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Research Article

Nature's Cancer Combatants: Bioactive Compounds Disrupting Tumour Metabolism

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Abstract:
Metabolic reprogramming in cancer cells has been well-characterised as a hallmark of tumorigenesis and therapeutic resistance. Cancer cells exhibit enhanced glycolysis, glutaminolysis, dysregulated oxidative phosphorylation (OXPHOS), and aberrant lipid metabolism to support their rapid proliferation and survival under various unfavourable conditions. Natural products are one of the richest pools for potentially disrupting numerous metabolic pathways, and thus modulating these routes has recently come to light as a new cancer treatment strategy. This chapter is a comprehensive and systematic review of the evidence published in the last 20 years, about natural chemicals and cancer metabolism. Investigation on natural substances such as resveratrol, curcumin, berberine, quercetin and epigallocatechin gallate (EGCG) is being extensively conducted with the potential to modify key metabolic pathways implicated in cancer metastasis. The efficacy of these molecules comes from the ability to target glycolytic enzymes (e.g., pyruvate kinase M2 (PKM2), hexokinase 2 (HK2)), lipid biosynthesis (fatty acid synthase [FASN], stearoyl-CoA desaturase 1[SCD1]), oxidative phosphorylation and mitochondria function, and glutaminolysis through glutamine utilization. The work of this article was used extensively for those mechanistic experiments of this research paper such as a Western Blot, Enzymatic Test, Metabolomic Profiling and Mitochondrial Function. The findings reveal that natural products help inhibit tumour growth and enhance the response of cancer cells to radiation and chemotherapy, without induced relapse. While promising, there is still work to be done before these preclinical results can be translated into a clinical setting, primarily because each cancer has a unique tumour metabolism and the possibility of off-target effects remains concerning. However, the promise of natural chemicals as future therapeutic agents in cancer treatment is highlighted by their capacity to influence diverse metabolic pathways and reduce toxicity profiles. More clinical research and dose strategy optimisation is essential to reap the benefits of these natural substances fully.

Keywords: Cancer metabolism, Natural compounds, Metabolic reprogramming, Glycolysis inhibition, Mitochondrial dysfunction

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I. Introduction:

Cancer remains one of the deadliest diseases globally, with millions losing their lives to it every year. That is because it is, in fact, a constellation of diseases characterized by the out-of-control growth and invasion of otherwise normal cells as opposed to being any one illness. Cancer Research Despite many advances over the last few decades in how cancer is studied, available treatments are often not sufficient to control the disease long-term, with side effects, drug resistance and even non-specific targeting of 'cancer' cells all being issues associated with current treatment strategies./PubMed

Accordingly, the study of cancer specific biology has emerged and highlighted unique characteristics that may be harnessed to create highly specific and efficacious treatments. Of these characteristics, cancer metabolism has emerged as an especially compelling domain of investigation.

Cancer Metabolism: The Warburg Effect and Beyond

One of the most distinctive features of cancer cells is their altered metabolism. Unlike normal cells, which rely primarily on oxidative phosphorylation to generate energy in the presence of oxygen, cancer cells often shift their metabolism towards aerobic glycolysis—a phenomenon known as the Warburg effect. This metabolic shift enables cancer cells to rapidly produce ATP and metabolic intermediates required for biomass synthesis, despite being energetically less efficient than oxidative phosphorylation. In doing so, cancer cells meet the heightened demands of their rapid proliferation.

The Warburg effect is not the sole metabolic adaptation in cancer cells. Tumour cells also exhibit increased glutaminolysis (the breakdown of glutamine for energy and biosynthetic purposes) and enhanced fatty acid synthesis, processes that fuel their relentless growth and survival in nutrient-deprived and hypoxic environments. These altered metabolic pathways are now recognized as key drivers of cancer progression and resistance to therapy. By reprogramming their metabolism, cancer cells gain advantages such as the ability to survive under stress, evade cell death, and metastasize to distant organs. Therefore, targeting cancer-specific metabolic pathways has become an attractive strategy for developing more precise and effective cancer therapies.

Natural Compounds as Therapeutic Agents

Natural compounds, which are bioactive substances derived from plants, marine organisms, and fungi, have a long history of use in traditional medicine and modern pharmacology. Many of the drugs used today, including the chemotherapy agents paclitaxel and vincristine, were originally derived from natural sources. In recent years, there has been renewed interest in the use of natural compounds for cancer therapy, particularly for their ability to target cancer metabolism. The rich diversity of structures and mechanisms of action found in natural compounds makes them ideal candidates for modulating complex biological processes like metabolism.

Unlike synthetic drugs, which are often designed to target a single molecule or pathway, natural compounds tend to have multiple molecular targets. This poly-pharmacology is particularly advantageous in cancer treatment, as it allows for the simultaneous modulation of several metabolic pathways that are essential for tumour growth and survival. Moreover, natural compounds are generally less toxic to normal cells, making them attractive alternatives or complement to conventional chemotherapy.

Challenges of Traditional Cancer Therapies

Traditional cancer treatments like chemotherapy and radiotherapy, while effective in many cases, have significant limitations. These treatments often cause severe side effects due to their indiscriminate toxicity to both cancer and healthy cells. Additionally, cancer cells can develop resistance to these treatments, leading to treatment failure and disease relapse. The metabolic flexibility of cancer cells further complicates treatment, as they can adapt to therapeutic pressure by reprogramming their metabolism.

Targeting cancer metabolism offers a promising approach to overcome these limitations. By specifically targeting metabolic pathways crucial for cancer cell growth and survival, therapies can selectively kill cancer cells while sparing normal tissues. Moreover, metabolic pathways often sit upstream of oncogenic signalling networks, making them attractive targets for a broader impact on cancer progression. By disrupting energy production, biosynthesis, and redox balance, natural compounds can effectively suppress tumour growth while minimizing the risk of resistance and adverse side effects.

Mechanisms of Natural Compounds in Targeting Cancer Metabolism

A growing body of evidence supports the ability of natural compounds to interfere with cancer-specific metabolic pathways. For example, resveratrol, a polyphenol found in grapes and red wine, inhibits glycolysis by downregulating key enzymes and activating AMPK. Curcumin, a polyphenol derived from turmeric, impairs mitochondrial function, inhibits fatty acid synthesis, and modulates other metabolic pathways. Berberine, an alkaloid, reduces glucose uptake and activates AMPK, while quercetin inhibits glycolysis and promotes mitochondrial dysfunction. These compounds often have minimal toxicity to normal cells, making them promising candidates for cancer therapy.

The Synergistic Potential of Natural Compounds

Natural compounds can also enhance the effectiveness of existing cancer therapies. Studies have shown that combining natural compounds with conventional chemotherapy or radiotherapy can result in synergistic effects, where the combined treatment is more effective than either therapy alone. For instance, quercetin has been shown to sensitize cancer cells to the chemotherapeutic agent doxorubicin by inhibiting glycolysis and promoting oxidative stress. Similarly, curcumin has been found to enhance the effects of radiotherapy by disrupting cancer cell metabolism and increasing ROS production.

This synergistic potential is particularly important in the context of drug resistance, which remains a major obstacle in cancer treatment. By targeting cancer metabolism, natural compounds can overcome the metabolic adaptations that often lead to resistance to conventional therapies.

Review of Literature

Cancer metabolism has gained significant attention in recent decades due to the recognition that metabolic reprogramming is a hallmark of cancer. Tumour cells undergo numerous alterations in metabolic pathways to support their rapid growth, proliferation, and survival in hostile environments. These metabolic changes provide potential therapeutic targets that can be exploited for cancer treatment. Among various approaches, natural compounds have emerged as promising agents for targeting cancer metabolism due to their diverse bioactivity, relatively low toxicity, and potential for synergistic effects with conventional therapies. This literature review explores the mechanisms through which natural compounds modulate cancer metabolism, highlighting key studies that have advanced the field.

Cancer Metabolism: An Overview

Cancer cells exhibit a high degree of metabolic flexibility, which allows them to adapt to environmental changes and sustain their rapid growth. One of the most well-known metabolic alterations in cancer cells is the Warburg effect, where cancer cells prefer aerobic glycolysis over oxidative phosphorylation, even in the presence of oxygen. This metabolic shift enables rapid ATP production, intermediate generation for biosynthesis, and redox balance maintenance. In addition to the Warburg effect, cancer cells upregulate glutaminolysis, lipid metabolism, and the pentose phosphate pathway, allowing them to thrive in nutrient-poor environments and contributing to therapy resistance. Targeting these unique metabolic pathways offers a promising avenue for developing selective cancer therapies.

Natural Compounds and Cancer Metabolism

Natural compounds, including polyphenols, flavonoids, alkaloids, terpenoids, and marine-derived compounds, have shown great potential in modulating cancer metabolism. These compounds act on multiple metabolic pathways, including glycolysis, oxidative phosphorylation, lipid metabolism, and redox balance, thereby offering a multifaceted approach to cancer therapy.

Polyphenols: Modulating Glycolysis and Oxidative Phosphorylation

Polyphenols, a diverse class of plant-based compounds, have emerged as promising agents in cancer therapy. These natural compounds, abundant in fruits, vegetables, tea, wine, and other plant-based foods, exhibit potent anticancer properties by targeting key metabolic pathways in cancer cells. Resveratrol, a stilbene found in grapes and red wine, inhibits glycolysis by downregulating key enzymes and reducing glucose uptake. It also disrupts mitochondrial function, leading to reduced ATP production and increased oxidative stress. Curcumin, derived from turmeric, targets multiple metabolic pathways, including glycolysis and oxidative phosphorylation. It downregulates glycolytic enzymes, impairs mitochondrial function, and modulates signalling pathways like mTOR and AMPK. Epigallocatechin gallate (EGCG), found in green tea, inhibits glucose uptake, reduces the expression of key glycolytic enzymes, and impairs mitochondrial function, leading to apoptosis. By targeting both glycolysis and mitochondrial respiration, these polyphenols disrupt the metabolic flexibility of tumour cells, making them potent anticancer agents.

Flavonoids, a subclass of polyphenols, are widely distributed in plants and possess diverse pharmacological properties, including anticancer effects. Quercetin, a flavonoid found in apples, onions, and tea, inhibits glycolysis by downregulating key enzymes and glucose transporters. It also impairs mitochondrial function, leading to reduced ATP production and increased oxidative stress. Additionally, quercetin disrupts glutaminolysis, a metabolic pathway crucial for cancer cell growth and survival, by inhibiting glutaminase. Kaempferol, another flavonoid found in broccoli, spinach, and other leafy greens, also inhibits glycolysis and impairs mitochondrial function, leading to apoptosis in cancer cells. Furthermore, kaempferol inhibits fatty acid synthesis, a process upregulated in many cancers to support growth and energy storage.

Alkaloids: Inhibiting Glycolysis and Oxidative Phosphorylation

Alkaloids, a class of nitrogen-containing compounds found in plants, have demonstrated potent anticancer activity by targeting cancer metabolism. Berberine, an iso-quinoline alkaloid, inhibits glycolysis by downregulating glucose uptake and key glycolytic enzymes. It also disrupts mitochondrial function, leading to reduced ATP production and increased oxidative stress. Additionally, berberine activates AMPK, which inhibits anabolic processes and promotes catabolism, further impairing cancer cell growth. Vinca alkaloids, such as vinblastine and vincristine, are well-known chemotherapeutic agents that target microtubule formation. However, they also exhibit effects on cancer metabolism, inhibiting glycolysis and impairing mitochondrial function, leading to reduced energy production and increased ROS levels in cancer cells. By targeting both the cytoskeleton and metabolism, vinca alkaloids effectively inhibit cancer cell proliferation and induce apoptosis.

Terpenoids: Modulating Mitochondrial Function and Redox Balance

Terpenoids, a diverse class of plant-derived compounds, target mitochondrial function and redox balance in cancer cells. Betulinic acid, a triterpenoid found in birch bark, induces apoptosis by disrupting mitochondrial function and increasing ROS production. Paclitaxel, a diterpenoid, inhibits oxidative phosphorylation and induces ROS production, leading to mitochondrial dysfunction and apoptosis.

Marine-Derived Compounds: Disrupting Energy Metabolism

Marine organisms, such as algae, sponges, and marine bacteria, are a rich source of bioactive compounds with unique anticancer properties. Fucoidans, sulphated polysaccharides found in brown algae, inhibit glycolysis

and induce apoptosis in cancer cells by reducing the expression of glycolytic enzymes and impairing mitochondrial function. Trabectedin, a marine-derived compound, targets multiple metabolic pathways. It inhibits oxidative phosphorylation, induces mitochondrial dysfunction, and disrupts nucleotide synthesis, effectively inhibiting cancer cell growth and survival.

Synergistic Effects of Natural Compounds with Conventional Therapies

Natural compounds offer a promising approach to enhance the efficacy of conventional cancer therapies. By targeting metabolic pathways crucial for tumour survival, these compounds can sensitize cancer cells to chemotherapy and radiotherapy. For example, quercetin enhances the effects of doxorubicin by inhibiting glycolysis and promoting ROS production, leading to increased apoptosis. Similarly, curcumin enhances the effects of radiotherapy by disrupting cancer cell metabolism and increasing oxidative stress. This synergistic effect of natural compounds with conventional therapies offers a promising strategy to overcome drug resistance and improve treatment outcomes.

II. Methodology:

Method for Studying Natural Compounds Targeting Cancer Metabolism

Understanding how natural compounds target cancer metabolism requires a multidisciplinary approach that integrates molecular biology, biochemistry, pharmacology, and oncology. The following section outlines a structured method to investigate the role of natural compounds in modulating cancer metabolism, from the selection of compounds to experimental techniques for studying their effects on metabolic pathways.

1. Selection of Natural Compounds

The first step is identifying and selecting the natural compounds to be studied. These compounds can be derived from plants, marine organisms, fungi, or other natural sources. Commonly studied categories of natural compounds include **Polyphenols** (e.g., resveratrol, quercetin), **Flavonoids** (e.g., apigenin, luteolin), **Alkaloids** (e.g., berberine, vincristine), **Terpenoids** (e.g., artemisinin), **Saponins** (e.g., ginsenosides), etc. The selection of anticancer compounds involves several key criteria. Firstly, compounds with prior evidence of anticancer activity are prioritized. Secondly, the compound's ability to target specific metabolic pathways like glycolysis, oxidative phosphorylation, or lipid metabolism is considered. Thirdly, structural characteristics that facilitate interactions with metabolic enzymes or mitochondrial functions are sought. Lastly, the compound's availability in sufficient quantities and high purity is essential for reliable experimental outcomes.

2. In Vitro Studies (Cell Culture Models)

The next step involves evaluating the effects of the selected natural compounds on cancer cell metabolism using in vitro models. These studies provide initial insights into how natural compounds influence key metabolic pathways and cellular behaviour.

Cell Line Selection

To study the effects of natural compounds on cancer cell metabolism, researchers often utilize human cancer cell lines representing various cancer types, such as breast (MCF-7), colon (HCT116), lung (A549), and glioblastoma (U87MG). These cell lines exhibit metabolic adaptations commonly observed in cancer cells, making them ideal models for investigating metabolic disruptions. Non-cancerous cell lines, such as fibroblasts, are typically used as controls to assess the specificity and potential toxicity of the compounds towards cancer cells.

Treatment Protocol

To prepare natural compounds for treatment, they are first dissolved in suitable solvents like DMSO or ethanol and then diluted to the desired working concentrations. Cancer cells are seeded in multi-well plates and allowed to adhere before being treated with various concentrations of the natural compounds for a duration of 24 to 72 hours. This allows for the assessment of dose-response relationships. Untreated cells or cells treated with the solvent alone serve as control groups to evaluate the specific effects of the compounds.

Metabolic Assays in Cell Lines

To assess the impact of natural compounds on cancer cell metabolism, various assays are employed. Glycolysis assays, often utilizing colorimetric or fluorescence-based methods, measure glucose uptake and lactate production to evaluate glycolytic activity. Mitochondrial function is assessed using the Seahorse XF Analyzer, which measures oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) in real-time, providing insights into oxidative phosphorylation and glycolysis. Changes in intracellular ATP levels, indicative of metabolic reprogramming, are measured using luminescence-based ATP assays. Additionally, natural compounds may induce oxidative stress by disrupting mitochondrial function, leading to increased reactive oxygen species (ROS) production. ROS levels are quantified using fluorescent dyes like DCFDA. Finally, cell viability assays, such as MTT, resazurin, or trypan blue exclusion, are used to correlate the metabolic effects of the compounds with their impact on cancer cell survival.

3. In Vivo Studies (Animal Models)

Once in vitro, efficacy is demonstrated, the next step is to evaluate how natural compounds affect cancer metabolism in vivo using animal models.

Animal Model Selection

To further investigate the efficacy of natural compounds in a more complex and physiologically relevant setting, researchers often employ animal models. Xenograft models involve implanting human cancer cells into immunocompromised mice, such as nude or SCID mice, to generate tumours. This approach allows for the

assessment of the systemic effects of natural compounds on cancer metabolism. Alternatively, genetically engineered mouse models (GEMMs) are utilized. These mice are genetically modified to develop cancer spontaneously due to specific genetic mutations, closely mimicking human cancer development and its associated metabolic reprogramming.

Compound Administration

Natural compounds can be administered to animal models through various routes, including oral gavage, intraperitoneal injection, or intravenous injection. The choice of administration route depends on factors such as the compound's pharmacokinetic properties and solubility. To ensure therapeutic efficacy and minimize toxicity, careful dose optimization is crucial. The appropriate dosage is determined based on factors like the compound's potency, the animal model's physiology, and the desired therapeutic outcome.

Metabolic and Tumour Monitoring

To monitor the effectiveness of natural compounds on tumour growth and metabolism, various techniques are employed. Tumour size and volume are regularly measured using callipers or non-invasive imaging methods like MRI or PET scans. At the conclusion of the treatment period, tumour tissues are harvested for metabolomic analysis. Metabolites involved in key metabolic pathways, including glycolysis, glutaminolysis, lipid metabolism, and the TCA cycle, are quantified using mass spectrometry or NMR spectroscopy. Histological analysis, involving immunohistochemistry (IHC), is performed to assess markers of apoptosis (e.g., cleaved caspase-3) and proliferation (e.g., Ki-67), as well as the expression of metabolic enzymes (e.g., HK2, PKM2). These combined approaches provide a comprehensive evaluation of the impact of natural compounds on tumour growth and metabolic reprogramming.

4. Enzyme Activity and Gene Expression Assays

To further elucidate the mechanisms by which natural compounds target cancer metabolism, enzyme activity assays and gene expression studies are conducted.

Enzyme Activity Assays

Natural compounds often exert their anticancer effects by targeting key metabolic enzymes. Hexokinase 2 (HK2), a crucial enzyme in glycolysis, catalyses the initial step of glucose metabolism. Inhibiting HK2 reduces glycolytic flux, hindering cancer cell growth. Pyruvate kinase M2 (PKM2), another glycolytic enzyme frequently upregulated in cancer, promotes anabolic processes. Its inhibition leads to decreased tumour growth. Glutaminase, an enzyme that converts glutamine to glutamate, is essential for cancer cells reliant on glutaminolysis. Inhibiting glutaminase disrupts glutamine metabolism, impairing cancer cell survival. To assess the impact of natural compounds on these enzymes, researchers employ colorimetric or fluorometric assays that measure the production of metabolites, such as ATP or NADH, associated with enzymatic reactions. These assays provide valuable insights into the mechanism of action of natural compounds and their potential as anticancer agents.

Gene Expression Analysis

To gain a deeper understanding of the transcriptional changes induced by natural compounds, researchers often analyze the expression levels of genes associated with cancer metabolism. Quantitative PCR (qPCR) is employed to quantify the mRNA levels of metabolic enzymes like HK2, PKM2, LDHA, and GLS, as well as transporters such as GLUT1 and MCT4. Additionally, Western blotting is utilized to quantify the protein levels of key metabolic regulators, including AMPK, mTOR, and HIF-1α, which play crucial roles in metabolic reprogramming in cancer cells. By examining these changes in gene and protein expression, researchers can elucidate the molecular mechanisms through which natural compounds modulate metabolic pathways and exert their anticancer effects. To understand the transcriptional changes induced by natural compounds, the expression levels of genes related to cancer metabolism are measured using:

5. Metabolomic Profiling

Metabolomic profiling is a powerful tool used to identify and quantify small molecules (metabolites) in cells, tissues, or biofluids following treatment with natural compounds. This provides a comprehensive view of the metabolic alterations induced by the compounds.

Techniques for Metabolomic Profiling

To comprehensively profile the metabolic changes induced by natural compounds, researchers often employ two primary techniques: mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. MS-based metabolomics is widely used due to its high sensitivity and ability to quantify a vast array of metabolites involved in various metabolic pathways, including glycolysis, the TCA cycle, lipid metabolism, and amino acid metabolism. NMR spectroscopy, while less sensitive than MS, offers non-invasive, quantitative data on metabolic changes. It provides valuable insights into the metabolic alterations induced by natural compounds, aiding in the understanding of their mechanisms of action and potential therapeutic applications

Data Analysis

Metabolomic data are analyzed to identify key metabolic pathways that are altered following treatment with natural compounds. Statistical analyses (e.g., principal component analysis, heatmaps) are employed to compare the metabolomic profiles of treated and control groups, highlighting significant metabolic changes.

6. Synergistic Studies with Conventional Therapies

To maximize the therapeutic potential of natural compounds, researchers often explore their combinatorial use with conventional cancer therapies such as chemotherapy and radiotherapy. The Chou-Talalay method is frequently employed to calculate the

Combination Index (CI) value, which determines whether the combination of treatments is synergistic, additive, or antagonistic. Additionally, various treatment schedules, including sequential and simultaneous administration, are investigated to optimize the efficacy of the combined therapy. By combining natural compounds with conventional therapies, researchers aim to enhance therapeutic outcomes while potentially reducing adverse side effects.

III.Results and Discussion:

Based on the methodology outlined, this section discusses the findings from studies on natural compounds targeting cancer metabolism, as well as an analysis of their potential impact on various metabolic pathways. The results are categorized based on the major metabolic pathways—glycolysis, oxidative phosphorylation, glutaminolysis, and lipid metabolism—and provide a comparative evaluation of how different natural compounds modulate these processes. Additionally, the in vitro, in vivo, and clinical trial results are examined, followed by a discussion on the implications and limitations of the findings.

1. Impact on Glycolysis

Natural compounds have emerged as promising agents for targeting the glycolytic pathway, a hallmark of cancer metabolism. Studies have demonstrated that compounds like resveratrol, curcumin, and quercetin can significantly inhibit glycolysis in various cancer cell lines. For instance, resveratrol downregulates glucose transporter 1 (GLUT1) and hexokinase 2 (HK2), reducing glucose uptake and lactate production. Curcumin inhibits pyruvate kinase M2 (PKM2), a key glycolytic enzyme, leading to decreased glycolytic flux and ATP production. Quercetin lowers the expression of lactate dehydrogenase A (LDHA), resulting in reduced lactate production and decreased tumour viability. In vivo studies have corroborated these findings, with resveratrol treatment reducing tumour size and lactate levels in mouse models of breast cancer. While these findings are promising, it's important to note that the efficacy of these compounds may vary across different cancer types. Additionally, while glycolytic inhibition is a promising strategy, compensatory metabolic pathways may be upregulated, necessitating combination therapies for more effective outcomes.

2. Modulation of Oxidative Phosphorylation

Natural compounds have also demonstrated significant effects on oxidative phosphorylation (OXPHOS), a key metabolic process for ATP generation in mitochondria. Berberine, for instance, inhibits complex I of the electron transport chain, leading to reduced ATP production, increased ROS generation, and mitochondrial dysfunction in pancreatic and ovarian cancer cells. Epigallocatechin gallate (EGCG) modulates mitochondrial biogenesis by upregulating PGC-1α, leading to altered OXPHOS and increased ROS in melanoma cells. In vivo studies with berberine have shown reduced tumour growth, decreased mitochondrial respiration, and increased oxidative stress in xenograft models. While targeting OXPHOS offers a promising strategy for cancer therapy, particularly in cancers that rely on mitochondrial respiration, it's crucial to address potential toxicity to non-cancerous cells. Optimizing dosing and delivery strategies is essential to maximize anticancer efficacy while minimizing off-target effects.

3. Inhibition of Glutaminolysis

The glutaminolysis pathway, which involves the metabolism of glutamine to support cancer cell growth, has emerged as another key target for natural compounds. Genistein, an isoflavone found in soy, inhibits glutaminase, the enzyme responsible for converting glutamine to glutamate, in prostate cancer cells. This inhibition reduces the production of TCA cycle intermediates, leading to energy stress and apoptosis. Similarly, sulforaphane, a compound found in cruciferous vegetables, downregulates c-Myc, a transcription factor that regulates glutaminase expression, in colon cancer cells. This results in reduced glutamine uptake and inhibited tumour growth. Targeting glutaminolysis offers a promising therapeutic strategy, as cancer cells often rely heavily on glutamine for their metabolic needs, while normal cells are less dependent on this amino acid. However, the variability in glutamine dependency among different cancers highlights the need for further research to identify the most suitable patient populations for glutaminolysis-targeting therapies.

4. Effects on Lipid Metabolism

Lipid metabolism, encompassing fatty acid synthesis and β-oxidation, has emerged as a critical target for natural compounds in cancer therapy. Ginsenosides, derived from ginseng, inhibit fatty acid synthase (FASN), an enzyme involved in lipogenesis, leading to reduced lipid droplet formation and impaired cancer cell survival in breast and ovarian cancer cells. Garcinol, a compound found in Garcinia species, inhibits stearoyl-CoA desaturase-1 (SCD1), involved in fatty acid desaturation, leading to decreased cell proliferation and increased apoptosis in liver cancer cells. In vivo studies have confirmed these findings, with ginsenosides reducing tumour growth and lipid accumulation in breast cancer xenografts, and garcinol reducing lipid content and increasing apoptosis in tumours. While targeting lipid metabolism offers a promising strategy, the variability in lipid metabolism among different cancer types necessitates further research to identify the most suitable patient populations for these therapies. Additionally, exploring combination therapies with other targeted agents may enhance the efficacy of natural compounds in disrupting lipid metabolism and inhibiting cancer cell growth.

5. Synergistic Effects with Conventional Therapies

The combination of natural compounds with conventional therapies like chemotherapy and radiotherapy has shown promising results in enhancing treatment efficacy. For instance, curcumin combined with 5-FU demonstrated synergistic effects in colon cancer cells by inhibiting glycolysis and increasing oxidative stress. Resveratrol, when combined with

cisplatin, showed improved outcomes in ovarian cancer models by targeting both glycolysis and mitochondrial respiration, making cancer cells more susceptible to chemotherapy-induced apoptosis. Clinical trials have also supported these findings, with studies showing improved progression-free survival and reduced side effects in cancer patients treated with combinations of natural compounds and chemotherapy. While these findings are encouraging, further validation in larger clinical trials is necessary to fully assess the long-term benefits and safety profiles of these combinations. By targeting multiple aspects of cancer metabolism, natural compounds have the potential to revolutionize cancer therapy and improve patient outcomes.

IV. Conclusion:

Cancer metabolism has emerged as a promising target for cancer therapy, offering a unique opportunity to selectively attack the metabolic vulnerabilities of cancer cells. Natural compounds, derived from diverse sources such as plants, marine organisms, and fungi, have shown significant potential in modulating cancer metabolism. These compounds often target multiple metabolic pathways, including glycolysis, oxidative phosphorylation, glutaminolysis, and lipid metabolism, thereby disrupting energy production, biosynthesis, and redox balance in cancer cells.

By understanding the mechanisms through which natural compounds target cancer metabolism, researchers can develop more effective and targeted therapies. In vitro and in vivo studies have demonstrated the ability of natural compounds to inhibit tumor growth, induce apoptosis, and sensitize cancer cells to conventional therapies. However, further research is needed to fully elucidate the molecular mechanisms of action and to address potential challenges such as drug delivery, toxicity, and resistance.

The synergistic potential of natural compounds with conventional therapies offers a promising avenue for improving cancer treatment outcomes. By combining the strengths of natural compounds with existing therapies, it may be possible to achieve greater efficacy with fewer side effects. As research in this field continues to advance, natural compounds hold the promise of becoming valuable tools in the fight against cancer.

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