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EMERGING ANTITUMOR MECHANISMS OF PLANT SECONDARY METABOLITES: BEYOND CLASSICAL CYTOTOXICITY

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ABSTRACT

Plant secondary metabolites have historically been invaluable sources of anticancer drugs, with compounds such as paclitaxel, vincristine, and camptothecin serving as mainstays of chemotherapy. Classical anticancer mechanisms have focused on direct cytotoxicity through microtubule disruption, topoisomerase inhibition, and DNA intercalation. However, emerging research has revealed that plant secondary metabolites exert pleiotropic anticancer effects through diverse mechanisms beyond classical cytotoxicity. This review critically examines emerging antitumor mechanisms of plant secondary metabolites, including the regulation of apoptosis, metastasis inhibition, autophagy modulation, reversal of multidrug resistance, targeting of cancer stem cells, epigenetic modulation, and immunomodulatory effects. We synthesize current understanding of the molecular pathways targeted by plant-derived compounds, including the PI3K/AKT/mTOR pathway, MAPK/ERK signaling, and the NF-κB inflammatory cascade. Case studies of selected compounds, including curcumin, resveratrol, and epigallocatechin gallate, illustrate the diversity of anticancer mechanisms. Despite significant advances, challenges including poor bioavailability and the need for predictive biomarkers persist. This review identifies promising research directions and discusses the potential for combination therapies targeting multiple pathways.

Keywords: Anticancer; Plant Secondary Metabolites; Apoptosis; Metastasis; Multidrug Resistance; Signal Transduction

1 INTRODUCTION

Cancer remains a leading cause of mortality worldwide, with an estimated 19.3 million new cases and 10 million deaths annually (Talib et al., 2022). Despite significant advances in targeted therapies and immunotherapies, chemotherapy continues to play a central role in cancer treatment. Plant secondary metabolites have contributed substantially to the anticancer pharmacopoeia, with clinically important agents including paclitaxel from Taxus species, vincristine and vinblastine from Catharanthus roseus, and camptothecin derivatives from Camptotheca acuminata (Talib et al., 2022).

Classical anticancer mechanisms of plant-derived compounds have focused on direct cytotoxicity through microtubule disruption, topoisomerase inhibition, and DNA intercalation (Chaudhry et al., 2022). However, emerging evidence has revealed that plant secondary metabolites exert pleiotropic effects through diverse mechanisms beyond classical cytotoxicity. These emerging mechanisms include the regulation of apoptosis, inhibition of metastasis, modulation of autophagy, reversal of multidrug resistance, targeting of cancer stem cells, epigenetic modulation, and

immunomodulatory effects (Talib et al., 2022; Fakhri et al., 2022). The identification of these additional mechanisms has expanded the therapeutic potential of plant-derived compounds and opened new avenues for drug development.

The diversity in chemical structure and the relatively low toxicity make plant-derived natural products a promising source for the development of new and more effective anticancer therapies that have the capacity to target multiple hallmarks in cancer (Talib et al., 2022). This review provides a comprehensive examination of emerging antitumor mechanisms of plant secondary metabolites, evaluating the molecular pathways targeted and discussing implications for cancer therapy.

2 CLASSICAL ANTICANCER MECHANISMS: A BRIEF OVERVIEW

2.1 Microtubule Interference

Microtubule-targeting agents, including paclitaxel and vinblastine, disrupt the dynamic instability of microtubules, causing mitotic arrest and subsequent apoptosis. Paclitaxel, a potent mitotic inhibitor discovered from Taxus brevifolia, suppresses cell growth and arrest, induces apoptosis, and inhibits proliferation (Chaudhry et al., 2022). These compounds remain widely used in the treatment of breast, ovarian, and lung cancers.

2.2 Topoisomerase Inhibition

Topoisomerase inhibitors, including camptothecin and its derivatives, disrupt DNA replication by stabilizing the topoisomerase-DNA cleavage complex. Irinotecan and topotecan are clinically used for colorectal and ovarian cancers, respectively. These compounds induce DNA damage and subsequent apoptosis in rapidly dividing cells.

2.3 DNA Intercalation

Certain plant alkaloids intercalate between DNA base pairs, disrupting replication and transcription. While DNA intercalators are effective anticancer agents, their clinical utility is limited by cardiotoxicity and other side effects.

Table 1: Classical Anticancer Mechanisms of Plant Secondary Metabolites

Compound Class	Examples	Mechanism of Action	Clinical Application
Taxanes	Paclitaxel, Docetaxel	Microtubule stabilization *(inhibits depolymerization)*	Breast, ovarian, and lung cancers
Vinca Alkaloids	Vincristine, Vinblastine	Microtubule disruption *(inhibits tubulin polymerization)*	Leukemia, lymphoma, and childhood cancers
Camptothecins	Irinotecan, Topotecan	Topoisomerase I inhibition *(induces DNA strand breaks)*	Colorectal, ovarian, and small cell lung cancers
Epipodophyllotoxins	Etoposide, Teniposide	Topoisomerase II inhibition *(causes double-strand DNA cleavage)*	Lung cancer, testicular cancer, and refractory leukemias

3 EMERGING ANTITUMOR MECHANISMS

3.1 Regulation of Apoptosis

Apoptosis induction is a more profound mechanism of cell death triggered by naturally isolated anti-cancer agents (Chaudhry et al., 2022). Plant secondary metabolites modulate apoptosis through both intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Evading apoptosis is the major hurdle in killing cancer cells, a mechanism mainly regulated as intrinsic and extrinsic pathways (Chaudhry et al., 2022).

Curcumin from Curcuma longa induces apoptosis through the upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins, including Bcl-2 and survivin (Vadukoot et al., 2022). Curcumin exerts its anti-proliferative properties via a variety of mechanisms, including the suppression of intrinsic and extrinsic apoptotic signaling pathways and the stoppage of the cell cycle (Fan et al., 2022). Resveratrol from grapes and berries activates the intrinsic apoptotic pathway through mitochondrial membrane potential disruption and cytochrome c release (Yang et al., 2022).

Flavonoids, including quercetin and apigenin, induce apoptosis through diverse mechanisms, including caspase activation and p53 upregulation. Various extracts and fractions successfully induce apoptosis, cell-cycle modulation,

and anti-proliferative activity (Chaudhry et al., 2022). The ability of plant-derived compounds to overcome apoptotic resistance in cancer cells has been demonstrated through modulation of the PI3K/AKT/mTOR pathway.

3.2 Inhibition of Metastasis

Metastasis, the spread of cancer to distant organs, is the primary cause of cancer mortality. Epithelial-mesenchymal transition (EMT) is a biologic process that epithelial cells alter to mesenchymal cells and acquire fibroblast-like properties (Ghalehno et al., 2022). EMT plays a significant role in cancer metastasis, motility, and survival (Ghalehno et al., 2022).

Plant secondary metabolites inhibit metastasis through diverse mechanisms, including the regulation of epithelial-mesenchymal transition (EMT), matrix metalloproteinase inhibition, and angiogenesis suppression. Natural products could interfere with the different processes implicated in cancer drug resistance by reversing the EMT process (Ghalehno et al., 2022). Various studies on the relationship between EMT and resistance to chemotherapy agents have been reviewed, and different anticancer natural products with EMT inhibitory properties and drug resistance reversal effects have been compared (Ghalehno et al., 2022).

Curcumin inhibits EMT through regulation of Snail, Slug, and Twist transcription factors, reducing cancer cell migration and invasion. Resveratrol inhibits matrix metalloproteinase expression and activity, reducing extracellular matrix degradation required for metastasis. Sulforaphane from cruciferous vegetables suppresses angiogenesis through inhibition of VEGF signaling.

3.3 Autophagy Modulation

Autophagy is a highly conserved process that allows cells to degrade aggregated/misfolded proteins, dysfunctional or superfluous organelles, and damaged macromolecules, in order to recycle them for biosynthetic and/or energetic purposes to preserve cellular homeostasis and health (Martelli et al., 2022). Changes in autophagy are correlated with several pathological disorders such as neurodegenerative and cardiovascular diseases, infections, cancer, and inflammatory diseases (Martelli et al., 2022).

Recent evidence has shown that several natural products can modulate (induce or inhibit) the autophagy pathway (Martelli et al., 2022). Natural products may target different regulatory components of the autophagy pathway, including specific kinases or phosphatases (Martelli et al., 2022). Macroautophagy (autophagy) controls both apoptosis and the unfolded protein response in the cells; therefore, any changes in the autophagy pathway will affect both the unfolded protein response and apoptosis (Martelli et al., 2022).

Targeted autophagy activation has shown significant promise in the fight against tumor drug resistance (Yao et al., 2022). Several research groups have examined the ability of natural products such as alkaloids, terpenoids, polyphenols, and anthraquinones to serve as autophagy inhibitors or activators (Yao et al., 2022). The data support the capacity of natural products that promote lethal autophagy or inhibit pro-survival autophagy from being employed against tumor drug resistance (Yao et al., 2022).

Resveratrol induces autophagic cell death in certain cancer cell types through mTOR inhibition (Yang et al., 2022). Curcumin promotes autophagy through AMPK activation, leading to growth inhibition in cancer cells. However, autophagy induced by some compounds may promote survival, suggesting the need for careful therapeutic targeting.

3.4 Reversal of Multidrug Resistance

Multidrug resistance (MDR) has shown to be one of the leading threats faced currently in many chemotherapeutic agents (Shah et al., 2023). Permeability glycoprotein (P-gp) is an efflux transporter in membrane, an integral part of ATP-binding cassette transporters widely distributed in the body for cellular uptake (Shah et al., 2023). It is present enormously in cancerous cells and is in charge of generating transporter-mediated resistance to treatments of tumorous cells in addition to blocking the entry of chemotherapeutic drugs into the cell (Shah et al., 2023).

Natural P-gp inhibitors are derived from natural plant sources possessing basic structures like alkaloids, flavonoids, phenolics, terpenoids, saponins, sapogenins, sterols, coumarins, and miscellaneous structures acting on P-gp substrate for inhibition of multi-drug resistance via inhibiting the efflux pump (Shah et al., 2023). They do not depict their action on the healthy cells and thus it is proven to be more effective and less toxic than synthetic P-gp inhibitor leading to enhancement in bioavailability of chemotherapeutic drugs (Shah et al., 2023).

Curcumin inhibits P-glycoprotein function and expression, restoring sensitivity to chemotherapeutic agents in resistant cancer cells. Flavonoids, including quercetin and kaempferol, modulate P-glycoprotein activity through competitive

inhibition and downregulation. Plant-derived compounds can also regulate alternative resistance mechanisms, including other ABC transporters and survival signaling pathways.

3.5 Cancer Stem Cell Targeting

Cancer stem cells (CSCs) are a subpopulation of cells with self-renewal capacity and tumor-initiating potential, often responsible for tumor recurrence and therapy resistance. Natural products derived from major natural sources, including food, botanical, and marine species, have shown effects on CSCs in pre-clinical and clinical settings (Di Franco et al., 2022).

Natural compounds are promising players in cancer therapy through their ability to destroy the shield of cancer stem cells (Di Franco et al., 2022). Research has been conducted on the mechanisms through which natural compounds kill CSCs and the potential use of natural compounds in the inhibition of CSCs (Erkisa et al., 2022).

Curcumin suppresses CSC properties through inhibition of Wnt/β-catenin and Notch signaling pathways. Resveratrol reduces CSC populations through inhibition of STAT3 signaling and induction of differentiation. Sulforaphane targets CSCs through epigenetic modulation, including histone deacetylase inhibition.

3.6 Epigenetic Modulation

Emerging evidence indicates that plant secondary metabolites modulate epigenetic processes, including DNA methylation and histone modification. Natural products isolated from medicinal plants such as flavonoids and phenolic acids have shown their ability to exhibit several actions on epigenetic modifiers, such as the inhibition of DNA methyltransferase (DNMT) (Javaid et al., 2022).

Phytochemicals can mitigate cancer through metabolic remodeling and epigenetics reprogramming (A New Frontier, 2022). Curcumin, resveratrol, and indole-3-carbinol have been studied for their regulation of micro-RNA and epigenetic factors in the treatment of cancers (Javaid et al., 2022).

Curcumin modulates histone acetylation and DNA methylation patterns, regulating gene expression in cancer cells. Resveratrol activates SIRT1, a NAD-dependent deacetylase, and inhibits HDAC activity. Sulforaphane inhibits HDAC activity, promoting histone acetylation and transcription of tumor suppressor genes.

3.7 Immunomodulatory Effects

Plant-derived natural products have shown potential as immunomodulators and therefore as novel immunotherapies for cancer treatment (Natural biomolecules, 2022). Natural products and their derivatives have been investigated as immune checkpoint inhibitors, targeting cytokine/chemokine signaling in cancer (Natural products and their derivatives, 2022).

Herbal medicine-derived natural products targeting cytokine/chemokines and immune checkpoints have been summarized (Natural products and their derivatives, 2022). The modulation function of herbal medicines and natural products on tumor immunosurveillance has been reviewed, providing scientific insight into further research on molecular mechanisms and potential clinical applications (Leukocyte modulation, 2022).

Table 2: Emerging Antitumor Mechanisms of Plant Secondary Metabolites

Mechanism	Compound Examples	Key Molecular Targets	Key References
Apoptosis Regulation	Curcumin, Resveratrol	Downregulation of Bcl-2 and Survivin; Activation of Caspases	Vadukoot et al., 2022; Yang et al., 2022
Metastasis Inhibition	Curcumin, Sulforaphane	Suppression of Snail, Slug, and Matrix Metalloproteinases (MMPs)	Ghalehno et al., 2022
Autophagy Modulation	Resveratrol, Curcumin	Regulation of mTOR pathway and activation of AMPK	Martelli et al., 2022; Yao et al., 2022
MDR Reversal	Curcumin, Quercetin	Inhibition of P-glycoprotein (P-gp) and ATP-binding cassette (ABC) transporters	Shah et al., 2023
Cancer Stem Cell (CSC) Targeting	Curcumin, Sulforaphane	Downregulation of Wnt/β-catenin and STAT3 signaling pathways	Di Franco et al., 2022; Erkisa et al., 2022

Epigenetic Modulation	Curcumin, Resveratrol	Modulation of DNA Methyltransferases (DNMT), Histone Deacetylases (HDAC), and SIRT1	Javaid et al., 2022
Immunomodulation	Various polyphenols	Regulation of cytokine profiles and modulation of immune checkpoints	Natural biomolecules, 2022

4 SIGNALING PATHWAYS TARGETED BY PLANT SECONDARY METABOLITES

4.1 PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway is frequently hyperactivated in cancer and promotes cell proliferation, survival, and metabolism. Plant secondary metabolites target this pathway through diverse mechanisms. Curcumin has shown reliable anticancer function and low toxicity, thereby offering broad research prospects, including the induction of apoptosis and autophagy and arrest of the cell cycle (Fan et al., 2022). Resveratrol inhibits AKT phosphorylation and mTOR activity through AMPK activation (Yang et al., 2022).

4.2 MAPK/ERK Signaling

The MAPK/ERK pathway is involved in cell proliferation and is frequently dysregulated in cancer. Plant secondary metabolites modulate this pathway through regulation of ERK phosphorylation. Curcumin inhibits ERK phosphorylation, reducing cell proliferation and inducing apoptosis. Resveratrol activates ERK signaling in certain contexts, suggesting complex and context-dependent effects.

4.3 NF-κB Pathway

NF-κB is a transcription factor involved in inflammatory responses and cancer progression. Plant secondary metabolites inhibit NF-κB activation through regulation of IKK activity and IκB degradation. Curcumin is a well-characterized NF-κB inhibitor, blocking IKK activity and preventing NF-κB translocation to the nucleus. Resveratrol inhibits NF-κB through SIRT1 activation and downregulation of inflammatory mediators.

4.4 Long Non-Coding RNA Modulation

Long non-coding RNAs (lncRNAs) appear to be promising targets for the treatment of cancer (Almeida et al., 2022). Their deregulation has already been related to a variety of clinical-pathological parameters (Almeida et al., 2022). Terpenoids and flavonoids are the main examples of secondary metabolites involved with lncRNA activity (Almeida et al., 2022). lncRNAs including H19, CASC2, HOTAIR, NKILA, CCAT1, MALAT1, AFAP1-AS1, MEG3, and CDKN2B-AS1 can be highlighted as important targets in the search for new anti-tumor agents since they act as modulating pathways related to cell proliferation, cell cycle, apoptosis, cell migration, and invasion (Almeida et al., 2022).

4.5 Cellular Senescence Pathways

Cellular senescence suppresses tumor growth while also developing a tumorigenic state in nearby cells that is mediated by senescence-associated secretory phenotypes (SASPs) (Fakhri et al., 2022). The dual function of cellular senescence stresses the need for identifying multi-targeted agents directed towards the promotion of cell senescence in cancer cells and suppression of the secretion of pro-tumorigenic signaling mediators in neighboring cells (Fakhri et al., 2022). Natural secondary metabolites have shown favorable anticancer responses in recent decades, as some have been found to target the senescence-associated mediators and pathways (Fakhri et al., 2022). Phenolic compounds and polyphenols, terpenes and terpenoids, alkaloids, and sulfur-containing compounds have shown to be promising anticancer agents through the regulation of paracrine and autocrine pathways (Fakhri et al., 2022).

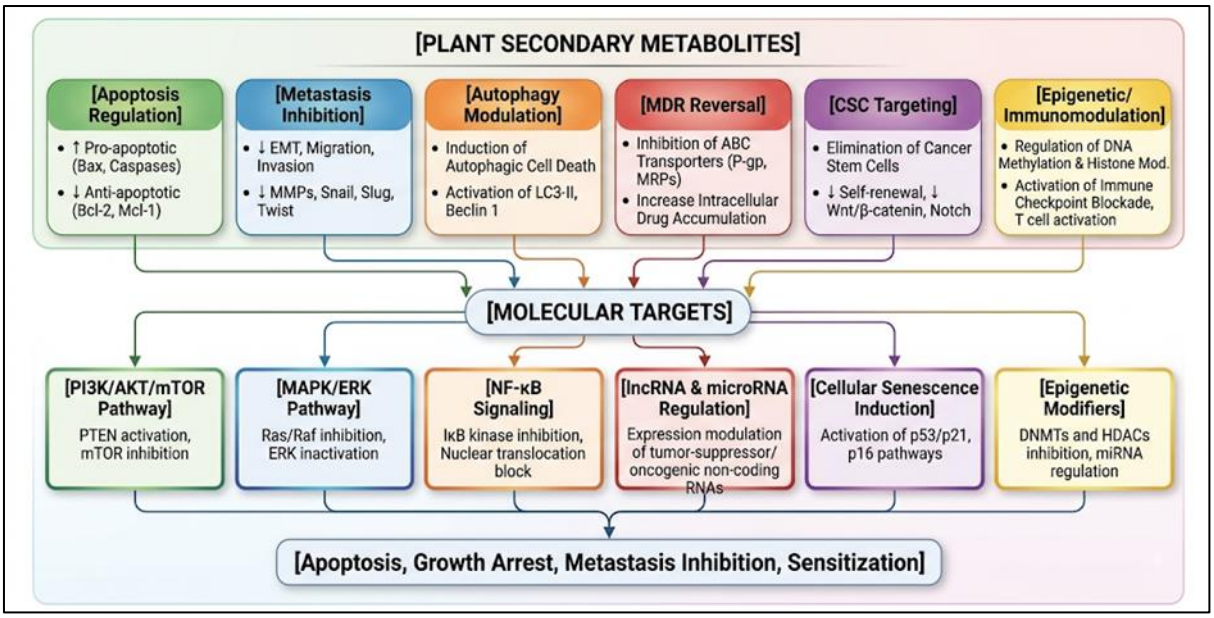

Figure 1: Emerging Antitumor Mechanisms of Plant Secondary Metabolites

5 CASE STUDIES

5.1 Curcumin

Curcumin, a hydrophobic polyphenol extracted from the rhizome of Curcuma longa, has shown reliable anticancer function and low toxicity, thereby offering broad research prospects (Fan et al., 2022). Due to its potency to affect multiple targets of different cellular pathways, it is considered a promising agent to tackle various cancers alone or in combination with the existing chemotherapies (Vadukoot et al., 2022). Curcumin exerts its anti-proliferative properties against cancer cell lines in vitro and in vivo via a variety of mechanisms, including the suppression of intrinsic and extrinsic apoptotic signaling pathways, the stoppage of the cell cycle (Fan et al., 2022), and the regulation of lncRNA expression (Almeida et al., 2022). Despite promising preclinical data, clinical translation has been limited by poor bioavailability.

5.2 Resveratrol

Resveratrol, a plant polyphenol, has demonstrated anticancer effects through diverse mechanisms, including apoptosis induction, autophagy modulation, and immunomodulation (Yang et al., 2022). Resveratrol could modulate apoptosis and autophagy, and autophagic genes (Yang et al., 2022). The anticancer mechanisms of resveratrol in breast cancer include the inhibition of cell proliferation and reduction of cell viability, invasion, and metastasis (Behroozaghdam et al., 2022). Resveratrol also counteracts multidrug resistance in acquired drug-resistant cancer cell lines (Resveratrol-Induced Resensitization, 2022). The compound has shown chemopreventive activity in preclinical models.

5.3 Epigallocatechin Gallate (EGCG)

EGCG, the major catechin in green tea, has demonstrated neuroprotective and anticancer effects through diverse mechanisms. The compound inhibits protein aggregation, reduces inflammation, and modulates epigenetic processes. EGCG has been studied as a cancer epigenetic regulator (Dou, 2022). Bioavailability and metabolism are major challenges for clinical translation.

6 CHALLENGES AND LIMITATIONS

6.1 Bioavailability

Poor bioavailability is a major limitation for many plant-derived compounds, particularly those with limited aqueous solubility and rapid metabolism. Curcumin and resveratrol are notable examples with low oral bioavailability (Vadukoot et al., 2022; Yang et al., 2022). Nanotechnology-based delivery and synthetic modifications are being explored to overcome this limitation. The low yield, selectivity index, and undesirable pharmacokinetic parameters were emphasized as a difficulty for obtaining these compounds on a large scale and for improving the potency of its biological effect (Almeida et al., 2022).

6.2 Off-Target Effects

The pleiotropic effects of plant-derived compounds, while potentially beneficial, may also contribute to off-target effects and toxicity. The complex pharmacological profiles require careful evaluation of therapeutic indices and side effect profiles.

6.3 Predictive Biomarkers

The clinical utility of plant-derived compounds would benefit from predictive biomarkers identifying patients most likely to respond. The identification of molecular signatures correlating with response to specific plant-derived compounds is an important research direction.

6.4 Clinical Translation Challenges

Challenges for the use of natural products as commercial drugs include the low yield, selectivity index, and undesirable pharmacokinetic parameters (Almeida et al., 2022). However, the synthesis and/or development of formulations were suggested as a possible approach to solve these problems (Almeida et al., 2022). A multitude of preclinical findings have shown the function of botanicals in regulating cell autophagy and its potential impact on cancer therapy; however, the number of related clinical trials to date remains low (Martelli et al., 2022).

7 FUTURE PERSPECTIVES

The future of plant-derived anticancer agents lies in the elucidation of additional mechanisms and the development of improved formulations. The application of genomic and proteomic approaches will enable identification of novel targets and biomarkers. The integration of plant-derived compounds with immunotherapies represents a promising direction. The development of nanotechnology-based delivery systems may enhance bioavailability and tumor targeting. Personalized medicine approaches, guided by molecular biomarkers, may improve patient selection and outcomes.

Further pre-clinical and clinical studies are warranted to better clarify the utility of natural compounds and their modulatory effects on autophagy, as fine-tuning of autophagy could be translated into therapeutic applications for several cancers (Martelli et al., 2022). The potential applications of natural products that regulate autophagy in the fight against tumor drug resistance warrant further investigation, along with consideration of some limitations of the current studies and future research needs and priorities (Yao et al., 2022).

8 CONCLUSION

Plant secondary metabolites exert pleiotropic antitumor effects through diverse mechanisms beyond classical cytotoxicity. Emerging mechanisms include the regulation of apoptosis, metastasis inhibition, autophagy modulation, reversal of multidrug resistance, targeting of cancer stem cells, epigenetic modulation, and immunomodulatory effects. These compounds target multiple signaling pathways, including PI3K/AKT/mTOR, MAPK/ERK, and NF-κB, and modulate epigenetic processes and lncRNA expression. Clinical translation has been challenged by bioavailability and off-target effects, but emerging strategies are addressing these limitations. The continued elucidation of mechanisms, development of improved formulations, and integration with immunotherapies promise to enhance the therapeutic potential of plant-derived anticancer agents.

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