Targeting Cancer Signaling Pathways with Plant-Derived Agents: A Review

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ABSTRACT

Cancer remains a global health challenge, and current therapies, including chemotherapy and radiation therapy, are often limited by serious side effects and drug resistance. These limitations have sparked increasing interest in natural alternatives, especially plant-based compounds with diverse biological actions. Several phytochemicals, such as curcumin, epigallocatechin-3-gallate (EGCG), withaferin-A, kaempferol, and quercetin, have been shown to inhibit important signaling pathways that cancer cells rely on for growth, survival, and metastasis. These natural agents, which often target multiple cellular pathways rather than a single target, as many drugs do, are particularly valuable in the fight against drug-resistant cancers. Nevertheless, their clinical use is limited by issues such as low bioavailability, distinct pharmacokinetics, and tumor heterogeneity. In view of these challenges, the utilization of innovative drug delivery methods, such as nano-functionalized formulations, along with combination strategies, has been considered in recent studies. This evidence gives way to the development of network pharmacology and personalized medicine as valuable strategies in maximizing the therapeutic activity of medicinal plants; This review explores the mechanisms by which these agents exert their anticancer activity and highlights progress made in, as well as hurdles remaining toward, the integration of these strategies into contemporary oncology.

Keywords: signalling, anticancer, pharmacology, curcumin, epigallocatechin-3-gallate

INTRODUCTION

Globally, cancer stands out as a major health challenge that claims millions of lives each year, primarily due to dysregulated cellular proliferation and disruption of normal cellular functions (Lee et al., 2016; Shrihastini et al., 2021). Several traditional cancer therapies, such as radiation and chemotherapy, are most often associated with drug resistance and have serious negative impacts. Consequently, there is increasing interest in exploring alternative therapeutic methods, including the use of plant-derived compounds. These natural compounds, known for their potent bioactive properties, present a viable path for targeted cancer treatment by modulating the key signaling pathways involved in cancer development and progression (Farghadani & Naidu, 2021, Farooqi et al., 2020; Qattan et al., 2022). This review offers an in-depth examination of the current understanding of plant-derived medicines for targeting cancer signaling pathways, with particular emphasis on their mechanism of action, effectiveness, drawbacks, and future research directions.

Plant-Derived Compounds and Their Anti-Cancer Properties

Various compounds derived from plants have exhibited significant anticancer activity in both in vivo and in vitro studies (Asgharian et al., 2021; Farghadani & Naidu, 2021; Qattan et al., 2022). These compounds, often classified as phytochemicals, exhibit a broad spectrum of chemical structures and biological functions. For example, flavonoids such as kaempferol and quercetin (Qattan et al., 2022, Asgharian et al., 2021) possess notable anti-inflammatory, anticancer, and antioxidant properties. These compounds exert their effects by modulating various cancer-related mechanisms, including metastasis, angiogenesis, oxidative stress, apoptosis,

proliferation, and cell cycle regulation (Qattan et al., 2022). Other important secondary metabolites with different mechanisms of action and therapeutic potential include curcumin, epigallocatechin-3-gallate (EGCG), and withaferin-A (Farghadani & Naidu, 2021; I. Lee et al., 2016; Farooqi et al., 2020). Although further investigation is required to comprehensively clarify their mechanisms of action, alkaloids, another class of phytochemicals, also shows promising effect for cancer treatment (Tilaoui et al., 2021).

Mechanisms of Action

Medicines obtained from plants play an important role in exhibiting anticancer effects by disrupting oncogenic signaling pathways crucial for cancer cell survival, growth, and spread. These compounds frequently target multiple pathways simultaneously, thereby enhancing their effectiveness (Farghadani & Naidu, 2021; Farooqi et al., 2020). For instance, curcumin has been shown to affect the phosphatidylinositol 3-kinase (PI3K)/ Protein Kinase B (Akt)/ mammalian target of rapamycin (mTOR), Janus Kinase (JAK)/ transducers, Activators of Transcription (STAT), MAPK, NF-κB, p53, and Wnt/β-catenin pathways in hormone-independent breast cancer (Farghadani & Naidu, 2021). Similarly, EGCG regulates the Janus Kinase (JAK)/ Transducers and Activators of Transcription (STAT), Wnt/β-catenin, TGF/SMAD, SHH/GLI, and NOTCH pathways in different cancers (Farghadani et al., 2021). Kaempferol affects several pathways involving phosphatidylinositol 3-kinase (PI3K)-(AKT) Protein Kinase B, VEGF, STAT, p53, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Qattan et al., 2022). By modulating these pathways, which are often disrupted in cancer cells, plant-based medicines can inhibit metastasis, trigger apoptosis, and prevent cell proliferation (Farghadani & Naidu, 2021; Qattan et al., 2022). Furthermore, certain phytochemicals may exert their anticancer effects via epigenetic pathways by affecting DNA methylation, histone modification and chromatin remodeling (Bouyahya et al., 2022). However, certain mechanisms of action can differ based on the compound, form of cancer, and cellular environment (Chirumbolo et al., 2018).

Targeting Specific Signaling Pathways

Phosphoinositide 3-kinase (PI3K)/Protein Kinase B (Akt)/Mammalian Target of Rapamycin (mTOR) Pathway

This signaling pathway is often activated in various cancers, facilitating cell growth, survival, and the formation of new blood vessels (Tarik Regad., 2015; Farghadani & Naidu, 2021). Various plant-derived compounds have been shown to be effective in blocking this pathway (Tarik Regad., 2015; Farghadani & Naidu, 2021; Qattan et al., 2022). For example, curcumin inhibits the activities of PI3K, Akt, and mTOR, leading to reduced growth and enhanced apoptosis in breast cancer cells (Farghadani & Naidu, 2021). Similarly, the anticancer effects of kaempferol include its ability to inhibit the PI3K-AKT signaling pathway (Qattan et al., 2022). The use of plant-derived treatments to target this pathway holds significant promise for cancer therapy.

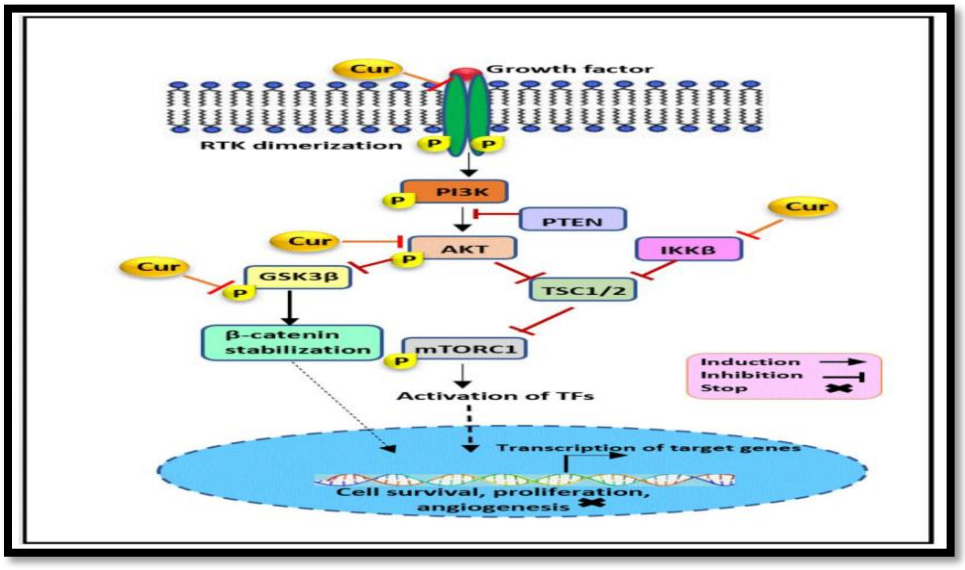

Figure 1. Curcumin Targets the PI3K/Akt/mTOR Signaling Cascade to Inhibit Growth and Metastasis in Hormone Receptor-Negative Breast Cancer. (Farghadani & Naidu, 2021).

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Janus Kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) Pathway

Dysregulation of this pathway is commonly observed in diverse cancers (Farghadani & Naidu, 2021; Farooqi et al., 2020). Research has indicated that curcumin and EGCG inhibit the JAK/STAT pathway, thereby impeding cancer cell development and promoting apoptosis. furthermore, the compound derived from the plant *Brassinin* influences the JAK/STAT pathway in colorectal cancer cells (Yang et al., 2021). additionally, investigation is warranted to explain the function of this pathway in cancer and explore the ability of plant-derived compounds as effective therapeutic agents (Fig.2).

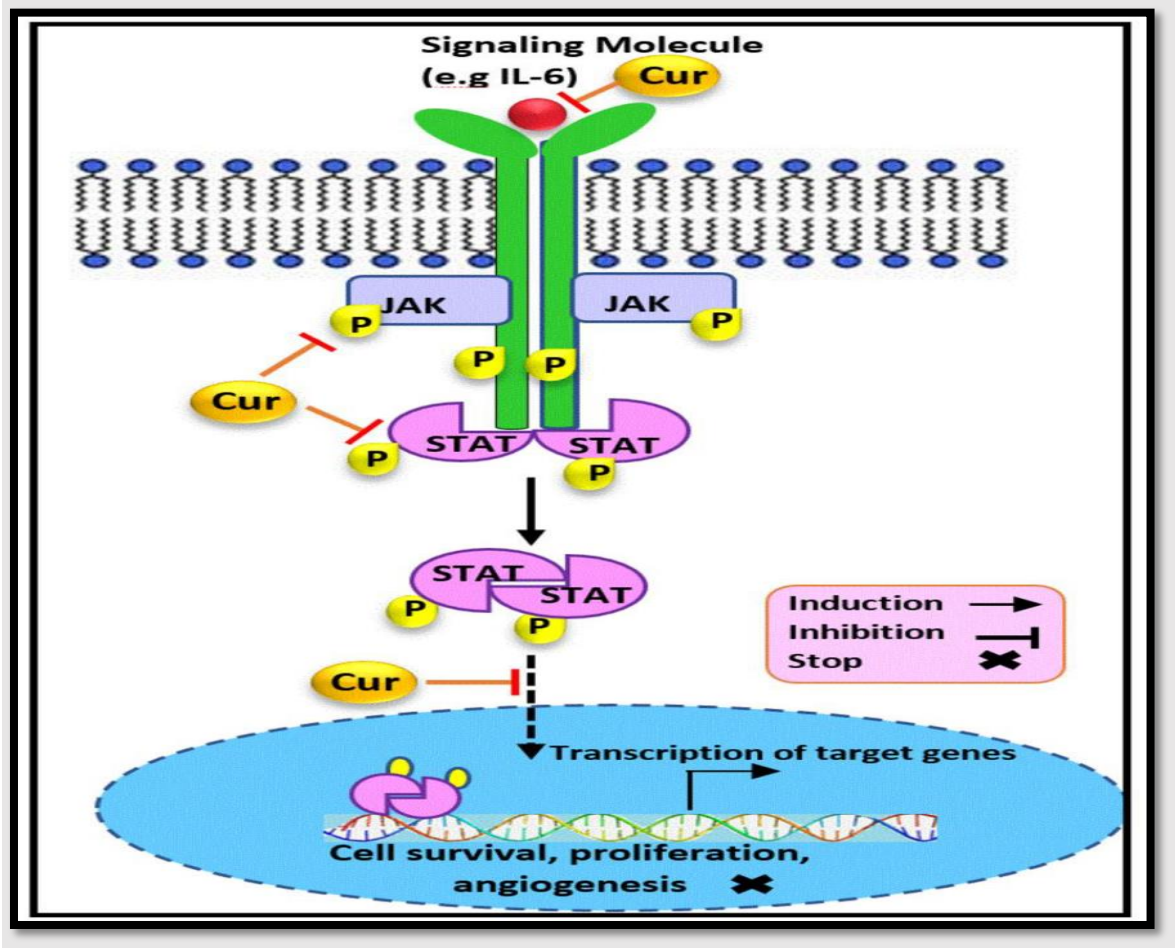

Figure 2. Curcumin Inhibits the IL-6/JAK/STAT3 Signaling Axis to Suppress Growth and Metastasis in Hormone Receptor-Negative Breast Cancer (Farghadani & Naidu, 2021).

Mitogen-Activated Protein Kinase (MAPK) Pathway

The mitogen-activated protein kinase pathway is a crucial signaling sequence that notably affects cell growth, differentiation, and survival. This pathway is aberrantly activated in cancer, resulting in unrestricted cell growth and tumor development (Tarik Regad., 2015; Choi et al., 2010; Farghadani & Naidu, 2021). Curcumin inhibits the MAPK pathway, contributing to its anticancer effects (Farghadani & Naidu, 2021). Additional investigations are needed to elucidate the specific mechanisms by which plant-derived compounds affect the MAPK pathway and their potential therapeutic advantages. Recent studies have examined the effects of other plant-derived compounds on the MAPK pathway, yielding promising findings for cancer prevention and treatment. Organic materials, such as resveratrol from grapes and EGCG from green tea, have been shown to affect numerous elements of the MAPK cascade. Understanding how these secondary metabolites interact with the MAPK pathway at the molecular level could pave the way for the development of new targeted treatments for cancer and other illnesses associated with aberrant MAPK signaling (Fig. 3).

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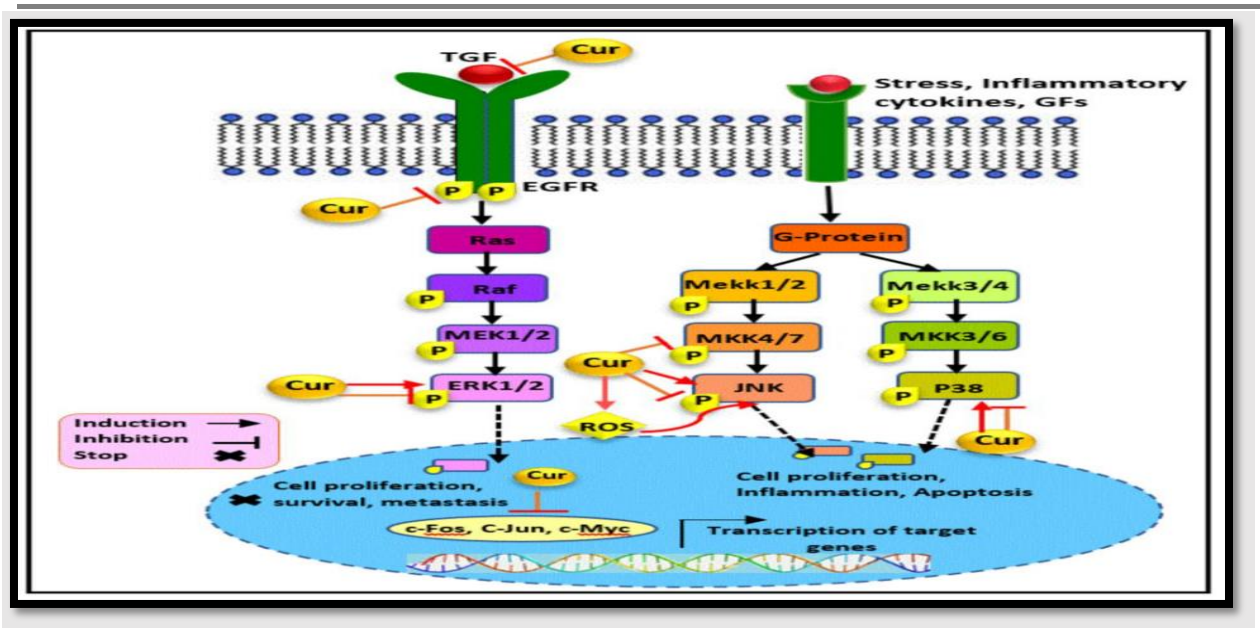

Fig. 3. Curcumin-Mediated Inhibition of MAPK Signaling Suppresses Tumor Progression in Hormone Receptor-Negative Breast Cancer (Farghadani & Naidu, 2021).

Wnt/β-catenin Pathway

Alterations in the Wnt/β-catenin pathway provide great opportunities for cancer treatment using naturally occurring compounds. Combination therapies involving several organic substances that target this pathway may enhance their anticancer effectiveness. Moreover, elucidating the molecular mechanisms by which these compounds interact with the Wnt/β-catenin pathway (Farghadani & Naidu, 2021) could facilitate the development of effective and targeted treatment strategies. The Wnt/β-catenin pathway plays a fundamental role in regulating cell growth, differentiation, and stem cell maintenance. Abnormal triggering of this pathway has been repeatedly observed in numerous cancers, encouraging tumor growth and metastasis (Farghadani & Naidu, 2021; Farooqi et al., 2020; Liu et al., 2020). Curcumin and EGCG have been proven to inhibit the Wnt/β-catenin pathway, thereby reducing cancer cell augmentation and amplifying apoptosis (Farghadani & Naidu, 2021; Farooqi et al., 2020). Another plant-derived substance that comes from plants, phenol, also targets this pathway in colorectal cancer cells (Liu et al., 2020). Further examination is call for to explore the therapeutic efficacy of plant derived agents targeting this pathway (Fig. 4).

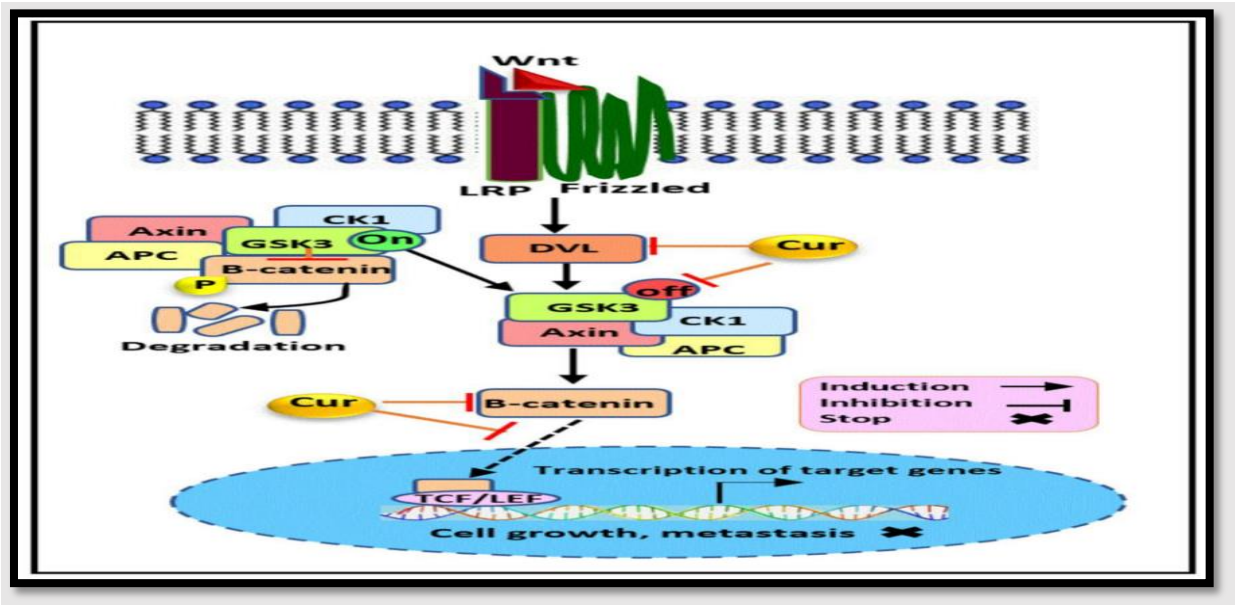

Fig 4. Curcumin Suppresses Wnt/β-Catenin Signaling to Inhibit Tumor Growth and Metastasis in Hormone Receptor-Negative Breast Cancer (Farghadani & Naidu, 2021).

Other Signaling Pathways

Other cancer-related signaling pathways, such as p53, NF-κB (Denlinger et al., 2004; Farghadani & Naidu, 2021; Qattan et al., 2022; Singh et al., 2026), and different receptor tyrosine kinase (RTK) signaling pathways, have also been shown to be regulated by plant-derived agents. These pathways play important roles in managing cell growth, apoptosis, and survival, and their dysregulation contributes to the development and progression of cancer. Alteration of these pathways by plant-derived compounds can subdue cancer cell growth, induce apoptosis, and inhibit metastasis (Tarik Regad., 2015; Choi et al., 2010; Denlinger et al., 2004).

Clinical Significance and Future Directions

Despite several preceding studies demonstrating the efficacy of plant-derived materials as anti-cancer drugs and their clinical delivery proves to be challenging (Asgharian et al., 2021; Farghadani & Naidu, 2021; Farooqi et al., 2020; I. Lee et al., 2016; Qattan et al., 2022) due to complex pharmacokinetics and bio-accessibility patterns, the need for innovative drug delivery systems, and the inherent heterogeneity of cancer (Farooqi et al., 2020; Mondal et al., 2023). Furthermore, these drugs and their multifaceted properties are associated with challenges in delineating their exact mechanisms of action and predicting clinical success, despite the fact that they benefit many pathways (Chirumbolo et al., 2018; I. Lee et al., 2016). Current investigations, however, are addressing these limitations. A prominent research area is the development of nano-formulations for enhanced bioavailability and targeted delivery of medicinal agents (Farooqi et al., 2020; Mondal et al., 2023). To counteract drug resistance and enhance therapeutic efficacy, combination therapies based on plant-derived compounds in combination with traditional chemotherapeutic agents or other targeted therapies are being researched (Sauter E. R., 2020; Uzoigwe et al., 2012; Yang et al., 2021). In addition, network pharmacology enhances our understanding of the complex relationships between plant compounds and their molecular targets, which assists in the development of more effective and individualized cancer therapies (Jenča et al., 2024; Zheng et al., 2018).

Overcoming Challenges in Clinical Translation

One of the obstacles to translating promising preclinical results into clinical success is. The low bioavailability and poor absorption of several plant-derived compounds are key barriers. This requires innovative drug delivery systems, such as nano functionalization, to improve their absorption and distribution within the body (Farooqi et al., 2020; Mondal et al., 2023). One key challenge is the heterogeneity of cancer, as different types of tumors have different genetic and molecular characteristics. This requires the development of personalized therapies tailored to the specific molecular profile of each patient's tumor (Farghadani & Naidu, 2021; Wang et al., 2020). Furthermore, it is challenging to predict the clinical efficacy and possible unfavorable effects of plant-derived medicines because of their pleiotropic effects, even though they may be advantageous in addressing many pathways. Thus, thorough preclinical research is necessary to work out the best dosage, delivery method, and possible medication interactions (Chirumbolo et al., 2018; I. Lee et al., 2016)

Nanotechnology and Drug Delivery

Nanotechnology can enhance the delivery of plant-derived compounds to cancer cells (Singh et al., 2026). By summarizing these substances, nanoparticles can prevent deterioration and increase bioavailability. Additionally, to minimize off-target effects, nanoparticles can be modified with targeting ligands to accurately deliver plant-derived compounds to cancer cells (Farooqi et al., 2020; Mondal et al., 2023). This targeted delivery approach can notably increase therapeutic effectiveness and reduce side effects. Research on the application of natural polymeric nano-biocomposites for drug delivery is exciting. These biocompatible and biodegradable substances provide a secure and environmentally friendly alternative to artificial nanoparticles (Mondal et al., 2023).

Combination Therapies

The use of plant-based agents in combination with traditional cancer therapies or other targeted agents holds important promise for improving treatment outcomes (Sauter E. R., 2020, 2020; Siddiqui et al., 2025; Singh et

al., 2026; Uzoigwe et al., 2012; Yang et al., 2021). The combination of these agents can result in synergistic effects, enhancing their anticancer activity and overcoming drug resistance. For instance, brassinin amplifies the anticancer effects of paclitaxel in colorectal cancer cells. This symbiotic effect can be attributed to the ability of plant-based agents to regulate numerous signaling pathways, often distinct from those targeted by traditional therapies. To determine the best combinations of plant-based drugs and traditional medications and to understand the underlying processes of their synergistic interactions, further studies are required (Sauter E. R., 2020; Uzoigwe et al., 2012; Yang et al., 2021).

Network Pharmacology and Personalized Medicine

Network pharmacology offers an effective approach for understanding the complex interactions between plant-derived agents and their molecular targets in cancer cells (Siddiqui et al., 2025; Zheng et al., 2018). This systems biology perspective allows for the identification of the principal pathways and networks involved in the anticancer effects of these compounds . Network pharmacology can integrate proteomic, genomic and metabolomic data to elucidate the mechanism of action and synergistic interactions among components present in plant-based agents. These details are instrumental in the development of customized therapies tailored to the specific molecular characteristics of individual patients' tumors. Network pharmacology can also help identify useful biomarkers for predicting treatment outcomes and refining therapeutic approaches (Zheng et al., 2018).

Specific Plant-Derived Agents and Their Targets

This section uses solid examples of plant-derived agents and their mechanisms to highlight the most researched compounds in the available literature investigating target cancer signaling pathways. However, it is important to note that this is not an exhaustive list, as many other plant-based agents are currently under investigation. These agents have demonstrated promising preclinical and clinical activity, suggesting their potential application in antitumor therapy. The compounds investigated in this study were selected based on their ability to modulate important signaling pathways regulating cancer progression, including angiogenesis, cellular proliferation, and apoptosis. Researchers hope to develop more effective targeted treatments with fewer side effects than current chemotherapy by understanding how these agents derived from plants work.

Curcumin

Among these potential chemotherapeutic agents, curcumin, a polyphenol isolated from turmeric, has received considerable attention owing to its broad spectrum of anticancer effects (Farghadani & Naidu, 2021; Jenča et al., 2024; Tsai et al., 2016). It controls several signalling pathways, such as JAK/STAT, PI3K/Akt/mTOR, NF-κB, p53, MAPK, and Wnt/β-catenin. Curcumin inhibits cell proliferation, angiogenesis, survival, and metastasis in most hormone-independent breast cancers. Despite these beneficial effects, its clinical efficacy is limited by low bioavailability and rapid metabolism. Current research is focused on new formulations that improve absorption efficiency and enhance therapeutic potential (Farghadani & Naidu, 2021).

Epigallocatechin-3-gallate (EGCG)

Catechuic acid, a compound found in tea, is another promising plant-derived agent with anticancer properties. It influences several key signaling pathways, including JAK/STAT, Wnt/β-catenin, NOTCH, TGF/SMAD, and SHH/GLI (Farghadani & Naidu, 2021; Farooqi et al., 2020a). EGCG has been shown to slow cancer cell growth, trigger apoptosis, and suppress metastasis in different cancer types. However, like curcumin, its low bioavailability remains a major challenge for clinical use. To address this, researchers have developed nano-formulations aimed at improving drug delivery and enhancing therapeutic effectiveness (Farooqi et al., 2020).

Kaempferol

Kaempferol, a flavonoid present in many fruits and vegetables, exhibits strong anticancer activity. It regulates several signaling pathways, including VEGF, STAT, NF-κB, p53, and P13K-AKT (Qattan et al., 2022; Tsai et al., 2016). It inhibits cell proliferation and triggers apoptosis and angiogenesis in different cancer cell lines. To fully realize its therapeutic potential, further research is required to assess its clinical applications and optimize its delivery methods (Qattan et al., 2022).

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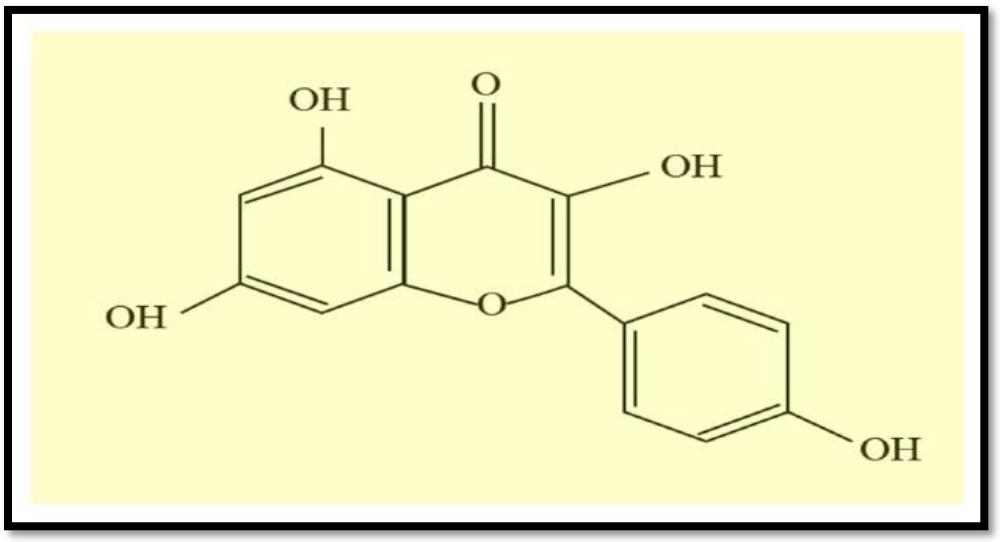

Figure 5. Chemical structure of Kaempferol (Qattan et al., 2022).

Withaferin-A

Withaferin-A, a steroidal lactone derived from *Withania somnifera*, has shown promise as an anticancer agent (I. Lee et al., 2016; Tsai et al., 2016). It acts by modulating multiple signaling pathways, leading to reduced cell growth, induction of apoptosis, and greater sensitivity of cancer cells to standard chemotherapy drugs. However, more research is needed to fully understand its toxicity and potential side effects before it can be safely applied in clinical settings (Jenča et al., 2024; I. Lee et al., 2016; Tsai et al., 2016).

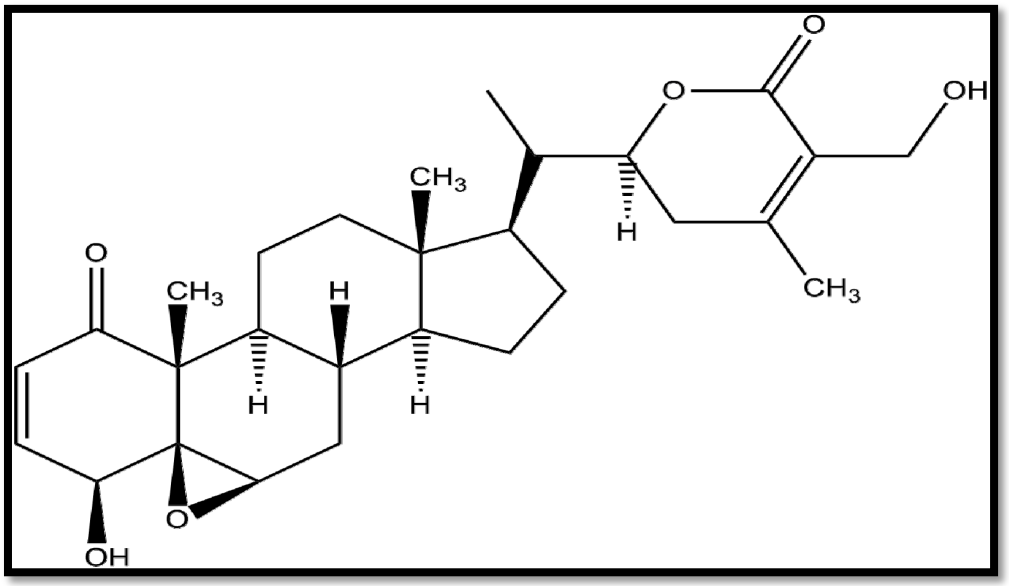

Fig 6. Structure of withaferin-A (I. Lee et al., 2016).

Quercetin

Quercetin is a flavonoid that is abundant in plants and exhibits potent anticancer effects in various cancers, including pancreatic cancer. It affects several cellular processes, including autophagy, apoptosis, inhibition of cell growth, epithelial mesenchymal transition (EMT), and oxidative stress, and sensitizes cancer cells to chemotherapy. The results demonstrate its activity in cancer cell lines and animal models and suggest that this drug has potential as a supportive therapy, especially when administered in conjunction with other treatments. However, many flavonoid compounds are plagued by barriers such as bioavailability and clinical translation, which warrant further investigation (Asgharian et al., 2021) (Table 1).

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Table 1: A number of pharmacological activities of quercetin reported in recent studies (Asgharian et al., 2021).

Sr. no.	Activity	Administration	Model	Dose (in)
1	Apoptosis induction and anticancer effect	Direct treatment	MCF-7 and MDA-MB-231	25 μM (Asgharian et al., 2021)
2	autophagy and promoted cell survival	Direct treatment	Human umbilical vein endothelial cells (HUVECs)	20 μM (Asgharian et al., 2021)
3	ROS and free radical scavenging activity	Direct treatment	Erythrocystes	5.7 Mm DPPH Assay
4	Supressed autophagic flux, decreased liver injury by ethanol consumption	gavage	C57BL/6J mice on ethanol containing liber De Carli liquid diet	100 mg kg^{-1} (Asgharian et al., 2021)
5	Antimicrobial effect against *streptococcus suis*	Subcutaneous	*Streptococcus suis* infected mice	100 mg kg^{-1} (Asgharian et al., 2021)
6	Decreased fat accumulation in liver (ethanol induced)	Oral	Chronic ethanol feeding C57BL/6J MICE	100 mg kg^{-1} (Asgharian et al., 2021)
7	Higher insulin levels, improved dyslipidaemia, reduced serum blood glucose levels, decreased oxidative stress	Intraperitoneal	STZ induced diabetic rats	30 mg kg^{-1} (Asgharian et al., 2021)
8	Controlled insulin resistance, reduced blood sugar, pancreatic cells protection	Oral	STZ induced diabetic wistar rats	100- 200 mg kg^{-1} (Asgharian et al., 2021)
9	Controlled body weight and blood glucose, performance in the Morris water test	Oral	STZ induced diabetic rats	5- 20 mg kg^{-1} (Asgharian et al., 2021)
10	Enhanced the time spent by mice in the target quadrant in the Morris water maze task	Oral	STZ induced diabetic mice in the Morris water maze task	40 mg kg^{-1} (Asgharian et al., 2021)

Other Intriguing Agent

Many other compounds derived from plants are currently being investigated for their ability to target signaling pathways in cancer. These include, but are not limited to, resveratrol, genistein, and other flavonoids and polyphenols (Mohan Shankar et al., 2022). The diverse chemical structures and biological activities of phytochemicals offer significant potential for the development of novel cancer therapies. Further studies are needed to fully interpret their mechanisms of action, effectiveness, and safety profiles before clinical application.

Limitations and Future Research Directions

Although there has been considerable advancement in understanding the anti-cancer properties of plant-based compounds, several obstacles persist. Further investigation is required to better understand the bioavailability and pharmacokinetics of these compounds to maximize their therapeutic potential (Farghadani & Naidu, 2021).

Developing targeted drug delivery systems, such as nano-functionalized formulations, is essential for improving their delivery to cancer cells while reducing unintended effects (Farooqi et al., 2020; Mondal et al., 2023).

Furthermore, different types of cancer cells are used for the development of customized and personalized treatments tailored to tumors with unique and different molecular characteristics (Farghadani & Naidu, 2021; Singh et al., 2026; Wang et al., 2020). Further studies are required to identify predictive biomarkers for treatment response and to comprehend the interaction between compounds derived from plants and the tumor microenvironment (Farghadani & Naidu, 2021; Wang et al., 2020). Plant-derived agents, in combination with traditional treatment strategies, may have synergistic effects, leading to therapeutic advantages and possibly helping to overcome drug resistance. Nevertheless, clinical trials are important for determining the safety and efficacy of these natural agents in various cancer types and for verifying their possible utility as anticancer drugs. Identifying bioactive compounds and understanding their molecular targets through high-throughput screening may enable the discovery of novel pharmacological avenues for cancer therapy. Key takeaway: Interdisciplinary approaches are crucial for the future development of plant-derived cancer therapies. Network pharmacology is a novel approach that integrates computer-aided analysis and experimental systems to provide insights into the interactions between these compounds and their molecular targets in complex biological pathways . This strategy may aid in the identification of protective biomarkers and lead to more tailored therapies (Zheng et al., 2018). The development of unique drug delivery systems (including nano-functionalization and other cutting-edge technologies) is needed to improve bioavailability, allowing these compounds to reach their target sites (Farooqi et al., 2020; Mondal et al., 2023). Additionally, the use of botanicals in conjunction with traditional cancer therapies or other forms of targeted agents has considerable promise for augmenting the results of metastatic treatment (Sauter E. R., 2020; Uzoigwe et al., 2012; Yang et al., 2021). However, can be challenging to overcome and new research avenues must be pursued in order to improve we al like the potent anticancer properties of plant-based agents.

CONCLUSION

Plant-derived compounds are a potent alternative to conventional cytotoxic anti-cancer therapies as they exert robust in vitro and in vivo anti-cancer effects by activating critical signalling pathways. Their capacity to act on multiple pathways simultaneously, coupled with their lower toxicity than standard chemotherapy, makes them particularly interesting candidates for treating reinforcing behaviour. Nonetheless, there are obstacles to overcome, such as improving bioavailability and accurate delivery while unravelling their complex behaviour within the tumor microenvironment. These challenges should be addressed in future studies by employing innovative drug delivery systems, personalized medicine strategies, and/or network pharmacology. Integrating these approaches can optimize the therapeutic potential of plant-based agents in cancer treatment, thereby improving the quality of life of patients.

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