticancer impact. RA and anti-MUC1 dramatically increase Bax protein and Bad mRNA, and they also block Gal-3. The combination activity of RA and anti-MUC1 efficiently suppresses Bcl-2 mRNA [268].

4. Translational and Clinical Findings

Although preclinical studies show promising anticancer effects of plant-derived compounds, clinical evidence remains limited and mixed (Table 3). Some trials report good tolerability and potential benefits, whereas others have not demonstrated clear improvements in clinical outcomes. Poor bioavailability and rapid metabolism may partly explain this gap. Because human clinical studies investigating plant-derived compounds in cancer are limited, relevant studies identified during the literature search were considered irrespective of their specific phytochemical class to provide a broader overview of the available translational evidence. Further well-designed clinical trials using standardized formulations are needed to establish their safety and efficacy in cancer treatment.

The clinical studies summarized in Table 3 vary in study design, patient populations, formulations, doses, treatment durations, and outcome measures, limiting direct comparisons. The findings are also inconsistent: curcumin showed potential benefits when combined with paclitaxel, while two green tea extract trials reported different outcomes for colorectal adenoma prevention. Small studies of resveratrol and sulforaphane reported preliminary findings, although the sulforaphane trial did not achieve its primary endpoint. Lycopene increased plasma levels but did not significantly affect PSA or Ki-67. These differences, together with the small sample sizes of several studies, highlight the preliminary nature of the available clinical evidence. The included compounds represent different phytochemical classes: curcumin (curcuminoid), EGCG (flavonoid), resveratrol (stilbenoid), sulforaphane (isothiocyanate), and lycopene (carotenoid). Although sulforaphane and lycopene are not polyphenols, they were included to provide a broader overview of the limited human clinical evidence on plant-derived compounds in cancer. Larger, well-designed clinical trials are needed to establish their clinical relevance.

Table 3. Clinical studies of selected plant-derived compounds in cancer.

Compound	Cancer Type	Study Design	Sample Size	Dose	Treatment Duration	Main Outcome	Safety Finding	Clinical Development Status	References
Curcumin (CUC-1®)	Advanced/ metastatic breast cancer	RCT, double-blind, placebo-controlled	150	300 mg IV/week + paclitaxel 80 mg/m^2	12 weeks, with 3-month follow-up	Curcumin + paclitaxel improved ORR and physical performance, suggesting potential adjunctive benefits in advanced breast cancer.	No major safety issues; less fatigue	Clinical-stage; not approved	[269]
Green tea extract (EGCG)	Colorectal adenoma/ CRC prevention	RCT, double-blind, placebo-controlled	1001 enrolled; 879 randomized	GTE standardized to 150 mg EGCG twice daily	3 years	GTE showed no significant chemopreventive benefit against colorectal adenomas.	Well tolerated; no major AE difference	Clinical trial; chemopreven-tion not established	[270]
Green tea extract (GTE)	Colorectal adenoma prevention	Randomized controlled trial	176 enrolled; 143 completed	0.9 g GTE/day	12 months	Lower incidence of metachronous colorectal adenomas, representing an reduction compared with controls.	No major safety concerns reported	Clinical trial; promising chemopreven-tive evidence	[271]
Resveratrol	Colorectal cancer	Human preoperative intervention study	20	Oral, 0.5 or 1 g/day	8 doses before surgery	Reduced tumor cell proliferation; potential chemopreventive activity	Well tolerated	Early clinical investigation; investigational	[272]
Sulforaphane-rich extract	Recurrent prostate cancer	Phase II clinical trial	20	200 µmol/day	≤20 weeks	Primary endpoint not achieved; PSA doubling time increased	Well tolerated	Phase II; investigational	[273]
Lycopene	Localized prostate cancer	Phase II randomized controlled trial	45	15, 30 or 45 mg/day	Approxi-mately 30 days	Increased plasma lycopene; no significant effect on PSA or Ki-67	No toxicity observed	Phase II; investigational	[274]

5. Pharmacokinetics and Bioavailability of Flavonoids and Phenolic Acids

Pharmacokinetics describes how bioactive compounds are absorbed, distributed, metabolized, and excreted (ADME) in the body [275]. Although dietary phenolic compounds are not drugs, they undergo pharmacokinetic processes similar to pharmaceuticals and interact with cellular targets (e.g., receptors, ion channels, transporter proteins, etc.) to exert biological and therapeutic effects. Consequently, their efficacy largely depends not only on their bioavailability and pharmacodynamic properties but also on their intrinsic activity, which determines the extent to which they reach relevant tissues and remain available at the site of action [276].

Bioavailability refers to the rate and extent to which a bioactive compound is absorbed and reaches its site of action [277]. It includes bioaccessibility, digestion, absorption, tissue distribution, metabolism, and physiological response. Notably, the metabolites of a phenolic compound may exhibit bioavailability and biological activity distinct from those of their parent compound [278]. Despite their health benefits, flavonoids generally exhibit low and highly variable bioavailability. Their bioavailability is influenced by several factors, including chemical structure, solubility, food matrix interactions, processing methods, and individual characteristics such as age, genetics, metabolic capacity, and gut microbiota composition [279,280]. Structural features, including glycosylation, methoxylation, and the number and position of hydroxyl groups, markedly affect their absorption and metabolism. Phenolic acids and isoflavones generally show higher bioavailability than many other flavonoid subclasses [281].

The chemical form in which phenolic compounds occur in foods also influences their absorption. Compounds present as esters, polymers, or glycosides are usually poorly absorbed and often require enzymatic or microbial transformation before becoming bioavailable [278]. In addition, gut microbiota play a crucial role in metabolizing dietary polyphenols and generating bioactive metabolites, particularly phenolic acids, thereby contributing significantly to their overall biological activity and health-promoting effects [282]. Bioaccessibility, defined as the fraction of a phytochemical released from the food matrix in an absorbable form, is a key determinant of bioavailability. It is influenced by the food matrix, physicochemical properties of the compound, and gastrointestinal processes, particularly digestion, which governs the release and subsequent absorption of phenolic compounds [281].

Importantly, the concentrations effective in vitro may not be reached at the target site in vivo. Differences in absorption, metabolism, and tissue distribution can affect drug exposure and, consequently, the translation of these preclinical findings to clinical settings.

5.1. Digestion

During digestion, mechanical and chemical actions break down food matrices and disrupt cell structures, releasing phenolic compounds into the gastrointestinal tract. Digestive enzymes and changes in pH facilitate the release of free and conjugated phenolics, whereas insoluble-bound phenolics often show low bioaccessibility. Only a small portion of phenolic compounds is absorbed in the small intestinal epithelium, while the remainder enters the circulatory system to exert biological effects or reaches the colon. In the colon, gut microbiota further metabolize them. Gastrointestinal digestion may also modify the phenolic structure, thereby influencing their stability, bioavailability, and biological activity [279].

5.2. Absorption

Dietary flavonoids are liberated from plant foods during mastication and gastrointestinal digestion before being absorbed across the intestinal epithelium. Their absorption is strongly influenced by food matrix characteristics, processing conditions, molecule size, configuration, lipophilicity, solubility, and chemical structure [283]. Gastric acid may initially modify certain polyphenols during the absorption process [284]. Following absorption, phenolic compounds are transported to the liver through the portal circulation, where they

often undergo conjugation reactions such as methylation, glucuronidation, and sulfation before entering systemic circulation. Unabsorbed compounds may be excreted or further metabolized by intestinal microbiota [285].

5.3. Distribution

After absorption, phenolic compounds are transported through systemic circulation and distributed to various tissues and organs where they exert their biological activities [286]. Their distribution is strongly influenced by physicochemical characteristics as well as their intricate interactions with protein transporters and carriers, such as GLUT, SGLT1, ABC transporters, albumin, fibrinogen, organic anion and cation transporters, and MATE1 [287]. In circulation, phenolic compounds commonly exist as glucuronidated, methylated, or sulfated conjugates, bound to plasma proteins such as albumin. These metabolites are subsequently distributed to different tissues and organs, including the liver, kidneys, heart, lungs, and brain [288].

5.4. Metabolism

Phenolic compounds undergo extensive metabolic transformation and transportation in the intestine, liver and other tissues through the action of xenobiotic-metabolizing enzymes. These metabolic reactions largely determine their bioavailability, biological activity, tissue distribution, and excretion. Most phenolics undergo phase II conjugation reactions, including methylation, sulfation, and glucuronidation, catalyzed by enzymes like catechol-O-methyltransferase (COMT), sulfotransferases (SULTs), and UDP-glucuronyl transferase (UGT). The extent of these biotransformation processes can significantly affect the therapeutic potential and biological activity of individual phenolic compounds at target tissues [289,290]. Although some conjugated metabolites may retain biological activity, rapid metabolism and excretion can often reduce half-life and concentrations of parent compounds at target sites [289]. Therefore, the form and concentration of a compound reaching the target tissue should be considered when interpreting anticancer effects observed in preclinical models.

5.5. Excretion

After absorption and metabolism, most polyphenols are rapidly excreted as glucuronides and sulfate esters through urine and bile. The non-absorbed polyphenols and returned polyphenols in the gut lumen become metabolized to simple phenolic compounds that are primarily eliminated in feces [291]. The extent of excretion varies according to molecular size, degree of polymerization of individual polyphenols, nature of the phenolic binding, etc. [292].

However, translating these findings to the clinic remains challenging, as the concentrations that show anticancer effects in vitro may not be reached at the tumor site in vivo. The pharmacokinetic factors can influence the concentrations reaching target tissues and should therefore be considered when interpreting preclinical findings and their potential clinical relevance.

6. Risk, Toxicity and Safety Consideration of Flavonoids and Phenolic Acids

Although polyphenols possess numerous health benefits, excessive intake or inappropriate use may result in adverse effects. Higher concentrations of polyphenols can interfere with digestive enzymes, alter intestinal microbiota, interact with drugs, cause hormonal imbalance, impair iron uptake, develop anemia, and cause other physiological disturbances. Some polyphenols exhibit mutagenic effects, carcinogenic potential, genotoxic effects and prooxidative activity [293]. Polyphenols can interact with conventional medications by modulating the activity of phase I and phase II drug-metabolizing enzymes, including cytochrome P450 enzymes, glutathione S-transferase,

UDP-glucuronosyltransferase, sulfotransferase, N-acetyltransferase, methyltransferase, epoxide hydrolase, and NAD(P)H:quinone oxidoreductase, thereby altering drug absorption, metabolism, and therapeutic efficacy [293,294].

Further, they can alter function, structure, solubility, hydrophobicity, thermal stability, isoelectric point, and sensitivity of proteins to digestive enzymes. Thus, they can modify the activity of digestive enzymes [295,296]. Although many herbal products have a long history of traditional use, their safety cannot be assumed, as evidence regarding their mechanisms of action, toxicity, contraindications, and potential drug interactions remains limited for many products [297].

Many herbal products are still not adequately tested or properly regulated, making it difficult to fully understand their possible side effects, contraindications, and interactions with conventional medicines and functional foods. Therefore, stronger regulatory oversight is needed to ensure their safety, quality, and appropriate use [298].

The safety of natural bioactive molecules depends on dose, duration of use, and individual patient characteristics. A relatively safe compound can become harmful when consumed at excessive doses. Improper use or prolonged consumption, contamination, and interactions with other drugs may increase the risk of adverse effects [299,300]. Therefore, comprehensive evaluation of toxicity, pharmacokinetics, and long-term safety remains essential to ensure their safe and effective clinical application.

7. Combined Effects of Polyphenolic Compounds with Anticancer Drugs and Other Polyphenols

Conventional cancer therapies like chemotherapy and radiation therapy are often limited due to drug resistance, which contributes to cancer progression and treatment failure. To overcome these limitations, combinatorial therapies using natural bioactive compounds have gained considerable attention. Polyphenols can be combined with other polyphenols, anticancer drugs, vitamins, or other bioactive compounds. Such an approach can inhibit tumor growth more efficiently, increase apoptosis, reduce drug resistance, and modulate multiple cancer-related signaling pathways [301].

7.1. Combined Effects of Different Polyphenolic Compounds

Numerous studies have demonstrated that combinations of polyphenols exhibit greater anticancer efficacy than individual compounds alone. For example, the anthocyanin-rich OptiBerry formulation, derived from several berry extracts, showed strong anti-angiogenic and antitumor effects with minimal toxicity. These effects were linked to suppression of VEGF, NF-κB, and MCP-1 signaling pathways, resulting in reduced angiogenesis, inflammation, and metastasis [302,303]. Similarly, the combination of ellagic acid and quercetin significantly inhibited cell proliferation and promoted apoptosis in MOLT-4 human leukemia cells, accompanied by marked alteration in cell-cycle progression [304].

In MOLT-4 human leukemia cells, quercetin combined with ellagic acid reduced cell growth and viability and increased apoptosis. Isobolographic analysis confirmed a synergistic effect, suggesting that the combination was more effective than the individual compounds under the tested conditions [305].

Curcumin combined with resveratrol exhibited improved inhibitory effects against colon cancer cells in both in vitro and in vivo models by suppressing tumor growth and cellular proliferation [306]. Likewise, the combination of curcumin and catechins in colorectal cancers considerably reduced cell proliferation and increased apoptosis compared to individual compounds alone [307]. Other promising combinations include genistein and sulforaphane, which decreased cell viability and induced cell-cycle arrest in breast cancer cells [308]. The protective effects of grape seed extract, resveratrol, ellagic acid, and ursolic acid were associated with

antioxidant activity, inhibition of cell proliferation, induction of apoptosis, and protection against DNA damage. In experimental models of skin carcinogenesis, their combination may help suppress tumor initiation and progression more effectively [309].

Apigenin and naringenin showed enhanced antiproliferative effects in A549 and H1299 lung cancer cells, with combination index values below 1. Their combination induced cell-cycle arrest, increased oxidative stress and mitochondrial dysfunction, and promoted apoptosis. Further studies are needed to establish the clinical relevance of these findings [310]. A combination of curcumin and resveratrol in primary prostate cancer cells in B6C3F1/J mice suppressed tumor growth and reduced cell proliferation [311]. Another study showed the combinatorial effect of genistein and sulforaphane decreased cell viability and encouraged cell death and cell cycle arrest at the G1 phase in MCF-7 cells and at the G2/M phase in MDA-MB-231 breast cancer cells [308].

7.2. Combined Effects of Polyphenolic Compounds with Anticancer Drugs

Polyphenols have shown potential to enhance the effects of conventional anticancer drugs and modulate drug resistance in preclinical studies, although their clinical benefits remain uncertain. Their ability to reduce treatment-related adverse effects and improve clinical outcomes remains to be established. Flavonoids and phenolic acids may improve the effects of other natural compounds or anticancer drugs through complementary actions on multiple cellular targets [Figure 4]. However, enhanced activity with a combination does not necessarily indicate pharmacological synergy. Apigenin has shown enhanced anticancer activity when combined with several chemotherapeutic agents, including cisplatin, paclitaxel, and gemcitabine, in prostate and pancreatic cancer models [312–314].

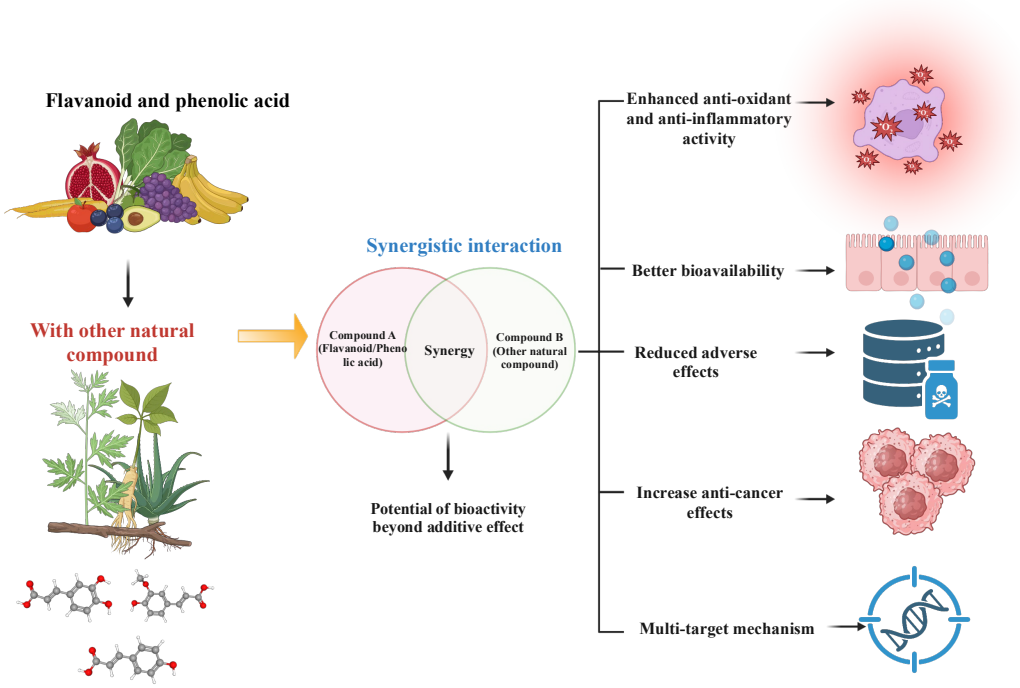


Figure 4. Potential interactions between flavonoids, phenolic acids, and other natural compounds. Their combined effects may enhance antioxidant, anti-inflammatory, and anticancer activities through complementary mechanisms and modulation of multiple molecular targets. However, enhanced combined activity does not necessarily indicate pharmacological synergy, which requires appropriate quantitative assessment. Proposed benefits, including improved bioavailability, reduced adverse effects, and increased anticancer efficacy, require further experimental and clinical validation. Created in BioRender. Rahmani, A.H. (2026) https://BioRender.com/0awy6qz (accessed on 25 October 2026).

Similarly, curcumin has enhanced the anticancer effects of conventional drugs in preclinical studies. Combination treatment with curcumin and dasatinib effectively inhibited colon cancer progression and improved therapeutic outcomes in preclinical studies [315]. Likewise, curcumin combined with gemcitabine significantly suppressed pancreatic tumor growth and reduced tumor-forming potential [316].

Collectively, these predominantly preclinical findings suggest that polyphenol-based combination therapies may have potential to enhance the efficacy of conventional cancer treatments and modulate treatment resistance. However, further clinical studies are needed to establish their therapeutic benefits in humans.

8. Discussion

As one of the leading causes of death, cancer continues to be a major global health concern. Conventional cancer treatments, such as radiation, chemotherapy, and surgery, have made significant strides, but they are not without drawbacks. Patients' quality of life can be greatly impacted by the severe side effects they frequently face [317]. Tumor heterogeneity is now well understood thanks to recent technical developments in multi-omics platforms. However, intra-tumoral and inter-patient heterogeneity might be linked to treatment failure, which is a major issue for effective cancer treatment. In this sense, early cancer detection can lower the chance of dying from the disease, screen for likely malignancies before symptoms manifest, and has more potential advantages than disadvantages [318,319].

However, high treatment costs and drug resistance are further limitations. Further, the efficacy of some therapies against metastatic diseases is still noticeably lacking. Therefore, it is necessary to investigate supplementary and alternative therapy approaches to improve patient health and survival [317].

While cancer remains notoriously difficult to manage due to its adaptive nature, it is clear that oxidative stress is involved in several stages of tumor development and progression, but its effects can vary depending on the tumor type, cellular context, and redox balance [320]. Natural products, particularly those derived from plants, have emerged as promising candidates for further anticancer drug development. The vast structural diversity of these compounds, along with their selective cytotoxicity toward cancer cells observed in experimental models, makes them promising candidates for further investigation, although their therapeutic selectivity and safety in humans remain to be established. Their selective cytotoxic effects may vary with the compound, concentration, tumor type, and cellular context. Additionally, many plant-derived compounds exhibit multifaceted mechanisms of action, which may help in overcoming resistance issues commonly associated with conventional treatments. However, their therapeutic potential and safety require further evaluation in relevant preclinical models and clinical studies [317].

By reducing the antioxidant capacity of cancer cells, several natural compounds may make them more susceptible to oxidative stress brought on by chemotherapy and radiation. Tumors that have their antioxidant defense compromised are less able to counteract oxidative damage, which leads to cell death. However, one should keep in mind that, depending on concentration, cell type, exposure duration, and environmental factors, a single natural chemical frequently exhibits both pro-oxidant and antioxidant qualities [321].

Natural antioxidants have gained traction as potential therapeutics. Their anticancer properties are associated with antioxidant activity, regulation of cellular functions, induction of apoptosis, and enhanced sensitivity to chemotherapy [322]. Recent evidence suggests that natural bioactive compounds may enhance the effects of conventional chemotherapy and help reduce treatment-related toxicity. However, further clinical studies are needed to confirm these benefits and establish their safety in cancer treatment [323].

However, further clinical studies and standardized quality control are needed to establish the safety and clinical feasibility of these approaches. Further, the potential of plant-derived products to enhance the efficacy of conventional chemotherapy also remains to be confirmed in well-designed preclinical and clinical studies [324,325]. Their pharmacological potential can be increased through structural alterations, alternate formulations, and/or the use of increasingly efficient delivery methods. Plant drug-functionalized nanodiamonds and other nanocarriers based on anticancer drugs are examples of recent biotechnological solutions that offer a new promise for cancer therapy using nanotech approaches. Concurrently, they offer an additional advancement in the effective application of secondary metabolites for cancer treatment [325]. Importantly, the therapeutic effects of plant-derived compounds depend on their ability to modulate redox balance in a context-dependent manner rather than simply their antioxidant activity [326]. The antioxidant and pro-oxidant activities of plant-derived polyphenols represent a context-dependent, double-edged effect in cancer therapy. Depending on concentration and the cellular redox environment, these compounds may either reduce oxidative stress or promote reactive oxygen species accumulation and cancer cell death. Importantly, their antioxidant activity may also interfere with certain chemotherapy or radiotherapy regimens that depend on oxidative damage, highlighting the need to evaluate these effects in the context of specific treatments [294].

The effects of combining polyphenols with chemotherapy or radiotherapy can differ depending on the compound, dose, and treatment conditions, and clinical evidence is still limited [327,328]. Several preclinical studies have reported enhanced effects when polyphenols are combined with drugs such as cisplatin, doxorubicin, 5-fluorouracil, gemcitabine, and paclitaxel. However, the outcomes are not always positive. For example, curcumin enhanced the effects of trastuzumab at lower concentrations but showed antagonistic effects at higher concentrations [329]. This suggests that polyphenols do not always improve treatment outcomes, and their effects need to be assessed carefully for each combination.

One of the main challenges in translating these findings into clinical practice is that the concentrations effective in laboratory studies may be difficult to achieve in humans. Although in vitro studies often use high micromolar concentrations, oral intake of natural polyphenols may result in much lower blood levels because of poor solubility, rapid metabolism, and extensive breakdown in the liver [330]. Moreover, plasma levels do not necessarily reflect the amount of the compound reaching target tissues or producing its biological effect [325].

Some phenolic acids and flavonoids may cause liver toxicity at certain doses. For example, epigallocatechin-3-gallate (EGCG), a tea flavonoid, caused toxicity in isolated rat liver cells, mainly through mitochondrial damage and increased reactive oxygen species (ROS) production. Liver injury was also observed in mice given tea phenolics by intraperitoneal injection [331]. Therefore, safety considerations should distinguish between dietary exposure, purified phytochemicals, standardized extracts, whole herbal preparations, and pharmacological-dose supplementation, as these can differ in dose, composition, bioavailability, and systemic exposure. Accordingly, safety depends not only on the compounds but also on dose, duration, and formulation. At higher exposures, some polyphenols may affect endocrine function, iron absorption, or drug metabolism, while certain compounds have shown toxic or pro-oxidant effects in experimental studies. Potential interactions with anticancer drugs should also be considered, particularly at pharmacological doses. Overall, safety findings should therefore be interpreted in the context of specific compounds and levels of exposure rather than generalized across all natural products as a whole [293].

Polyphenols may influence drug metabolism by altering the activity of cytochrome P450 (CYP) enzymes, particularly CYP3A4, which plays an important role in the metabolism of many drugs. They may also affect drug transporters, including P-glycoprotein, poten-

tially changing drug absorption and circulating concentrations. These interactions may increase drug toxicity or reduce therapeutic effectiveness, highlighting the need to assess the safety of polyphenols used alongside anticancer treatments, particularly at pharmacological doses [332]. However, these experimental findings should be interpreted cautiously, as they do not necessarily reflect the effects of normal dietary intake.

Large-scale initiatives such as the NCI Program for Natural Products Discovery (NPNPD) support the identification and development of promising natural product candidates. Combining these efforts with further preclinical and clinical studies may help translate promising plant-derived compounds into effective cancer therapies. The future of polyphenol-based cancer therapies will depend on a better understanding of their mechanisms, improved delivery and bioavailability, and stronger clinical evidence [325,333].

A comparison of in vitro effective concentrations with human plasma levels further highlights the challenges of translating experimental findings into clinical settings (Table 4). The differences observed may partly reflect limited absorption, rapid metabolism, and low systemic availability of unchanged compounds, emphasizing the need to consider pharmacokinetic factors when interpreting their anticancer potential.

Table 4. Comparison of in vitro effective concentrations and reported human plasma levels of selected polyphenols, highlighting their major pharmacokinetic limitations.

Compound	In Vitro Effective Concentration	Reported Human Plasma Concentration	Main Pharmacokinetic Limitation
Quercetin	10 μM (pancreatic cancer cells) [59]	0.63 ± 0.72 μM (after enzymatic hydrolysis of plasma) [334]	Extensive glucuronidation and sulfation; free quercetin was not detected in plasma [334]
Apigenin	10–35.15 μM (reported growth-inhibitory concentrations) [91,92]	0.127 ± 0.081 μM (following a high parsley intake) [335]	Poor aglycone absorption, extensive glucuronidation and sulfation, and glycosylation-dependent bioavailability [336]
EGCG	1 μg/mL EGCG (approximately 2.18 μM) [337]	0.310 ± 0.117 μM (free EGCG, 1 h after green tea consumption); 0.080 μM fasting after 7 days of regular intake [338]	Low systemic exposure, extensive conjugation during regular intake, and low fasting plasma concentrations of free EGCG [338]
Resveratrol	42.5 μM (IC_{50} in HCT116 cells) and 100 μM (IC_{50} in DLD1 cells) after 72 h [339]	491 ± 90 ng/mL (approximately 2 μM; resveratrol plus metabolites); unchanged resveratrol was below 5 ng/mL [340]	Rapid intestinal and hepatic sulfate and glucuronide conjugation, resulting in very low systemic availability of unchanged resveratrol despite high oral absorption [340]

Overall, plant-derived polyphenols have shown potential in preclinical cancer research; however, their clinical potential remains uncertain due to limited bioavailability, dose-dependent effects, possible interactions with conventional therapies, and the limited clinical evidence available to date. Further research should clarify how these compounds affect drug transporters and influence the efficacy and toxicity of chemotherapy and radiotherapy. Better-standardized formulations and well-designed clinical trials are needed to establish their safety and therapeutic value. Large-scale initiatives such as the NCI Program for Natural Products Discovery may also help identify promising compounds for further investigation.

9. Conclusions

Natural phytochemicals are being investigated as potential adjuncts to conventional cancer therapies, particularly in preclinical studies exploring their effects on treatment efficacy and toxicity. However, their clinical benefits remain to be fully established. Numerous plant-derived bioactive compounds have demonstrated promising anticancer activities through the modulation of oxidative stress, inflammation, apoptosis, angiogenesis, metastasis, and multiple cellular signaling pathways. Some approved anticancer drugs, such as taxanes and vinca alkaloids, are derived from plants. However, the flavonoids and phenolic acids discussed in this review are not yet established treatments for cancer, and most remain under preclinical or clinical investigation. Their safety and effectiveness in patients still need to be confirmed through further clinical studies. Additionally, their broad clinical applications continue to be restricted by well-documented limitations. Bridging this translational gap will require thorough interdisciplinary collaboration across medicinal chemistry, pharmacology, biochemistry, and biology to decode mechanisms of action and combinational effects. Therefore, this review aimed to compile current knowledge regarding phytochemicals used in cancer therapy, identify promising therapeutic opportunities, and discuss the major limitations and future challenges associated with the development of safer and more effective anticancer strategies based on natural compounds.

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