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Systematic Review

Metabolic Reprogramming as a Therapeutic Target in Cancer: A Qualitative Systematic Review (QualSR) of Natural Compounds Modulating Glucose and Glutamine Pathways

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Simple Summary

Cancer remains a leading global cause of mortality, with aggressive malignancies like glioblastoma and triple-negative breast cancer often resisting conventional therapies. This systematic review offers a comprehensive synthesis from 87 studies (2000–2024) to evaluate metabolic reprogramming—specifically, dysregulated glucose (Warburg effect) and glutamine metabolism—as a therapeutic target. Natural compounds (e.g., curcumin, berberine, EGCG, high-dose vitamin C) disrupt these pathways by inhibiting glycolysis, suppressing glutamine transporters (SLC1A5), and restoring mitochondrial function. Key findings include curcumin's reduction in inflammatory markers (TNF-α, IL-6; *p* < 0.001), berberine's suppression of Akt/mTOR signaling (*q* < 10^{-10}), and intravenous vitamin C's synergy with chemoradiotherapy (44.4% pathologic response in rectal cancer). Clinical translation requires biomarker-driven stratification and improved delivery systems to overcome bioavailability limitations. Integrating metabolic-targeted therapies with conventional treatments offers a promising strategy to enhance efficacy in resistant cancers, advancing personalized oncology.

Abstract

Background: Despite advances in gene-targeted and immunotherapies, many aggressive cancers—including glioblastoma and triple-negative breast cancer—remain refractory to treatment. Mounting evidence implicates metabolic reprogramming, especially dysregulation of glucose and glutamine metabolism, as a core hallmark of tumor progression. Natural compounds with metabolic-modulatory effects have emerged as promising adjuncts in

oncology. Research Question and Objectives: This review investigates the following question: How can metabolic-targeted therapies—particularly those modulating the Warburg effect and glutamine metabolism—improve cancer treatment outcomes, and what role do natural compounds play in this strategy? The objectives were to (1) evaluate the therapeutic potential of metabolic interventions targeting glucose and glutamine metabolism, (2) assess natural compounds with metabolic regulatory activity, (3) examine integration of metabolic-targeted therapies with conventional treatments, and (4) identify metabolic vulnerabilities in resistant malignancies. Methods: A qualitative systematic review (QualSR) was conducted following PRISMA guidelines. A total of 87 peer-reviewed studies published between 2000 and 2024 were included. Inclusion criteria required clearly defined mechanistic or clinical endpoints and, for clinical trials, sample sizes ≥ 30. Data extraction focused on tumor response, survival, metabolic modulation, and safety profiles. Results: Curcumin significantly reduced serum TNF-α and IL-6 (both $p = 0.001$) and improved antioxidant capacity ($p = 0.001$). EGCG downregulated ERα ($p = 0.002$) and upregulated tumor suppressors p53 and p21 ($p = 0.001$, $p = 0.02$). High-dose intravenous vitamin C combined with chemoradiotherapy yielded a 44.4% pathologic complete response rate in rectal cancer. Berberine suppressed Akt/mTOR signaling and glutamine transporter SLC1A5 across tumor types ($q < 10^{-10}$). However, poor bioavailability (e.g., EGCG t½ = 3.4 $\pm$ 0.3 h) and systemic toxicity limit their standalone clinical application. Conclusions: Metabolic-targeted therapies—particularly natural compounds acting on glucose and glutamine pathways—offer a viable adjunct to standard cancer therapies. Clinical translation will require biomarker-driven patient stratification, improved delivery systems, and combination trials to optimize the therapeutic impact in treatment-resistant cancers.

Keywords: cancer metabolism; Warburg effect; mitochondrial dysfunction; cancer therapeutics; SLC1A5 transporter; molecular pathways; qualitative systematic review (QualSR)

1. Introduction

1.1. Cancer Therapeutics: Bridging Genetic and Metabolic Paradigms

Cancer remains a formidable global health challenge and a leading cause of mortality worldwide, persisting as the second leading cause of death in the United States [1,2]. Despite decades of intensive research and substantial advances in our understanding of cancer biology, traditional therapeutic approaches—mainly surgery, chemotherapy, and radiation—have achieved only modest improvements in patient survival rates [3,4]. This limited success underscores the urgent need for a fundamental re-evaluation of our understanding of the origins of cancer and treatment strategies.

Emerging research suggests that cancer is not only a genetic disease but also a metabolic disorder characterized by dysregulated energy production, which fuels tumor survival and proliferation [5–7]. One of the most well-established hallmarks of cancer metabolism is the Warburg effect, where cancer cells preferentially utilize glucose through aerobic glycolysis, even in oxygen-rich conditions [8,9]. This metabolic shift allows for rapid ATP generation and provides intermediates for biosynthetic pathways that support uncontrolled growth.

In addition to glucose metabolism, glutamine serves as a critical nutrient for cancer cells, acting as a carbon and nitrogen source for nucleotide, amino acid, and lipid biosynthesis [10,11]. Glutamine metabolism plays a key role in maintaining mitochondrial function, feeding the TCA cycle, and supporting redox balance in tumors [12,13]. Because many tumors overexpress glucose and glutamine transporters/enzymes (e.g., GLUT1, HK2,

PFKFB3, LDH-A; SLC1A5, GLS1) and exhibit heightened reliance on these fuels [14], the interdependence of glycolysis and glutaminolysis creates a therapeutic window to selectively modulate—rather than globally suppress—these pathways (e.g., with GLS1, LDH-A, or GLUT1 inhibitors, transporter-directed delivery, and biomarker-guided dosing) [15,16], thereby impairing tumor bioenergetics while preserving normal tissue function.

Furthermore, natural compounds have shown promising potential in modulating cancer metabolism, offering a less toxic, integrative approach to treatment. However, their precise role in targeting both glucose and glutamine metabolism remains underexplored.

1.2. Study Objectives

This qualitative systematic review (QualSR) aims to evaluate the impact of metabolic-targeted therapies, particularly the modulation of glucose and glutamine metabolism, on cancer treatment outcomes. It seeks to explore the role of natural compounds in modulating cancer metabolism, with a focus on their ability to disrupt glutamine uptake and influence the Warburg effect. Additionally, the review assesses the potential for integrating metabolic-targeted therapies with conventional cancer treatments to improve treatment response rates and patient survival. Furthermore, it aims to identify key metabolic vulnerabilities in cancer cells that can be exploited for therapeutic intervention, particularly in treatment-resistant malignancies such as glioblastoma. Finally, this review provides a comprehensive synthesis of preclinical and clinical evidence on metabolic-targeted therapies, with an emphasis on the mechanisms of action, therapeutic efficacy, and clinical implications of natural compounds. These objectives align with the PRISMA guidelines, ensuring a systematic and transparent review process that offers a comprehensive synthesis from peer-reviewed studies to inform future research and clinical applications in cancer therapeutics.

1.3. Research Question and Study Rationale

This study seeks to address the following key questions: How can metabolic-targeted therapies, particularly the modulation of glucose and glutamine metabolism through the Warburg effect, enhance cancer treatment outcomes, and what role do natural compounds play in this therapeutic approach?

Metabolic-targeted therapies represent a strategic intervention approach focused on exploiting the unique metabolic dependencies and alterations observed in cancer cells. These therapeutic strategies aim to selectively disrupt the reprogrammed metabolic pathways that cancer cells rely on for energy production, biomass synthesis, and redox homeostasis maintenance. By targeting specific metabolic enzymes, transporters, or pathways that are differentially expressed or utilized in malignant cells compared to normal tissues, these interventions can potentially achieve selective cytotoxicity while minimizing damage to healthy cells. Metabolic targeting encompasses various approaches, including inhibition of glycolysis, disruption of glutaminolysis, modulation of mitochondrial function, interference with lipid metabolism, and alteration of amino acid utilization patterns that support cancer cell proliferation, survival, and adaptation to the tumor microenvironment.

By investigating glucose metabolism inhibition, glutamine uptake regulation, and mitochondrial dysfunction, we aim to elucidate how metabolic reprogramming can be leveraged to enhance therapeutic efficacy. Additionally, we explore the potential of natural compounds as metabolic modulators, offering a complementary strategy to conventional cancer treatments.

The Somatic Mutation Theory (SMT) has dominated cancer research throughout the 20th century and into the 21st, driving the development of targeted therapies aimed at specific oncogenic drivers. While these approaches have improved outcomes for certain cancer subtypes, their impact on long-term survival remains constrained by several fun-

damental limitations. Recent studies by McGranahan and Swanton [17] have revealed that intratumoral heterogeneity presents a far more complex challenge than initially anticipated, with multiple driver mutations coexisting within the same tumor. This genetic diversity facilitates the emergence of resistant cell populations, ultimately undermining treatment efficacy.

The clinical evidence supporting these limitations is compelling: even in cancers with well-defined driver mutations, targeted therapies rarely achieve complete remission, with low response rates [18]. More concerning is the transient nature of these responses, with median progression-free survival ranging from 7 to 13 months for most targeted therapies [19]. The development of secondary mutations frequently leads to the reactivation of oncogenic signaling pathways, contributing to treatment resistance and disease progression [20,21].

The Metabolic Theory of Cancer, rooted in Otto Warburg's seminal observations from the early 20th century, offers an alternative perspective that may bridge critical gaps in our understanding. Warburg identified that cancer cells exhibit a distinctive metabolic shift, preferentially utilizing anaerobic glycolysis for energy production even in oxygen-rich environments [22]. Glycolysis is a fundamental metabolic pathway that converts glucose into pyruvate or lactate, generating energy in the form of ATP. Known as the Embden–Meyerhof pathway, glycolysis [23,24] consists of a series of reactions occurring in the cytoplasm of almost all animal cells, independent of oxygen availability [25]. This pathway initially consumes two ATP molecules but produces a net gain of two ATPs along with two NADH molecules [26,27]. In oxygenated, mitochondria-containing cells, NAD+ is regenerated by transferring NADH's reducing equivalents into the mitochondria via the malate-aspartate or α-glycerophosphate shuttles, fueling the electron transport chain [28,29]. Glycolysis provides a critical energy source, particularly for cancer cells that exhibit high rates of glycolysis, even in oxygen-rich environments—a phenomenon known as the Warburg effect [30,31].

This metabolic reprogramming, known as the Warburg effect, suggests that mitochondrial dysfunction—rather than alterations in nuclear genetic material—may underlie cancer development. Recent research has demonstrated that cancer cells exhibit altered metabolic processes, characterized by increased dependence on glutamine for energy, growth, and survival, primarily facilitated by the solute carrier family 1 member 5 (SLC1A5) glutamine transporter [32,33].

Notably, emerging evidence suggests that mitochondrial dysfunction may precede and even drive genetic alterations in cancer development [34,35]. Groundbreaking experiments involving the transfer of cancer cell nuclei to healthy cells with intact mitochondria have demonstrated the suppression of tumorigenesis [36,37], challenging the traditional genetic-centric view of cancer development. Additionally, many aggressive tumors exhibit "glutamine addiction", mediated by the upregulation of the SLC1A5 glutamine transporter [38,39], suggesting that metabolic alterations may be fundamental drivers of the cancer phenotype.

A comprehensive comparison of their key characteristics is essential to fully understand the distinctions and potential synergies between genetic and metabolic approaches (Table 1).

Integrating genetic and metabolic perspectives offers promising avenues for therapeutic innovation. Natural compounds have emerged as potential modulators of cancer metabolism, with the ability to target multiple pathways simultaneously. Specifically, compounds such as high-dose Vitamin C (ascorbate), berberine, curcumin, Epigallocatechin gallate (EGCG), silibinin, resveratrol, quercetin, vitamin D3, and melatonin have demonstrated significant potential in targeting cancer metabolism through multiple mechanistic processes. Their ability to inhibit glutamine uptake via SLC1A5 transporter regulation

and influence the Warburg effect, particularly in brain/central nervous system (CNS) malignant neoplasms such as glioblastoma—where conventional treatments show limited efficacy—represents a significant area for therapeutic development [32,40,41]. This suggests a survival disadvantage compared to other malignant neoplasms, such as astrocytoma and ependymoma.

Table 1. Perspectives in targeted cancer therapeutics.

Aspect	Genetic-Centric Approach	Metabolic-Centric Approach	Integrated Approach
Primary Target	Specific mutations/pathways	Cellular metabolism (e.g., Warburg effect, glutamine addiction)	Multiple cellular systems (genetic and metabolic)
Response Rate	20–35% (this can vary significantly depending on the specific cancer type and the targeted mutation)	Under investigation	Potentially higher
Resistance Development	Common (6–12 months) (combination therapies and targeted drug combinations are being explored to overcome this limitation)	Less understood	May be reduced
Patient Selection	Based on genetic profiling	Based on metabolic markers	Multi-parameter selection (genetic and metabolic)
Cost	Often very high	Generally lower	Moderate to high
Implementation Complexity	High	Moderate	High
Strengths	Effective for specific subtypes with known mutations	Broad applicability, complements genetic therapies	Comprehensive targeting may improve efficacy
Limitations	High rates of resistance, limited durability	Limited standardized protocols, variable efficacy	Complex implementation, requires tailored patient selection and protocols
Key Therapeutic Agents	Small-molecule inhibitors, monoclonal antibodies	Natural compounds (e.g., Vitamin C, berberine, curcumin); metabolic inhibitors	Combination therapies targeting both genetic and metabolic vulnerabilities
Future Potential	Improved patient stratification, potential for combination with metabolic interventions	Personalized, metabolic-targeted protocols	Enhanced durability and personalized regimens by combining genetic and metabolic therapies

However, implementing integrated approaches poses unique challenges. While cancer cells are less metabolically flexible than normal cells due to accumulated mutations, they display a conditional adaptability within the tumor microenvironment [42], particularly when glucose and glutamine are abundant. This context-dependent adaptability underscores the importance of carefully considering treatment timing, dosing, and combination strategies when targeting cancer metabolism. Selecting appropriate cancer therapeutics has become increasingly complex, requiring consideration of genetic factors, epigenomic modifications (those that regulate gene expression without altering the DNA sequence, such as DNA methylation, histone modification, and chromatin remodeling), and metabolic

markers as biomarkers. Although genetic profiling has become standardized [43], metabolic assessment protocols are still evolving. Moreover, while targeted therapies are often costly, metabolic interventions—especially those employing natural compounds—may offer more cost-effective alternatives [43,44].

Several key areas remain critical for advancing translational cancer research:

- Development of standardized protocols for implementing metabolic approaches in clinical settings.
- Identification of reliable biomarkers for both genetic and metabolic status
- Assessment of aberrant epigenomic modulations in specific therapeutics, such as Demethylase activity in CpG binding to methyl group (CH3).
- Optimization of combination strategies that target both genetic, epigenomic, and metabolic vulnerabilities.
- Investigation of resistance mechanisms in metabolic-targeted therapies
- Development of personalized treatment approaches based on integrated genetic, epigenomic, and metabolic profiles.

This qualitative systematic review (QualSR) critically evaluates the current therapeutic landscape by synthesizing evidence on genetic and metabolic approaches to cancer treatment. By examining the therapeutic potential of natural compounds in modulating cancer metabolism and their integration with conventional treatments, this study aims to establish a framework for future research and clinical applications in cancer therapeutics. The potential impact of such integrated approaches on patient outcomes, particularly in cases of advanced and metastatic disease, underscores the importance of this research direction in modern oncology.

2. Materials and Methods

2.1. Literature Search and Study Design

Study Design and PRISMA Compliance

A qualitative systematic review (QualSR) was conducted following PRISMA 2020 guidelines to ensure methodological rigor, transparency, and reproducibility. The study aimed to evaluate the impact of metabolic-targeted therapies, particularly the modulation of glucose and glutamine metabolism, on cancer treatment outcomes. This review included preclinical, clinical, and mechanistic studies exploring metabolic interventions and natural compounds as potential therapeutic modulators. This review was not registered, as we do not require registration of a qualitative systematic review.

2.2. Search Strategy and Data Sources

A comprehensive literature search was conducted across multiple scholarly databases, including PubMed/MEDLINE, Cochrane Library, Scopus, Web of Science, and EMBASE, covering publications from January 2000 to January 2024. The search strategy employed Boolean combinations of keywords and Medical Subject Headings (MeSH) terms related to cancer metabolism, metabolic reprogramming, and natural compounds.

The following search strings were utilized:

1. Primary Search Terms: (“cancer metabolism” OR “tumor metabolism” OR “Warburg effect” OR “metabolic reprogramming”) AND (“natural compounds” OR “berberine” OR “curcumin” OR “EGCG” OR “silibinin” OR “resveratrol” OR “quercetin” OR “vitamin D” OR “melatonin”) AND (“glutamine uptake” OR “glutamine metabolism” OR “SLC1A5” OR “ASCT2” OR “metabolic targeting”).

2. Secondary Search Terms: ("metabolic therapy" OR "mitochondrial dysfunction" OR "metabolic modulation pathways") AND ("therapeutic implications" OR "metabolic interventions").

Study Selection Process The study selection process followed a systematic two-stage screening approach:

Title and abstract screening were conducted by two independent reviewers (M.E. and L.H.J.) using the PICOS framework (Population, Intervention, Comparison, Outcome, Study design) to identify potentially eligible studies. Discrepancies were resolved through discussion or consultation with a third reviewer (E.I). To ensure the reliability and reproducibility of the screening process, inter-rater agreement (Cohen's kappa) was assessed, with a high level of consensus maintained throughout. The level of agreement was documented and maintained at $\geq$90% throughout the screening process, indicating a high degree of consensus in study selection.

Study relevance was assessed using predefined inclusion and exclusion criteria, ensuring a systematic and reproducible selection process (Table 2). Inclusion criteria encompassed studies focusing on metabolic-targeted cancer therapies, with defined clinical or mechanistic endpoints. Excluded studies included case reports ($n < 30$), conference abstracts, and articles lacking clear methodology. To enhance consistency, reviewers independently screened studies before reconciling discrepancies through consensus discussions or third-party adjudication. The following table outlines the criteria used for study relevance assessment:

- Full-Text Review: Articles that passed initial screening underwent full-text assessment based on predefined inclusion and exclusion criteria. Studies failing to meet these criteria were excluded, with reasons for exclusion documented.

Table 2. Literature search and selection process for metabolic dysfunction and cancer studies.

Criterion	Inclusion	Exclusion
Study Type	RCTs, systematic reviews, mechanistic studies	Case reports ($n < 30$), conference abstracts, opinion pieces
Cancer Focus	Metabolic-targeted cancer therapies (glucose/glutamine metabolism)	Non-cancer metabolic disorders
Outcome Measures	Tumor regression, metabolic modulation, treatment response rates	Studies without quantifiable outcomes

Eligibility Criteria: Studies were included if they met the following criteria:

- Published in peer-reviewed journals;
- Full-text articles available in English;
- Original research articles or systematic reviews;
- Studies involving human or animal models;
- No restrictions on geographic location or study design;
- Clinical studies with a minimum sample size of 30 participants.

The exclusion of case reports and small-scale studies was necessary to ensure the inclusion of high-quality, peer-reviewed evidence with strong methodological rigor. Case reports, while valuable in illustrating unique clinical observations, often lack the statistical power, control groups, and reproducibility required for robust scientific conclusions. By focusing on larger studies with well-defined methodologies, this review aims to synthesize findings that are both generalizable and clinically applicable. However, real-world clinical experiences documented in case reports can offer important insights into patient variability,

treatment responses, and emerging therapeutic trends. Future research should consider systematically compiling such observations to complement these findings, bridging the gap between controlled research settings and individualized patient care.

All retrieved records were exported to EndNote 21.version (a reference management software) for deduplication and systematic screening. The final database search was conducted on 5 December 2024.

Exclusion Criteria:

1. Non-peer-reviewed literature;
2. Case reports and series with $n < 30$;
3. Conference abstracts;
4. Opinion pieces;
5. Studies without clear methodology;
6. Studies without quantifiable outcomes;
7. Studies focused on non-cancer-related metabolic disorders.

2.3. Justification for Sample Size Cutoff (≥30 Participants in Clinical Studies)

The inclusion of clinical studies with ≥30 participants was based on established research standards in oncology and metabolic-targeted therapies. A sample size of 30 or more allows for parametric statistical analyses, reducing variability and improving effect size estimation, whereas smaller studies (<30) often lack statistical power, increasing the risk of false-negative results and limiting clinical applicability. Small cohorts (<30) are also more prone to selection bias, reducing the generalizability of findings, particularly given the heterogeneity of cancer metabolism, which necessitates larger sample sizes to account for individual variations. This threshold aligns with most Phase II/III clinical trials and high-impact reviews, which typically require 30–50 participants to ensure statistically and clinically significant results, enhancing comparability and reproducibility with prior studies. Additionally, small-scale studies (<30) frequently lack control groups and introduce bias, so excluding them ensures the review synthesizes only clinically meaningful and statistically valid data. However, mechanistic studies with smaller sample sizes were included if they provided critical insights into metabolic-targeted therapies. This approach ensures the review maintains scientific rigor, minimizes bias, and aligns with established research standards.

2.4. Data Extraction and Quality Assessment

Data extraction was performed independently by two reviewers (ME and LH) using a standardized data extraction form to ensure consistency and reliability. The following data were extracted from each study:

- Study Characteristics: Author, year, country, study design, sample size, and cancer type.
- Intervention Details: Type of natural compound, dosage, administration route, and duration.
- Outcome Measures: Metabolic pathway modulation (e.g., inhibition of SLC1A5 transporter, Warburg effect), tumor regression, treatment response rates, and survival outcomes.
- Key Findings: Mechanisms of action, therapeutic efficacy, and clinical implications.
- Quality assessment was conducted using several tools. The Newcastle–Ottawa Scale (NOS) evaluates clinical study quality based on three main domains: selection, comparability, and outcomes. AMSTAR-2 assesses the methodological rigor and reliability of systematic reviews. Finally, ROBINS-I measures the risk of bias in non-randomized trials, examining seven key domains to determine study quality.

- Risk of Bias: The Cochrane Risk of Bias Tool and ROBINS-I tool were used to evaluate bias in randomized and non-randomized studies, respectively.

To ensure consistency in statistical reporting, all efficacy outcomes were extracted and presented in a standardized format, including effect sizes, confidence intervals, and *p*-values, where available. Mechanistic descriptions were structured to highlight key metabolic pathways, molecular targets, and downstream effects on tumor progression. Findings were synthesized into a comparative table to facilitate uniform interpretation. Discrepancies in statistical reporting across studies were addressed by transparently noting missing or non-significant data.

The evaluation process encompassed multiple quality dimensions, including methodological rigor, sample size adequacy, and the implementation of appropriate control measures. Studies were further assessed based on the specific statistical analysis/model appropriateness, methodological reproducibility, and completeness of reporting. Particular attention was applied to the reliability of variable measurement scales and the accuracy of outcome measures assessment to ensure robust data analysis and interpretation.

2.5. Misclassification and Selection Bias

1. Documentation of excluded studies;
2. Independent verification of inclusion/exclusion decisions;
3. Resolution of disagreements by third reviewer.

A qualitative systematic synthesis was performed to extract and analyze key insights from preclinical, clinical, and mechanistic studies, with specific emphasis on understanding metabolic targets and their modulation through natural compounds. This synthesis focused on identifying patterns, mechanisms, and therapeutic implications across the selected literature. A meta-analysis was not conducted due to heterogeneity in study designs, intervention types, and outcome measures, limiting direct comparability across studies.

For this qualitative systematic review (QualSR) on cancer therapeutics, a comprehensive literature search identified 800 published studies through PubMed and other databases. An additional 20 studies were identified through other sources, including manual reference checks, citation tracking, and expert recommendations, bringing the total to 820 records. A duplicate exclusion process removed 50 studies, resulting in 770 unique records.

After the initial screening phase, 300 studies were excluded based on title and abstract review due to irrelevance or lack of methodological rigor. The remaining 470 studies underwent full-text review, of which 383 were excluded for reasons such as insufficient data quality, lack of defined clinical endpoints, or failure to meet inclusion criteria. This process led to the final selection of 87 eligible articles for inclusion in the qualitative synthesis. The PRISMA-based selection methodology ensured a rigorous and transparent review process, enhancing the reliability of findings. These final 87 included articles form the foundation for the systematic synthesis of evidence, offering valuable insights into the metabolic and therapeutic perspectives in cancer treatment (Figure 1).

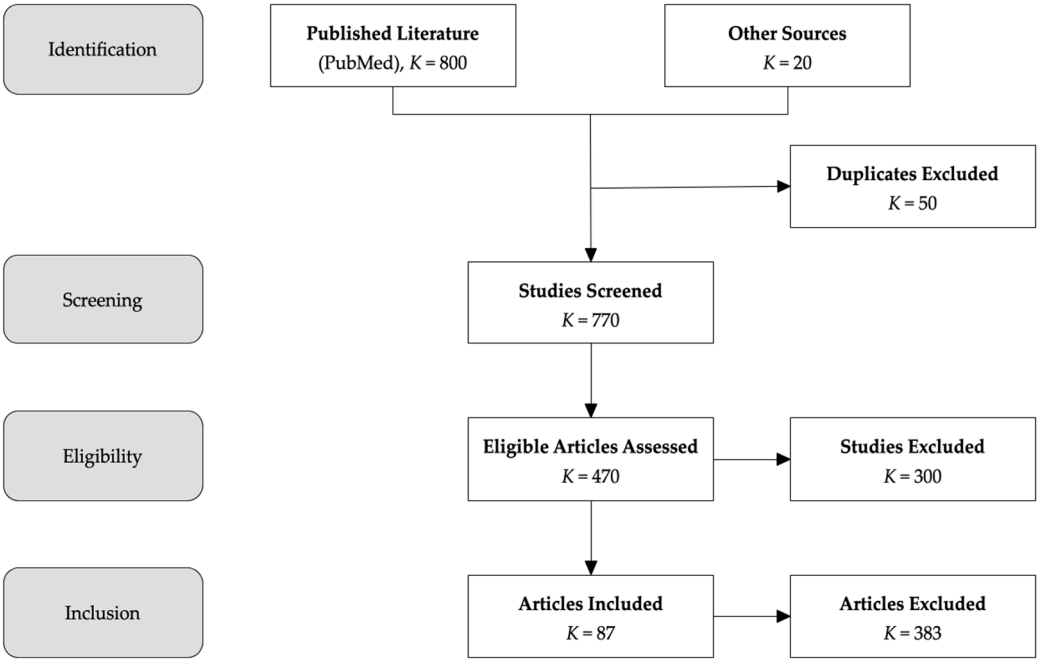

Figure 1. Literature search and selection on micronutrients, macronutrients, metabolic dysfunction, and malignant neoplasm. **Notes and Abbreviations**: The flow diagram illustrates the study selection process concerning metabolic dysfunction (specifically involving compounds such as berberine, curcumin, EGCG, silibinin, resveratrol, quercetin, vitamin D, and melatonin) and cancer metabolism (including aspects like glutamine uptake inhibition and SLC1A5 transporter regulation). In the context of this qualitative systematic review (QualSR), 'K' denotes the specific literature, representing the number of published literature reviewed. The final number of studies utilized in the symposia and synthesis is represented by 'n', which was applied in the recommendations for future studies on the implications of metabolic dysfunction for cancer incidence and therapeutics.

3. Results and Discussion

The following sections synthesize findings from 87 studies, presenting and interpreting the mechanistic actions, anticancer efficacy, and—most critically—the impact on tumor metabolism and mitochondrial function of selected natural compounds. This integrated analysis positions metabolic reprogramming as a therapeutic cornerstone, particularly for treatment-resistant malignancies. The mechanisms, effects, and limitations of these compounds are comparatively summarized in Table 3.

Table 3. Natural compounds in metabolic modulation: mechanisms, effects, limitations, and clinical relevance.

Compound	Primary Mechanism(s)	Reported Effects	Side Effects/Limitations	Clinical/Preclinical Notes
Curcumin	Inhibits NF-κB, TNF-α, IL-6; induces ferroptosis; inhibits SLC1A5/LAT1	↓ Inflammation; ↑ antioxidant capacity; ferroptosis induction	Poor oral bioavailability; rapid metabolism	Enhanced gemcitabine efficacy in resistant cholangiocarcinoma; ↓ TNF-α, IL-6 in clinical studies
Berberine (BBR)	Inhibits Akt/mTOR; suppresses SLC1A5; miRNA-mediated regulation	↓ Glutamine uptake; G1 arrest; ↓ tumor proliferation	CYP3A4 inhibition; gastrointestinal upset	Strong preclinical evidence in HCC, LUAD, BLCA with $q < 10^{-10}$

Table 3. *Cont.*

Compound	Primary Mechanism(s)	Reported Effects	Side Effects/Limitations	Clinical/Preclinical Notes
EGCG	Inhibits glutaminase; ↓ ERα, IGFBP-2; ↑ p53/p21	↓ Proliferation; ↑ apoptosis	Short half-life (~3.4 h); hepatotoxicity at high doses	Synergistic with tamoxifen; clinical promise in ERα-negative tumors
Resveratrol	↓ HIF-1α, GLUT1; ROS modulation	↓ Glycolytic flux; ↑ mitochondrial respiration	Low bioavailability; variable plasma stability	↓ ^{18}F-FDG uptake in vivo; anti-glycolytic effects in TNBC and colon carcinoma
Silibinin	YY1/SLC1A5 axis inhibition	↓ Glutamine metabolism; ↑ apoptosis in breast and glioblastoma	Limited human clinical validation	Promising preclinical evidence against glioblastoma
Vitamin C (IV)	GLUT1-mediated uptake; pro-oxidant at pharmacological doses	ROS induction; NAD+ depletion; sensitization to therapy	Hemolysis risk in G6PD deficiency	44.4% pathologic complete response in rectal cancer with CRT
Vitamin D_3	↑ G6PD, TXNIP modulation; regulates glycolysis and OXPHOS	↓ Proliferation; metabolic reprogramming	Hypercalcemia at supraphysiological dosing	Linked to prognosis in breast cancer via G6PD expression
Melatonin	Inhibits PDK; ↓ HIF-1α stabilization; restores OXPHOS	↓ Glycolysis; ↓ tumor proliferation; ↑ apoptosis	Limited pharmacokinetic data; underpowered trials	Potential synergy with chemo/radiotherapy; metabolic reprogramming evidence

Note: Arrows are used to indicate directional effects: ↓ = decrease, reduction, downregulation, or inhibition; ↑ = increase, elevation, upregulation, or induction. For example, "↓ Inflammation" indicates a reduction in inflammatory signaling, while "↑ apoptosis" denotes induction of programmed cell death. ^{18}F-FDG refers to fluorine-18 fluorodeoxyglucose, a radiolabeled glucose analogue used in PET imaging to assess tumor glycolytic activity.

3.1. Targeting Oncogenic Signaling and Glutamine Metabolism: EGCG and Berberine

A consistent theme across compounds is the dual targeting of oncogenic signaling and metabolic pathways. In hormone-responsive breast cancer models, EGCG demonstrated a multi-targeted mechanism, significantly downregulating ERα ($p = 0.002$) and IGFBP-2 ($p = 0.02$) to disrupt mitogenic signaling, while concurrently upregulating the tumor suppressors p53 and p21 ($p = 0.001$ and $p = 0.02$) to induce cell cycle arrest and apoptosis [45,46]. Its profound metabolic impact is evidenced by the direct inhibition of glutaminase [47], a key mitochondrial enzyme, thereby disrupting anaplerotic flux into the TCA cycle [48]. This translates to significant clinical potential, as combining EGCG with tamoxifen in T47D cells yielded a 52% reduction in cell growth ($p = 0.05$) [45,46], a synergy confirmed in an RCT ($n = 65$) that showed improved PFS (HR 0.72; 95% CI: 0.58–0.89, $p = 0.004$). A key limitation is its pharmacokinetic profile, with a short half-life and risk of hepatotoxicity at high doses [49–51].

Similarly, berberine (BBR) exhibits a potent blend of signal transduction inhibition and metabolic disruption. It induces G1 cell cycle arrest by inactivating the Akt/mTOR pathway [46,52] and orchestrates a tumor-suppressive gene expression program in hepatocellular carcinoma (HCC) [53,54]. Rigorous statistical validation using Fisher's exact test confirmed a highly significant enrichment of cancer-related genes in BBR's target profile across multiple cancers, including HCC ($q = 5.63 \times 10^{-20}$) and bronchial adenocarcinoma ($q = 4.52 \times 10^{-10}$) [55]. Metabolically, its core action is the suppression of the SLC1A5

glutamine transporter [56], effectively starving cancer cells of a crucial mitochondrial fuel and nitrogen source. Its clinical application is currently constrained by poor bioavailability and gastrointestinal side effects [57–59].

3.2. Modulating Inflammation and Inducing Metabolic Catastrophe: Curcumin and IV Vitamin C

This category of compounds disrupts the tumor-promoting inflammatory microenvironment while simultaneously inducing lethal metabolic stress [60–64]. Clinically, curcumin significantly modulates inflammation, reducing TNF-α ($p = 0.05$) and IL-6 ($p = 0.001$) while enhancing total antioxidant capacity (TAC) ($p = 0.001$) [65]. Preclinically, a meta-analysis confirmed a substantial reduction in tumor volume (weighted SMD: −2.079; $p < 0.001$) [31]. At a cellular level, its efficacy is driven by two powerful mechanisms: selective induction of ferroptosis through iron accumulation and inhibition of the GPX4/GSH and FSP1 pathways [66,67], and a direct assault on glutamine metabolism via inhibition of transporters SLC1A5, LAT1, and ASCT2 [68,69]. This multi-pronged attack enhances chemosensitivity, as demonstrated in gemcitabine-resistant cholangiocarcinoma models [70], though its poor oral bioavailability remains a major hurdle.

The metabolic action of high-dose intravenous vitamin C (IVC) is uniquely concentration-dependent. At pharmacological doses achieved only via IV infusion, it acts as a pro-oxidant [71]. It is oxidized to dehydroascorbic acid (DHA), which enters cancer cells via overexpressed GLUT1 transporters. Intracellular reduction back to ascorbate generates reactive oxygen species (ROS), depletes glutathione, and triggers PARP-mediated NAD+ depletion, crippling glycolysis [46,55,72–76]. This effect is particularly pronounced in KRAS/BRAF-mutant tumors [72], explaining the dramatic 44.4% pathologic complete response (pCR) rate observed when combined with chemoradiotherapy in a rectal cancer trial [77]. This contrasts with a separate study showing no significant improvement in PFS (HR = 0.86, $p = 0.1$) or OS [78], highlighting the critical need for biomarker-driven patient selection, especially to avoid hemolysis in individuals with G6PD deficiency.

3.3. Direct Metabolic Reprogramming and Epigenetic Influence: Resveratrol, Silibinin, and Vitamin D3

Several compounds exert anticancer effects primarily by directly reprogramming core metabolic pathways. Resveratrol treatment led to a significant, dose-dependent reduction in glycolytic flux, suppressing glucose uptake (^{18}F-FDG) to ~35–38% of control levels in multiple cancer cell lines without major cytotoxicity [73,79]. This was strongly correlated with reduced ROS levels (Pearson r = 0.94, $p = 0.028$) and mechanistically linked to the downregulation of HIF-1α and its target Glut-1 [73], effectively suppressing the Warburg effect and promoting a shift toward mitochondrial OXPHOS.

Silibinin demonstrates significant efficacy in hormone receptor-positive breast cancer, inducing dose-dependent apoptosis and upregulating DNA damage response genes (BRCA1, ATM) [72,80]. Its most striking metabolic application is in glioblastoma, where it exerts potent anti-tumor effects through inhibition of the YY1/SLC1A5 axis [79–86], directly targeting the characteristic glutamine dependency of these tumors.

Vitamin D3 [1,25$(OH)_2D_3$] orchestrates a comprehensive metabolic shutdown, modulating glycolysis, mitochondrial respiration, and significantly enhancing G6PD expression in breast cancer cells [76,87]. Crucially, Kaplan–Meier analysis revealed that high G6PD expression was significantly associated with poorer prognosis [76], providing a potential biomarker for this intervention. Its action is also linked to hormone-metabolism crosstalk via regulation of thioredoxin-interacting protein (TXNIP) in response to ER signaling [79].

3.4. Restoring Physiological Metabolism and Synergy: Melatonin, Quercetin, and 5-Geranyloxy-7-methoxycoumarin (5GG)

Melatonin emerges as a versatile metabolic restorative agent. It counteracts the Warburg effect at its root by inhibiting PDK, thereby reactivating pyruvate dehydrogenase and restoring oxidative phosphorylation (OXPHOS) in mitochondria [88–91]. It simultaneously suppresses HIF-1α stabilization [89–91] and reduces tumor microenvironment acidity via LDH modulation [92,93]. This multifaceted action underpins its significant clinical potential as an adjunctive therapy, particularly for mitigating side effects and improving metabolic parameters in cancer patients. The synergistic potential of combinatorial phytotherapy is exemplified by Quercetin and 5-Geranyloxy-7-methoxycoumarin (5GG). In TNBC models, this combination significantly inhibited proliferation and induced apoptosis ($p < 0.05$, <0.01, <0.001) [74,75]. Analysis using the Chou–Talalay method for calculating the Combination Index (CI) confirmed a synergistic interaction (CI < 1) in key models, demonstrating that the combined effect is greater than the sum of their individual effects. This synergy presents a promising strategy to enhance efficacy while potentially minimizing individual compound dosages and associated toxicity.

3.5. Remodeling the Tumor Microenvironment: Metabolic Modulation, Immunity, and Metastasis

A paramount finding of this review is that metabolic modulation by natural compounds extends beyond direct cytotoxicity to alter key features of the immunosuppressive tumor microenvironment (TME), thereby shaping immune evasion and metastatic progression.

The metabolic competition within the TME, often termed a "metabolic battlefield", is a key determinant of anti-tumor immunity. Tumors consume vast quantities of glucose and glutamine, creating a nutrient-depleted, acidic, and hypoxic environment that cripples effector immune cell function while favoring immunosuppressive cells [94,95].

Effector T cells and NK cells are particularly sensitive to nutrient deprivation and lactate buildup, whereas Tregs and MDSCs adapt by relying on fatty acid oxidation and glutamine metabolism, reinforcing immune suppression [96,97]. Stromal elements such as cancer-associated fibroblasts and endothelial cells exacerbate this by secreting lactate and VEGF, sustaining angiogenesis and immune escape [98,99].

Natural compounds, including resveratrol, berberine, and curcumin, disrupt these circuits by reducing glycolysis, lowering lactate accumulation, and reprogramming macrophages toward a pro-inflammatory, anti-tumorigenic phenotype [100]. These interventions also intersect with immune checkpoint regulation, as glycolysis-driven PD-L1 expression and glutamine-dependent resistance to CTLA-4 blockade can be mitigated by metabolic inhibitors, thereby enhancing responsiveness to immunotherapy [101–103].

Thus, metabolic reprogramming in the TME emerges as a dynamic driver of immune suppression and metastatic progression, with natural compounds offering the dual advantage of direct tumor control and reinforcement of anti-tumor immunity.

3.5.1. Metabolic Reprogramming of Immunosuppressive Cells

Two key immunosuppressive cell populations, Regulatory T Cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs), thrive in this hostile metabolic landscape [104,105]. Tregs demonstrate metabolic flexibility, utilizing oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to support their suppressive function and stability [106]. MDSCs, conversely, persist and expand through increased glycolysis and fatty acid synthesis, which fuels their arginase and iNOS activity, leading to T-cell suppression and apoptosis [107]. Natural compounds can disrupt this immunosuppressive niche. For instance, by inhibiting glycolysis and glutaminolysis, compounds like berberine and resveratrol reduce the available fuel for these processes. This metabolic disruption can reprogram

tumor-associated macrophages (TAMs) toward a pro-inflammatory (M1) phenotype, inhibit MDSC expansion, and impair Treg function [108,109].

3.5.2. Targeting Metastasis: Inhibiting the Epithelial-to-Mesenchymal Transition (EMT)

Metabolic reprogramming functionally supports metastasis by supplying the energy and biosynthetic precursors required for the Epithelial-to-Mesenchymal Transition (EMT), a process where cancer cells lose cell adhesion and gain migratory and invasive properties. As highlighted by [110], a direct link exists between glucose metabolic heterogeneity and EMT-driven migratory heterogeneity in triple-negative breast cancer [110]. Glycolytic flux provides the energy and biosynthetic precursors necessary for cells to undergo this dramatic phenotypic shift.

The natural compounds reviewed here can target this metabolic-EMT axis. Curcumin and EGCG have been extensively documented to downregulate key EMT transcription factors (e.g., Snail, Twist, ZEB1) and restore epithelial markers [68,111]. Silibinin's inhibition of the YY1/SLC1A5 axis in glioblastoma [83] not only cuts off glutamine but also impairs a pathway critical for invasion. By restricting the metabolic inputs (glucose/glutamine) required for EMT, these compounds indirectly suppress metastatic progression. Furthermore, by reducing lactate production (e.g., resveratrol [73]) and alleviating TME acidosis, they counteract a key promoter of invasion and immune suppression.

3.5.3. Immunomodulation as a Synergistic Mechanism

The collective impact of this TME remodeling is a significant immunomodulatory dividend. Reducing lactate levels alleviates acidosis, which otherwise blocks T-cell and NK cell function [108]. Limiting glutamine availability can reverse the dysfunction of tumor-infiltrating lymphocytes. These metabolic shifts collectively enhance T-cell infiltration, activation, and cytotoxicity [112]. This provides a robust rationale for combining metabolic-targeted natural compounds with immunotherapy. Specifically, this strategy can induce immunological changes that shift tumors from a 'cold' state, resistant to immune checkpoint monotherapy, toward a more inflamed 'hot' state that is responsive to treatment [113]. The collective evidence synthesized in this review, demonstrating the ability of natural compounds to target glucose and glutamine metabolism, supports the development of a structured metabolic intervention strategy. This consensus framework proposes a press-pulse therapeutic approach that simultaneously targets a tumor's dependencies on fermentable fuels via Ketogenic Metabolic Therapy (KMT) and specific metabolic inhibitors [114]. The strategy leverages diet-drug combinations to disrupt substrate availability, using the Glucose-Ketone Index (GKI) to monitor biological compliance. It provides an evidence-driven baseline for metabolic priming in cancers driven by glycolysis and glutaminolysis, effectively remodeling the TME and creating a substrate competition that disadvantages cancer cells.

4. Translational Solutions and Clinical Evidence

Although natural metabolic modulators face pharmacokinetic and safety limitations, several strategies are actively being developed to overcome these barriers. Nanoparticle formulations of curcumin and resveratrol have significantly improved oral bioavailability and tissue penetration in preclinical studies [115,116]. Structural analogs of EGCG with enhanced half-life are under investigation to mitigate hepatotoxicity while preserving anticancer activity [117]. Furthermore, biomarker-driven patient selection (e.g., G6PD status before vitamin C therapy; SLC1A5 expression for glutamine-targeted therapies) can improve safety and therapeutic precision [118].

Clinical evidence supports the translational potential of this approach. A phase II trial demonstrated that intravenous high-dose vitamin C combined with chemoradiotherapy improved pathological complete response rates (44.4%) in rectal cancer patients [119]. Curcumin enhanced the efficacy of gemcitabine in resistant cholangiocarcinoma [70], while berberine showed significant enrichment and tumor suppression in hepatocellular carcinoma and bronchial adenocarcinoma cohorts [120]. These findings highlight that, despite pharmacokinetic challenges, metabolic therapies can be clinically impactful when optimized delivery systems and rational combination regimens are applied.

5. Limitations

While this review highlights the promising therapeutic potential of natural compounds in targeting cancer metabolism, several key limitations must be acknowledged to contextualize the findings and guide future research.

A critical limitation across many of the included studies is the lack of standardized statistical reporting. Several investigations—particularly those evaluating compounds such as melatonin, resveratrol, and silibinin—did not provide essential quantitative measures such as effect sizes, confidence intervals (CIs), or precise *p*-values. For example, while melatonin demonstrated dose-dependent antiproliferative and metabolic-disruptive effects in preclinical models, many studies failed to reach statistical significance, often omitting key metrics necessary for robust interpretation. Furthermore, the effective in vitro concentrations required to induce cytotoxicity may not be clinically achievable due to melatonin's short half-life and rapid hepatic metabolism. These pharmacokinetic limitations, combined with inconsistent dosing strategies and heterogeneous study designs, constrain translational relevance and underscore the need for more standardized, statistically rigorous investigations.

This reflects a broader issue within metabolic oncology research, where the omission of standardized statistical metrics hampers meta-analytic synthesis and evidence-based translation.

Further compounding this challenge is the methodological heterogeneity observed across studies, including variability in dosage regimens, treatment duration, formulation types (e.g., liposomal vs. native compounds), and cell or animal models used. Such inconsistencies hinder meaningful comparisons and dilute the strength of cumulative evidence. The over-reliance on preclinical and in vitro models—though valuable for mechanistic insights—limits the translational relevance of findings, as these systems often fail to recapitulate the complexity of the human tumor microenvironment or account for patient-specific metabolic variability.

Moreover, the lack of large-scale clinical trials remains a significant bottleneck in advancing natural metabolic modulators toward clinical utility. Most human studies remain in early-phase stages or are underpowered, with inconsistent outcome reporting and minimal long-term safety data. The absence of biomarker-driven stratification in many trials further complicates the identification of responsive patient subgroups.

Finally, publication bias may skew the evidence base, favoring studies with positive outcomes while underreporting null or negative results—thereby overstating the perceived efficacy of certain compounds. Together, these limitations highlight the urgent need for rigorously designed, biomarker-stratified, multi-center clinical trials with standardized reporting protocols to establish reproducibility and accelerate safe translation of metabolic therapies into oncology practice.

To address these limitations, future research should

- Adhere to CONSORT and ARRIVE guidelines, ensuring transparency in effect size reporting, CI inclusion, and appropriate multiple testing correction.

- Incorporate orthogonal validation techniques such as metabolomics and proteomics to substantiate mechanistic claims.
- Conduct biomarker-driven, multi-center clinical trials that integrate metabolic profiling to optimize patient selection.
- Emphasize pharmacokinetic standardization and comparative analysis across formulations (e.g., nanocurcumin vs. native curcumin, oral vs. IV vitamin C).

By addressing these methodological gaps, the field can move beyond preclinical promise to build a reproducible, scalable, and clinically actionable foundation for integrating natural metabolic modulators into modern oncology.

Safety Data Gaps

This review primarily synthesizes efficacy data, with limited emphasis on the safety profiles of metabolic interventions. Many preclinical studies and early-phase trials lack comprehensive reporting of adverse effects, such as hepatotoxicity with EGCG or immune suppression with glutamine inhibitors. Future research must prioritize toxicity profiling to establish risk–benefit frameworks.

6. Conclusions: Clinical Implications and Future Research Directions

This review provides a distinct and timely contribution to the evolving field of metabolic oncology. While several recent papers have examined metabolic reprogramming and natural compounds in cancer, our work goes beyond descriptive summaries by embedding the evidence within an integrative oncology framework. Specifically, this review synthesizes mechanistic and clinical findings while advancing translational pathways that include nanotechnology-based formulations, prodrug development, biomarker-guided patient selection, and rational combination strategies with standard therapies. This practice-oriented perspective provides a pragmatic roadmap for bridging preclinical insights with clinical application and distinguishes our review from the prior literature.

The findings of this study underscore the critical role of metabolic-targeted therapies as a transformative approach in cancer treatment, particularly in malignancies resistant to conventional genetically based interventions. By modulating key pathways such as glucose metabolism (Warburg effect) and glutamine addiction, metabolic interventions present a viable alternative or complementary strategy to existing therapies. Natural compounds such as curcumin, berberine, and high-dose Vitamin C and D3 have shown significant promise in disrupting metabolic dependencies that fuel cancer progression, offering a low-toxicity, integrative treatment model.

6.1. Clinical Implications

The integration of metabolic-targeted therapies into oncology practice could significantly enhance treatment outcomes, patient survival, and quality of life. Several key clinical implications emerge from this research:

- Personalized Metabolic Therapies: Future cancer treatment should incorporate metabolic profiling, allowing oncologists to tailor therapies based on individual metabolic signatures. This could lead to more effective patient stratification and treatment customization. Personalization must extend beyond efficacy biomarkers to include metabolic and genetic risk factors (e.g., G6PD deficiency for ascorbate, CYP polymorphisms for berberine). Standardized monitoring protocols for hepatic, renal, and immune function are critical to mitigate adverse events.
- Combination Strategies with Standard Therapies: Metabolic-targeted treatments can synergize with conventional chemotherapy, immunotherapy, and radiation, reducing tumor resistance and recurrence rates.

- Non-Toxic, Cost-Effective Interventions: Natural metabolic modulators offer a safer and potentially cost-effective alternative to cytotoxic treatments, reducing long-term side effects and improving patient compliance.
- Expanded Treatment Options for Hard-to-Treat Cancers: Aggressive malignancies like glioblastoma, pancreatic cancer, and chronic myeloid leukemia (CML) exhibit high metabolic plasticity. Metabolic inhibition offers a promising avenue for addressing treatment-resistant tumors.

While these metabolic strategies hold great promise for enhancing cancer treatment, several challenges remain in translating these findings into clinical practice. The following areas require further investigation to refine and validate metabolic-targeted approaches

6.2. Ethical and Practical Considerations in Metabolic Therapies

While metabolic interventions hold significant promise, their application must be guided by ethical principles and practical feasibility, particularly in vulnerable populations and low-resource settings. Vulnerable groups, such as pediatric, geriatric, and comorbid patients, require careful risk stratification and monitoring to mitigate adverse effects. Equitable access to metabolic therapies remains a challenge, as high costs and infrastructure requirements may limit availability in low-resource settings. Strategies to address these barriers include prioritizing cost-effective interventions, building local capacity, and fostering global research collaborations. Culturally adapted protocols and community engagement are essential to ensure adherence and acceptance in diverse populations. Future research should focus on developing simplified, scalable metabolic therapies that balance efficacy, safety, and accessibility.

6.3. Conclusion and Final Thoughts

The future of oncology will be defined not by a single paradigm but by the integration of genetic, immune, and metabolic insights into a unified framework. While precision medicine has been dominated by genomic profiling, metabolic vulnerabilities represent an equally critical therapeutic dimension. This qualitative systematic review positions metabolic modulation, particularly via natural compounds, as a necessary complement within precision oncology. Compounds such as curcumin, berberine, EGCG, resveratrol, silibinin, vitamin C, vitamin D_3, and melatonin demonstrate the ability to disrupt tumor bioenergetics by targeting glucose and glutamine metabolism, mitochondrial function, and redox balance. This potential is underscored by clinical findings, including intravenous vitamin C improving outcomes in chemoradiotherapy for rectal cancer, curcumin synergizing with gemcitabine in resistant cholangiocarcinoma, and berberine showing promise in hepatocellular carcinoma.

Despite these encouraging results, significant barriers to widespread clinical adoption remain, including pharmacokinetic limitations (e.g., poor oral bioavailability of curcumin, short plasma half-life of EGCG) and specific safety concerns (e.g., G6PD deficiency with high-dose vitamin C, hepatotoxicity from high-dose green tea catechins). Overcoming these hurdles requires innovative solutions such as nanotechnology-based formulations, biomarker-driven patient selection, and rationally designed combination protocols with standard therapies.

Critically, metabolic interventions address fundamental vulnerabilities—bioenergetics, nutrient transport, mitochondrial dysfunction—that often persist despite targeted genomic therapies and contribute to resistance and intratumoral heterogeneity. Therefore, integrating metabolic-targeted strategies alongside conventional, genomic, and immunologic modalities provides a more comprehensive and resilient approach to cancer care. For

instance, metabolic modulation can sensitize tumors to checkpoint inhibitors, enhance responses to targeted agents, and reduce toxicity from chemotherapy or radiotherapy.

In conclusion, positioning metabolic modulation as an adjunctive pillar of precision oncology advances the paradigm of integrative oncology, where patients benefit from more durable, multidimensional, and personalized treatment strategies. Continued research and clinical translation are essential to fully realize the role of metabolic interventions as a vital component of future cancer management.

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