JEMUR

JOURNAL OF EMERGING MINDS IN UNDERGRADUATE RESEARCH

Volume 1 · Issue 1 · 2026 | jemur.org

REVIEW ARTICLE

Natural Products as Multi-Target Agents in Cancer Prevention and Progression

İrem Kumru ÖZ[1*]

[1] *Department of Molecular Biology and Genetics, Faculty of Arts and Sciences, Bursa Uludağ University, Bursa, Türkiye*

[*] **Corresponding Author:** rmkumru@gmail.com

DOI: 10.5281/zenodo.22086209

Submitted: 6 July 2026 **Accepted:** 24 August 2026 **Published:** 31 August 2026

ABSTRACT

Plant-derived natural products have long been an invaluable source of anticancer agents for the prevention and treatment of cancer. Although numerous modern and costly treatment strategies are currently used to combat cancer, factors such as treatment resistance, systemic toxicity, and tumor heterogeneity continue to be major obstacles to successful clinical outcomes. To overcome these limitations, bioactive natural products stand out as potential therapeutic agents due to their high molecular diversity and multi-targeted biological activities. Various classes of phytochemicals, including polyphenols, flavonoids, terpenoids, and alkaloids, represent promising candidates for new complementary anticancer strategies due to their ability to simultaneously modulate multiple cellular mechanisms. This review focuses on the roles of ten bioactive compounds-curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), sulforaphane, carvacrol, berberine, luteolin, apigenin, honokiol and propolis-which have shown efficacy in experimental and clinical settings and are among the most widely investigated compounds in contemporary research, in the context of cancer progression. This study provides an overview of the classification and mechanism-based evaluation of these compounds based on their effects on apoptosis avoidance, metastasis, epithelial-mesenchymal transition (EMT), and tumor microenvironment. Furthermore, the current opportunities and limitations of translating these compounds into clinical applications are discussed.

Keywords: *natural products; phytochemicals; cancer hallmarks; apoptosis evasion; epithelial–mesenchymal transition; tumor microenvironment*

To cite this article: Öz, İ. K. (2026). Natural products as multi-target agents in cancer prevention and progression. *Journal of Emerging Minds in Undergraduate Research, 1*(1), 57-76. https://doi.org/10.5281/zenodo.22086209

1. Introduction

Cancer remains one of the most significant global health challenges based on current data, due to its increasing incidence, complex biology, and limitations in treatment strategies (Sung et al., 2026). Worldwide, cancer ranks as the second leading cause of death. According to the latest GLOBOCAN 2024 estimates, approximately 20.6 million new cancer cases and 9.8 million cancer-related deaths were reported globally, highlighting the growing burden of cancer on health systems worldwide (Sung et al., 2026). Moreover, the global cancer burden is expected to increase substantially in the coming decades. The rise in cancer incidence is largely driven by genetic predispositions as well as modifiable risk factors, including tobacco use, a sedentary lifestyle associated with modern living, unhealthy dietary habits, and environmental pollution. The complex and molecularly intricate nature of cancer underscores the necessity for effective prevention and therapeutic strategies (Anand et al., 2008).

Cancer development and progression are governed by a complex interplay of genetic, epigenetic, and microenvironmental alterations that enable malignant cells to acquire distinct biological capabilities (Hanahan & Weinberg, 2011). The hallmarks of cancer provide a comprehensive framework for understanding these interconnected processes, including sustained proliferative signaling, resistance to cell death, metastatic progression, angiogenesis, immune evasion, and continuous remodeling of the tumor microenvironment. These interrelated mechanisms enable cancer cells to survive under adverse conditions and contribute to tumor progression and therapeutic resistance (Hanahan & Weinberg, 2011; Hanahan, 2022).

One of the most critical and challenging features of cancer cells is their ability to evade programmed cell death (apoptosis). Dysregulation of apoptotic mechanisms, including alterations in mitochondrial signaling, pro- and anti-apoptotic regulators, and caspase activation, allows tumor cells to escape normal cellular elimination processes (Fuchs & Steller, 2011). In addition, metastatic dissemination mediated through epithelial–mesenchymal transition (EMT), extracellular matrix remodeling, and angiogenic adaptation represents another key determinant of cancer progression (Pastushenko & Blanpain, 2019). Furthermore, the tumor microenvironment (comprising immune cells, stromal components, extracellular matrix, and signaling molecules) actively contributes to tumor growth, immune suppression, and therapeutic resistance (Baghban et al., 2020).

Despite significant advances in cancer therapy, limitations such as drug resistance, systemic toxicity, and tumor heterogeneity continue to constrain treatment efficacy (Vasan et al., 2019). Therefore, multi-target therapeutic approaches capable of modulating several cancer-related processes have gained increasing attention. Natural products and plant-derived bioactive compounds represent promising candidates due to their structural diversity and their ability to regulate multiple molecular and cellular mechanisms involved in cancer progression (Newman & Cragg, 2020). Phytochemicals such as polyphenols, flavonoids, terpenoids, alkaloids, and other bioactive molecules exert anticancer effects by modulating apoptosis, metastatic behavior, oxidative stress balance, inflammation, and tumor microenvironment interactions (Aggarwal & Shishodia, 2006). Unlike single-target therapeutic approaches, these compounds can simultaneously influence multiple cancer hallmarks, providing a rationale for their investigation as complementary or preventive strategies in cancer therapy (Aggarwal & Shishodia, 2006; Newman & Cragg, 2020). In this context, the molecular-level investigation of

target phytochemicals, particularly regarding their potential to suppress tumor survival pathways and reactivate apoptotic mechanisms, is of considerable importance.

In this review, ten bioactive compounds that have demonstrated substantial therapeutic potential in experimental and clinical studies and represent the most frequently researched agents in current literature (curcumin, resveratrol, quercetin, epigallocatechin gallate [EGCG], sulforaphane, carvacrol, berberine, luteolin, apigenin, and honokiol), along with propolis (a natural bee product) were examined as multi-target agents in cancer prevention and therapy strategies. Compound selection was guided by three primary inclusion criteria: (i) demonstrated evidence in experimental and/or clinical models, (ii) representation of distinct chemical classes (polyphenols, flavonoids, terpenoids, and alkaloids), and (iii) prominent coverage in current cancer literature. Conversely, the exclusion criteria were defined as compounds with insufficient experimental data, poorly defined molecular mechanisms, or efficacy strictly restricted to a single cancer cell line. These compounds were categorized based on their abilities to target apoptosis evasion, suppress metastatic and EMT-related processes, and modulate oxidative stress and tumor microenvironment dynamics.

In this review, we comprehensively summarize recent studies and mechanistic insights regarding the therapeutic potential of natural products in cancer prevention and therapy, focusing predominantly on literature published between 2010-2026 years. (pivotal older sources were also cited where appropriate). Literature searches were conducted across major electronic databases, including PubMed, Web of Science, ScienceDirect, Scopus, Google Scholar, and ClinicalTrials.gov (last accessed in July 2026) This study provides critical insights into the multi-target mechanisms and anticancer efficacy of ten selected bioactive compounds: curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), sulforaphane, carvacrol, berberine, luteolin, apigenin, and honokiol, alongside propolis, aiming to inform future translational and clinical applications.

The review offers an integrated perspective on the anticancer potential of these agents by detailing key evidence from in vitro, in vivo, and clinical models across various malignancy types. Specifically, this work synthesizes their multi-target actions into key operational axes, including the modulation of: (I) apoptosis reactivation and survival pathway inhibition, (II) metastatic dissemination and epithelial–mesenchymal transition (EMT), (III) oxidative stress dynamics, (IV) tumor microenvironment remodeling, and (V) potential synergistic effects with conventional chemotherapeutics. Compounds were selected based on robust experimental validation, mechanistic clarity, structural diversity (encompassing polyphenols, flavonoids, terpenoids, and alkaloids), and high relevance in contemporary oncological research. Consequently, this review serves as a comprehensive resource for researchers aiming to exploit multi-target natural agents for innovative cancer treatment and prevention strategies.

2. Multi-Target Mechanisms of Natural Bioactive Agents in Cancer

Natural products and plant-derived bioactive compounds offer significant therapeutic advantages in oncology because of their structural diversity and ability to simultaneously modulate multiple oncogenic signaling pathways. Rather than acting on a single molecular target, these multi-target agents exert pleiotropic effects that collectively intersect with the core hallmarks of cancer development and progression. (Newman & Cragg, 2020)

As illustrated in Figure 1, ten representative natural bioactive compounds, along with propolis, have gained prominent attention in current oncological research owing to their distinct chemical classes and multi-target capabilities.p

Cancer is not merely a disease characterized by uncontrolled cell proliferation; rather, it is a complex process that arises from the accumulation of numerous biological alterations that enable tumor cell survival, invasion of surrounding tissues, and development of therapeutic resistance. The “hallmarks of cancer” framework, a fundamental concept in understanding cancer biology, systematically defines the essential characteristics acquired by malignant cells and facilitates the understanding of the mechanisms involved in tumor development and progression (Hanahan, 2022).

Within this framework, cancer cells acquire fundamental biological capabilities, including sustained proliferative signaling, evasion of growth suppressor mechanisms, resistance to programmed cell death (apoptosis), replicative immortality, induction of angiogenesis, activation of invasion and metastasis, evasion of immune surveillance, and establishment of a tumor-supportive microenvironment (Hanahan, 2022). These characteristics do not represent independent processes; rather, they constitute a complex network of interacting mechanisms that collectively drive tumor development.

The ability of cancer cells to evade apoptotic mechanisms provides a significant advantage in the early stages of tumor development. Dysregulation of apoptotic signaling pathways, including increased expression of anti-apoptotic proteins, suppression of mitochondrial death signaling, and inhibition of caspase activation, enables cells to escape normal elimination processes (Pistritto et al., 2016). In addition, epithelial–mesenchymal transition (EMT), extracellular matrix remodeling, and angiogenic adaptations play critical roles in metastatic progression by facilitating the dissemination of cancer cells to distant tissues (Mittal, 2018).

The tumor microenvironment is a complex system comprising dynamic interactions among cancer cells, stromal cells, immune cells, extracellular matrix components, and various signaling molecules. This microenvironment supports tumor growth through chronic inflammation, immune suppression, angiogenesis, and development of therapeutic resistance (Hinshaw & Shevde, 2019). Therefore, therapeutic approaches that target multiple hallmarks of cancer have become an important area of research in contemporary cancer therapy.

2.1. Natural Products as Multi-Target Therapeutic Agents

The multifactorial and heterogeneous nature of cancer limits the effectiveness of therapeutic approaches directed toward a single molecular target. Therefore, there is growing interest in multi-target therapeutic strategies capable of regulating different biological processes. Plant-derived natural products have emerged as important candidates in cancer research because of their extensive chemical diversity and their ability to modulate multiple cellular mechanisms (Newman & Cragg, 2020).

Plant-derived bioactive compounds, including polyphenols, flavonoids, terpenoids, and alkaloids, can modulate processes that play critical roles in cancer development, such as cell proliferation, apoptosis, oxidative stress, inflammation, metastasis, and regulation of the tumor microenvironment (Šemeláková et al., 2026). Curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), berberine, and other natural compounds have been reported

to suppress tumor progression by exerting simultaneous effects on multiple cancer hallmarks (Anand et al., 2008; Šemeláková et al., 2026).

The multi-target mechanisms of natural products offer potential advantages, particularly in overcoming major challenges in cancer treatment, including tumor heterogeneity and therapeutic resistance. However, low bioavailability, metabolic instability, and limitations associated with clinical translation remain important challenges that must be addressed for their therapeutic application (Newman & Cragg, 2020)

Therefore, investigating the regulatory effects of natural products on cancer hallmarks may contribute to the development of novel complementary therapeutic approaches for cancer prevention and the control of cancer progression.

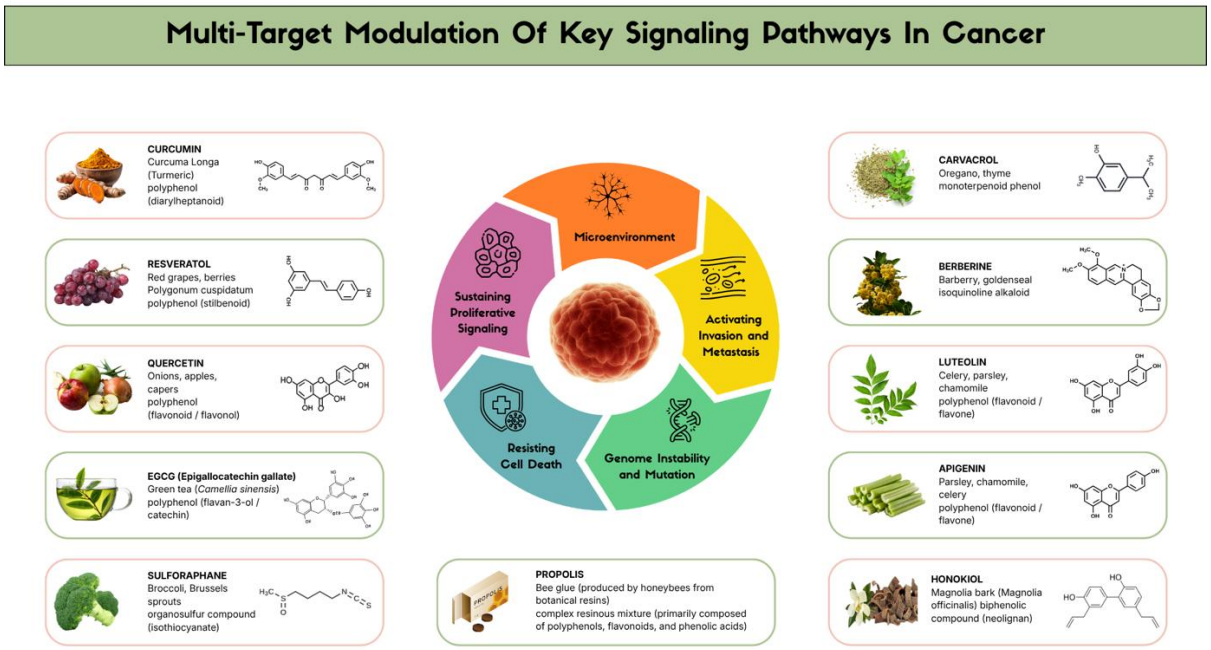

Figure 1 Schematic overview of the ten selected natural bioactive compounds and propolis, categorized by their chemical classes, and their multi-target modulation across key functional hallmarks of cancer progression. The central diagram illustrates the five core operational axes targeted by these compounds: sustaining proliferative signaling, resisting cell death, genome instability and mutation, activating invasion and metastasis, and tumor microenvironment remodeling.

2.2. Natural Products Targeting Apoptosis Evasion

To systematically evaluate the anticancer potential of plant-derived natural products, ten representative bioactive compounds (curcumin, resveratrol, quercetin, EGCG, sulforaphane, carvacrol, berberine, luteolin, apigenin, and honokiol) alongside propolis were analyzed based on their distinct chemical classes and multi-target capabilities. Rather than acting via a single molecular pathway, these agents exert broad biological effects that directly intersect with major hallmarks of cancer progression, including apoptosis evasion, metastatic dissemination, genomic instability, and tumor microenvironment remodeling.

To provide a structured and comprehensive overview, the chemical classifications, primary molecular targets, key signaling cascades, and affected cancer hallmarks for each selected agent are systematically summarized in Table 1, supported by representative recent literature

Table 1 Chemical classification, primary molecular targets, key signaling cascades, and affected cancer hallmarks of the ten selected natural bioactive compounds and propolis.

Compound	Chemical Class	Primary Molecular Targets & Key Signaling	Cancer Hallmarks Affected	References
Curcumin	Polyphenol (Diarylheptanoid)	NF-κB, PI3K/Akt, Bcl-2 family, Caspase-3/9, XIAP	Resisting cell death, Sustaining proliferative signaling	Demirci et al. (2025); Farghadani & Naidu (2021)
Resveratrol	Polyphenol (Stilbenoid)	MMP-2/9, TGF-beta, Wnt beta-catenin, COX-2	Activating invasion and metastasis, Sustaining proliferative signaling	Batırel et al. (2025); Ren et al. (2021); Song et al. (2019)
Quercetin	Polyphenol (Flavonoid / Flavonol)	PI3K/Akt/mTOR axis, p53, p21/WAF1, Bad, Survivin	Resisting cell death, Sustaining proliferative signaling	Russo et al. (2012); Tang et al. (2020); Reyes-Farias & Carrasco-Pozo (2019)
EGCG (Epigallocatechin gallate)	Polyphenol (Flavan-3-ol / Catechin)	ROS machinery, NF-κB, MMPs, Angiogenic drivers	Genome instability and mutation, Resisting cell death	Khan & Mukhtar (2019); Li et al. (2024); Negri et al. (2018)
Sulforaphane	Organosulfur compound (Isothiocyanate)	Nrf2/Keap1 axis, ARE signaling, HDACs, Phase II enzymes	Genome instability and mutation, Sustaining proliferative signaling	Su et al. (2018); Mangla et al. (2020)
Carvacrol	Monoterpenoid phenol	Mitochondrial lipid bilayer, ROS generation, Cytochrome c, PARP	Resisting cell death, Sustaining proliferative signaling	Besli et al. (2026); Sharifi-Rad et al. (2018); Khan et al. (2017)
Berberine	Isoquinoline alkaloid	EMT transcription factors, AMPK, Cell motility machinery	Activating invasion and metastasis, Resisting cell death	Rauf et al. (2021); Samadi et al. (2020)
Luteolin	Polyphenol (Flavonoid / Flavone)	MAPK/ERK, PI3K/Akt, Snail, Twist, E-cadherin	Activating invasion and metastasis, Resisting cell death	Qin et al. (2021); Imran et al. (2019)
Apigenin	Polyphenol (Flavonoid / Flavone)	TNFR1, Fas (CD95), DR4/DR5, Caspase-8/9/3, PARP	Resisting cell death, Activating invasion and metastasis	Sung et al. (2016); Imran et al. (2020); Pan et al. (2021)
Honokiol	Biphenolic compound (Neolignan)	STAT3, Sonic Hedgehog (Shh), Oct4, Sox2, Nanog	Resisting cell death, Microenvironment alterations	Ong et al. (2020); Avtanski et al. (2014)
Propolis	Complex resinous mixture (Polyphenols, flavonoids, and phenolic acids)	IL-6, NF-κB, VEGF, MMP-2/9, Caspases	Resisting cell death, Sustaining proliferative signaling, Microenvironment alterations, Activating invasion and metastasis	Sforcin (2016); Li et al. (2021); Zhu et al. (2024)

3. Molecular Mechanisms and Hallmark-Targeted Actions of Bioactive Agents

3.1. Dysregulation of Apoptotic Mechanisms in Cancer

Apoptosis is a genetically programmed cell death mechanism required for maintaining cellular homeostasis, tissue development, and removing oncogenic cells (Cavalcante et al., 2019). In malignant cells, the evasion of apoptosis drives unconstrained clonal expansion, survival under metabolic stress, and therapeutic resistance (Pistritto et al., 2016). As illustrated in Figure 2, this survival phenotype is governed by hyperactivated prosurvival signaling pathways, including Nuclear Factor-kappa B (NF-κB) and Phosphoinositide 3-kinase/Akt (PI3K/Akt), alongside upregulation of anti-apoptotic Bcl-2 proteins and suppression of endogenous caspase activation (Kale et al., 2018; Pfeffer & Singh, 2018).

Intrinsic apoptotic dysregulation primarily involves an altered balance between pro- and anti-apoptotic Bcl-2 family members (Kale et al., 2018). Upregulation of anti-apoptotic Bcl-2 prevents mitochondrial outer membrane permeabilization (MOMP), blocking the release of pro-apoptotic factors into the cytosol (Cavalcante et al., 2019). Concurrently, executioner caspase signaling is inhibited by inhibitor of apoptosis proteins (IAPs) and functional mutations in the TP53 tumor suppressor gene (Marei et al., 2021).

Natural bioactive compounds (specifically curcumin, carvacrol, quercetin, and apigenin) can reverse this apoptotic resistance through targeted molecular interventions (Figure 2). These agents lower mitochondrial membrane potential, stimulate cytosolic cytochrome c release, induce downstream activation of initiator caspase-9 and executioner caspase-3, and trigger DNA fragmentation, ultimately driving malignant cells toward apoptotic cell death (Pfeffer & Singh, 2018; Marei et al., 2021).

3.1.1. Curcumin: Induction of Apoptosis and Prosurvival Death Signaling

Curcumin, a natural polyphenolic diarylheptanoid derived from the rhizomes of Curcuma longa, induces apoptosis across various human cancer cell lines through the modulation of survival pathways and executioner apoptotic cascades (Tomeh et al., 2019; Farghadani & Naidu, 2021). The primary mechanism of curcumin-induced cell death involves the suppression of constitutive survival signaling networks. Specifically, curcumin inhibits Nuclear Factor-kappa B (NF-κB) and Phosphoinositide 3-kinase/Akt (PI3K/Akt) pathways, leading to the downregulation of downstream anti-apoptotic targets, including cyclin D1, c-Myc, and X-linked inhibitor of apoptosis protein (XIAP) (Demirci et al., 2025).

At the organelle level, curcumin targets mitochondrial integrity by altering the expression balance of the Bcl-2 family (Figure 2). It upregulates pro-apoptotic Bax while suppressing anti-apoptotic Bcl-2 and Bcl-xL, which leads to a loss of mitochondrial membrane potential and the subsequent cytosolic release of cytochrome c (Farghadani & Naidu, 2021). Cytosolic cytochrome c facilitates apoptosome assembly, triggering sequential cleavage and activation of initiator caspase-9 and executioner caspase-3, which culminates in nuclear DNA fragmentation (Figure 2). Additionally, curcumin promotes cell death by inducing intracellular reactive oxygen species (ROS) accumulation and activating the c-Jun N-terminal kinase (JNK) pathway, enhancing its capacity to sensitize chemoresistant tumor phenotypes to programmed cell death (Tomeh et al., 2019)

3.1.2. Carvacrol: Disruption of Mitochondrial Potential and Intrinsic Death Signaling

Carvacrol, a monoterpenoid phenol abundant in the essential oils of Lamiaceae species such as oregano and thyme, induces intrinsic apoptosis in cancer cells through mitochondrial membrane disruption (Besli et al., 2026; Khan et al., 2017). Due to its lipophilic structure, carvacrol integrates into cellular membranes and targets the inner mitochondrial membrane, causing a loss of mitochondrial membrane potential (Figure 2).

This disruption impairs the mitochondrial electron transport chain, promoting intracellular reactive oxygen species (ROS) accumulation and oxidative stress in malignant cells (Sharifi-Rad et al., 2018). Increased oxidative stress alters the Bax/Bcl-2 expression ratio, facilitating outer mitochondrial membrane permeabilization and the cytosolic release of cytochrome c and Smac/DIABLO (Figure 2). Once in the cytosol, these factors neutralize inhibitor of apoptosis

proteins (IAPs) and activate the caspase-9/caspase-3 proteolytic cascade, leading to poly(ADP-ribose) polymerase (PARP) cleavage and nuclear DNA fragmentation (Sharifi-Rad et al., 2018; Khan et al., 2017). Furthermore, carvacrol-induced mitochondrial impairment activates endoplasmic reticulum (ER) stress pathways and disrupts intracellular calcium homeostasis, contributing to the suppression of tumor cell survival (Besli et al., 2026).

3.1.3. Quercetin: Modulation of Prosurvival Kinases and Cell Cycle Arrest

Quercetin, a polyphenolic flavonoid abundant in onions, apples, and berries, inhibits tumor growth by targeting prosurvival kinase cascades and restoring cell cycle checkpoints (Tang et al., 2020; Reyes-Farias & Carrasco-Pozo, 2019). A central mechanism of quercetin-induced cytotoxicity is the suppression of the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) axis (Figure 2). By inhibiting Akt phosphorylation, quercetin blocks the inactivation of pro-apoptotic Bad and glycogen synthase kinase-3β (GSK-3β), enabling Bad translocation to the mitochondria to promote apoptotic death (Russo et al., 2012; Tang et al., 2020).

Concurrently, quercetin downregulates the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway, resulting in decreased expression of anti-apoptotic proteins such as Mcl-1 and survivin (Reyes-Farias & Carrasco-Pozo, 2019). In cells with wild-type p53 status, quercetin activates the p53 tumor suppressor pathway, inducing transcriptional upregulation of p21/WAF1. This leads to cell cycle arrest at the G2/M phase and directs damaged cells toward programmed apoptotic cell death (Figure 2). Through these combined kinase-inhibitory and cell cycle-regulatory mechanisms, quercetin sensitizes malignant cells to apoptotic elimination (Tang et al., 2020; Reyes-Farias & Carrasco-Pozo, 2019).

3.1.4. Apigenin: Activation of Death Receptors and Caspase Cascades

Apigenin, a natural trihydroxyflavone present in parsley, celery, and chamomile, induces programmed cell death in hematologic and solid malignancies by activating both extrinsic and intrinsic apoptotic pathways (Imran et al., 2020; Pan et al., 2021). The primary mechanism involves upregulating cell-surface death receptors, including tumor necrosis factor receptor 1 (TNFR1), Fas (CD95), and death receptors 4/5 (DR4/DR5). This leads to the recruitment of Fas-associated death domain (FADD) and the activation of initiator caspase-8 (Figure 2).

Concurrently, apigenin activates the intrinsic mitochondrial pathway by altering the Bax/Bcl-2 expression ratio, causing mitochondrial membrane potential loss and downstream activation of initiator caspase-9 (Sung et al., 2016). These extrinsic and intrinsic cascades converge at the activation of executioner caspases-3 and-7. Activated caspase-3 cleaves poly(ADP-ribose) polymerase (PARP), impairing cellular DNA repair mechanisms and inducing nuclear DNA fragmentation (Figure 2). Through this multi-caspase activation, apigenin suppresses tumor cell survival and promotes apoptotic death across resistant cancer cells (Imran et al., 2020; Pan et al., 2021).

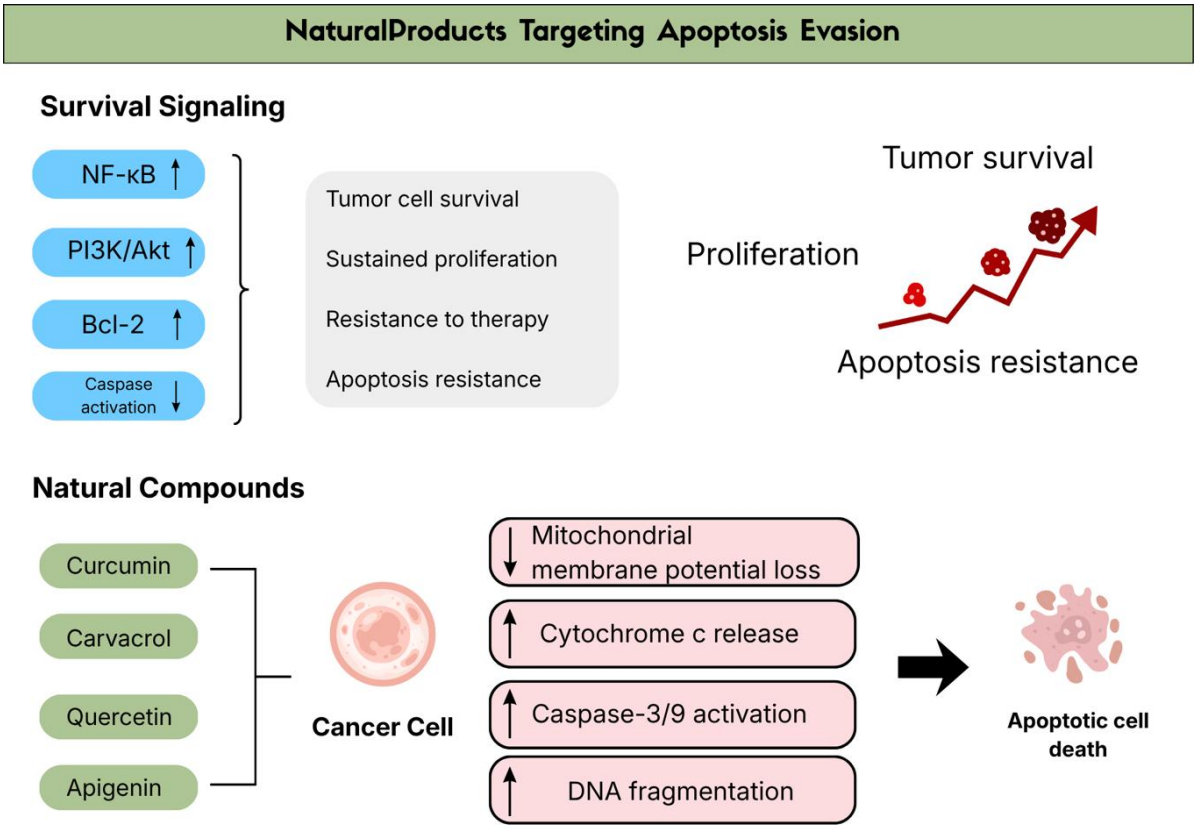

Figure 2 Schematic representation of apoptosis evasion mechanisms via survival signaling and their reversal by natural compounds.

3.2. EMT and the Metastatic Cascade in Cancer Progression

The metastatic cascade remains the primary cause of cancer-related mortality, converting localized primary tumors into systemic disease (Pastushenko & Blanpain, 2019; Welch & Hurst, 2019). This process involves a series of sequential steps: local tissue invasion, intravasation into the blood or lymphatic circulation, survival within the bloodstream, extravasation into distant tissues, and subsequent metastatic colonization (Pastushenko & Blanpain, 2019; Welch & Hurst, 2019).

A critical biological driver of tumor invasion and motility is epithelial–mesenchymal transition (EMT), a cellular reprogramming process in which polarized epithelial cells lose cell–cell adhesion junctions and acquire a migratory, invasive mesenchymal phenotype (Dongre & Weinberg, 2019). At the molecular level, EMT is characterized by the loss of epithelial markers, primarily E-cadherin (encoded by CDH1) and the concurrent upregulation of mesenchymal markers, including N-cadherin, vimentin, and extracellular matrix-degrading matrix metalloproteinases (MMP-2 and MMP-9) (Pastushenko & Blanpain, 2019; Georgescu et al., 2020).

This phenotypic transition is governed by a conserved network of core EMT-inducing transcription factors, including Snail, Slug, Twist, and ZEB1/2, alongside key oncogenic signaling pathways such as Transforming Growth Factor-beta (TGF-beta), Wnt-beta-catenin, and STAT3 (Dongre & Weinberg, 2019; Georgescu et al., 2020). Inhibiting the EMT transcriptional program and suppressing invasive signaling cascades prior to distant colonization represents an important therapeutic axis in preventing metastatic progression.

3.2.1. Resveratrol: Suppression of Extracellular Matrix Remodeling and Invasion

Resveratrol, a polyphenolic stilbenoid present in grapes, berries, and Polygonum cuspidatum, inhibits metastatic progression by modulating extracellular matrix (ECM) degradation and epithelial–mesenchymal transition (EMT) signaling (Ren et al., 2021; Batırel et al., 2025). A principal mechanism of resveratrol-mediated anti-metastatic activity is the downregulation of matrix metalloproteinases, specifically MMP-2 and MMP-9 (Figure 3). By suppressing MMP expression and enzymatic activity, resveratrol reduces extracellular matrix proteolysis, thereby limiting tumor cell invasion into adjacent tissues and vascular structures (Ren et al., 2021).

In addition to enzymatic suppression, resveratrol inhibits key signaling pathways that drive EMT, including Transforming Growth Factor-beta (TGF-beta) and Wnt-beta-catenin networks (Figure 3). Inhibition of these cascades prevents the nuclear translocation and accumulation of beta-catenin, leads to the upregulation of membrane-bound E-cadherin, and represses mesenchymal markers such as N-cadherin and vimentin (Song et al., 2019). Through the dual regulation of ECM-degrading enzymes and EMT-inducing transcription factors, resveratrol attenuates cellular migration, invasion, and distant metastatic dissemination (Batırel et al., 2025).

3.2.2. Luteolin: Transcriptional Regulation of EMT Drivers and Cadherin Expression

Luteolin, a polyphenolic flavone found in celery, parsley, and chamomile, represses the epithelial–mesenchymal transition (EMT) program in cancer cells by targeting upstream kinase networks and EMT-inducing transcription factors (Qin et al., 2021; Imran et al., 2019). Mechanistically, luteolin inhibits the Mitogen-Activated Protein Kinase (MAPK/ERK) and Phosphoinositide 3-kinase (PI3K/Akt) signaling pathways, resulting in the transcriptional downregulation of primary EMT drivers, specifically Snail and Twist (Figure 3).

By suppressing Snail and Twist expression, luteolin relieves transcriptional repression at the CDH1 promoter, restoring membrane-bound E-cadherin levels (Figure 3). This upregulation of E-cadherin stabilizes cell–cell adhesion, reduces vimentin expression, and blocks the transition of tumor cells toward a migratory, mesenchymal phenotype (Qin et al., 2021; Pan et al., 2022). Consequently, luteolin impairs tumor cell motility, matrix invasion, and metastatic dissemination across human cancer models (Imran et al., 2019; Pan et al., 2022).

3.2.3. Honokiol: Inhibition of Cancer Stemness and Self-Renewal Signaling

Honokiol, a natural biphenolic neolignan isolated from the bark of Magnolia officinalis, represses cancer stem cell (CSC) phenotypes and self-renewal pathways that drive tumor recurrence, metastasis, and therapeutic resistance (Ong et al., 2020; Avtanski et al., 2014). Cancer stem cells represent a subpopulation within tumors possessing embryonic self-renewal properties and high invasive capacity. Mechanistically, honokiol suppresses core embryonic transcription factors, including Oct4, Sox2, and Nanog, that maintain the CSC stemness state (Figure 3).

This transcriptional suppression is mediated by the inhibition of constitutively active self-renewal cascades, particularly Signal Transducer and Activator of Transcription 3 (STAT3) and Sonic Hedgehog (Shh) signaling pathways (Figure 3). By disrupting these signaling networks, honokiol reduces the side population fraction, impairs mammosphere and tumorsphere formation in vitro, and sensitizes chemoresistant cell lines to conventional therapeutics (Ong et

al., 2020). Through the targeted suppression of CSC self-renewal and stemness drivers, honokiol attenuates metastatic colonization and tumor persistence (Avtanski et al., 2014).

3.2.4. Berberine: Attenuation of Cellular Migration and Invasive Capacity

Berberine, an isoquinoline alkaloid isolated from *Berberis* species, suppresses tumor cell migration and metastatic colonization by targeting EMT-associated signaling cascades and matrix degradation (Rauf et al., 2021; Samadi et al., 2020). Berberine inhibits AMPK-mediated pathways and represses key transcription factors regulating EMT, resulting in reduced vimentin expression and restoration of E-cadherin levels (Figure 3). Furthermore, berberine downregulates MMP-2 and MMP-9 activity, impairing matrix degradation and vascular intravasation (Rauf et al., 2021). Through these actions, berberine suppresses distant metastatic organ colonization across solid tumor models (Samadi et al., 2020).

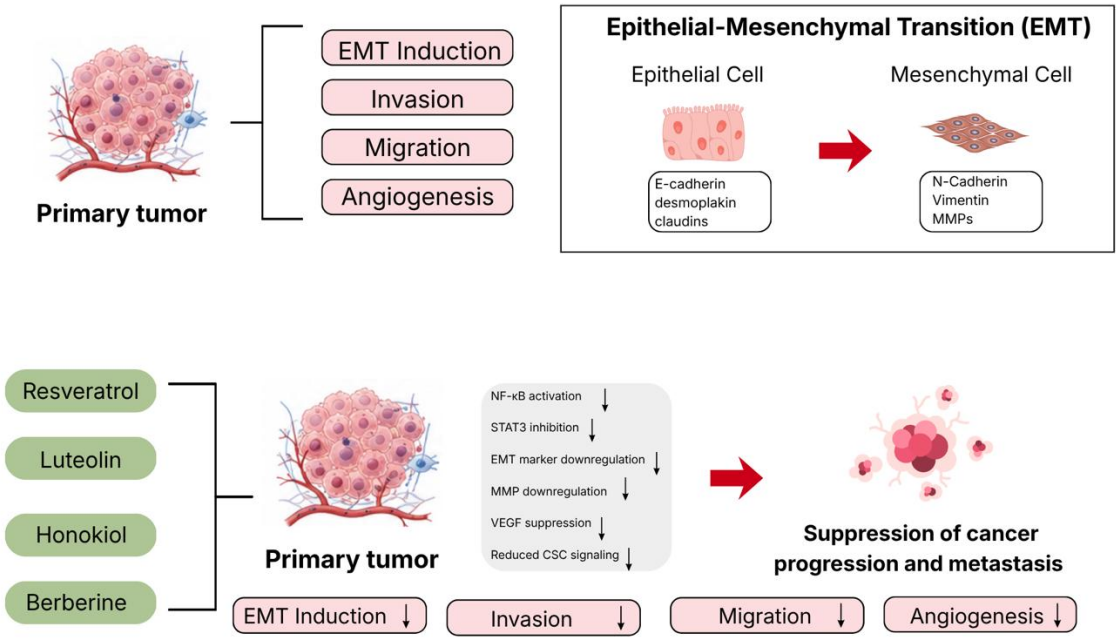

Figure 3 Schematic illustration of the epithelial-mesenchymal transition (EMT) in primary tumors and its suppression by natural plant products.

3.3. The Role of Oxidative Stress and Redox Imbalance in Malignancy

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and cellular antioxidant defense capacity, regulates both tumorigenesis and cancer progression (Hayes et al., 2020). Under physiological conditions, regulated ROS levels act as second messengers in cell proliferation and signaling. However, in malignant cells, metabolic rewiring, mitochondrial dysfunction, and chronic inflammatory cues cause a persistent elevation of intracellular ROS (Negri et al., 2018).

This sustained oxidative environment promotes genomic instability, induces DNA damage, and leads to the constitutive activation of oncogenic transcription factors, particularly Nuclear Factor-kappa B (NF-κB) and Hypoxia-Inducible Factor-1 alpha (HIF-1α) (Figure 4). Furthermore, chronic oxidative stress remodels the tumor microenvironment by activating tumor-associated fibroblasts, driving extracellular matrix remodeling, and stimulating Vascular

Endothelial Growth Factor (VEGF)-mediated angiogenesis (Figure 4). Consequently, modulating cellular redox homeostasis and targeting microenvironmental survival signaling represent key approaches to suppressing tumor adaptation and progression (Negri et al., 2018; Hayes et al., 2020).

3.3.1. Epigallocatechin Gallate (EGCG): Tumor Redox Regulation and Pro-Oxidant Effects

Epigallocatechin gallate (EGCG), the primary polyphenolic catechin isolated from green tea (Camellia sinensis), regulates cellular redox balance and ROS-dependent signaling cascades in human malignancies (Khan & Mukhtar, 2019; Negri et al., 2018). EGCG exhibits cell type-dependent dual redox activities. In non-transformed physiological tissues, EGCG functions as an antioxidant free radical scavenger that upregulates cytoprotective enzymes to limit oxidative DNA damage. Conversely, within the altered metabolic environment of cancer cells, EGCG exerts pro-oxidant actions, promoting intracellular ROS accumulation (Figure 4).

This targeted ROS elevation leads to mitochondrial outer membrane permeabilization, cytochrome c release, and induction of intrinsic apoptosis (Li et al., 2024; Negri et al., 2018). Concurrently, EGCG suppresses constitutively active Nuclear Factor-kappa B (NF-κB) and Hypoxia-Inducible Factor-1 alpha transcriptional networks (Figure 4). Through the inhibition of these factors, EGCG downregulates downstream matrix metalloproteinases (MMP-2 and MMP-9) and Vascular Endothelial Growth Factor (VEGF), suppressing tumor invasion, extracellular matrix remodeling, and angiogenic sprouting within the tumor microenvironment (Khan & Mukhtar, 2019; Negri et al., 2018).

3.3.2. Propolis: Neutralization of Inflammatory Signaling and Angiogenic Factors

Propolis, a complex resinous mixture produced by honeybees (Apis mellifera) from diverse botanical origins, modulates tumor–microenvironment interactions through its high concentration of polyphenols, flavonoids, and phenolic esters (Sforcin, 2016; Li et al., 2021). As a multi-component natural product, propolis targets parallel signaling nodes within the tumor microenvironment. At the cellular level, propolis attenuates chronic inflammatory signaling by downregulating Interleukin-6 (IL-6), Signal Transducer and Activator of Transcription 3 (STAT3), and Nuclear Factor-kappa B (NF-κB) activation, thereby suppressing inflammation-driven tumor progression (Figure 4) (Li et al., 2021; Zhu et al., 2024).

Simultaneously, propolis targets tumor vascularization by suppressing Vascular Endothelial Growth Factor (VEGF) expression and secretion (Figure 4) (Sforcin, 2016; Zhu et al., 2024). Inhibition of VEGF signaling reduces endothelial cell proliferation, migration, and capillary tube formation, limiting nutrient supply to the primary tumor mass. Through these combined anti-inflammatory and anti-angiogenic actions, propolis disrupts supportive stromal signaling and impairs tumor adaptation (Li et al., 2021; Zhu et al., 2024).

3.3.3. Sulforaphane: Activation of Nrf2-Mediated Cytoprotective Responses

Sulforaphane, an organosulfur isothiocyanate abundant in cruciferous vegetables such as broccoli and Brussels sprouts, regulates cytoprotective signaling and cellular detoxification networks in human malignancies (Mangla et al., 2020). The primary mechanism of action involves the activation of the Nuclear Factor Erythroid 2–Related Factor 2 (Nrf2) signaling pathway, a central regulator of the cellular antioxidant response (Figure 4).

Mechanistically, sulforaphane reacts with specific cysteine residues on Kelch-like ECH-associated protein 1 (Keap1), inducing a conformational change that disrupts the Keap1–Nrf2 interaction (Figure 4). This allows stabilization and nuclear translocation of Nrf2, where it heterodimerizes with Small Maf proteins and binds to Antioxidant Response Elements (ARE) in target gene promoters (Su et al., 2018; Mangla et al., 2020). This transcriptional binding induces Phase II detoxification enzymes including heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), and glutathione S-transferases (GSTs) which neutralize reactive oxygen species (ROS) and electrophiles (Figure 4).

Through Nrf2 pathway activation, sulforaphane reduces oxidative DNA damage in non-transformed cells while selectively triggering cell cycle arrest and intrinsic apoptosis in malignant phenotypes (Su et al., 2018; Mangla et al., 2020).

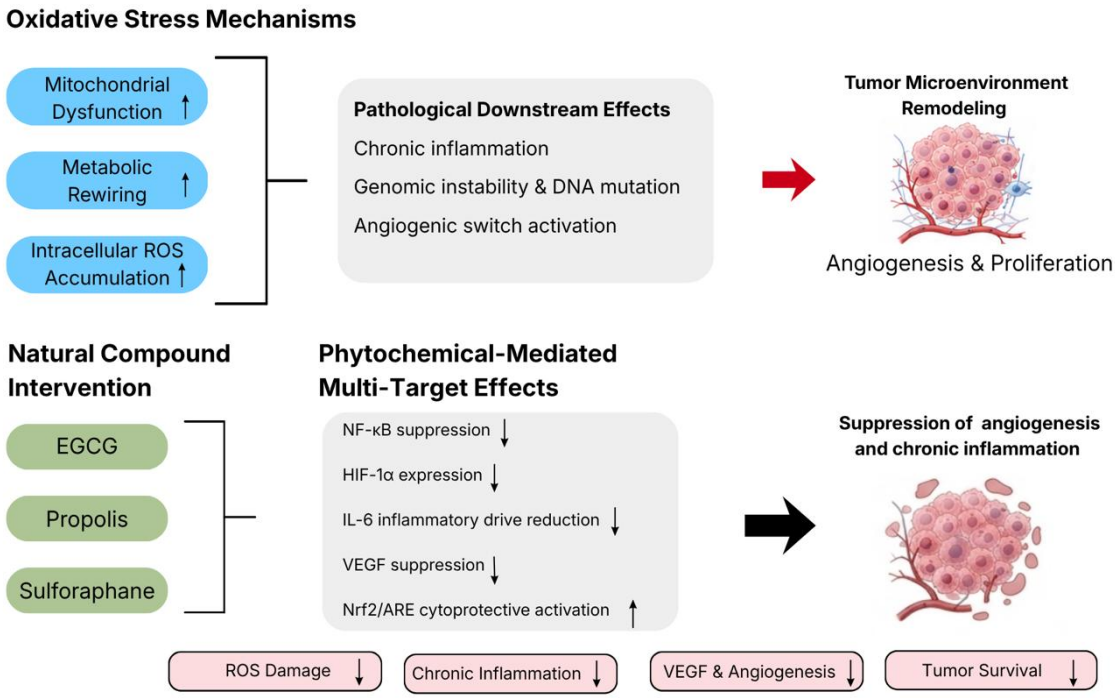

Figure 4 Schematic representation of oxidative stress and tumor microenvironment remodeling in cancer progression and their targeted modulation by EGCG, propolis, and sulforaphane

4. Challenges and Limitations of Natural Products in Cancer Therapy

Despite preclinical efficacy observed across in vitro and in vivo models, several pharmacological and biopharmaceutical limitations obstruct the clinical translation of plant-derived bioactive agents (Tomeh et al., 2019; Atanasov et al., 2021). Phytochemicals including curcumin, resveratrol, and quercetin exhibit poor systemic bioavailability, primarily restricted by low aqueous solubility, extensive first-pass hepatic metabolism (via rapid glucuronidation and sulfation), and rapid systemic clearance (Tomeh et al., 2019; Del Rio et al., 2013). Consequently, achieving therapeutic concentrations within target tumor tissues remains a major barrier using unformulated administration routes. Although numerous in vitro models demonstrate potent multi-targeted regulations, such as the inhibition of IKK-mediated NF-kB activation and blockade of nuclear translocation, translating these specific mechanisms into human systems requires overcoming these pharmacokinetic barriers.

In addition, tumor heterogeneity and potential herb–drug interactions complicate the clinical pharmacokinetics of natural compounds. Select phytochemicals modulate cytochrome P450 (CYP450) enzyme isoforms and drug efflux transporters (such as P-glycoprotein), potentially altering the clearance and systemic exposure of co-administered chemotherapeutic agents (Atanasov et al., 2021; Yeung et al., 2018).

A further challenge involves transitioning natural products from crude nutraceuticals to pharmaceutical-grade therapeutics. Although multi-component matrices such as propolis are widely consumed as functional foods, clinical implementation demands rigorous chemical standardization, batch-to-batch reproducibility, identification of primary active constituents, and validated dose–response relationships (Sforcin, 2016; Atanasov et al., 2021). Chemical variability driven by geographical origin and extraction methodologies presents regulatory hurdles regarding quality control and safety profiling, necessitating standardized nano-formulation approaches (e.g., micelles, liposomes, and polymeric nanoparticles) to protect these compounds from premature degradation and to establish safe therapeutic windows in ongoing Phase I and II clinical trials (Sforcin, 2016; Tomeh et al., 2019).

5. Future Perspectives

The translational viability of natural products in oncology depends on addressing their inherent biopharmaceutical and pharmacological limitations. Transitioning plant-derived bioactive agents from experimental settings toward clinical evaluation requires multidisciplinary approaches that integrate materials science, medicinal chemistry, and computational biology. Advanced delivery platforms, such as polymeric nanoparticles, liposomes, and nanomicelles, are being investigated to address low aqueous solubility, rapid metabolic clearance, and limited tumor tissue targetability observed in compounds like curcumin, resveratrol, and quercetin. In parallel, targeted medicinal chemistry approaches, including semi-synthetic modifications and structure–activity relationship optimization, offer opportunities to improve the pharmacodynamics, metabolic stability, and target selectivity of molecules such as carvacrol, apigenin, and honokiol. Furthermore, the integration of artificial intelligence, machine learning algorithms, and multi-omics profiling with network pharmacology facilitates the systematic analysis of multi-target natural products, aiding in candidate selection and the design of potential combination strategies with standard chemotherapeutics or immunotherapies. Combining nano-formulation approaches, structural optimization, and computational target identification may enhance the translational feasibility and therapeutic potential of natural bioactive compounds in cancer management.

6. Conclusion

The rising global burden and structural heterogeneity of cancer highlight the clinical need for multi-target therapeutic strategies capable of modulating complex biological networks. Evasion of apoptosis, metastatic dissemination, and microenvironmental redox alterations represent interconnected mechanisms that contribute to tumor resistance against conventional single-target therapies. As reviewed, plant-derived bioactive compounds and complex natural matrices provide a polypharmacological framework for targeting these survival cascades at multiple regulatory checkpoints.

Specifically, compounds such as curcumin, carvacrol, quercetin, and apigenin promote apoptotic susceptibility by modulating Bcl-2 family expression and triggering caspase-dependent proteolysis. Concurrently, agents including resveratrol, luteolin, and honokiol attenuate invasive and metastatic potential by repressing epithelial-mesenchymal transition (EMT) transcription factors and cancer stemness pathways. Furthermore, EGCG, sulforaphane, and multi-component matrices such as propolis regulate tumor microenvironment dynamics and cellular redox homeostasis by suppressing pro-inflammatory signaling and modulating cytoprotective responses. Although biopharmaceutical limitations regarding oral bioavailability, metabolic stability, and pharmaceutical standardization remain to be addressed through advanced nano-delivery systems and structural optimization, these natural agents present a valuable framework for contemporary oncological research. Driven by expanding research efforts and translational studies, these bioactive scaffolds continue to gain significance in modern oncology underscoring that comprehensive, multi-targeted paradigms in future cancer therapy will increasingly rely on the strategic integration of these versatile natural molecules.

Declarations

Ethics Statement

Research and publication ethics were strictly observed throughout the preparation of this manuscript. As this work is a literature-based review and did not involve human participants, animal experimentation, or biological tissue samples, formal ethical committee approval was not required.

Conflict of Interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support, grants, or institutional funding for the research, authorship, and/or publication of this article.

Acknowledgements

I would like to thank my sister, Fatma ÖZ, for her support, dedication, and efforts throughout the preparation of this manuscript.

Use of Artificial Intelligence

The author used AI-assisted tools for language editing, translation and reference formatting checks. All scientific content, analytic decisions, interpretations, and final wording were determined and verified by the author, who takes full responsibility for every claim in the manuscript.

References

Aggarwal, B. B., & Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochemical Pharmacology,* 71(10), 1397–1421. https://doi.org/10.1016/j.bcp.2006.02.009

Anand, P., Kunnumakara, A. B., Sundaram, C., Harikumar, K. B., Tharakan, S. T., Lai, O. S., Sung, B., & Aggarwal, B. B. (2008). Cancer is a preventable disease that requires major lifestyle changes. *Pharmaceutical Research*, 25(9), 2097–2116. https://doi.org/10.1007/s11095-008-9661-9

Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., the International Natural Product Sciences Taskforce, & Supuran, C. T. (2021). Natural products in drug discovery: Advances and opportunities. *Nature Reviews Drug Discovery*, 20(3), 200–216. https://doi.org/10.1038/s41573-020-00114-z

Avtanski, D. B., Nagalingam, A., Bonner, M. Y., Arbiser, J. L., Saxena, N. K., & Sharma, D. (2014). Honokiol inhibits epithelial–mesenchymal transition in breast cancer cells by targeting signal transducer and activator of transcription 3/Zeb1/E-cadherin axis. *Molecular Oncology*, 8(3), 565–580. https://doi.org/10.1016/j.molonc.2014.01.004

Baghban, R., Roshangar, L., Jahanban-Esfahlan, R., Seidi, K., Ebrahimi-Kalan, A., Jaymand, M., Kolahian, S., Javaheri, T., & Zare, P. (2020). Tumor microenvironment complexity and therapeutic implications at a glance. *Cell Communication and Signaling,* 18, 59. https://doi.org/10.1186/s12964-020-0530-4

Batırel, S., Çetinkaya, B., & Yılmaz, A. M. (2025). The inhibitory effects of resveratrol on tumor growth and metastasis in esophageal adenocarcinoma. *Clinical and Experimental Health Sciences*, 15(3), 629–635. https://doi.org/10.33808/clinexphealthsci.1646378

Besli, N., Ercin, N., Tokocin, M., Boluk, S. E., Kalkan Cakmak, R., Ozdogan, K., Aktokmakyan, T. V., Toprak, M., Ercan, G., Beker, M., Celik, U., Capkinoglu, E., & Tutar, Y. (2026). Carvacrol selectively induces mitochondria-related apoptotic signaling in primary breast cancer-associated fibroblasts. *Pharmaceuticals*, 19(1), 142. https://doi.org/10.3390/ph19010142

Cavalcante, G. C., Schaan, A. P., Cabral, G. F., Santana-da-Silva, M. N., Pinto, P., Vidal, A. F., & Ribeiro-dos-Santos, Â. (2019). A cell's fate: An overview of the molecular biology and genetics of apoptosis. *International Journal of Molecular Sciences,* 20(17), 4133. https://doi.org/10.3390/ijms20174133

Del Rio, D., Rodriguez-Mateos, A., Spencer, J. P. E., Tognolini, M., Borges, G., & Crozier, A. (2013). Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxidants & Redox Signaling*, 18(14), 1818–1892. https://doi.org/10.1089/ars.2012.4581

Demirci, Z., Islek, Z., Ilhan Siginc, H., Sahin, F., Ucisik, M. H., & Bolat, Z. B. (2025). Curcumin-loaded emulsome nanoparticles induces apoptosis through p53 signaling pathway in pancreatic cancer cell line PANC-1. *Toxicology in Vitro*, 102, 105958. https://doi.org/10.1016/j.tiv.2024.105958

Dongre, A., & Weinberg, R. A. (2019). New insights into the mechanisms of epithelial–mesenchymal transition and implications for cancer. *Nature Reviews Molecular Cell Biology*, 20(2), 69–84. https://doi.org/10.1038/s41580-018-0080-4

Farghadani, R., & Naidu, R. (2021). Curcumin: Modulator of key molecular signaling pathways in hormone-independent breast cancer. *Cancers*, 13(14), 3427. https://doi.org/10.3390/cancers13143427

Fuchs, Y., & Steller, H. (2011). Programmed cell death in animal development and disease. *Cell*, 147(4), 742–758. https://doi.org/10.1016/j.cell.2011.10.033

Georgescu, S. R., Tampa, M., Mitran, C. I., Mitran, M. I., Caruntu, C., Caruntu, A., Lupu, M., Matei, C., Constantin, C., & Neagu, M. (2020). Tumour microenvironment in skin carcinogenesis. In A. Birbrair (Ed.), *Tumor microenvironments in organs: From the brain to the skin—Part A* (pp. 123–142). Springer. https://doi.org/10.1007/978-3-030-36214-0_10

Hanahan, D. (2022). Hallmarks of cancer: New dimensions. *Cancer Discovery*, 12(1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell*, 144(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

Hayes, J. D., Dinkova-Kostova, A. T., & Tew, K. D. (2020). Oxidative stress in cancer. *Cancer Cell*, 38(2), 167–197. https://doi.org/10.1016/j.ccell.2020.06.001

Hinshaw, D. C., & Shevde, L. A. (2019). The tumor microenvironment innately modulates cancer progression. *Cancer Research*, 79(18), 4557–4566. https://doi.org/10.1158/0008-5472.CAN-18-3962

Imran, M., Aslam Gondal, T., Atif, M., Shahbaz, M., Batool Qaisarani, T., Hanif Mughal, M., Salehi, B., Martorell, M., & Sharifi-Rad, J. (2020). Apigenin as an anticancer agent. *Phytotherapy Research*, 34(8), 1812–1828. https://doi.org/10.1002/ptr.6647

Imran, M., Rauf, A., Abu-Izneid, T., Nadeem, M., Shariati, M. A., Khan, I. A., Imran, A., Orhan, I. E., Rizwan, M., Atif, M., Gondal, T. A., & Mubarak, M. S. (2019). Luteolin, a flavonoid, as an anticancer agent: A review. *Biomedicine & Pharmacotherapy*, 112, 108612. https://doi.org/10.1016/j.biopha.2019.108612

Kale, J., Osterlund, E. J., & Andrews, D. W. (2018). BCL-2 family proteins: Changing partners in the dance towards death. *Cell Death & Differentiation*, 25, 65–80. https://doi.org/10.1038/cdd.2017.186

Khan, F., Khan, I., Farooqui, A., & Ansari, I. A. (2017). Carvacrol induces reactive oxygen species (ROS)-mediated apoptosis along with cell cycle arrest at G0/G1 in human prostate cancer cells. *Nutrition and Cancer*, 69(7), 1075–1087. https://doi.org/10.1080/01635581.2017.1359321

Khan, N., & Mukhtar, H. (2019). Tea polyphenols in promotion of human health. *Nutrients*, 11(1), 39. https://doi.org/10.3390/nu11010039

Li, J., Liu, H., Liu, X., Hao, S., Zhang, Z., & Xuan, H. (2021). Chinese poplar propolis inhibits MDA-MB-231 cell proliferation in an inflammatory microenvironment by targeting enzymes of the glycolytic pathway. *Journal of Immunology Research,* 2021, 6641341. https://doi.org/10.1155/2021/6641341

Li, X., Hou, Y., Han, G., Yang, Y., Wang, S., Lv, X., & Gao, M. (2024). S100A4/NF-κB axis mediates the anticancer effect of epigallocatechin-3-gallate in platinum-resistant ovarian cancer. *iScience*, 27(2), 108885. https://doi.org/10.1016/j.isci.2024.108885

Mangla, B., Neupane, Y. R., Singh, A., Kumar, P., Shafi, S., & Kohli, K. (2020). Lipid-nanopotentiated combinatorial delivery of tamoxifen and sulforaphane: Ex vivo, in vivo and toxicity studies. *Nanomedicine, 15*(26), 2563–2583. https://doi.org/10.2217/nnm-2020-0277

Marei, H. E., Althani, A., Afifi, N., Hasan, A., Caceci, T., Pozzoli, G., Morrione, A., Giordano, A., & Cenciarelli, C. (2021). p53 signaling in cancer progression and therapy. *Cancer Cell International*, 21, 703. https://doi.org/10.1186/s12935-021-02396-8

Mittal, V. (2018). Epithelial mesenchymal transition in tumor metastasis. Annual Review of Pathology: *Mechanisms of Disease*, 13, 395–412. https://doi.org/10.1146/annurev-pathol-020117-043854

Negri, A., Naponelli, V., Rizzi, F., & Bettuzzi, S. (2018). Molecular targets of epigallocatechin-gallate (EGCG): A special focus on signal transduction and cancer. *Nutrients*, 10(12), 1936. https://doi.org/10.3390/nu10121936

Newman, D. J., & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of Natural Products,* 83(3), 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285

Ong, C. P., Lee, W. L., Tang, Y. Q., & Yap, W. H. (2020). Honokiol: A review of its anticancer potential and mechanisms. *Cancers*, 12(1), 48. https://doi.org/10.3390/cancers12010048

Pan, F.-F., Zheng, Y.-B., Shi, C.-J., Zhang, F.-W., Zhang, J.-F., & Fu, W.-M. (2021). H19-Wnt/β-catenin regulatory axis mediates the suppressive effects of apigenin on tumor growth in hepatocellular carcinoma. *European Journal of Pharmacology*, 893, 173810. https://doi.org/10.1016/j.ejphar.2020.173810

Pan, J., Cai, X., Zheng, X., Zhu, X., Feng, J., & Wang, X. (2022). Luteolin inhibits viability, migration, angiogenesis and invasion of non-small cell lung cancer vascular endothelial cells via miR-133a-3p/purine rich element binding protein B-mediated MAPK and PI3K/Akt signaling pathways. *Tissue and Cell*, 75, 101740. https://doi.org/10.1016/j.tice.2022.101740

Pastushenko, I., & Blanpain, C. (2019). EMT transition states during tumor progression and metastasis. *Trends in Cell Biology,* 29(3), 212–226. https://doi.org/10.1016/j.tcb.2018.12.001

Pfeffer, C. M., & Singh, A. T. K. (2018). Apoptosis: A target for anticancer therapy. *International Journal of Molecular Sciences,* 19(2), 448. https://doi.org/10.3390/ijms19020448

Pistritto, G., Trisciuoglio, D., Ceci, C., Garufi, A., & D'Orazi, G. (2016). Apoptosis as anticancer mechanism: Function and dysfunction of its modulators and targeted therapeutic strategies. *Aging*, 8(4), 603–619. https://doi.org/10.18632/aging.100934

Qin, T., Zhao, J., Liu, X., Li, L., Zhang, X., Shi, X., Ke, Y., Liu, W., Huo, J., Dong, Y., Shen, Y., Li, Y., He, M., Han, S., Li, L., Pan, C., & Wang, C. (2021). Luteolin combined with low-dose paclitaxel synergistically inhibits epithelial–mesenchymal transition and induces cell apoptosis on esophageal carcinoma in vitro and in vivo. *Phytotherapy Research,* 35(11), 6228–6240. https://doi.org/10.1002/ptr.7267

Rauf, A., Abu-Izneid, T., Khalil, A. A., Imran, M., Shah, Z. A., Bin Emran, T., Mitra, S., Khan, Z., Alhumaydhi, F. A., Aljohani, A. S. M., Khan, I., Rahman, M. M., Jeandet, P., & Gondal, T. A. (2021). Berberine as a potential anticancer agent: A comprehensive review. *Molecules*, 26(23), 7368. https://doi.org/10.3390/molecules26237368

Ren, B., Kwah, M. X. Y., Liu, C., Ma, Z., Shanmugam, M. K., Ding, L., Xiang, X., Ho, P. C. L., Wang, L., Ong, P. S., & Goh, B. C. (2021). Resveratrol for cancer therapy: Challenges and future perspectives. *Cancer Letters*, 515, 63–72. https://doi.org/10.1016/j.canlet.2021.05.001

Reyes-Farias, M., & Carrasco-Pozo, C. (2019). The anti-cancer effect of quercetin: Molecular implications in cancer metabolism. *International Journal of Molecular Sciences*, 20(13), 3177. https://doi.org/10.3390/ijms20133177

Russo, M., Spagnuolo, C., Tedesco, I., Bilotto, S., & Russo, G. L. (2012). The flavonoid quercetin in disease prevention and therapy: Facts and fancies. *Biochemical Pharmacology,* 83(1), 6–15. https://doi.org/10.1016/j.bcp.2011.08.010

Samadi, P., Sarvarian, P., Gholipour, E., Shams Asenjan, K., Aghebati-Maleki, L., Motavalli, R., Hojjat-Farsangi, M., & Yousefi, M. (2020). Berberine: A novel therapeutic strategy for cancer. *IUBMB Life*, 72(10), 2065–2079. https://doi.org/10.1002/iub.2350

Šemeláková, M., Hudáková, T., Solár, P., Šalagovič, J., & Židzik, J. (2026). Plant-derived bioactive compounds and their therapeutic potential in cancer. *International Journal of Molecular Sciences, 27*(10), 4275. https://doi.org/10.3390/ijms27104275

Sforcin, J. M. (2016). Biological properties and therapeutic applications of propolis. *Phytotherapy Research,* 30(6), 894–905. https://doi.org/10.1002/ptr.5605

Sharifi-Rad, M., Varoni, E. M., Iriti, M., Martorell, M., Setzer, W. N., del Mar Contreras, M., Salehi, B., Soltani-Nejad, A., Rajabi, S., Tajbakhsh, M., & Sharifi-Rad, J. (2018). Carvacrol and human health: A comprehensive review. *Phytotherapy Research*, 32(9), 1675–1687. https://doi.org/10.1002/ptr.6103

Song, Y., Chen, Y., Li, Y., Lyu, X., Cui, J., Cheng, Y., Zheng, T., Zhao, L., & Zhao, G. (2019). Resveratrol suppresses epithelial-mesenchymal transition in GBM by regulating Smad-dependent signaling. *BioMed Research International, 2019*, 1321973. https://doi.org/10.1155/2019/1321973

Su, X., Jiang, X., Meng, L., Dong, X., Shen, Y., & Xin, Y. (2018). Anticancer activity of sulforaphane: The epigenetic mechanisms and the Nrf2 signaling pathway. *Oxidative Medicine and Cellular Longevity*, 2018, 5438179. https://doi.org/10.1155/2018/5438179

Sung, B., Chung, H. Y., & Kim, N. D. (2016). Role of apigenin in cancer prevention via the induction of apoptosis and autophagy. *Journal of Cancer Prevention,* 21(4), 216–226. https://doi.org/10.15430/JCP.2016.21.4.216

Sung, H., Filho, A. M., Laversanne, M., Ferlay, J., Siegel, R. L., Soerjomataram, I., Jemal, A., & Bray, F. (2026). Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries. *CA: A Cancer Journal for Clinicians,* 76(4), e70090. https://doi.org/10.3322/caac.70090

Tang, S.-M., Deng, X.-T., Zhou, J., Li, Q.-P., Ge, X.-X., & Miao, L. (2020). Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects.

Biomedicine & Pharmacotherapy, 121, 109604. https://doi.org/10.1016/j.biopha.2019.109604

Tomeh, M. A., Hadianamrei, R., & Zhao, X. (2019). A review of curcumin and its derivatives as anticancer agents. *International Journal of Molecular Sciences*, 20(5), 1033. https://doi.org/10.3390/ijms20051033

Vasan, N., Baselga, J., & Hyman, D. M. (2019). A view on drug resistance in cancer. *Nature*, 575(7782), 299–309. https://doi.org/10.1038/s41586-019-1730-1

Welch, D. R., & Hurst, D. R. (2019). Defining the hallmarks of metastasis. *Cancer Research,* 79(12), 3011–3027. https://doi.org/10.1158/0008-5472.CAN-19-0458

Yeung, K. S., Gubili, J., & Mao, J. J. (2018). Herb-drug interactions in cancer care. *Oncology*, 32(10), 516–520.

Zhu, H., Li, C., Jia, L., Qiao, J., El-Seedi, H. R., Zhang, Y., & Zhang, H. (2024). Supercritical CO_2 extracts of propolis inhibits tumor proliferation and enhances the immunomodulatory activity via activating the TLR4-MAPK/NF-κB signaling pathway. *Food Research International,* 196, 115137. https://doi.org/10.1016/j.foodres.2024.115137