Regulatory Mechanism of Cancer Cell Metabolism by Natural Compounds

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Abstract

Cancer cell metabolism has emerged as a promising target for cancer therapy due to its fundamental role in supporting tumor growth and survival. Natural compounds derived from plants and other sources have gained attention as potential regulators of cancer cell metabolism. This review article explores the regulatory mechanisms by which natural compounds modulate cancer cell metabolism. This study discusses the various groups of natural substances, including polyphenols, alkaloids, flavonoids, and terpenoids, as well as their effects on key metabolic pathways such as glycolysis, oxidative phosphorylation, and fatty acid metabolism. We delve into the underlying molecular mechanisms through which these natural compounds exert their effects, including modulation of oncogenic signaling pathways, alteration of enzyme activity, and regulation of gene expression. Furthermore, current breakthroughs in the identification and development of natural chemicals as prospective treatments targeting cancer cell metabolism were discussed. We discuss preclinical and clinical studies that have demonstrated the efficacy and safety of natural compounds in inhibiting tumor growth, inducing apoptosis, and sensitizing cancer cells to conventional therapies. This comprehensive review provides valuable insights into the regulatory mechanisms of cancer cell metabolism by natural compounds. Understanding the interactions between natural compounds and cancer cell metabolism will facilitate the development of novel therapeutic strategies that exploit the metabolic vulnerabilities of cancer cells, potentially leading to more effective and targeted cancer treatments.

Keywords: Natural compound; cancer cell metabolism; tumor growth; cancer therapy; CARs: Chimeric antigen receptors; CAFs: Cancer-associated fibroblasts.

Targeting Metabolism Modifications in Cancer:

One of the earliest biological pathways linked to cancer is deregulated metabolism. Despite Warburg’s groundbreaking findings on the effects of the altered energy metabolism in cancer cells, the precise significance and the selective benefits brought on by this deregulation are still up for discussion today. There is little doubt that a number of factors have considerably slowed progress in this field of study. The two most obvious changes in the characteristics of cancer cells, namely their prolonged and uncontrolled growth and their capacity to evade death; have been the subject of intense research for many years in the hunt for novel anticancer treatment drugs. As a result, we have helped create many types of therapeutic drugs that inhibit the growth of cancer cells or cause them to die throughout the years. These studies focused mostly on how differently healthy and cancerous cells responded to these treatments. But as time has gone on, we have also come to understand this approach’s limitations in light of the high rate of therapeutic failure and the frequent emergence of systemic toxicity. Recently, the variety and polymorphism of cancer have made it possible to think of it as a continuous, heterogeneous system that interacts and communicates with its environment in complicated ways. It has become clear that if we wish to successfully treat cancer, entrenched cancer characteristics like continued and unchecked cell proliferation and resistance to cell death need to be reassessed in a far more complicated modulatory environment.

The potential of cancer cells to alter their cellular energy metabolism is undergoing a rebirth that is important in cancer science for these sections concerning basic biochemistry in the wake of this new perspective. This fresh interest is being stoked by the identification of unanticipated interactions between modulators of separate activities and famous metabolic variables. On the one hand, non-canonical regulatory roles for particular metabolic enzymes or substrates are beginning to emerge; in contrast, oncogenes, tumour suppressors, and other modulators controlling activities typically modified at the start of cancer...
progression, such as immune system response, cell proliferation, or cell death, appear in the dual roles of controllers of metabolic processes.

There are two significant ramifications of decoding the functions of metabolic alterations occurring during carcinogenesis and finding the main nodes that distinguish between diseased and healthy behavior: novel prediction biomarkers and new medication development methods. Additionally, substances that target metabolic processes may also be potentially exploited for chemotherapeutic reasons. As a result, new information may provide tools to troubleshoot frequent chemotherapeutic failures. Since this field of study is very young, finding drugs that are metabolically active is a timely issue. Biologically active substances with a wide range of pharmacological potential are abundant in nature. Amazingly, fungi, microbes, and plants account for over 80% of all anticancer chemicals. Each of the cancer hallmarks [1, 2] recently categorised by Hanahan and Weinberg [3] can be inhibited by both natural and chemically altered molecules (to increase stability, specificity, and/or activity). Cancer metabolism is another area where evidence is mounting [2]. Surprisingly, several of these substances are found in food or have long been used in traditional medicine. As a result, they have a favourable profile for absorption and metabolism in the body with minimal toxicity.

1. Benefits of Altering Metabolism in Cancer Cells Compared with Normal Cells

1.1 Mitochondrial respiration to glycolysis metabolic switch

Otto Warburg was the first to identify the preferred transition from aerobic glycolysis to oxidative phosphorylation, which is the most studied and debated metabolic trait in cancer cells.

He had earlier proposed mitochondrial dysfunction as the likely cause. Cancer cells have flaws in the enzymatic respiratory chain [4], but there is no direct link between the prevalence of mitochondrial dysfunction and the metabolic transition to glycolysis, which is frequently observed in cancer cells. Cancer tissues and cells, on the other hand, frequently rely on mitochondrial respiration to make ATP [5]. Additionally, under some conditions, cancer cells could potentially be made to restart their mitochondrial energy production [6]. These findings substantiate the theory that cancer cells’ propensity to intensify the glycolytic pathway while decreasing oxidative phosphorylation must be an active strategy offering significant advantages despite the obvious energetic inefficiency of glycolysis. They also demonstrate that mitochondria are generally functional in cancer cells. However, identifying these selective benefits is a challenging undertaking that is actually up for discussion.

Theoretically, metabolic changes during carcinogenesis might offer a number of advantages since cancer cells require constant access to macromolecule precursors to sustain their high rate of multiplication. In reality, the decrease in mitochondrial respiration results in the buildup of precursors needed for the main cellular synthesis pathways leading to amino acids, nucleotides, and lipids instead of the full breakdown of glucose into carbon dioxide (CO2) and water. This metabolic change unavoidably feeds these anabolic pathways as a result. Second, cancer cells have moderately to severely decreased oxygen tension; therefore, the fact that they choose to use glycolysis to generate energy in this environment is an intriguing adaptation. So, in response to low oxygen levels, overexpression or stabilisation of the hypoxia-inducible factor (HIF) stimulates the transcription of multiple essential glycolytic enzymes and glucose transporters, hence promoting the glycolytic process [7]. Increased glycolytic flow typically entails increased overexpression and/or activity of certain isoforms of numerous enzymes involved in glycolysis. The upregulation of important enzymes such as hexokinase II (HKII), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase (LDH), and the isoform M2 of pyruvate kinase (PKM2) in cancer cells has led to suggestions of these enzymes as prospective therapeutic targets [8, 9]. It’s interesting to note that some of these enzymes are also beginning to have nonglycolytic functions, and the new roles they have been given actually increase the aggressiveness of cancer. For instance, GAPDH, LDH, or PKM2 may also activate gene expression by acting as direct transcriptional factors or by interacting with and subsequently modulating the activity of other nuclear proteins [10–12] (such as HIF-1 and the Signal Transducer and Activator of Transcription 3 (STAT3) [13, 14]) necessary for the transcription of genes particularly associated with cell proliferation (such as, MEK5, histones H2A and H2B, cyclin D1, c-Myc, and androgen receptor [10, 13–15]).

Lactate overproduction serves two purposes. In order to regenerate nicotinamide adenine diphosphate (NAD+), it activates the glycolytic pathway. On the other hand, it is secreted outside the cells, where it encourages angiogenesis and the spread of cancer cells away from their original site. Events regulating lactate synthesis and the synthesis of proangiogenic agents are mutually regulated. For instance, extracellular acidification brought on by lactate transfer and H+ extrusion encourages the activation of HIF-1 [16, 17]. The LDH-A promoter is then transactivated by HIF-1 [16]. Additionally, acidic environments disrupt the immune system’s functioning, which aids in the invasion of cancer. The function of some immune cells, such as cytotoxic T lymphocytes, and the synthesis of cytokines are in fact compromised by lactate secretion [18]. Additionally, it enhances cell motility by regulating the degree to which matrix components are expressed [19, 20].

There are other benefits to the Warburg effect, and mitochondria play a role in several fascinating theories. Reactive oxygen species (ROS) buildup may inevitably be reduced by reducing mitochondrial metabolism. Rapidly proliferating cell systems may benefit from the inhibition of ROS generation because these cells may be better shielded from the possibility of DNA damage during DNA synthesis [21]. The finding that healthy, highly proliferating systems briefly convert to glycolysis before entering S-phase [22] appears to support this concept. Further promoting this flip concurrently with the arrival into S-phase is c-Myc, which increases transcription of the glycolytic enzymes.

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2.2 Important Affected Metabolic Pathways in Cancer

One of the main problems with reprogrammed metabolism is the cancer cells’ selective exploitation of aerobic glycolysis. It is becoming more and more obvious that other metabolic pathways or mediators may be crucial in the development of cancer. The capacity to investigate the metabolic profile of cancer cells using modern, sophisticated experimental methods has made it possible to identify an astounding number of changes. They mostly relate to the status, levels of expression, or accumulation of certain enzymes or intermediary substrates that are engaged in certain anabolic processes. Despite the clear benefit of these alterations within the anabolic process in which they are primarily active, other noncanonical roles have evolved, such as regulation of redox homeostasis or certain signalling events that enable the high rate of cellular proliferation. In this part, we will briefly go over two important routes that can be targeted for therapeutic purposes.

2.2.1. Amino Acid Metabolism

Cancer cells commonly use glutamine metabolism in addition to glucose metabolism. The mitochondria are where this amino acid is initially transformed into glutamate (by a mitochondrial glutaminase) after being taken up by particular transporters. After being further converted to α-ketoglutarate in a process mediated by glutamate dehydrogenase (GIDH), glutamate subsequently serves as fuel for the tricarboxylic acid cycle (TCA). Exceeding substrates from the TCA cycle may reappear in the cytosol, where they serve as the building blocks for a number of anabolic pathways that produce lipids, additional amino acids, and nucleotides. In addition to its important function in anabolic pathways, glutamine metabolism can exacerbate glycolysis, glutaminolysis, and nicotinamide adenine dinucleotide phosphate oxidase (NAPDH) generation, the latter of which further protects cells from potential oxidative stress. This is because lactate is accumulated through malate formation. Studies show that some cancers, such as glioblastoma, have an incredibly high rate of glutamine metabolism that exceeds their actual nitrogen requirements, which raises the possibility that glutamine consumption in cancer cells serves as a quick and preferential carbon source to replenish a number of biosynthetic pathways. Other proteins, such as the NRF2-related factor (NRF2), whose expression level is changed in cancer cells, may help to further enhance this preferential usage of glutamine. These findings collectively suggest that glutamine metabolism may become a drug of choice for cancer cells to sustain their high rate of proliferation. Targeting their capacity to breakdown glutamine may therefore have therapeutic value, particularly in cancers that depend on glutamine.

2.2.2. Lipid Metabolism

A growing amount of research shows that disturbed lipid homeostasis plays a crucial role in promoting the phenotype of cancer cells. The pattern of modifications described leads one to believe that lipid metabolism has several functions in cancer. Beyond the significance of metabolic changes that favour lipogenesis and therefore particular anabolic activities, lipid-related variables seem crucial in regulating redox homeostasis and the buildup of particular lipid messengers, such as prostaglandins and lysophosphatidic acid. As a result, as we shall discuss later, various transcription factors and enzymes that regulate lipogenesis and lipid homeostasis are overexpressed in cancer. The importance of steroid hormone-dependent pathways in the reported altered lipid metabolism was confirmed by the earliest identification of these abnormalities in hormone-dependent cancers, such as those affecting the breast and prostate. Other cancer cell lines originating from melanoma, osteosarcoma, colorectal, lung, and hematopoietic cancer cells, as well as melanoma, osteosarcoma, colorectal, lung, and colorectal cancer cells, have all recently been found to exhibit similar patterns of changes. The phosphatidylinositol-3-kinase (PI3K)/Akt pathway [41, 42], the H-ras [41], and AMP-activated protein kinase, or AMPK (AMP-activated protein kinase), have already been found to exhibit similar patterns of changes. The phosphatidylinositol-3-kinase (PI3K)/Akt pathway [41, 42], the H-ras [41], and AMP-activated protein kinase, or AMPK (AMP-activated protein kinase), [43] are
other modulatory upstream pathways that were discovered as a result of these cellular settings. The sterol regulatory element-binding protein (SREBP), a lipid-related transcription factor, is also increased in cancer, and its target genes encourage malignant aggression [44]. It is generally known that too much glucose causes mitochondrial citrate concentrations to rise, which activates fatty acid neosynthesis. Citrate is then transformed in the cytoplasm into palmitoyl-CoA, a precursor to the production of triglycerides and phospholipids. After hunger, the buildup of triglycerides may be reversed when a drop in the lipogenic intermediate malonyl-CoA triggers the reactivation of carnitine palmitoyltransferase-1 (CPT-1), which then triggers mitochondrial fatty acid oxidation [45].

De novo fatty acid synthesis is maintained in cancer cells, and numerous lipogenic enzymes are frequently increased. The benefit of further aggravated extrabiosynthetic anabolic activities facilitating cell development is provided by the subsequent surge in lipidogenesis. Cancer cells commonly overexpress the enzymes ATP-citrate lyase (ACL), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FAS) [46]. Particularly, FAS was suggested as a possible cancer biomarker for therapeutic reasons [47, 48]. FAS inhibitors suppress carcinogenesis in in vivo procarcinogenic models of breast [50] and lung [38] tissues, and they also cause cell death in a number of cancer cell lines [34, 47, 51–53], all without affecting healthy lipogenic tissues [54]. These findings support the dual clinical potential of FAS inhibitors. Additionally, FAS targeting, in conjunction with chemotherapeutic drugs, reduces chemoresistance since FAS expression is correlated with the development of metastases [35, 55]. These numerous anticancer properties, along with the finding that FAS is overexpressed in premalignant lesions [56, 57], strongly support the idea that this enzyme may actually be regarded as an oncoenzyme because of its early role in carcinogenesis [58–60].

Additionally, lysophosphatidic acid, a phospholipid, is synthesised preferentially by cancer cells rather than triglycerides [49]. Lipid messengers are accumulated as a result of the biosynthetic diversion of lipid precursors, which promotes cancer cell proliferation, survival, and migration to different tissues [61]. The procarcinogenic effects that proinflammatorysignalling events play during carcinogenesis are strengthened by an increase of prostaglandins, including prostaglandin E [62]. Surprisingly, lipid metabolism and control of the expression of the primary proinflammatory mediator cyclooxygenase 2 (COX-2), which is constitutively overexpressed in cancer, have a close relationship [62, 63]. The fact that lipolytic enzymes, such as monoacylglycerol lipase ( MAGL) [64], are overexpressed in cancer and may directly regulate prostaglandin levels [65] is consistent with these data. Given current research on the functions of lipid metabolism in cancer, we are certain that additional findings will only increase the significance of these pathways for the treatment and prevention of cancer.

2.3 Impact of Modified Metabolism on Promoting Cancer Hallmarks

Angiogenesis and cell death susceptibility are two crucial mechanisms that affect the growth and survival of tumours [66–68]. The metabolism of cancer cells is tightly correlated with these separate mechanisms [67, 69]. The latest research has shown that mitochondria regulate these two important pathways and support metabolic balance in cancer cells [70]. For cellular survival and maintenance, the mitochondrion serves as the most significant coordinator of both energy generation and the accumulation of biosynthetic precursors.

By influencing cancer cell metabolism, reducing mitochondrial-dependent apoptosis, and promoting angiogenesis, altered mitochondrial bioenergetics and functions play a significant role in carcinogenesis [66, 70–72]. When compared to healthy cells, cancer cells usually exhibit a mitochondrial metabolic shift from glucose oxidation (GO) to glycolysis [73]. As a result, they assimilate more glucose. By controlling the metabolic key enzymes that control the balance between GO and glycolysis and by reducing the entry of pyruvate into mitochondria, cancer cells refuel themselves with phosphorylated intermediates necessary for growth and proliferation [17, 73, 74]. During aerobic glycolysis, the stored pyruvate is partially transformed into lactate and secreted to maintain glycolysis. Extracellular lactate that is secreted affects the extracellular matrix by reducing the pH of the tumour environment, allowing the matrix to reorganise itself, and triggering blood vessel invasion in response to angiogenic factors produced by the tumour [17]. Due to the activation of HIF-1 being triggered by decreased mitochondrial efficiency, angiogenesis, cell migration, enhanced cell survival, and energy metabolism may all ensue [75, 76]. On the other hand, HIF-1 is inhibited by the restoration of mitochondrial function [77–79]. In many cancer cell lines, it has been shown that dichloroacetate (DCA), which inhibits pyruvate dehydrogenase kinase (PDK), activates GO in the mitochondria and reduces tumour growth; this process is associated with the suppression of HIF-1 [69].

Modifications in mitochondrial activity affect both the metabolic state of the cell and the regulation of the redox status of cancer cells. The pentose phosphate pathway (PPP) is used to break down the vast amounts of glucose that are present in cells, creating nucleosides and NADPH [70, 73]. Modifications in mitochondrial activity affect both the metabolic state of the cell and the regulation of the redox status of cancer cells. NADPH fundamentally plays a role in redox regulation, defending cells from ROS. ROS levels that are high, such as those produced by cancer cells, can encourage oxidative damage-induced cell death. As a result, cancer cells increase the amount of NADPH they can make to lower ROS activity [73]. The differential in redox status between healthy cells and cancer cells may be a target for medications that produce ROS to kill cancer cells only. Therefore, it is possible to use the induction of ROS to cause cancer cells to die as a result of oxidative damage. The B-cell lymphoma-2 (Bcl-2) protein, which is overexpressed in a number of cancer cells, is another significant modulator of the redox status in cancer cells [80]. The antiapoptotic properties of Bcl-2 maintain the integrity of the outer mitochondrial membrane and prevent its permeabilization by sequestering the proapoptotic proteins BAX (B-cell lymphomaassociated X) and Bcl-2 homologous antagonist
killer (BAK). This is why Bcl-2 has the potential to be tumorigenic. Although Bcl-2 may modify the intracellular redox status in order to maintain the ROS potential at the most advantageous level for cancer cell survival, regulation of ROS levels by Bcl-2 has also been established [81, 82].

Another additional route that ensures the survival of cancer cells is autophagy. Additionally, autophagy is a key mechanism driving cell metabolism [67]. In the absence of exogenous nutrients, it provides intracellular ones. Because of inadequate vascularization, cancer cells are put in an environment devoid of nutrition and oxygen, unlike normal cells. By supplying the endogenous metabolic substrates required to fuel glycolysis, ATP generation, and mitochondrial metabolism with pyruvate, autophagy may aid cancer development [67]. The breakdown products that come from the recycling of intracellular organelles by autophagy help to manufature energy and create new proteins and membranes. By destroying protein, lipids, carbohydrates, nucleic acids, and proteins, autophagy does in fact supply an internal source of sugar, nucleosides, amino acids, and fatty acids [83]. Therefore, autophagy promotes cancer cell survival in nutrient-deficient tumours by maintaining cell metabolism and avoiding the development of mitochondrial malfunction in cancer cells [84].

Autophagy, oxidative stress, and impaired mitochondrial activity are all closely connected. A growing body of research highlights how significantly autophagy may impact mitochondrial functioning and ROS buildup [85]. Mitophagy is an autophagic mechanism that regulates mitochondrial number and health conditions. Overly damaged mitochondria form a substrate for autophagic breakdown through the mitochondrial quality control mechanism of mitophagy. Mitophagy can be induced by hypoxia and hypoxia-inducible factors (HIFs) [86]. ROS production, DNA damage induction, and cell death are all associated with dysfunctional mitochondria [87]. Therefore, mitophagy’s destruction of these damaged organelles may shield cells against the development of cancer. However, the autophagic pathways may be activated or inhibited in the context of cancer treatment. Because this modulation invariably reduces cancer cell viability, it has been shown that autophagy inhibitors may target autophagy-dependent cancer cells [88]. On the other hand, a high rate of autophagy can cause cell death. Because of this, cytotoxic cancer treatments that intensify autophagy may cause greater oxidative stress or severe cell damage, making cancer cells more susceptible to cell death (also known as apoptosis) [89]. It’s interesting to note that Bcl-2 controls both autophagy and apoptosis. By interacting with the proautophagy protein Beclin-1 and the proapoptotic protein Bax, Bcl-2 controls autophagy [72]. Therefore, it is crucial to take into account the interaction between autophagy and mitochondrial metabolism while developing a cancer treatment plan. Redox changes linked to mitochondrial dysfunctions may also play a crucial role in halting the development, spread, and establishment of cancer during the very earliest stages of carcinogenesis.

### 3. Potential Metabolic Pathways that Natural Molecules Can Target

The use of this information for both preventative and therapeutic reasons follows naturally from the clarification of the many roles that altered metabolism plays in cancer. The occurrence of certain modulation patterns also indicates prospective molecular targets for new types of anticaner drugs in the future. This section offers a summary of the natural substances controlling the most intriguing metabolic pathway intermediates.

#### 3.1. Carbohydrate metabolism related factors

##### 3.1.1. Glucose Transporters

A cancer cell needs to stimulate the glycolytic pathway in order to meet the anabolic requirement for regular supplies of intracellular glucose. By actively connecting to ion fluxes through the extrusion of Na+, some plasma membrane transporters that carry glucose into cells enable glucose internalization [90]. In cancer cells, certain isoforms of glucose transporters are frequently overexpressed. The solute carrier (SLC2) gene family’s facilitative glucose transporters (GLUTs) are commonly overexpressed. Information on isoforms 1, 3, 4, and 12 has been published consistently. Therefore, one effective tactic is to target anomalous expression or activity of such carriers. The possible modulators of glucose transporters have been identified in a number of natural substances (Figure 1). According to a critical analysis of the literature, these substances most likely indirectly influence the expression of glucose transporters by influencing upstream modulatory pathways. For natural chemicals, the same holds true. Long chained fatty acid derivatives known as anomalous acetogenins are derived from a variety of tropical plants, including the Graviola or Annonamuricata tree. Recent research has demonstrated that graviola extracts have a variety of anticaner effects on pancreatic cancer cell types [91]. The extract inhibits cell motility and induces necrosis, which lowers cell viability and proliferation. With mice xenograft models, the potential anticancer activities have been demonstrated. Graviola extract inhibits the growth of tumours and the development of metastases. The capacity of this molecule to block glucose absorption is highlighted by an investigation of metabolic parameters. In addition, it significantly lowers the expression levels of various metabolic actors, including GLUT1 and GLUT4, HKII, and LDH-A. This pattern of regulation results from the control of several components and pathways, including the suppression of ERK (extracellular-regulated kinase) and Akt activation as well as the decrease in HIF-1 and nuclear factor B (NF-B) expression levels. Finding compounds that influence the function of glucose transporters is an intriguing alternative to selectively targeting glucose transporter expression without influencing many other intracellular pathways, which is challenging. Several natural chemicals merit consideration in this area. Glucopiericidin A (GPA) has been isolated and characterised in the broth of the bacterial strain Lechevalieria sp. as a novel inhibitor of glycolysis following a natural product screening assay based on crude extracts of microbial origin intended to identify new inhibitors.
Figure 1: Metabolism that natural compounds can target. A list of the most important substances influencing the metabolic pathways of cancer cells. Many of these molecules are analogous to natural compounds, alternatively, they are chemical structures that have been identified as being active and might serve as a model for the discovery of prospective natural compounds that have comparable activity. The molecules in green and brown alter the expression level of the targeted enzyme, respectively, while the ones in blue affect enzymatic activity (+ or - stands for activators or inhibitors, respectively). Abbreviations: ATP citrate lyase, ACL; gallocat-echingallate, GCG; epigallocatechingallate (EGCG); fatty acid synthase, FAS; fructose-6-phosphate, F6P; fructose-1,6-biphosphate, FBP; hypoxia-inducible factor 1, HIF-1; glucose-6-phosphate, G6P; glutamine synthetase, GS; hexokinase II, HK2; glyceraldehyde-3-phosphate, G3P; glyceraldehyde-3-phosphate dehydrogenase, GAPDH; glucose transporter, GLUT; glutamate dehydrogenase, GDH; α-ketoglutarate (αKG); isocitrate dehydrogenase 1, IDH1; lactate dehydrogenase, LDH; nicotinamide adenine dinucleotide phosphate-oxidase, NADPH; pentose phosphate pathway; 3-phosphoglycerate, 3PG; phosphoenolpyruvate, PEP; pyruvate kinase isoform M2, PKM2.
of filopodia protrusion (special membrane structures involved in promoting metastasis) [92]. The researchers established that GPA promotes cellular absorption of glucose. Deoxyglucose (DG), a nonmetabolizable glucose analogue, accumulates as a result of the substance, although it has no effect on the essential glycolytic enzyme HK. Their findings imply that GPA could imitate a GLUT1 substrate in order to exert its effects.

3.1.2. Enzymes involved in Carbohydrate Metabolism

The initial enzymatic stage of glycolysis is controlled by the enzyme hexokinase (HK), which enables the intracellular phosphorylation of glucose (Figure 1). The major isoform in cancer cells, HKII, participates in the Warburg effect and promotes cell proliferation [96]. In close proximity to the ATP molecules necessary for HK’s enzymatic activity, HK forms an association with the outer mitochondrial membrane. The destabilisation of this physical contact has a detrimental impact on the energetics of the cancer cell as a whole. In addition, it severely disturbs the mitochondria, causing cytochrome c to be released and, thus, inducing apoptosis [97]. Some organic substances have been believed to encourage the separation of HK from mitochondria. Many plants, including rosemary (Rosmarinusofficinalis L.), olives (Olea europaea L.), and ginger (Zingiberofficinalis), generate methyl jasmonate, a plant stress hormone that binds to HK and disrupts its connection with the voltage-dependent anion channel (VDAC) in cancer cells [98]. Overall energy is compromised as a result of this occurrence, which also encourages the release of cytochrome c from mitochondria, inducing apoptosis. Its usage in conjunction with chemotherapeutic drugs or the antiglycolytic agent 2-deoxyglucose is now being researched [98].

A crucial glycolytic enzyme called glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is responsible for catalysing the conversion of glyceraldehyde-3-phosphate to glyceraldehyde-1,3-biphosphate and the subsequent production of NADH. There is proof that GAPDH may have a variety of noncanonical roles in cell growth and survival. Both adherent and nonadherent cancer cell cultures demonstrate antiproliferative effects in response to the bis-quinone alkyaloid saframycin, a bacterial result of fermentation. Similar to alkylating agents, this substance has properties. The Myers group has demonstrated that the antiproliferative activity attributed to this chemical [99] may be caused by saframycin forming a nuclear ternary complex with GAPDH and DNA.

In recent years, interest in using the embryonic isoform M2 (PKM2) for cancer diagnosis and treatment has increased [5]. The rate-limiting stage of glycolysis is catalysed by enzymes from the pyruvate kinase family, which results in the buildup of pyruvate from phosphoenolpyruvate in an ATP-producing process. Instead of adult M1, only cancer cells express the embryonic isoform M2. The preservation of aerobic glycolysis depends on this transition [8]. Additionally, cells that reproduce quickly only express PKM2. It’s important to note that PKM2 may exist in either a dimeric or tetrameric form; the latter effectively catalyses the synthesis of pyruvate, while the former is essentially inert. The dimeric form predominates in cancer cells. It is thought that this contradictory behaviour helps to further boost glycolysis and a number of anabolic processes.

Two primary PKM2 targeting methods are being examined at the moment. The initial effort entails finding substances that block PKM2. Three potential chemical structures linked to potential inhibitory activities on PKM2 have been identified as a result of high-throughput screenings using an enzymatic LDH assay to examine a compound library that includes molecules approved by the Food and Drug Administration (FDA) and purified natural products [100]. Thiazolidinediones are among the active substances, and natural compounds from the naphthoquinones family, such as shikonin, alkannin, and their derivatives (extracted from various plants, such as Arnebia sp. and Allannatinictoria), have recently been shown to be the most effective and focused inhibitors of PKM2 [101]. It is also known that these substances can disrupt PKM2 by decreasing lactate synthesis and glucose uptake [102]. However, their impact on cell survival is unrelated to their inhibitory effect on PKM2, which instead raises the possibility that the glycolytic metabolism is compromised. Despite the fact that PKM2 is essential for cancer cell survival [101], there is a chance that it might harm healthy PKM2-expressing cells as well. A second area of study is now focused on encouraging PKM2 to become active again in cancer cells. The Warburg effect is eliminated, and oxidative phosphorylation may be activated again when the ratio of tetrameric to dimeric PKM2 isoforms increases [103]. Few encouraging studies identifying some chemical scaffolds as possible PKM2 activators have been published yet. Sulphonamides, thieno[3,2-b]pyrrole[3,2-d]pyridazinones, and 1-(sulphonyl)-5-(arylsulfonyl)indolines are some of the small molecules that serve as allosteric modulators by binding to an enzyme’s surface pocket and encouraging the interaction of various PKM2 subunits. Even though PKM2 targeting seems to be a potential area for drug discovery, research is still in its early stages. Finding the initial chemical building blocks might lead to the discovery of naturally occurring molecules with similar structural properties.

3.2. Hypoxia-Inducible Factor-1

Without a doubt, the hypoxic redox switch HIF-1 plays a crucial role in regulating the generation of glucose transporters and important glycolytic enzymes (Figure 1). The finding of HIF-1 small-molecule inhibitors is thus a crucial tactic. Several attempts have used reporter gene constructs controlled by an HIF-1 response element in cell-based experiments. The aquatic plant Saururus chinensis [104] and (ii) the alpinumisoflavones [alpinumisoflavone and 4-O-methyl alpinumisoflavone] isolated from the tropical legumaceous plant Lonchocarpus glabrescens [105].These substances prevent the activation of HIF-1 caused by hypoxia, and they may also influence the expression of HIF-1 and HIF-1 target genes, including GLUT1 and/or VEGF. The cinnamic acid derivatives bacharin and drupanin, which were isolated from Brazilian green propolis, have also been recognised by the Nagasawa group as inhibitors of HIF-1-dependent luciferase activity [106]. They also have antiangiogenic properties and suppress the production of HIF-1 and its target genes (GLUT1, HKII, and VEGF).
2.3 Influencing mitochondrial function and metabolism

In addition to impacting cell death and angiogenesis, two crucial processes implicated in the development of cancer, it has been demonstrated that a number of natural substances can target mitochondrial metabolism and activities. Often used as a spice, curcumin is a natural substance obtained from the plant Curcuma longa. In a range of cancer models, its anticarcinogenic and chemopreventive activities target mitochondrial metabolism and function, causing cell death and angiogenesis [107]. Curcumin causes alterations in the mitochondrial membrane potential, procaspase-3 and 9 cleavage, and death in human colorectal cancer cells in a dose- and time-dependent manner, as well as the release of lactate dehydrogenase. It results in a cell cycle arrest in the S phase, the release of cytochrome c, a notable rise in the levels of Bax and p53, and a noticeably decreased level of Bcl-2 and survivin in LoVo cells [108]. By influencing mitochondrial malfunction brought on by oxidative stress, dimethoxycurcumin (Demc), a synthetic derivative of curcumin, causes cell cycle arrest in S phase and apoptosis in human breast cancer MCF-7 cells. Accordingly, it was shown that ROS production was enhanced and glutathione levels were decreased after DNA damage and apoptosis [109]. A drop in the mitochondrial membrane potential and a decline in the cellular energy status (ATP/ADP) due to ATP synthase inhibition were further signs of mitochondrial malfunction. As a result, alterations in the expression of apoptotic markers like Bax and Bcl-2 were linked with mitochondrial dysfunction [109]. Redox changes were identified in several investigations as a causal factor underlying mitochondrial dysfunction in cancer. The ROS-lysosomal mitochondrial pathway (LMP) is a new mechanism for curcumin control, and cathepsin B (cat B) and cathepsin D (cat D) were found to be important mediators of this system in apoptosis by Chen et al. Curcumin causes lysosomal membrane permeabilization, which occurs before mitochondrial changes, in lung cancer cell line A549 to trigger apoptosis [110]. Further research showed that in small cell lung cancer (SCLC) and NPC-TW 076 human nasopharyngeal carcinoma cells, curcumin-induced ROS generation decreases the mitochondrial membrane potential, followed by downregulation of Bcl-2 expression, Bax activation, and release of cytochrome c into the cytosol, paralleled by the activation of caspase-9 and -3 [111, 112]. The suppression of mitochondrial NADP(+)-dependent isocitrate dehydrogenase activity, which is crucial for providing NADPH for the antioxidant systems and plays a crucial role in the cell’s defense against oxidative stress, significantly increases the amount of apoptosis that curcumin induces in the colon cancer cell line HCT116 [113]. A significant apoptotic activity against a variety of cancer cell lines is shown by the amaryllidaceae alkaloid pancretatianthin, which was isolated from the bulb of Hymenocallis littoralis [114]. In breast cancer cells, pancratistatin induced ROS production and mitochondrial depolarization, which resulted in caspase-independent cell death. Pancratistatin lowered mitochondrial membrane potential and caused apoptotic nuclear morphology in colorectal carcinoma cell lines but not in non-cancerous colon fibroblast cells [114]. Resveratrol, a naturally occurring stilbene derived from grapes, blueberries, or cranberries, causes apoptosis in colon cancer cells by activating caspase and producing nitric oxide [115]. Resveratrol, on the other hand, promoted apoptosis in multiple myeloma cells by inhibiting NF-B activation and, as a result, downregulating specific genes such as interleukin-2 and Bcl-2, which resulted in cell cycle arrest [116].

A potential treatment method involves taking advantage of the interactions among mitochondria with the autophagic system. Numerous advantageous effects of resveratrol include neuroprotection and cytotoxicity in glioblastoma cell lines. Resveratrol has been shown to inhibit the formation of gliomas by inducing a crosstalk between autophagy and apoptosis [117]. In three human GBM cell lines, resveratrol does affect the production of autophagosomes, which is followed by an increase in the autophagic proteins Atg5 (Autophagy protein 5, beclin-1, and LC3-II [117]. The reduction of resveratrol-induced autophagy, however, resulted in an uptick in Bax expression and caspase-3 cleavage, which led to apoptosis. Only the suppression of both cell death pathways rendered resveratrol harmless. Thus, in order to make glioblastoma cancer cells more susceptible to death, resveratrol promotes autophagy by causing oxidative stress or cell damage [117]. Additionally, curcumin treatment of HepG2 cells obtained from the human liver results in a decrease in mitochondrial membrane potential and an activation of autophagy. Furthermore, it has been proven that curcumin stimulates mitophagy. This discovery highlights the significance of mitophagy in the mechanism by which nasopharyngeal cancer cells die [118].

HIF-1 is a crucial mechanism in mitochondrial dysfunction that contributes to the development of tumours, as was previously noted. Curcumin has been shown to be essential in the reduction of tumour growth in HepG2 hepatocellular carcinoma cells and MCF-7 breast cancer cells by inhibiting HIF-1-mediated angiogenesis [119, 120]. Curcumin’s anticancer properties are due to the inactivation of HIF-1 via the degradation of the ARNT (Aryl hydrocarbon nuclear translocator). The flavonoid bavachinin is another natural molecule with strong antiangiogenic properties. Human KB cancer created from HeLa cells was suppressed by bavachinin’s enhanced HIF-1 activity [121]. Bavachinin reduced the transcription of HIF-1-regulated angiogenesis and energy metabolism genes such as vascular endothelial growth factors (VEGFs), GLUT1, and HKII in human HOS osteosarcoma cells during hypoxia [121]. The medicinal drug avachinin can be used to prevent cancer angiogenesis. Indeed, in vivo research has shown that giving bavachinin injections dramatically decreased the tumour volume in naked mice receiving KB xenografts [121]. The main routes of action for naturally occurring substances that serve as mitochondrial modulators are summarised in Figure 2.
2.3 Additional Modified Metabolic Pathways Targeted in Cancer Cells

2.3.1 Amino Acid Metabolism

The two primary carbon sources that cancer cells employ to meet their anabolic requirements are glutamine and glucose. Published studies suggest that glutamine metabolism plays a part in the phenotype of malignant cells. As a result, efforts to target the enzymes thought to be involved in this process are being researched. Several cancer cell lines have a high rate of glutamine consumption. As demonstrated in glioblastoma cells using combinatorial therapies with drugs depleting cells of glucose or inhibiting certain kinase- (i.e., AKT-) dependent pathways, decreasing glutamate dehydrogenase (GDH) activity is an efficient anticancer method [122]. By identifying and binding to the location of the allosteric regulator ADP, green tea polyphenols such as epigallocatechingallate (EGCG) and catechingallate (CG) block GDH [123, 124]. These results give rise to curiosity regarding the possible application of these polyphenols and their increased bioavailability analogues in the management of glutamine-dependent cancers.

2.3.1. Lipid Metabolism

In cancer cells, FAS maintains abnormal lipid metabolism. Seven distinct functional domains make up the intricate structure of this enzyme [125]. The likelihood of reducing its enzymatic activity with various particular substances is increased by this characteristic. There are four main known selective FAS inhibitors [126]. Cerulenin, an antibiotic derived from the fungus Cephalosporiumcaerulens, inhibits the ketoacyl synthase domain noncompetitively [127]. Targeting the thioesterase domain of FAS is tetrahydrolipstatin, also referred to as Orlistat (a derivative of the natural chemical lipstatin) [128]. The activity of the enzyme enoyl-reductase is impacted by triclosan [129]. The most effective substance in vitro that is able to adversely influence all three of the aforementioned domains in a competitive, irreversible manner is the synthetic chemical derivative of cerulenin C75 [129]. The Food and Drug Administration (FDA) gave orlistat its OK because it can help people lose weight. Additionally, each of these compounds has anticancer properties by inhibiting cancer cell growth and inducing cancer cell death [126]. Their ability to modulate other enzymes, such as the increase in CPT-1 activity and the oxidation of fatty acids by cerulenin and C75, leading to weight loss [130, 131], their reduced bioavailability (such as Orlistat [126]), or their stability in vivo (such as the inactivation of C75 by intracellular glutathione and other small thiols [132]), however, prevents their actual application for treating cancer. Current research efforts are concentrated on the development of novel synthetic derivatives of this first group of molecules and the discovery of novel compounds of natural origin, both of which

Figure 2: Therapeutic targets for malfunctions of the mitochondria. Examples of organic substances that may be effective in the treatment of cancer. Their mode of action in relation to mitochondrial dysfunction is schematized in the figure. Different mitochondrial targets, including mitochondrial membrane potential (MMP), B Cell Lymphoma-2 (Bcl-2 family proteins (Bcl-2)), reactive oxygen species (ROS), HIF-1, mitochondrial metabolism (MM), and autophagy, are impacted by the chemicals addressed here.
may exhibit improved accuracy and bioavailability or stability in vivo.

A particularly intriguing approach in this situation is the potential discovery of new FAS inhibitors from natural compounds, especially by looking into compounds of vegetal origin that have the dual favourable profile of being regularly consumed in the diet and exhibiting both hypolipidemic and anticancer properties. Numerous types of polyphenols seem to be excellent candidates. It has been frequently demonstrated that black and green tea extracts are lipidogenic inhibitors [133]. In vitro tests of the FAS enzymatic activity [134, 135] have revealed catechingallate derivatives, such as ECGG, epicatechingallate (ECG), and catechingallate (CG), as particular FAS inhibitors. Because it directly interacts with and regulates the activity of the -ketocacylreductase domain of FAS, the galloyl moiety of catechins is crucial for the inhibitory effects of these molecules [134, 135]. Other polyphenolic substances share the FAS inhibiting action. Several flavonoids, including luteolin, quercetin, kaempferol, myricetin, fisetin, and baicalein, have been identified as inhibitors of the -ketocacylreductase domain by the Tian group [136]. In a comparison study with ECGG in prostate cancer, the flavone luteolin and the flavonols quercetin and kaempferol (and to a lesser extent the flavone apigenin and the flavanonetaxifolin) were shown to behave as effective inhibitors of lipogenesis. Their capacity to suppress FAS was validated by an in vitro FAS enzymatic activity test, although less effectively than ECGG [137]. Tian and colleagues proposed that the biphenyl core shared by all polyphenolic FAS inhibitors may be the cause of their documented inhibitory action [138]. Flavones like quercetin and kaempferol that contain hydroxyl groups at specific positions [137] show a reversible rapidly binding restricting activity, while ECGG and ECG show an irreversible slow binding activity. These potential distinctions may account for a structure-dependent mechanism of action.

However, it has been recognised that further heterogeneity may be related to the varying rates of absorption, metabolization, and inherent stability of the substances. The impacts on lipid metabolism may also be the outcome of several intracellular signalling processes that are controlled by polyphenolic chemicals and ultimately converge to affect lipid metabolism. It has been demonstrated that curcumin has an impact on FAS activity and lipid synthesis [139]. This capability could be partially explained by the substance’s known antagonistic action towards the NF-B-mediated pathway [140]. Additionally, it has recently been demonstrated that curcumin and its derivatives can modify the AMPK-SREBP pathway [141, 142]. Through modification of a P13K/AKT-dependent pathway, green tea extracts inhibit the overexpression of FAS brought on by EGF in MCF-7 [143]. Other polyphenolic substances that target the expression of FAS as well as transcription factors such as SREBP by altering certain pathways have been discovered to be lipidogenesis inhibitors. These results could potentially point to additional pertinent mechanisms that are involved in the regulation of lipid metabolism in cancer cells. The NAD-dependent deacetylasesirtuin 1 (SIRT-1) is activated by the stilbene resveratrol, which has hypolipidemic effects [144]. SIRT-1 activation then positively modulates AMPK, which in turn avoids lipid accumulation by controlling several processes, including FAS downregulation. Resveratrol’s activation of AMPK has also been verified in several investigations [145].

Furthermore, substances from other plants that exhibit hypolipidemic characteristics also share this characteristic, as was seen with extracts from Hibiscus sabdariffa [146]. Extra-virgin olive oil’s phenolic compounds, which have been shown to be an extremely potent inhibitor of FAS expression and a regulator of lipid production in breast cancer cell models [147], may possibly have promising and intriguing therapeutic implications. The most effective compounds appear to be those from the lignan family (1-[+]-pinoresinol and 1-[+]-acetoxypinoresinol), flavonoids (apigenin and luteolin), and secoiridoids (deacetoxyeupepinaglycone, ligstrosideaglycone, oleuropein glycoside, and oleuropeinaglycone) [147]. Similar to this, the extra-virgin olive oil polyphenols oleuropein and hydroxytyrosol inhibited FAS activity in colorectal cancer SW260 cells, and this result was associated with their antiproliferative potential [148]. Another colon model (HT-29) did not corroborate this impact, indicating a cell-type-specific effect and additional unrelated pathways [148]. Targeting lipid metabolism, particularly FAS activity, is still a viable option for reducing cancer cell survival. In addition, the silencing of FAS expression with FAS siRNA produced similar cellular alterations to luteolin [137], as demonstrated by Brusselmans and colleagues, who also demonstrated that palmitate added to the culture medium of prostate cancer cells allowed for bypassing the downstream effects of FAS inhibition by luteolin on lipid metabolism and prevented the cytotoxic effect of this compound. These results allow for the prediction of a causal role for FAS inhibition in the antiproliferative and cytotoxic effects of polyphenols, and they encourage further investigation into the relevance of polyphenol regulation of lipid metabolism in the anticancer properties associated with several of these substances.

Conclusion

A potential yet untapped area in anticancer treatments is the targeting of abnormal cell metabolism in cancer cells. We have emphasised in this review that many of these alterations occur during preneoplastic phases, which are relatively early in the carcinogenesis process. As a result, focusing on them might be a potent tool for chemoprevention. Further highlighting the significance of targeting specific metabolic-related aspects in future anticancer therapeutics, the literature indicates how cancer cells depend on a number of metabolic abnormalities in order to live and multiply.

The nature of prospectively pursueable molecular targets is defined by the identification of distinct aberrantly regulated metabolic keynotes with regard to the way they express and/or activate these factors. Despite all of these factors, the actual number of drugs being researched for antimetabolic uses is still quite low and in its very early stages. Superior differential toxicity against cancer cells compared to healthy cells, a decreased risk of systemic toxicity, and a favourable profile in particular...
pharmacological qualities such as bioavailability, half-life, and stability are all requirements for good candidates. By impacting nearly every cancer characteristic, several natural substances have thus far been found to be anticancer agents [2]. Surprisingly, we have provided several instances of dietary polyphenolic substances from fruits and vegetables that exhibit distinct antitumor properties in this article (Figure 1). Adsorption and bioavailability are two issues that limit promising natural chemicals from being employed for chemoprevention and therapeutic reasons, even if there is scientific evidence of many favourable biological characteristics for health. Additionally, information on the stability and clearance of naturally occurring substances is usually still unknown; additional work will be needed in the near future to clarify these crucial aspects.

A diverse and remarkably large “database” of molecular scaffolds may be found in nature. The identification of potential antitumor molecules, particularly those with dietary origins and fewer side effects, is made possible by the rapid improvement of innovative screening techniques that allow the investigation of huge databases of naturally occurring compounds. They are appealing for commercial goals because of the relatively low costs of their extraction and manufacture in large quantities, and they provide a solid foundation for chemical changes that might further enhance their anticancer properties and simplify their pharmacological usage.

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