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Metabolic Reprogramming of Cancer Cells By Phytochemicals: Multi-Target Approaches to Tumor Metabolism

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ABSTRACT

Background: Cancer cells undergo metabolic reprogramming to support rapid proliferation and survival under stress conditions, involving enhanced glycolysis (Warburg effect), glutaminolysis, and aberrant lipid metabolism. These metabolic alterations represent attractive therapeutic targets for precision oncology.

Objective: This review synthesizes current evidence on phytochemicals as multi-target agents capable of modulating cancer metabolism and overcoming therapeutic resistance through simultaneous pathway disruption.

Key Findings: Phytochemicals including flavonoids, alkaloids, terpenoids, and phenolics demonstrate unique properties enabling multi-pathway targeting unlike conventional single-target drugs. These compounds effectively modulate key metabolic nodes including glucose transporters (GLUT1), glycolytic enzymes (hexokinase 2, pyruvate kinase M2), glutaminase, and fatty acid synthesis enzymes (FASN, ACCA). Resveratrol, quercetin, curcumin, and EGCG exhibit particularly robust effects by simultaneously targeting glycolysis, glutaminolysis, lipid metabolism, and oxidative phosphorylation while modulating critical signaling pathways (PI3K/Akt/mTOR, HIF-1α, NF-κB). Beyond direct metabolic targeting, these compounds modulate the tumor microenvironment by reducing hypoxia, inflammation, and angiogenesis while enhancing immune cell function and disrupting cancer-associated fibroblast crosstalk.

Clinical Implications: Combination approaches utilizing phytochemicals with conventional metabolic inhibitors (metformin, 2-deoxy-D-glucose) demonstrate synergistic effects, enabling dose reduction and resistance prevention. The multi-target nature of phytochemicals addresses metabolic plasticity that underlies therapeutic resistance in cancer stem cells and metastatic disease.

Conclusion: Phytochemicals represent promising agents for metabolic cancer therapy through their ability to simultaneously disrupt multiple interconnected pathways, offering potential for personalized treatment strategies when integrated with precision medicine approaches and advanced drug delivery systems.

KEYWORDS: Metabolic reprogramming; phytochemicals; cancer metabolism; multi-target therapy; tumor microenvironment

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INTRODUCTION

Cancer cell metabolism has emerged as a critical hallmark of cancer, fundamentally distinct from that of normal cells. Tumors undergo metabolic reprogramming to meet the increased demands for energy, biosynthetic precursors, and redox balance necessary for rapid proliferation and survival under stressful conditions such as hypoxia and nutrient deprivation. Key alterations include enhanced glycolysis even in the presence of oxygen (the Warburg effect), up regulated glutaminolysis for nitrogen and carbon supply, and aberrant lipid metabolism supporting membrane biosynthesis and signaling. These metabolic adaptations are orchestrated by oncogenes and tumor suppressor genes, making metabolic enzymes and transporters attractive therapeutic targets. Given that metabolic reprogramming is often essential for tumor growth and metastasis, disrupting these pathways can sensitize cancer cells to therapies and address treatment resistance, offering a new frontier in precision oncology. **(**Cheong H et. al., 2012**,** Jang Met. al., 2013**,** Stine, Z.E., Schug, Z.T. et al.2022, Ganapathy-Kanniappan S 2017)

Phytochemicals and herbal medicines represent a promising class of therapeutic agents to target cancer metabolism due to their structural diversity and ability to simultaneously modulate multiple cellular pathways. Unlike conventional single-target drugs, phytochemicals such as flavonoids, alkaloids, terpenoids, and phenolics can interact with several metabolic nodes within cancer cells, thereby exerting pleiotropic effects. For example, some natural compounds inhibit glycolytic enzymes, while others regulate lipid synthesis or interfere with mitochondrial oxidative phosphorylation. Additionally, many phytochemicals possess antioxidant, anti-inflammatory, and immunomodulatory properties, which further contribute to their anticancer effects by modulating the tumor microenvironment and overcoming metabolic plasticity. (Jenča A et. al.,2024, Jha SK et. al.,2025, Monica S. J et. al.,2025, Shuvalov O et. al.,2023)

The relative safety profile, broad availability, and historical use of herbal compounds enhance their appeal for integration with standard cancer therapies. Importantly, many phytochemicals have demonstrated the ability to overcome therapeutic resistance by targeting alternative metabolic routes or compensatory pathways, potentially improving patient outcomes. As research advances, the integration of phytochemicals into metabolic targeting strategies holds great promise for developing more effective, less toxic, and personalized cancer treatments that exploit the metabolic vulnerabilities of tumors. This growing body of evidence underscores the need for comprehensive reviews and clinical validation efforts focused on multi-target metabolic modulation by herbal compounds. **(**Jha SK et. al., 2025, Shuvalov O et. al., 2023**,** Aljabali, A.A.A. et. al.2025)

HALLMARKS OF CANCER METABOLIC REPROGRAMMING

Cancer metabolic reprogramming is now recognized as a fundamental hallmark of cancer, crucial for sustaining the rapid proliferation and survival of tumor cells. Unlike normal cells, which primarily generate energy through oxidative phosphorylation, cancer cells exhibit altered metabolism characterized by increased glycolysis (even in the presence of oxygen), heightened glutaminolysis, and deregulated lipid metabolism. These changes enable tumors to fulfill elevated bioenergetics and biosynthetic demands, adapt to hostile microenvironments, and resist therapy. **(**Xu, X.et. al., 2023**,** Phan LM et. al., 2014, ward PS et. al., 2012)

Overview of Main Metabolic Pathways in Cancer

Glycolysis: Cancer cells prefer glycolysis over oxidative phosphorylation to produce ATP, a phenomenon called the Warburg effect. This

aerobic glycolysis supports rapid energy generation and provides metabolic intermediates for nucleotide, amino acid, and lipid synthesis. Key molecular players include glucose transporters (e.g., GLUT1), hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), and the hypoxia-inducible factor 1-alpha (HIF-1α), which promotes glycolysis under hypoxic tumor microenvironments**.** **(**Xu, X.et. al., 2023, ward PS et. al., 2012)

Glutaminolysis: Tumor cells often exhibit increased dependency on glutamine uptake and catabolism, which supplies carbon and nitrogen for the tricarboxylic acid (TCA) cycle, nucleotide biosynthesis, and antioxidant production. Enzymes like glutaminase (GLS) and transporters such as ASCT2 are frequently upregulated to support glutaminolysis, facilitating survival during nutrient stress. **(**Xu, X.et. al., 2023**,** Phan LM et. al., 2014,)

Lipid Metabolism: Aberrant lipid synthesis and fatty acid oxidation also typify cancer metabolism. Enhanced de novo lipogenesis provides essential components for membrane biogenesis and signaling molecules, while deregulated fatty acid oxidation supports energy homeostasis. Key targets include fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), and carnitinepalmitoyltransferase 1 (CPT1) **(**Xu, X.et. al., 2023**,** Phan LM et. al., 2014,)

Tumor Microenvironment and Metabolic Adaptation

The tumor microenvironment (TME) is characterized by hypoxia, low nutrient availability, acidity, and inflammatory signals, which impose additional metabolic pressures on cancer cells. Metabolic reprogramming enables tumor cells not only to survive but also to modify the TME, for example, through lactate production that modulates immune cell function and angiogenesis. Cancer-associated stromal cells, immune cells, and fibroblasts also undergo metabolic changes, creating complex metabolic crosstalk that promotes tumor progression and therapy resistance. (Xu, X.et. al., 2023**,** ward PS et. al., 2012)

In summary, cancer metabolic reprogramming involves dynamic and interconnected alterations in glycolysis, glutaminolysis, lipid metabolism, and TME adaptation. This metabolic plasticity provides multiple potential therapeutic targets for disrupting tumor growth and overcoming resistance. **(**Xu, X.et. al., 2023**,** Phan LM et. al., 2014, ward PS et. al., 2012)

MECHANISMS OF PHYTOCHEMICAL ACTION: MULTI-TARGET METABOLIC MODULATION

Phytochemicals exhibit unique properties that enable them to simultaneously modulate multiple metabolic pathways, making them powerful agents for targeting the complex metabolic rewiring observed in cancer cells. Unlike highly selective small-molecule drugs, phytochemicals often act as multi-target agents that simultaneously suppress glycolysis, glutaminolysis, lipid metabolism, and other interconnected metabolic processes, thus reducing the likelihood of resistance development and enhancing therapeutic efficacy. (Shuvalov O et. al., 2023)

Properties Enabling Multi-Pathway Targeting

Structural Diversity: Phytochemicals encompass diverse chemical classes such as flavonoids, phenolic acids, phytosterols, stilbenes, and carotenoids that interact with various enzymes and signaling proteins involved in metabolism.

Pleiotropic Activity: Many phytochemicals affect several key signaling pathways (e.g., PI3K/Akt/mTOR, c-Myc, HIF-1α) that regulate multiple metabolic routes, thus exerting broad anticancer effects.

Modulation of Enzyme Activity and Gene Expression: They can inhibit metabolic enzymes directly (e.g., hexokinase 2, fatty acid synthase) and alter expression of genes controlling metabolic flux.

Redox Regulation: Through antioxidant and pro-oxidant activities, phytochemicals influence cellular redox balance, impacting metabolism and inducing cancer cell death or senescence**.** (Shuvalov O et. al., 2023)

Role of Specific Phytochemical Classes

Flavonoids: Flavonoids like quercetin and kaempferol inhibit glycolytic enzymes (HK2, PKM2), suppress glutamine transporters, and down-regulate fatty acid synthesis enzymes (FASN), affecting energy production and biomolecule synthesis. They also modulate oncogenic signaling pathways that control metabolism.

Phenolic Acids: Compounds such as caffeic acid exhibit inhibitory effects on glycolysis and lipid metabolism by targeting key enzymes and signaling mediators involved in these pathways. (Shuvalov O et. al., 2023)

Phytosterols: These plant sterols interfere with lipid metabolism by inhibiting cholesterol synthesis enzymes and modulating lipid raft-associated signaling critical for cancer cell survival. **(**Angela R et. al., 2018)

Stilbenes: Resveratrol, a well-studied stilbene, regulates glucose uptake and metabolism through inhibition of GLUT1 and HIF-1α and suppresses lipogenesis and mitochondrial respiration, exerting broad metabolic control.

Carotenoids: These compounds modulate mitochondrial function and oxidative phosphorylation, impacting tumor energy metabolism while also providing antioxidant protection. (Shuvalov O et. al., 2023)

Together, these phytochemical classes orchestrate a multi-targeted assault on cancer metabolism, intervening at various nodes of glycolysis, glutaminolysis, lipid synthesis, and associated signaling pathways, thereby disrupting tumor growth and progression. (Shuvalov O et. al., 2023, Angela R et. al., 2018)

This multi-faceted modulation explains why phytochemicals hold promising potential as complementary or alternative metabolic cancer therapies, capable of overcoming the limitations of single-target inhibitors by addressing the metabolic plasticity of cancer cells simultaneously.

TARGETING GLYCOLYSIS IN CANCER: MOLECULAR TARGETS AND PHYTOCHEMICALS EXAMPLES

Cancer cells rely heavily on glycolysis for energy and biosynthesis even in oxygen-rich conditions, a phenomenon known as the Warburg effect. This metabolic reprogramming involves several key molecular targets **(**Ganapathy-Kanniappan S et. al., 2013**)**

GLUT1 (Glucose Transporter 1): Facilitates glucose uptake, a critical step for fueling glycolysis. GLUT1 is overexpressed in many tumors, supporting their high glucose consumption**. (**Ganapathy-Kanniappan S et. al., 2013)

HK2 (Hexokinase 2): Catalyzes the first step of glycolysis, converting glucose into glucose-6-phosphate. HK2 binds to mitochondria in cancer cells, promoting glycolysis efficiency and evasion of apoptosis. (Ganapathy-Kanniappan S et. al., 2013)

LDHA (Lactate Dehydrogenase A): Converts pyruvate to lactate and regenerates NAD+ necessary for sustained glycolysis. Elevated LDHA contributes to acidification of the tumor microenvironment and tumor aggressiveness (Ganapathy-Kanniappan S et. al., 2013)

PKM2 (Pyruvate Kinase M2): Regulates the final glycolytic step; exists in active and less active forms to balance energy production and biosynthesis. Cancer cells often express the less active PKM2 isoform to support anabolic processes Ganapathy-Kanniappan S et. al., 2013)

HIF1α (Hypoxia-Inducible Factor 1 alpha): A transcription factor activated under hypoxia that induces expression of glycolytic enzymes including GLUT1 and LDHA, enabling cancer cells to adapt metabolically under low oxygen**.** (Ganapathy-Kanniappan S et. al., 2013)

Phytochemical Compounds Targeting Glycolysis

Resveratrol: Downregulates GLUT1 and HK2 expression, inhibits HIF1α activity, and suppresses LDHA and PKM2, thereby disrupting glycolytic flux and cancer cell energy production (Zhao Y et. al., 2022)

Quercetin: Inhibits HK2 and PKM2 as well as signaling pathways like PI3K/Akt that regulate glycolysis and glucose uptake, leading to reduced lactate secretion and ATP generation(Zhao Y et. al.,2022)

Curcumin: Suppresses HIF1α and downstream glycolytic enzymes, impeding glycolysis and energy metabolism in cancer cells. Also modulates oncogenic signaling pathways impacting metabolism. (Zhao Y et. al., 2022)

EGCG (Epigallocatechin-3-gallate): Inhibits HK2 and LDHA activities, reduces glucose uptake, and activates AMPK to suppress glycolytic and anabolic metabolism, exerting anticancer effects. (Zhao Y et. al., 2022)

TARGETING GLUTAMINOLYSIS AND AMINO ACID METABOLISM

Tumor cells are highly dependent on glutamine, a phenomenon known as "glutamine addiction," and targeting key players in glutaminolysis and amino acid metabolism—such as transporters (ASCT2, SLC7A11) and enzymes (GLS1, GLS2)—has become a promising strategy in cancer therapy. Molecular targeting of these pathways impairs tumor growth and increases sensitivity to therapy by altering redox homeostasis, nutrient supply, and immune modulation**. (**Zou W et. al.,2025, Jin J et. al., 2023, Fan Y et. al.,2024, Wang Z et. al.,2020, Dong-Hwan Kim,Dong Joon Kim et. al.,2025, ShutianGuo et. al., 2024)

Tumor Dependency and Molecular Targets

Rapidly proliferating tumors exhibit high levels of glutamine uptake via ASCT2 (SLC1A5), the most studied glutamine transporter in cancer, and GLS1, the glutaminase enzyme responsible for converting glutamine to glutamate— the first step in glutaminolysis. (Zou W et. al.,2025, Jin J et. al., 2023, Fan Y et. al.,2024, Dong-Hwan Kim,Dong Joon Kim et. al.,2025, ShutianGuo et. al., 2024)

- Inhibiting ASCT2 reduces glutamine influx and can compromise tumor antioxidant defenses, induce apoptosis, and delay tumor growth.(Zou W et. al.,2025, Dong-Hwan Kim,Dong Joon Kim et. al.,2025, ShutianGuo et. al., 2024)
- GLS1 inhibition disrupts the entry of glutamine into the TCA cycle, increases oxidative stress, and resensitizes tumors to chemotherapy**(**Jin J et. al., 2023, Wang Z et. al.,2020, Anthony, Josephine et. al.,2024**)**
- Tumor resistance to glutaminolysis inhibition occurs through upregulation of alternative pathways (e.g., ASNS, GAD branches, compensation via other amino acid transporters), necessitating combination strategies. **(**Zou W et. al.,2025, Fan Y et. al.,2024)

Phytochemicals Influencing Glutaminolysis

- Quercetin and resveratrol, two phytochemicals, have been reported to interfere with glutaminolysis in cancer cells, largely by reducing GLS1 transcription and transporter activity or by influencing regulatory signaling pathways. These agents disrupt the glutamine fueling of malignant cells, leading to elevated oxidative stress and cell death.
- Quercetin appears to reduce glutaminase activity, decrease glutathione biosynthesis, and enhance tumor cell susceptibility to oxidative injury.
- Resveratrol impairs glutamate and glutathione production, aggravating redox imbalance and amplifying the cytotoxic effect of chemotherapy.
- These phytochemicals have demonstrated potential in preclinical settings, but further clinical studies are necessary to confirm their efficacy as adjuncts in targeting tumor metabolism.**(** Wang Z et. al.,2020)

Supporting Evidence from Recent Reviews and Research

Reviews and research articles from journals like Nature Communications, Frontiers in Pharmacology, and others confirm the critical role of ASCT2 and GLS1 as druggable targets that control glutamine flow and metabolism in cancer, with disruption of these targets yielding antitumor effects. **(**Jin J et. al., 2023, Fan Y et. al.,2024, Wang Z et. al.,2020, Dong-Hwan Kim,Dong Joon Kim et. al.,2025)

Combination therapies targeting multiple transporters and utilizing GLS inhibitors or phytochemicals are under investigation for overcoming resistance and optimizing antitumor efficacy. **(**Zou W et. al.,2025, Fan Y et. al.,2024, Dong-Hwan Kim,Dong Joon Kim et. al.,2025)

TARGETING LIPID METABOLISM

Fatty acid synthesis and oxidation are crucial metabolic hallmarks that support tumor growth, facilitate metastasis, and promote cancer cell survival. Inhibiting key lipid metabolic enzymes—such as FASN, ACCA, and CPT1—disrupts these processes, and phytochemicals have emerged as potent

modulators of these targets in preclinical cancer models. (Zhao J et. al., 2021, Li H et. al., 2020, Lei Y et. al., 2025)

Fatty Acid Synthesis and Oxidation in Cancer

Tumors show markedly enhanced de novo fatty acid synthesis and elevated activity of enzymes like fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACCA), satisfying requirements for rapid membrane biosynthesis, signaling, and energy provision. (Zhao J et. al., 2021, Li H et. al., 2020, Lei Y et. al., 2025, Koundouros et. al., 2020)

Fatty acid oxidation, driven predominantly by carnitinepalmitoyltransferase 1 (CPT1), enables cancer cells to survive metabolic stress and promotes metastasis by supplying ATP and reducing equivalents like NADPH (Zhao J et. al.,2021, Li H et. al.,2020, Lei Y et. al.,2025)

These alterations provide energy for highly proliferating cells, affect cancer stem cell maintenance, and may contribute to therapy resistance (Zhao J et. al., 2021, Li H et. al., 2020, Lei Y et. al., 2025, Koundouros et. al., 2020)

Inhibitory Effects of Phytochemicals

- Multiple phytochemicals, including resveratrol, quercetin, EGCG, curcumin, and luteolin, have been demonstrated to suppress cancer cell lipid metabolism by downregulating the expression or activity of FASN, ACCA, and CPT1
- Quercetin and resveratrol decrease FASN and ACCA expression, leading to reduced fatty acid synthesis and impaired cancer cell proliferation.
- EGCG and curcumin also target FASN and ACCA, impacting both lipid synthesis and related oncogenic signaling pathways. (Li H et. al.,2020)
- Certain phytochemicals lower CPT1 expression, thereby reducing fatty acid oxidation, weakening cancer cell survival under stress, and sensitizing cells to therapy.
- These inhibitory effects are supported by preclinical studies showing reduced tumor growth and metastasis associated with the use of these compounds.

Table 1: Key Metabolic Targets and Phytochemical Effects

Target	Cancer Role	Phytochemical Effect
FASN	Fatty acid synthesis, growth	Downregulated by quercetin, resveratrol, EGCG
ACCA	Rate-limiting in FA synthesis	Downregulated by quercetin, curcumin, EGCG
CPT1	Fatty acid oxidation, survival	Inhibited by select phytochemicals (EGCG, quercetin)

Phytochemicals offer promising adjuncts to conventional therapies by targeting lipid metabolic vulnerabilities specific to cancer cells, particularly through FASN, ACCA, and CPT1 inhibition (Li H et. al., 2020, Lei Y et. al., 2025, Koundouros et. al., 2020)

MODULATION OF FURTHER PATHWAYS

Cancer cells exhibit remarkable metabolic plasticity, utilizing multiple interconnected pathways to sustain their growth and survival. Beyond glycolysis and glutaminolysis, two critical metabolic pathways—the pentose phosphate pathway (PPP) and oxidative phosphorylation (OXPHOS)—serve as essential targets for phytochemical intervention, with several compounds demonstrating multi-pathway effects across these systems. (Shuvalov O et. al.,2023, Jin L et. al.,2019, Patra KC et. al.,2014, Zhao Z et. al.,2022, TeSlaa T et. al.,2023)

Pentose Phosphate Pathway (PPP)

The PPP serves as a critical parallel pathway to glycolysis, generating NADPH for biosynthetic processes and ribose-5-phosphate for nucleotide synthesis while providing antioxidant defense through glutathione regeneration. Cancer cells heavily depend on PPP flux to meet their high demands for nucleotide synthesis and to counteract oxidative stress generated during rapid proliferation (Jin L et. al., 2019, Patra KC et. al., 2014, TeSlaa T et. al., 2023, Cossu, V. et. al., 2020, Krushna CP et. al., 2014)

Key regulatory enzymes in the PPP include glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase

(6PGD), which control the oxidative branch, and transketolase (TK) and transaldolase (TALDO), which regulate the non-oxidative branch. The pathway operates in three distinct modes—pentose insufficiency, pentose overflow, and pentose cycling—depending on cellular metabolic demands. **(**Patra KC et. al., 2014, TeSlaa T et. al., 2023, Krushna CP et. al., 2014**)**

Phytochemical modulation of the PPP has been demonstrated with several compounds. Resveratrol downregulates key PPP enzymes including G6PD and transketolase, effectively reducing PPP flux in colon cancer cells. This inhibition compromises the cancer cell's ability to generate NADPH for biosynthetic processes and antioxidant defense, making them more vulnerable to oxidative stress and therapeutic intervention. **(**Shuvalov O et. al., 2023**,** TeSlaa T et. al., 2023)

OXPHOS and Mitochondrial Metabolism

Contrary to the traditional Warburg paradigm, many cancer cells maintain functional mitochondrial OXPHOS, particularly cancer stem cells and metastatic cells that rely heavily on mitochondrial respiration for energy production. OXPHOS contributes significantly to ATP production in various cancers, with some studies showing contributions ranging from 30-90% of total cellular ATP. (Zhao Z et. al., 2022, Zheng, J.2012, Passaniti A et. al., 2022, John Greene et. al., 2022)

Mitochondrial vulnerabilities in cancer include enhanced dependence on OXPHOS for survival under stress conditions, increased ROS production, and altered mitochondrial dynamics that support metastasis. Cancer stem cells, in particular, exhibit preferential reliance on OXPHOS over glycolysis, making them susceptible to mitochondrial-targeting strategies. **(**Zhao Z et. al., 2022, Passaniti A et. al., 2022, John Greene et. al., 2022)

Phytochemical targeting of OXPHOS occurs through multiple mechanisms:

Kaempferolsuppresses mitochondrial respiratory complex I, leading to energy failure and autophagy induction in cancer cells

Quercetin inhibits OXPHOS in melanoma cell lines, disrupting mitochondrial energy production

Resveratrol targets multiple OXPHOS proteins while simultaneously affecting glycolysis, demonstrating its multi-pathway effects

Arctigenin specifically inhibits mitochondrial complexes II and IV, selectively killing OXPHOS-dependent cancer cells **(**Shuvalov O et. al., 2023)

Table 2: Example Phytochemicals with Multi-Pathway Effects

Phytochemical		PPP Effects	OXPHOS Effects	Additional Pathways	Signaling Pathways
Resveratrol		G6PD↓, TK↓	Complex inhibition	Glycolysis↓, Lipogenesis↓	PI3K/Akt/mTOR↓ [36]
EGCG		Indirect modulation	Mitochondrial dysfunction	FASN↓, ACCA↓	AKT-mTOR↓ [36]
Curcumin		PPP enzyme inhibition	Complex targeting	Glycolysis↓, Glutaminolysis↓	NF-κB↓, MAPK↓ [37]
Quercetin		G6PD modulation	OXPHOS suppression	GLS1↓, FASN↓	Multiple pathways [38]

MODULATION OF TUMOR MICROENVIRONMENT METABOLISM BY PHYTOCHEMICALS

Phytochemicals are increasingly recognized for their ability to modulate various aspects of the tumor microenvironment (TME), including hypoxia, inflammation, angiogenesis, and interactions between cancer-associated fibroblasts (CAFs) and immune cells. These multitarget actions underpin their potential as adjuncts in cancer therapy by not only targeting tumor cells but also reprogramming the TME to restrict cancer progression. **(**Shuvalov O et. al.,2023, Paudel S et. al.,2023, Roy S et. al.,2020, Zhu Y et. al., 2022, Rujing Chen et. al., 2020)

Influence on Hypoxia, Inflammation, and Angiogenesis

Hypoxia and Angiogenesis

- Hypoxia within the TME stabilizes hypoxia-inducible factor 1α (HIF-1α), triggering the transcription of genes like VEGF, PDGF, and MMPs, which promote angiogenesis, tumor cell migration, and invasiveness. **(**Roy S et. al.,2020, Jiang X et.al 2020, Chen, Z et.al 2023, Liu, ZL et. al.,2023, Karen Acuña-Pilarte et. al.,2025)
- Several phytochemicals downregulate HIF-1α or disrupt its signaling:
  - **Kaempferol:** Induces degradation of HIF-1α via the ubiquitin–proteasome pathway, inhibiting hypoxia signaling and angiogenesis in cancer.**(** Shuvalov O et. al.,2023)
  - **Curcumin and Resveratrol:** Inhibit both HIF-1α and VEGF expression, decreasing new blood vessel formation, and normalizing aberrant tumor vasculature**. (**Shuvalov O et. al.,2023)
  - **Quercetin and EGCG:** Also reduce pro-angiogenic signaling and downregulate inflammatory cytokines, limiting tumor neovascularization. **(**Shuvalov O et. al.,2023, Paudel S et. al.,2023**)**
- By targeting hypoxia and HIF-1α, these compounds can also modulate extracellular acidosis, decrease MMP activity, and impair processes necessary for metastasis and TME remodeling.**(** Jiang X et.al 2020, Chen, Z et.al 2023, Karen Acuña-Pilarte et. al.,2025)

Inflammation

- Curcumin, resveratrol, quercetin, and others exhibit strong anti-inflammatory actions by inhibiting NF-κB signaling, suppressing pro-inflammatory cytokine release (TNF-α, IL-6), and blocking recruitment of immunosuppressive cells. **(**Shuvalov O et. al.,2023, Paudel S et. al.,2023**)**

The reduction in inflammation modulates the TME towards an anti-tumor phenotype and can also enhance immune cell infiltration and function.

Effects on Cancer-Associated Fibroblasts and Immune Cell Crosstalk

Cancer-Associated Fibroblasts (CAFs)

CAFs are central to remodeling the TME, influencing tumor cell metabolism, and supporting immunosuppression and metastasis **(**Zhu Y et. al., 2022, Rujing Chen et. al., 2020, Thiery J et. al., 2022)

Natural products such as curcumin, resveratrol, and other polyphenols have been shown to:

Inhibit CAF activation and signaling (e.g., through Hedgehog, TGF-β, and NF-κB pathways). **(**Shuvalov O et. al., 2023, Rujing Chen et.al2020)

Suppress paracrine pro-tumorigenic signals, reduce secretion of cytokines like IL-6, and interfere with the ability of CAFs to support tumor growth and therapy resistance. **(**Zhu Y et.al 2022, Rujing Chen et.al 2020)

Remodel the extracellular matrix (ECM) and suppress metabolic crosstalk between CAFs and cancer cells.

Immune Cell Metabolic Crosstalk

- **Phytochemicals** enhance anti-tumor immunity by:
- Restoring mitochondrial function and metabolic fitness in T cells, reversing hypoxia-induced suppression of cytotoxicity **(**Paudel S et. al.,2023, Chen, Z et.al 2023, AbouKhouzam R et. al.,2021)
- Increasing activation and cytotoxic capacity of NK cells and CD8+ T cells (e.g., via quercetin, silibinin, apigenin, curcumin), and decreasing numbers of immunosuppressive regulatory T cells and myeloid-derived suppressor cells (MDSCs). **(**Paudel S et. al.,2023
- Counteracting adenosine–A2A receptor and lactate-mediated immunosuppression in the hypoxic TME **(**Paudel S et. al.,2023, Roy S et. al.,2020, Chen, Z et.al 2023)

Table 3: Summary Table of Major Effects

Phytochemical	Impact on Hypoxia/HIF-1α	Anti-angiogenic Effects	CAF Modulation	Immune Crosstalk
Kaempferol	↓ HIF-1α, ↓ GLUT1	↓ VEGF, vessel density	Inhibits CAFs	Enhances immunity
Curcumin	↓ HIF-1α, ↓ cytokines	↓ VEGF, TGF-β	Inhibits TGF-β, ECM	↑ T/NK/CD8+ cells, ↓ Tregs/MDSCs
Resveratrol	↓ HIF-1α, ↓ inflammation	↓ Angiogenesis	Inhibits CAF signaling	↑ CD8+ T cells
Quercetin	↓ HIF-1α, ↑ T cell/NK	↓ VEGF, MMPs	Suppresses CAFs signaling	↑ CD8+/NK, ↓ Tregs
EGCG	↓ Inflammation	↓ VEGF	Reduces ECM remodeling	↑ CD8+ T/NK cells

OVERCOMING METABOLIC PLASTICITY AND THERAPEUTIC RESISTANCE:

Tumor Adaptation and Resistance Mechanisms

Metabolic Plasticity in Cancer Progression

Cancer cells demonstrate extraordinary metabolic flexibility that fundamentally contributes to therapeutic resistance. This metabolic plasticity manifests through several key mechanisms **(**Fendt SM et. al., 2020, Wu P et.al 2021)

Dynamic Metabolic Switching: Cancer cells can alternate between glycolysis and oxidative phosphorylation (OXPHOS) depending on environmental pressures and therapeutic interventions. This metabolic flexibility allows tumors to survive under various stressful conditions, including chemotherapy, radiation, and nutrient deprivation. **(**Fendt SM et. al., 2020**,** Desbats MA et. al., 2020**)**

Cancer Stem Cell Metabolic Heterogeneity: Cancer stem cells (CSCs) exhibit particularly high metabolic plasticity, enabling dynamic transitioning between different metabolic phenotypes. These cells can switch from OXPHOS to glycolysis when mitochondrial function is compromised, allowing tumors to regain growth following therapy. **(**Fendt SM et. al., 2020, Liu S et. al., 2024**)**

Micro-environmental Adaptation: The tumor microenvironment significantly influences metabolic adaptation potential. Stromal cells, immune cells, and extracellular matrix components create metabolic gradients that promote adaptive resistance through various mechanisms including exosome-mediated metabolite transfer and inflammatory signaling. **(**Wu P et.al 2021)

Specific Mechanisms of Metabolic Reprogramming

Energy Production Flexibility: Tumors demonstrate the ability to utilize multiple fuel sources beyond glucose, including lactate, fatty acids, glutamine, and amino acids. This metabolic versatility ensures continued energy production even when primary pathways are therapeutically targeted **(**Fendt SM et. al., 2020, Gouirand V et. al., 2018**)**

Redox Homeostasis Management: Cancer cells maintain antioxidant defense systems through metabolic reprogramming, particularly via the pentose phosphate pathway and glutamine metabolism, enabling survival under oxidative stress induced by therapies. (Liu S et. al., 2024)

Drug Efflux Enhancement: Metabolic reprogramming supports increased expression and activity of ATP-binding cassette (ABC) transporters, particularly P-glycoprotein, MRP1, and BCRP, leading to enhanced drug efflux and reduced intracellular drug concentrations.**(**Tinoush B et. al.,2020)

Phytochemicals as Modulators to Overcome Resistance

ATP-Binding Cassette Transporter Modulation

Phytochemicals represent the most extensively studied natural approach to reversing multidrug resistance through ABC transporter modulation: (Tinoush B et. al., 2020)

Direct Inhibition Mechanisms: Flavonoids such as quercetin, apigenin, and EGCG directly

inhibit P-glycoprotein function by competing with chemotherapeutic agents for binding sites, thereby increasing intracellular drug accumulation. Alkaloids including berbamine, tetrandrine, and harmine demonstrate potent inhibitory effects on multiple ABC transporters simultaneously. (Tinoush B et. al., 2020)

Expression Downregulation: Phytochemicals like curcumin and resveratrol suppress ABC transporter gene expression through modulation of transcription factors such as NF-κB and AP-1. This approach provides longer-lasting effects compared to direct inhibition alone. (Tinoush B et. al., 2020)

Synergistic Enhancement: Natural compounds exhibit synergistic interactions with conventional chemotherapeutics, allowing for dose reduction while maintaining or enhancing therapeutic efficacy. **(**Wang P et. al., 2015, Zou JY et.al 2024)

Metabolic Pathway Disruption

AMPK/PGC-1α Pathway Targeting: Phytochemicals regulate cancer metabolism through modulation of the AMPK/PGC-1α signaling pathway, which controls energy homeostasis, mitochondrial biogenesis, and metabolic flexibility. Resveratrol, quercetin, and curcumin activate AMPK while modulating PGC-1α expression to disrupt metabolic adaptation**. (**Fakhri S et. al., 2024)

Glycolysis Inhibition: Compounds like corosolic acid and catechin target key glycolytic enzymes, forcing cancer cells to rely on less efficient metabolic pathways. This metabolic stress particularly affects rapidly proliferating cancer cells and those with high glucose dependence**. (**Wang Q et. al., 2025)

Mitochondrial Function Modulation: Phytochemicals can both enhance and disrupt mitochondrial function depending on the cancer type and metabolic state, with compounds like isoliquiritigenin and EGCG promoting mitochondrial dysfunction in resistant cancer cells**. (**Fakhri S et. al., 2024)

Cancer Stem Cell Targeting

Phytochemicals demonstrate particular efficacy against cancer stem cells, which exhibit the highest metabolic plasticity:

Stemness Marker Suppression: EGCG, sulforaphane, and genistein reduce expression of stem cell markers (CD133, CD44, and ALDH1) and transcription factors (Oct4, Sox2, Nanog) essential for stem cell maintenance.

Self-Renewal Inhibition: Natural compounds disrupt key signaling pathways (Wnt/β-catenin, Notch, and Hedgehog) that maintain cancer stem cell self-renewal capacity, forcing differentiation and reducing tumorigenic potential.

EMT Reversal: Phytochemicals like pterostilbene and genistein reverse epithelial-mesenchymal transition, a process closely linked to stemness and metastatic capacity.**(** Liskova A et. al.,2019)

Apoptosis and Autophagy Regulation

Caspase Activation: Resveratrol, curcumin, and quercetin restore apoptotic sensitivity in resistant cancer cells by activating both intrinsic and extrinsic apoptotic pathways. This includes modulation of Bcl-2 family proteins and p53-dependent signaling.

Autophagy Modulation: Phytochemicals exhibit dual roles in autophagy regulation - promoting protective autophagy in normal cells while inducing lethal autophagy in cancer cells through mTOR pathway modulation. **(**Rahman MA et.al 2021)

Death Resistance Reversal: Natural compounds overcome resistance mechanisms including survivin overexpression, NF-κB activation, and DNA repair enhancement that typically protect cancer cells from therapeutic intervention.**(**Wu P et. al.,2021)

Novel Mechanisms and Emerging Targets

Epigenetic Modulation: Phytochemicals modify DNA methylation patterns and histone modifications to reverse epigenetic silencing of tumor suppressor genes and restore drug sensitivity.

DNA Repair Sensitization: Natural compounds can inhibit DNA repair mechanisms, particularly homologous recombination and non-homologous end joining, making cancer cells more susceptible to DNA-damaging therapies. **(**Rahman MA et. al., 2021)

Metabolic Enzyme Targeting: Specific phytochemicals target key metabolic enzymes such as fatty acid synthase, acetyl-CoA carboxylase, and glutaminase to disrupt cancer cell energy production and biosynthesis **(**Fakhri S et. al., 2024)

Clinical Translation and Therapeutic Applications

Combination Strategies

The most promising approach involves combining phytochemicals with conventional therapies rather than using them as monotherapy. This strategy allows for:

Dose Reduction: Lower doses of toxic chemotherapeutics while maintaining efficacy

Resistance Prevention: Multiple targeting prevents development of single-pathway resistance

Enhanced Selectivity: Preferential targeting of cancer cells while protecting normal tissues **(**Wang P et. al., 2015, Wang Q et. al., 2025)

Delivery System Optimization

Novel drug delivery systems enhance phytochemical bioavailability and therapeutic efficacy:

Nanoformulations: Improve solubility and cellular uptake of poorly bioavailable compounds

Targeted Delivery: Direct phytochemicals to specific tissue types or cellular compartments

Sustained Release: Maintain therapeutic concentrations over extended periods **(**Fakhri S et. al., 2024)

COMBINATION APPROACHES: PHYTOCHEMICALS PLUS METABOLIC INHIBITORS

Synergistic Mechanisms and Molecular Rationale

AMPK-Mediated Synergy

The most extensively studied combination approach involves dual AMPK activation through metabolic inhibitors and phytochemicals. Metformin, the first-line diabetes medication, activates AMPK through mitochondrial complex I inhibition, while phytochemicals like curcumin, resveratrol, and EGCG provide additional AMPK stimulation through distinct mechanisms. **(**Rizeq B et. al., 2020, Zarei E et. al., 2021, Kim I et. al., 2013)

Key Molecular Events:

- Enhanced mTOR pathway suppression through additive AMPK phosphorylation
- Synergistic autophagy induction leading to autophagic cell death
- Improved tumor selectivity due to differential AMPK expression in cancer versus normal cells
- Coordinated metabolic reprogramming that prevents adaptive resistance

The combination of metformin plus curcumin demonstrates particularly strong synergistic effects (CI < 1) across multiple cancer types including gastric, breast, and hepatocellular carcinomas. This combination achieves complete inhibition of cancer cell viability at concentrations where individual agents show minimal effect, while selectively sparing normal cells. **(**Zarei, E et. al., 2021)

Glycolysis-OXPHOS Dual Targeting

2-Deoxy-D-glucose (2-DG) combined with various phytochemicals creates comprehensive metabolic shutdown by simultaneously targeting glycolysis and oxidative phosphorylation. This approach is particularly effective against metabolically flexible tumors that can switch between energy production pathways. **(**Singh R et. al., 2023**)**

Mechanistic Advantages:

- 2-DG inhibits hexokinase and accumulates as 2-DG-6-phosphate, blocking glycolysis
- Phytochemicals like berberine and resveratrol disrupt mitochondrial function
- Combined effect prevents metabolic switching and forces energy crisis
- Enhanced sensitivity in hypoxic tumor regions where glycolysis dependence is highest

The metformin plus 2-DG combination shows synergistic effects across multiple cancer types including B-cell lymphoma, breast cancer, glioblastoma, and ovarian cancer, with particular efficacy in preventing cyst formation in polycystic kidney disease models **(**Singh R et. al., 2023**)**

Cell Cycle-Metabolic Integration

Phytochemicals that target cell cycle machinery combined with metabolic inhibitors create dual checkpoint disruption. The metformin plus chrysin combination exemplifies this approach by simultaneously suppressing hTERT (telomerase) and cyclin D1 while depleting cellular energy. **(**Sara Rasouli et. al., 2018**)**

Synergistic Mechanisms:

- Energy depletion prevents DNA replication machinery assembly
- Cell cycle arrest compounds metabolic stress

- Apoptosis induction through p53-dependent and independent pathways
- Prevention of cell cycle checkpoint recovery

Combination Examples and Clinical Evidence

Metformin-Based Combinations

Metformin + Curcumin: This combination demonstrates the strongest clinical potential with evidence spanning gastric, breast, and liver cancers. Studies show synergistic inhibition of cell viability, migration, invasion, and colony formation. The combination enhances the cytotoxic effects of conventional chemotherapeutics including cisplatin, doxorubicin, docetaxel, and paclitaxel while maintaining selectivity for cancer cells. **(**Zarei, E et. al., 2021)

Metformin + Flavone: Research demonstrates synergistic apoptosis induction through PI3K/AKT pathway inhibition in breast cancer cells. The combination achieves enhanced tumor suppression at lower individual drug concentrations, reducing potential side effects (Zheng, Z et. al., 2018**)**

2-DG-Based Combinations

2-DG + Berberine: Demonstrates enhanced glycolysis suppression in lung cancer models with improved therapeutic index compared to single agents.

2-DG + Resveratrol: Shows additive to synergistic effects in neuroblastoma, combining glycolysis inhibition with enhanced oxidative stress and mitochondrial dysfunction.

2-DG + Ferulic Acid: This combination with radiation therapy enhances radiosensitization in non-small cell lung carcinoma through complementary DNA repair inhibition and energy depletion. **(**Singh R et. al., 2023**)**

Lonidamine Combinations

Lonidamine + Natural Compounds: While specific phytochemical combinations are less extensively studied, lonidamine's mechanism of inhibiting mitochondrial pyruvate carrier and lactate export provides a strong rationale for combination with phytochemicals targeting glycolysis or Complex I/II function. **(**Cervantes-Madrid et. al., 2015**,** Huang Y et. al., 2020**)**

Therapeutic Advantages and Clinical Rationale

Dose Reduction and Toxicity Mitigation

Combination approaches allow significant dose reduction of individual components while maintaining or enhancing therapeutic efficacy. This is particularly important for metabolic inhibitors like metformin and 2-DG, which can cause metabolic side effects at higher doses. **(**Zarei, E et. al., 2021**,** Singh R et. al., 2023**)**

Resistance Prevention

The multi-target approach prevents the development of single-pathway resistance mechanisms that commonly emerge with monotherapy. By simultaneously targeting AMPK, mTOR, glycolysis, and mitochondrial function, these combinations create multiple metabolic dependencies that are difficult for cancer cells to circumvent. **(**Rizeq B et. al., 2020, Kim I et. al., 2023)

Enhanced Tumor Selectivity

Cancer cells' high metabolic demands and altered energy production pathways make them preferentially sensitive to metabolic disruption compared to normal cells. The combination approach amplifies this selectivity by creating metabolic conditions that normal cells can better tolerate through metabolic flexibility. **(**Zarei, E et. al., 2021**,** Singh R et. al., 2023**)**

Broader Cancer Type Responsiveness

Different cancers exhibit varying metabolic dependencies, but combination approaches target fundamental metabolic processes shared across cancer types, potentially expanding the therapeutic window for metabolic cancer therapy.**(** Rizeq B et. al.,2020, Kim I et. al., 2023, Singh R et. al., 2023)

CLINICAL TRANSLATION AND CHALLENGES OF METABOLICALLY-ACTIVE PHYTOCHEMICALS IN CANCER THERAPY

Preclinical to Clinical Evidence for Metabolically-Active Phytochemicals

Phytochemicals such as sulforaphane, resveratrol, curcumin, epigallocatechingallate (EGCG), lycopene, and berberine have shown robust anticancer activity in preclinical models by modulating key pathways like autophagy and apoptosis, PI3K/Akt/mTOR, NF-κB, and MAPK signaling. (Rahman MA et. al., 2021,

Choudhari AS et. al., 2020, Monica S. J et. al., 2025)

Animal studies demonstrate tumor growth inhibition, apoptosis induction, and metastasis suppression through multi-target effects on cancer metabolism and cell survival pathways. **(**Rahman MA et. al., 2021**)**

Many phytochemicals have progressed to early-phase clinical trials assessing safety, bioactivity, and preliminary efficacy in various cancers such as breast, colorectal, prostate, lung, and neuroendocrine tumors. **(**Rahman MA et. al., 2021, Choudhari AS et. al., 2020**)**

Clinical trials mostly focus on phytochemical combinations with conventional chemo/radiotherapy to improve treatment response and reduce side effects.

Examples include berberine for colorectal cancer prevention (NCT03281096), curcumin in advanced breast cancer (NCT03072992), and sulforaphane in lung cancer risk (NCT03232138). **(**Choudhari AS et. al., 2020**)**

Bioavailability, Pharmacokinetics, Toxicity, and Regulatory Issues

- A major barrier to clinical translation is the limited bioavailability and rapid metabolism of many phytochemicals; nanoformulations and combination strategies are pursued to enhance delivery and stability.**(** Rahman MA et. al.,2021**,** Monica S. J et. al.,2025**)**
- Pharmacokinetic profiles vary widely across compounds, necessitating optimized dosing regimens and formulation improvements for clinical efficacy.**(** Rahman MA et. al.,2021**)**
- Toxicity profiles are generally favorable at clinically relevant doses, but long-term safety data are limited and require further systematic evaluation.**(** Rahman MA et. al.,2021**)**
- Interactions with conventional chemotherapy agents need careful assessment to avoid adverse herb-drug interactions.**(** Rahman MA et. al.,2021**)**
- Regulatory challenges include the classification of phytochemicals as dietary supplements versus drugs, varying global regulatory frameworks, and the need for standardized extracts and rigorous clinical trial designs.**(** Rahman MA et. al.,2021**,** Choudhari AS et. al.,2020**)**

Emerging Biomarkers for Clinical Use

- Phytochemical effects correlate with modulation of molecular biomarkers linked to metabolism and cancer progression, including autophagy markers (LC3, Beclin-1), apoptosis markers (caspase-3, Bcl-2), and signaling pathway components (phospho-mTOR, NF-κB activity).**(** Rahman MA et. al.,2021**,** Choudhari AS et. al.,2020**)**
- Epigenetic markers (DNA methylation changes), microRNAs, and metabolite profiles offer novel biomarker candidates to monitor phytochemical efficacy and patient stratification.**(** Rahman MA et. al.,2021)
- Multi-omics profiling combined with AI-based analysis improves identification of biomarker signatures predictive of treatment response in clinical settings.
- Companion diagnostic development integrated with phytochemical-based therapies is an emerging area to guide personalized treatment strategies and optimize outcomes. **(**Shuvalov O et. al., 2023, Monica S et. al.,2025)

FUTURE PERSPECTIVES AND NOVEL DIRECTIONS ON METABOLICALLY-ACTIVE PHYTOCHEMICALS IN CANCER THERAPY

Potential for Personalized Therapeutic Approaches

- Precision medicine tailors phytochemical treatments based on individual genetic, epigenetic, and metabolic tumor profiles, addressing intratumor heterogeneity and tumor microenvironment complexity for improved efficacy.**(** Zarei E et. al., 2021, Bhoyar N et. al., 2025)
- Network pharmacology and polypharmacology concepts enable multi-target strategies with phytochemicals attacking cancer-related molecular networks rather than single targets, reducing resistance development.**(73)**
- Bioinformatics and AI-driven approaches are advancing personalized prediction of phytochemical responsiveness and optimal combinations to maximize therapeutic benefits. **(**Efferth T et. al., 2017**)**

Integration with Precision Medicine, Nanotechnology, and Drug Delivery Systems

- Nanotechnology platforms improve phytochemical bioavailability, stability, and targeted delivery, overcoming limitations of poor solubility and rapid metabolism **(**Rahman MA et. al., 2021**,** Choudhari AS et. al., 2020**)**
- Smart drug delivery systems such as nanoparticles, liposomes, and exosomes facilitate controlled release and tumor-specific accumulation of phytochemicals and synergistic agents.(Choudhari AS et. al.,2020)
- Combining metabolically-active phytochemicals with molecular targeted therapies or immunotherapies offers opportunities for integrated precision medicine regimens. (Efferth T et. al.,2017)
- Emerging approaches include biomarker-guided phytochemical nanoformulations personalized to patients' metabolic and molecular tumor landscape. (Rahman MA et. al.,2021, Efferth T et. al., 2017)

Underexplored Phytochemicals and Possible Breakthroughs

- Many phytochemicals with promising preclinical metabolic modulation properties remain under-investigated clinically, including lesser-known polyphenols, alkaloids, terpenoids, and sulfur-containing compounds. (Shuvalov O et. al.,2023, Monica S et. al., 2025)
- Novel compounds like epigallocatechingallate (EGCG), sulforaphane, and piperlongumine demonstrate unique regulatory effects on cancer cell metabolism, redox balance, and epigenetic modifications, paving avenues for new therapies. (Efferth T et. al., 2017)
- Systems pharmacology and multi-omics analyses combined with AI modeling have potential to identify new phytochemical candidates and combinations for breakthrough metabolically-targeted treatments.
- Collaborative large-scale clinical trials incorporating metabolomics and biomarker strategies are essential to translate promising phytochemicals into effective personalized cancer therapies. (Efferth T et. al., 2017)

The future of metabolically-active phytochemicals in cancer precision medicine lies in personalized multi-targeted approaches, aided by cutting-edge bioinformatics, nanotechnology, and integration with standard therapies. This promises new breakthroughs by expanding the repertoire of phytochemicals from bench research to clinical application.

CONCLUSION

Phytochemicals offer significant potential in cancer therapy by targeting the metabolic reprogramming that underlies tumor growth and therapeutic resistance. These natural compounds—including flavonoids, terpenoids, and alkaloids—can disrupt multiple cancer-associated metabolic pathways, such as glycolysis, glutaminolysis, and lipid metabolism, while also modulating the tumor microenvironment and immune responses. Their multi-targeted mechanisms help overcome cancer cells' metabolic plasticity, making phytochemicals valuable adjuncts to standard therapies. Continued research and clinical validation are essential to optimize their use, but current evidence supports their integration into personalized, less toxic treatment strategies for effective cancer management.

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