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Review Article

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Potential of Plant Bioactive Compounds for the Treatment of Cancer

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ABSTRACT

Cancer remains one of the leading causes of mortality worldwide. Despite recent advances, current chemotherapeutic options often have undesirable side effects, and the development of resistance limits their long-term effectiveness. The botanical kingdom contains a vast repository of phytochemicals with varying biological activities. This review examines the anticancer potential of various classes of plant bioactive compounds. Specific alkaloids like berberine demonstrate remarkable apoptosis induction through mitochondrial stress and caspase activation in numerous cancer cell lines. Curcumin modulates multiple oncogenic pathways, including PI3K/Akt, Wnt/β-catenin, and MAPK signaling. Resveratrol elicits favorable anti-tumor responses through intrinsic apoptosis, autophagy stimulation, and antiangiogenic effects. Promising preclinical studies have elucidated the underlying molecular mechanisms by which bioactive components such as quercetin, genistein, and epigallocatechin gallate exert chemopreventive effects. While intensive research is still required, progress in standardizing extracts, isolating marker compounds, and clinical testing validates nature's treasure as a source for novel anticancer options. Future studies should focus on overcoming translational barriers to move these promising compounds from bench to bedside.

INTRODUCTION

Epidemiology of Cancer

Cancer is a pathological condition caused by abnormal cell division and is a major contributor to global fatalities. Based on the data, it can be inferred that the emerging figures indicate a significant loss of lives, with an estimated 10 million fatalities occurring in the year 2020. Furthermore, globally, it is seen that a substantial number of individuals, ranging from 19 to 20 million, receive a cancer diagnosis every year. [1]. The specific factor responsible for cancer development varies among individuals and is contingent upon the type of cancer and geographical location. It is crucial to establish appropriate treatment strategies for each case. The rise in cancer incidence rates is believed to be linked to changes in the environment, including climate, resulting from industrialization, as well as lifestyle choices related to living and dietary habits[2].

Molecular Basis of Cancer Development

While there are many potential causes of cancer, the most widely held theory holds that oncogene and tumor suppressor gene mutations occur sequentially, making the development of cancer an extremely complicated illness

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[3]. Oncogenes are mutant genes with cancer-causing potential. Proto-oncogene is a term used for oncogenes that have a role in controlling normal cell division before they become mutated. When a proto-oncogene undergoes a mutation, it becomes an oncogene and drives unchecked cell division and proliferation, setting the stage for the development of cancer. Tumor suppressive genes, which are also present in normal cells but work to prevent cancer from developing, are crucial to the cell's normal growth and differentiation. There is a large group of genes called tumor suppressor genes that all share a single property: they all prevent neoplasia from developing in the body. For a cancer cell to multiply and survive, both copies of a tumor-suppressor gene must be dormant. When tumor-suppressor genes are missing or turned ineffective by mutations, cancer develops. Genes like p53 and retinoblastoma 1 (RB1) are examples of tumor-suppressor genes [4]. DNA damage is a regular occurrence caused by both internal (endogenous) and external (exogenous) factors. Different DNA repair mechanisms identify and eliminate the damage. When DNA damage is left unaddressed, checkpoints in the cell cycle can impede its progression or trigger cellular senescence or apoptosis. Mistaken restoration or replicative bypass of lesions can lead to genetic alterations and abnormalities in chromosomes. When alterations occur in tumor suppressor genes or oncogenes, cells can transform into cancerous cells [5].

Limitations of Conventional Cancer Therapies

Conventional cancer treatment approaches include surgical intervention, radiation therapy, and chemotherapy. The utilization of chemotherapy has been linked to the recurrence of cancer, the formation of resistance, the imposition of significant pressure on patients, and the development of numerous serious side effects [6, 7]. During Radiotherapy, the radiation exposure has been observed to lead to elevated levels of discomfort, anxiety, and depression among patients who are undergoing this treatment. While it is seen that the occurrence of these issues tends to diminish following the completion of RT, a notable proportion of patients continue to exhibit psychological consequences after their treatment [8]. Radiation exposure elicits a psychological impact that triggers a cascade of reactions to repair the tissues that are damaged. The reaction commences with the activation of when the damage occurs in DNA, as a result, it activates the mitotic cell death, cellular senescence, and apoptosis. Subsequently, a continuous cytokine cascade ensues, leading to the induction of inflammation and collagen deposition. Late adverse effects, specifically, tend to be persistent and frequently exhibit a progressive pattern, resulting in a decline after their treatment [9].

Despite extensive research on plant-derived bioactive compounds, their clinical translation into standardized anticancer therapies remains limited. Most available evidence is derived from in vitro and preclinical studies, with comparatively fewer well-designed clinical trials validating safety, dosage optimization, and long-term efficacy. Additionally, challenges such as poor bioavailability, pharmacokinetic variability, and lack of targeted delivery systems create a significant gap between experimental findings and clinical application. Therefore, a comprehensive evaluation of molecular mechanisms alongside translational limitations is essential to bridge the gap between bench research and bedside implementation.

Role of Phytochemicals in Cancer Treatment

To combat the aforementioned adverse effects associated with alternative cancer treatment modalities, it is plausible that plant extracts possess the capability to mitigate these risks. The botanical realm encompasses a wide array of plants that exhibit significant chemical diversity and possess versatile chemical properties, with the majority exhibiting favorable toxicity profiles. Hence, herb formulations, crude plant extracts, and dietary sources are widely employed as primary reservoirs of phytochemicals for cancer therapeutics. Undoubtedly, they have demonstrated unparalleled benefits in mitigating the adverse effects of anticancer drugs. Over 3000 plant species have been investigated for anticancer properties, and numerous phytochemicals have shown potential either as standalone agents or in synergy with standard therapies. Notably, compounds such as berberine and camptothecin have demonstrated strong anticancer activities. Additionally, broader classes such as polyphenols [e.g., resveratrol, quercetin] and terpenoids e.g., taxol, artemisinin have also received attention due to their antioxidant, anti-inflammatory, and immune-modulating properties [10]. Their integration into cancer therapies underscores their biocompatibility, target-specific activity, and potential to enhance therapeutic outcomes.

Plant-Derived Compounds in Cancer

The plants that are a good source of natural compounds and compounds which have the potential to fight against cancerous cells and which have more phytonutrients are medicinal plants, many of which have been traditionally applied for cancer treatment and are widely identified for their broad-spectrum treatment potential against a range of diseases. A substantial proportion of chemopreventive agents are derived from botanical sources, largely due to their favorable safety profiles and minimal adverse effects. Over the past several decades, plant-derived bioactive molecules such as flavonoids, polyphenols, alkaloids, and sesquiterpenes have been extensively studied and applied in anticancer strategies [11]. The following are some of the major plant extracts used in cancer treatment.

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Alkaloids

Alkaloids are a diverse class of naturally occurring compounds characterized by a cyclic structure that contains at least one nitrogen atom, which distinguishes them from other classes of phytochemicals. Alkaloids are mostly manufactured from amino acids and their precursors, including ornithine, arginine, lysine are most common, then they also have phenylalanine, tryptophan, and tryptophan. Widely distributed throughout the plant kingdom, alkaloids are especially abundant in families such as Leguminosae, Menispermaceae, Ranunculaceae, Loganiaceae, and Papaveraceae. They are of considerable significance for the discovery of drugs due to their potent biological activities.Numerous alkaloid compounds are obtained from mostly the herbs and medicinal plants have been investigated and shown to exhibit strong antiproliferative and anticancer properties in both in vitro and in vivo studies.Currently, several plant-derived alkaloids have received FDA approval and are commercially available as anticancer agents [12, 13].

Berberine

Berberine constitutes yet another isoquinoline alkaloid of natural provenance, sourced from numerous botanical families, including Papaveraceae, Berberidaceae, and Ranunculaceae. This bioactive compound can be extracted from diverse plant species, prominently including Goldenseal, Barberry, Coptis, tree turmeric, and Oregon grape [14]. Berberine [BBR] has exhibited many effects on cancer cells, encompassing the modification of the cell cycle, induction of apoptosis, stimulation of autophagy, and influence on the tumor microenvironment. In light of the current emphasis on tumor immunotherapy and the considerable expense associated with immune-suppressing medications, BBR, a cost-effective Chinese traditional medicine exhibiting notable immunomodulatory characteristics, exhibits potential as a viable contender for extensive clinical application in the field of immunotherapy [15]. The promotion of apoptosis through the activation of caspases has been demonstrated by BBR. BBR has the potential to cause cell death in leukemia and hepatoma cells by upregulating the expression of caspase-8 and caspase-9 while simultaneously downregulating the expression of bcl-2 through the activation of caspase-3 [16](Figure 1)(Table 1).

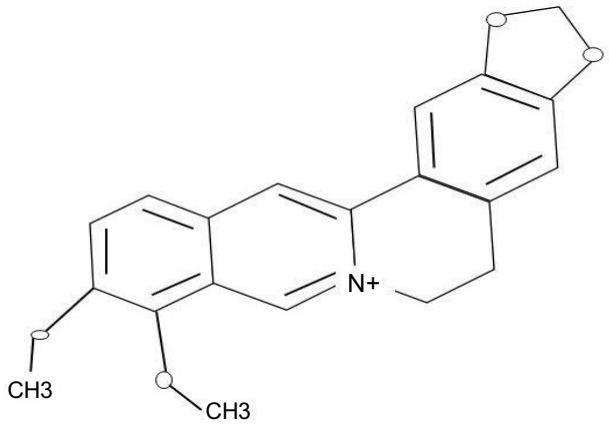

Figure 1: Structural Formula of Berberine

The main role play to control and regulate the apoptosis by controlling membrane permeability and initiating downstream signaling cascades is done by mitochondria. Through many studies, it is proven that external stimuli increase mitochondrial membrane permeability, resulting in the activation of caspase-dependent pathways that lead to programmed cell death. Notably, berberine (BBR) has been reported to enhance apoptosis by promoting the acetylation of FOXO1/3a, thereby reinforcing its role as a key regulator of mitochondria-dependent apoptosis [17]. Additionally, BBR uses a variety of signaling pathways to cause autophagy in tumor cells. The AMPK/mTOR/ULK1 axis, which affects JNK phosphorylation, is the precise target in glioblastoma. This modification stimulates Beclin-1 release in hepatocellular carcinoma and aids in the dissociation of the Bcl-2/Beclin-1 complex in breast cancer cells. The ULK1/mTOR signaling pathway is also activated by BBR by improving the interaction, which mediates this mechanism. Given that autophagy plays a part in drug resistance, cancer development, and apoptosis evasion, BBR's capacity to activate autophagic processes points to its substantial therapeutic promise in oncology [18]. Tissue and organ degradation brought on by unchecked cell proliferation and the invasive expansion of tumor cells accounts for a major portion of cancer-associated mortality. The breast cancer proliferation and spreading are controlled and prevented by targeting the ephrin-B2, and simultaneously downregulate the production of metalloproteinases MMP-2 and MMP-9 [19]. The MMPs are downregulated as a result of the suppression of the COX-2/PGE2-JAK2/STAT3 signaling cascade [20]. Additionally, by reducing the expression of Snail-1, a transcription factor crucial to the epithelial-mesenchymal transition, BBR prevents metastasis. Together, our results highlight how BBR modulates cancer-related signaling pathways and regulatory proteins to have anti-cancer effects [18, 20, 21]. Apart from its anti-metastatic and cytotoxic qualities, BBR has demonstrated potential in tumor immunotherapy. TNF-α and IL-1, BBR functions as a dopamine receptor

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antagonist and improves the immunological profile in the tumor microenvironment. Additionally, it suppresses CD4+ T cell proliferation and, by blocking STAT 1 phosphorylation, lowers the production of indoleamine 2,3-dioxygenase (IDO1) triggered by interferon-gamma (IFN-γ). The therapeutic promise of BBR in cancer immunotherapy techniques is supported by these immunomodulatory actions [18] (Table 1).

Table 1: Key Alkaloids, Anti-Tumor Activities, and Underlying Mechanisms

Compounds	Class	Anticancer Mechanisms	Plant Sources	References
Berberine	Alkaloid	Apoptosis via mitochondrial stress, caspase activation	Goldenseal, barberry, Japanese goldthread	[18, 21, 23]
Camptothecin	Alkaloid	Topo I inhibition, DNA damage, and autophagy	Camptotheca acuminata tree	[24, 25, 26, 27]

It induces apoptosis by activation of p53, Bax, and caspases, and inhibits anti-apoptotic proteins like Bcl-2. BBR regulates cell cycle progression by affecting cyclins and CDKs, leading to cell cycle arrest. It promotes autophagy through AMPK/mTOR and Beclin 1 pathways and suppresses invasion and migration by downregulating MMP-2/9 and Snail-1 (Figure 2).

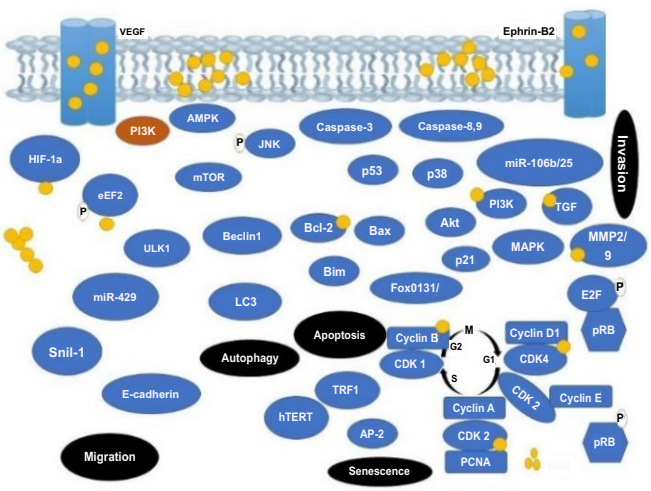

Figure 2: Berberine [BBR] exerts anticancer effects by modulating multiple signaling pathways.

Camptothecin [CPT]

Camptothecin [CPT] stands as a formidable contender among anticancer compounds. CPT belongs to the class of compounds that have a distinctive planar pentacyclic ring structure [27]. Camptothecin (CPT) is synthesized in numerous angiosperm plant species across various taxonomic groups [26]. Camptothecin (CPT) has demonstrated significant anticancer effects by selectively inhibiting intracellular topoisomerase I. The potential of CPT in therapeutic applications is restricted by various issues, such as the instability of its lactone ring and its insolubility in water. These limitations result in reduced oral solubility of the medicine and hinder its bioavailability in blood plasma. Different analogues of CPT are employed in the therapeutic management of lung cancer, ovarian, and colon [28]. The clinical trials of CPT in 1970 resulted, investigations into its mechanism of action have remained a subject of ongoing research. The initial discoveries about the mechanism of action of the CPT were made by Drs. Marshall and Susan Horwitz, who work as a collaborative team at Albert Einstein College of Medicine, with other researchers. The findings of their research demonstrated that CPT can impede the synthesis of DNA and RNA, particularly ribosomal RNA, while also causing DNA damage. The researchers made observations indicating that CPT exhibits its most efficacy during the S-phase of the cell cycle. Additionally, they hypothesized that the involvement of the DNA replication fork is likely in the mechanism behind cell death produced by CPT. Subsequent investigations have revealed that CPT effectively halts the progression of the cell cycle at both the S and G2 phases, which are crucial for the manifestation of CPT's cytotoxic effects [29]. Research findings have demonstrated that the analogue of CPT FL118 exhibits a specific inhibitory effect on the production of certain antiapoptotic proteins, namely survivin, Mcl-1, XIAP, and cIAP2. It was determined that FL118's inhibition of these proteins is not influenced by the state of the tumor suppressor p53, regardless of whether it is wild type, mutant, or null. This characteristic of FL118 holds significant importance, as the majority, if not all, of DNA-damaging medicines exhibit ineffectiveness in cases where p53 is mutated or absent [29, 30]. A camptothecin (CPT) analog in one of the analyses shows the potential to induce apoptosis in acute myeloid leukemia cell lines such as NB4 and U937. This apoptotic response is marked by the activation of caspase-3 and a disruption in mitochondrial membrane potential. The underlying mechanism involves the rapid activation of protein kinase C delta (PKCδ) following exposure to NSC606985. Notably, the pro-apoptotic effect of this compound can be completely abrogated by co-treatment with rottlerin, a selective PKCδ inhibitor [31]. In the NB4 cell line, a commonly used in vitro model of acute promyelocytic leukemia (APL), NSC706985 exhibited a pronounced inhibitory effect on cell proliferation. This restraint manifested with dependency on both time and concentration. Likewise, there was a marked reduction in cellular viability. It is noteworthy that this suppressive impact was evident even at exceedingly low concentrations [24]. CT-2106 is another very important chemical entity, the conjugation of camptothecin (CPT) with poly-L-glutamate. This conjugation is proposed to enhance the stability of the active lactone form of CPT and augment its aqueous solubility. Additionally, there was a

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hypothesis suggesting that the inclusion of the poly-L-glutamate component could potentially improve the transportation of CPT to tumor sites by capitalizing on the improved permeability and retention phenomenon. Nevertheless, the results of a clinical phase I trial indicated that the pharmacokinetic characteristics of the conjugated CPT did not exhibit substantial benefits in comparison to the unconjugated CPT [32]. Chimmitecan, a lipophilic derivative of camptothecin (CPT), has demonstrated significant cytotoxicity by effectively reducing the catalytic activity of Topoisomerase 1 (top1) and forming stable covalent complexes between Top1 and DNA. These effects are equivalent to the impact observed with top1 inhibition [33] (Table 1).

Indole Alkaloids

The heterocyclic aromatic chemical indole (C_8H_7N) is characterized by its weakly basic characteristics. Its fused structure, which consists of a pyrrole ring and a benzene ring, allows 10 pi electrons to delocalize over the entire molecule. Numerous well-known plant groups, such as the Apocynaceae, Rubiaceae, Nyssaceae, and Loganiaceae, have been found to contain indole-based alkaloids [35]. According to Muranaka and Saito [2010], these indole alkaloids are an important class of naturally occurring substances with strong pharmacological significance. Clinically, a range of indole alkaloids and their synthetic analogs are used to treat a number of cancers, including breast cancer, small-cell lung cancer, malignant lymphoma, and acute leukemia [35-37]. When it comes to signal transduction, mitogen-activated protein kinases (MAPKs) are crucial mediators that convert extracellular inputs into a variety of intracellular reactions. Among these pathways, the MAPK cascade is essential for transmitting signals from membrane receptors to intracellular targets, which has a significant impact on autophagy and other cellular functions. The three main MAPK branches-ERK1/2, JNK, and p38/MAPK-have been thoroughly studied in the control of cell destiny and homeostasis [36, 38]. Chinese medicinal plant Evodiae fructus causes human glioblastoma cells to undergo both autophagy and death. Reduced cytosolic calcium levels, alteration of the mitochondrial membrane potential, and increased apoptosis after calcium channel blocking are all indicators that evodiamine's pro-apoptotic mechanism includes the calcium signaling pathways. These results imply that the activation of a calcium-dependent JNK pathway is how evodiamine-induced autophagy functions [39]. Another indole-based alkaloid that was separated from Murraya Koenigii is isomahanine, which has been shown to have a variety of biological functions. Studies using the multidrug-resistant oral squamous cell carcinoma cell line CLS-354/DX have demonstrated that this chemical concurrently induces autophagy and apoptosis. These effects are linked to P38/MAPK signaling pathway activation and are most likely caused by stress reaction in the endoplasmic reticulum (ER) [40]. In mammalian systems, Beclin-1, which is encoded by a gene on chromosome 17q21, is an essential autophagy regulator. This 450-amino-acid, 60 kDa protein forms multi-protein complexes to carry out its autophagic actions. Its regulation mechanism includes interaction with Bcl-2 protein family members, including Bcl-2 and Bcl-XL, which bind to Beclin-1's BH3 domain and stop it from associating with the PI3KC3 complexes, so inhibiting autophagy [4, 42].

Taxol

Taxoids are a class of cyclic diterpenoids distinguished by their characteristic taxadiene core. These compounds have attracted considerable interest due to their strong anticancer properties, with paclitaxel-commonly referred to as Taxol, being the most well-known representative. Paclitaxel is predominantly obtained from the bark of yew trees [genus Taxus], which are slow-growing species. Paclitaxel has become one of the most widely employed chemotherapy drugs for treating a range of cancers [43, 44]. The pioneering research conducted by the Horwitz laboratory revealed the potent cytotoxic effects of Taxol, demonstrating its ability to inhibit HeLa cell proliferation at nanomolar concentrations. While cells exposed to the drug progressed through a normal S phase, Taxol induced a cell cycle arrest specifically at metaphase. The most remarkable and distinctive property of Taxol was its ability to enhance the polymerization of stable microtubules, a mechanism that underlies its antimitotic activity [45]. Beyond its clinical application in oncology, paclitaxel plays a crucial role in cell biology research. In unperturbed cells, the proper bipolar attachment of sister chromatids generates tension at kinetochores, facilitating the stabilization of kinetochore-microtubule interactions. This process, often referred to as sister chromatid exchange, ensures accurate chromosome segregation. However, paclitaxel treatment disrupts this dynamic by reducing the tension on kinetochores that maintain bipolar attachment. As a result, paclitaxel serves as a valuable experimental tool for inducing mitotic arrest and investigating the interplay between tension and attachment in the activation of the mitotic checkpoint [46].

Polyphenols

Polyphenolic compounds are one of the most diverse classes of secondary plant metabolites. They have several qualities that are beneficial to human health, such as antioxidant, anti-inflammatory, and antineoplastic actions. Previous research has demonstrated that it inhibits the growth of a wide variety of malignancies, making it an effective anticancer agent.The limited bioavailability of polyphenolic compounds is one of the issues that arises while using these kinds of substances.

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Upon ingestion, polyphenols must first be absorbed before undergoing biotransformation into their bioactive forms. Typically, following consumption, polyphenols undergo enzymatic hydrolysis of their carbohydrate moieties [if present], resulting in the release of aglycones. These aglycones then traverse the epithelial cells of the small intestine primarily through passive diffusion, facilitating their subsequent metabolism and systemic distribution. This happens after polyphenols have been broken down into their parts. Polyphenols exhibit antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, and anti-angiogenic properties. These compounds can modulate various molecular signaling pathways implicated in cancer development and progression, including the PI3K/Akt, MAPK, NF-κB, and Wnt/β-catenin pathways. For example, quercetin has been shown to suppress tumor growth in colon and breast cancer models by inducing apoptosis and cell cycle arrest, while EGCG from green tea can inhibit metastasis and reduce angiogenesis in prostate and lung cancers. If polyphenolic compounds are unable to be absorbed in this district, they will make their way to the colon, where the microbiota will metabolize them. Therefore, it is expected that an alteration in the gut microbiota will lead to a reduction in the amount of polyphenols that are absorbed by the human body, which will hurt human health. Nanomization has emerged as a prominent strategy among various formulation techniques aimed at enhancing the bioavailability of polyphenolic compounds. This approach utilizes diverse polymers and nanostructured carriers to develop polyphenolic compounds as potential anticancer agents, thereby improving their therapeutic efficacy. PLGA nanoparticles are comprised of polymers that can break down naturally. This polymer is made up of lactic acid and glycolic acid, both of which are acids that the body can digest [47-49].

Flavonoids

Flavonoids represent a diverse class of naturally occurring polyphenolic compounds characterized by the presence of a flavan core structure. They are structurally characterized by a 15-carbon skeleton consisting of two aromatic rings connected by a three-carbon bridge, forming a closed pyran ring C. This basic structure, known as the flavan nucleus, underlines the diversity of flavonoids, which are broadly classified into subgroups: flavones e.g., luteolin, apigenin, flavonols e.g., quercetin, kaempferol), flavanones e.g., naringenin, isoflavones e.g., genistein anthocyanins, and chalcones. They are abundantly distributed in a wide range of dietary sources, including fruits, vegetables, and plant-based beverages, rendering them one of the most prevalent groups of phytochemicals in the human diet. Flavonoids are widely famous for their broad spectrum of biological activities, notably their antioxidant, anticancer, anti-inflammatory, and antimutagenic properties. Due to their significant presence in commonly consumed foods and drinks, such as tea, wine, and various fruits and vegetables-they are considered promising candidates for therapeutic intervention in numerous diseases, including cancer. From a pharmacological perspective, flavonoids exhibit multifaceted anticancer properties by interfering with key pathways involved in carcinogenesis. These include antioxidant activity, which reduces oxidative stress and prevents DNA damage; anti-inflammatory effects, achieved through inhibition of NF-κB and COX-2 signaling; and induction of apoptosis by intrinsic and extrinsic pathways by modulating proteins such as Bcl-2, Bax, and caspases. Cell cycle arrest, particularly at G1 or G2/M phases, through modulation of cyclins and CDKs. Inhibition of angiogenesis, often by downregulating VEGF expression. Flavonoids exert anticancer effects by targeting multiple hallmarks of tumor development and progression, including the inhibition of invasion, metastasis, and angiogenesis, modulation shown in Figure [50, 51]. Flavonoids can't be used as an anticancer treatment because of things like their low bioavailability, poor stability and solubility, ineffective targeted delivery, and chemoresistance. Some famous examples of flavonoids and how they work are discussed below (Figure 3).

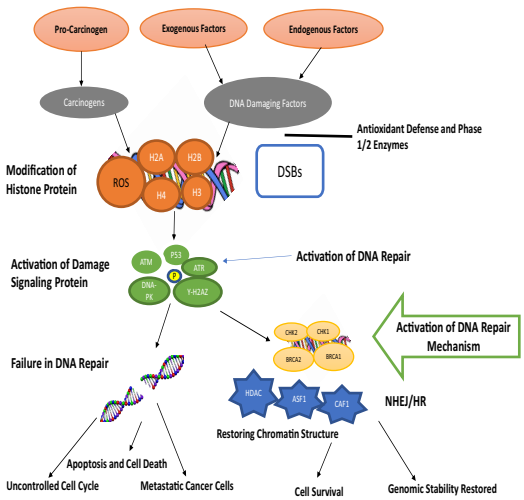

Figure 3: Cellular Mechanisms of Flavonoids on DNA Damage and Repair

Quercetin

Quercetin (Quer) is a widely distributed pentahydroxyflavone, predominantly present in many fruits and vegetables [52]. Querc holds significant importance, particularly due to its potential as an anticancer agent. The variable method of action is responsible for exhibiting varying efficacies, specificities, and targets in different types of malignancies [53]. Quercetin has been observed to impede the multiplication of cancer cells by the induction of apoptosis, hence diminishing the growth of various types of malignancies. The overexpression of cyclin-

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dependent kinase 6 [CDK6] has been closely linked to the onset and progression of several cancer types. Recent studies have highlighted quercetin as an effective natural inhibitor of CDK6. In a comparative analysis of various phytochemicals, including gallic acid, ferulic acid, caffeic acid, rosmarinic acid, capsaicin, tocopherol, limonene, and quercetin-quercetin showed the most pronounced inhibitory effect on CDK6 activity [54]. Research indicates that quercetin promotes apoptosis predominantly through the intrinsic [mitochondrial] pathway. This involves the activation of caspase-3 and caspase-9, the release of cytochrome c into the cytoplasm, and the subsequent cleavage of poly [ADP-ribose] polymerase [PARP]. These apoptotic events have been consistently observed in a variety of human cancer cell lines, including MCF-7 (breast cancer), CNE2 and HK1(nasopharyngeal carcinoma), HL-60 (leukemia), HPBALL (thymic lymphoma), and SCC-9 (oral squamous carcinoma). A key feature of this pathway is the disruption of mitochondrial membrane potential, which facilitates caspase activation and PARP cleavage initiated by quercetin [55; 54]. Quercetin's lipophilic nature enables it to cross cell membranes and modulate multiple intracellular signaling pathways involved in chemoprevention. It has been reported to inhibit cytochrome P450 (CYP) enzymes, which are essential for drug metabolism. Additionally, quercetin downregulates the expression of metastasis-associated proteins, particularly matrix metalloproteinases (MMPs), thereby impairing metastatic potential. Since angiogenesis supports tumor dissemination, quercetin's anti-angiogenic properties-evident through its suppression of neovascularization in the tumor microenvironment, further contribute to its anticancer effects. In the group of rats subjected to quercetin treatment, there was a notable reduction in the serum levels of inflammatory markers such as IL-1β, IL-1, IL-6, IL-8, and TNF-α, when compared to rats that were administered ethanol. However, it is noteworthy that IL-10 exhibited a distinct increase in the quercetin-treated group [56] (Table 2).

Genistein

The chemical name for genistein is 4',5,7-trihydroxyisoflavone. Genistein is considered the most basic isoflavonoid chemical within the Leguminosae family in terms of its biosynthesis. This compound serves as a pivotal intermediary in the production of intricate isoflavonoids, which play significant roles in either facilitating or impeding interactions between plants and microorganisms. The primary sources of genistein include legumes such as beans, alfalfa, peas, and soybeans [56]. Genistein exerts its anticancer effects through the modulation of a wide array of molecular signaling pathways. These include the regulation of microRNAs and the modulation of key proteins associated with apoptosis, transcription regulation, tumor suppression, kinase activity, growth factor signaling, and receptor functions [57]. A substantial body of evidence supports genistein's ability to trigger apoptosis by influencing the expression of proteins central to cell death mechanisms. In human cervical cancer (HeLa) cells, genistein enhances apoptosis by increasing the activity of caspase 9 and caspase 3. In addition, studies on LoVo and HT-29 colon cancer cell lines have shown that genistein induces cell death by inhibiting the NF-κB signaling cascade and altering the balance of apoptotic regulators-specifically, downregulating the anti-apoptotic protein Bcl-2 and upregulating the pro-apoptotic protein Bax. The pro-apoptotic effects of genistein in HT-29 cells have also been linked to this influence on the caspase-3 and p38 MAPK pathways, reinforcing its therapeutic potential as an anticancer compound, as depicted in Figure 4 [58, 59]. The process of cancer metastasis has been observed to be contingent upon increased expression levels of matrix metalloproteinases (MMPs). A research study conducted on nude mice demonstrated that genistein exerts inhibitory effects on the metastasis of salivary adenoid cystic carcinoma (ACC) cells. This suppression was associated with downregulating vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) expression. Furthermore, additional findings suggest that genistein effectively inhibits the migration of MAT-LyLu and AT-2 rat prostate cancer cells, further supporting its potential as an antimetastatic agent [59]. GEN downregulates the TLR4/MYD88/ NF-κB and EGFR/VEGFR pathways, thereby suppressing inflammatory mediators (e.g., TNF-α, STAT3, JAK) and transcription factors (NF-κB, C-Jun, ATF2), which leads to decreased expression of pro-inflammatory cytokines and matrix metalloproteinases [MMP-2, MMP-9] (Figure 4).

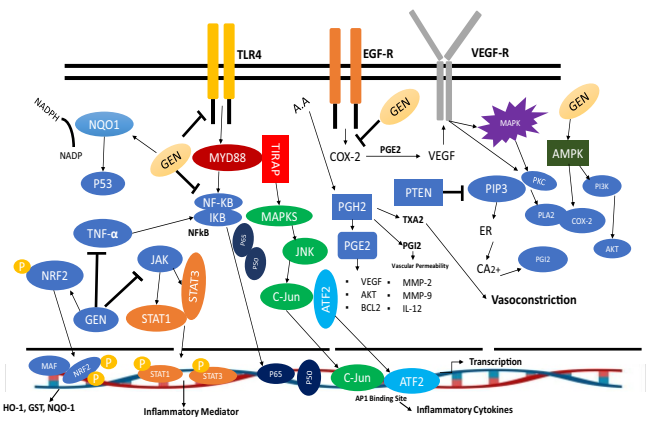

Figure 4: Schematic Diagram Illustrating the Inhibitory Effect of Genistein (GEN) on Key Signaling Pathways Involved in Cancer Metastasis, Inflammation, and Angiogenesis. Epigallocatechin Gallate (EGCG)

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Epigallocatechin-3-gallate (EGCG) is widely recognized as the most extensively investigated compound within the flavanol category. EGCG, a polyphenolic compound resulting from the esterification of epigallocatechin and gallic acid, is the predominant catechin with antioxidant properties found in green tea. Green tea and epigallocatechin gallate (EGCG) have shown promise as potential candidates for the prevention and control of various health conditions, including cancer, obesity, diabetes mellitus, cardiovascular illnesses, neurological diseases, and liver diseases. This is attributed to their notable antioxidant, anti-inflammatory, and anti-fibrogenic capabilities [60, 61]. DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) are enzymatic proteins that play a crucial role in the process of transcriptional gene silencing. On the other hand, histone acetyl transferases [HATs] are responsible for positively regulating gene expression. Multiple studies have demonstrated the involvement of EGCG in regulating epigenetic mechanisms, particularly through its influence on the expression and activity of DNMTs, HDACs, and HATs in various types of tumors. Epigallocatechin gallate (EGCG) exhibits binding affinity towards DNA methyltransferase (DNMT) and effectively hinders its enzymatic activity by competitive inhibition, as evidenced by a measured inhibition constant (Ki) of 6.89 μM. Consequently, this molecular interaction leads to the reactivation of genes that have been silenced through methylation in prostate cancer cells. The binding of EGCG to DNMT3B and HDAC1 was supported by molecular modeling and docking studies [62] (Table 2).

Table 2: Key Flavonoids, Anti-Tumor Activities, and Underlying Mechanisms

Compounds	Class	Anticancer Mechanisms	Plant Sources	References
Quercetin	Flavonoid	Apoptosis, cell cycle arrest, and anti-inflammatory	Fruits, vegetables, tea	[52, 56, 57, 68]
Genistein	Flavonoid	Apoptosis, autophagy, anti-anti-angiogenesis	Soybeans	[59, 63]
Apigenin	Flavonoid	Apoptosis, cell cycle arrest, anti-angiogenic	Parsley, thyme, chamomile	[64-68]
EGCG	Flavonoid	Apoptosis, auto -phagy, epigenetic modulation	Green tea	[60-62]

Curcumin

Curcumin, also known as diferuloylmethane, has the molecular formula C21H2006. The hydrophobic polyphenol in question is derived from the rhizome of perennial herbs of the Curcuma genus, which belongs to the Zingiberaceae family. *Curcuma longa* is a notable species in this group [69, 70]. Curcumin, a bioactive compound derived from *Curcuma longa,* has demonstrated considerable potential in inhibiting the progression of various cancer types. It effectively modulates critical processes involved in tumor development, including cell proliferation, invasion, angiogenesis, and metastasis. The anticancer activity of curcumin is primarily attributed to its regulatory influence on numerous cellular signaling pathways. Notably, curcumin has been reported to suppress the expression of oncogenic microRNAs (miRNAs) while enhancing the levels of tumor-suppressive miRNAs, thereby contributing to its therapeutic efficacy. Through its simultaneous modulation of these pathways, curcumin serves as a potent regulator of tumor progression and enhances the therapeutic response in cancer treatment strategies [71]. When growth factors and cytokines bind to receptors, downstream signaling pathways like PI3K/Akt, JAK/STAT, and MAPK are activated. These pathways affect cell survival (Table 3), (Figure 5).

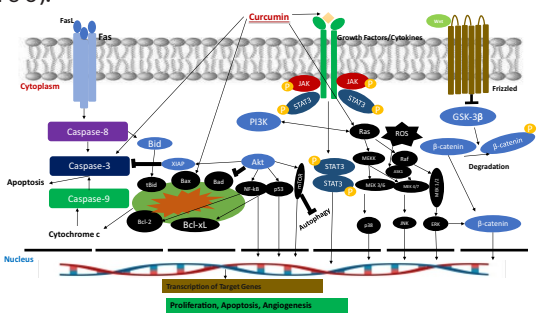

Figure 5: Signal Transduction Mechanisms Controlled by Curcumin Regulate Cancer Progression

Table 3: Key Non-Flavonoids, Anti-Tumor Activities, and Underlying Mechanisms

Compounds	Class	Anticancer Mechanisms	Plant Sources	References
Resveratrol	Non-flavonoid	Apoptosis, auto-phagy, anti- anti -angiogenesis	Grapes, berries	[72-74]
Curcumin	Non-flavonoid	Modulates PI3K/Akt, Wnt, NF-kB pathways	Turmeric	[70, 71,74]

Rhein

Rhein (1,8-dihydroxy-3-carboxyanthraquinone) is a naturally occurring anthraquinone derivative primarily found in plants belonging to the Polygonaceae family, notably *Rheum* [rhubarb] and *Reynoutria japonica* (Japanese knotweed). It has been extensively used in traditional Chinese medicine, largely due to its potent anticancer properties. Against HepG2 and Huh7, rhein has shown significant cytotoxic effects in liver cancer cell lines. Treatment with Rhein resulted in dose- and time-dependent alterations in cell morphology. Additionally, Rhein was found to induce double-stranded DNA breaks in these cells, further confirming its pro-apoptotic activity. A marked reduction in mitochondrial membrane potential (MMP) was also observed, suggesting early apoptotic events and compromised cellular integrity. One of the key mechanisms underlying Rhein's apoptotic effects is the

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elevation of intracellular reactive oxygen species (ROS). The ROS generated in response to Rhein exposure contributes to the initiation of apoptosis by activating redox-sensitive signaling pathways. Specifically, the JNK/Jun/caspase-3 cascade is activated, promoting programmed cell death. Furthermore, it activates multiple caspases, including caspase-1, -3, -8, -9, and -12, indicating a broad engagement of both intrinsic and extrinsic apoptotic pathways. Rhein also induces cell cycle arrest at the S-phase by downregulating cyclin A1, cyclin E1, cyclin D1, and CDK2. These results highlight Rhein's potential as a promising anticancer agent [75] (Table 4).

Table 4: Key Anthraquinones, Anti-Tumor Activities, and Underlying Mechanisms

Compounds	Class	Anticancer Mechanisms	Plant Sources	References
Emodin	Anthraquinone	ROS generation, JNK activation, and autophagy	Rhubarb, buckthorn	[77,78]
Rhein	Anthraquinone	Apoptosis via ROS,JNK/caspase signaling	Chinese rhubarb	[20; 75]

Limitations and Future Prospects

This review is limited by its reliance on published experimental and preclinical studies, as large-scale clinical validation of many phytochemicals remains insufficient. Variability in extraction methods, compound standardization, bioavailability issues, and potential drug–herb interactions further complicate therapeutic translation. Future research should prioritize well-structured clinical trials, nanotechnology-based delivery systems, molecular docking validation, and combination therapy strategies to enhance therapeutic precision and efficacy. Integrating phytochemicals with personalized medicine and targeted oncogenic pathway modulation may unlock their full potential as adjunct or standalone anticancer agents.

CONCLUSION

The pursuit of effective cancer therapies remains one of the most pressing challenges in modern medicine, necessitating innovative and multidisciplinary approaches. Among the strategies under investigation, the use of plant-derived extracts has emerged as a promising frontier that integrates traditional medicinal practices with contemporary biomedical research. This review explores the diverse and potent anticancer potential of various plant extracts, highlighting their multifaceted mechanisms of action. Plant-based compounds have been shown to exert anticancer effects through several pathways, including modulation of cell signaling, inhibition of enzymes crucial for tumor progression, and direct induction of apoptosis. These mechanisms often operate synergistically, enhancing therapeutic efficacy. Additionally, many plant extracts possess antioxidant and anti-inflammatory properties, further supporting their role in both cancer prevention and treatment. While plant extracts are not a universal solution to cancer, they significantly broaden the spectrum of available therapeutic options and offer renewed hope to patients worldwide.

Authors' Contribution

Conceptualization: HAA, MNA
Methodology: MA, JA
Formal analysis: JA
Writing and Drafting: HAA, AW, SAAS
Review and Editing: HAA, AW, SAAS, MNA, MA, JA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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