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Review Article

Potential role of natural bioactive compounds in targeting carbohydrate metabolism in cancer cells

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ABSTRACT

Cancer cells are in high demand for energy to sustain uncontrolled proliferation and survival. The alteration in the metabolic pathways is an adaption by the cancer cells to maintain the energy requirements as well as the synthesis of various macro molecules for cell growth and proliferation. Many plant-derived compounds have biomedical importance in the management of various diseases including cancer. In this review, we discuss various plant-derived compounds and their role in modulating the carbohydrate metabolism in cancer cells.

Several natural compounds effectively suppress the glycolytic activity in cancer cells. The role of several plant-derived compounds was reported to modulate glucose uptake, inhibition of glycolysis, and inhibition of pentose phosphate pathway as an indicator of reversing the Warburg effect.

Cancer cells have a higher rate of uptake of glucose and the amino acid glutamine than normal cells. This increased glucose uptake is also associated with a high rate of glycolysis resulting accumulation of lactate both in intracellular and extracellular spaces. The dependency of cancer cells on glycolysis even in the presence of abundant oxygen is first described by Otto Warburg and named after him as the Warburg effect. The Ammonia byproduct that is built up as a result of glutamine metabolism helps in the proliferation of cancer cells. Some phytocompounds show anticancer properties and reversing the Warburg effect. Characterization of plant-derived compounds for modulation of glucose uptake, inhibition of glycolysis, and inhibition of pentose phosphate pathway has promising prospects in the future.

1. Introduction

Cancer is one of the deadliest forms of disease in the current century and kills millions of lives every year. It is the second main cause of death worldwide, calculating an estimated 9.6 million deaths in 2018.[1,2] Several pieces of evidence indicate that carcinogenesis is a multistep process and involves genetic, epigenetic, or/and metabolic changes. Cancer cells show abnormal metabolism with an increased rate of glycolysis, increased fatty acid synthesis, and increased rates of glutamine metabolism.[3] Cancer cell proliferation requires sufficient supplies of nutrients including carbon sources and nitrogen sources which are obtained through metabolism. The cellular metabolism also helps cancer nill progression, metastasis, and resistance to chemotherapy (Figure 1). The intermediates of glycolysis provide the precursor for the biosynthesis of nucleotides, amino acids, and lipid which are required for the rapid cell division of cancer cells.[4] The study on cancer cell metabolism has attracted attention in recent years and is now considered as one of the hallmarks of cancer.[5] Plants are an important source of bioactive compounds and have the potential to modulate various cellular pathways. A growing list of evidence shows that plant-derived compounds interfere with cellular metabolism, cell proliferation, and viability. In this review, the list of phytocompounds

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Table 1 that modulate the activity of cellular metabolism is discussed.

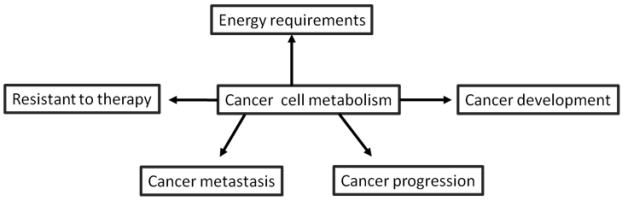

Figure 1: Role of metabolism in the process of carcinogenesis

1.1. Altered energy metabolism in cancer cells

The cancer cells mostly rely on aerobic glycolysis, where an increase in uptake of glucose and preferential production of lactate, a phenomenon termed "the Warburg effect." Besides aerobic glycolysis, *de novo* lipid biosynthesis, and glutamine-dependent anaplerosis, support cancer cells proliferation.[6] The increased uptake of glucose has been exploited in the diagnosis of cancer by the PET imaging system. The glucose transporters 1 and 3 (GLUT1 and GLUT3) are increased in many cancer.[7] The modification of lactate from glucose, instead of metabolizing it through glycolysis, is very less productive as very few amounts of ATP are produced per unit of glucose metabolized. Cancer cells can be killed in the absence of both glucose and oxygen or without energy. English biochemist, Herbert Crabtree, extended the work of Warburg and studied the heterogeneity of glycolysis in various types of tumors.[8] He agreed with Warburg's findings but later discovered that the intensity of respiration in tumors was not similar, it varies with many tumors exhibiting a considerable amount of respiration. Most cancer cells depend more on glycolysis rather than oxidative phosphorylation for glucose metabolism. Targeting glycolysis in cancer cells and its therapeutic deliberate has become a topic of great interest. Besides glycolytic enzymes, the mutation in isocitrate dehydrogenase 1 and 2 (IDH1/2) genes has been associated with multiple tumor types including glioma. Wild type IDHs convert isocitrate into alpha-ketoglutarate (α-KG), while mutant IDHs gain a new enzymatic activity of catalyzing α-KG into 2- hydroxyglutarate (2-HG). The 2-HG inhibits α-ketoglutarate-dependent dioxygenases and act as an oncometabolite for malignant transformation.[9] Therefore, it is important to think to target the carbohydrate metabolic pathways for cancer prevention and therapy.

1.2. Signaling pathways regulating carbohydrate metabolism

Studies indicate that multiple signaling pathways cross interact with each other and regulate various biological processes including metabolism. The altered metabolism in cancer cells is a result of altered growth factors signaling, oncogene activation, or repressor of tumor suppressor genes. The hypoxic environment in cancer cells also activates several pathways which collectively help the cancer cell to grow (Figure 2). Glucose transporters and some of the enzymes of glycolysis are regulated by various signaling pathways. The hexokinase 2, lactate dehydrogenase, and glucose transporter are mainly regulated by PI3/AKT,[10] HIF-1,[11] and GSK-3/TSC2/mTOR pathways[12] The activation of the HIF-1 pathway regulates many proteins such as glucose transporter 1, glucose transporter 3, hexokinase 1, hexokinase 2, phosphofructokinase L, aldolase A, aldolase C, glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase 1, enolase 1, pyruvate kinase M and lactate dehydrogenase A.[13] The glycolytic genes and GLUT1 are regulated by c-Myc oncogene.[14]

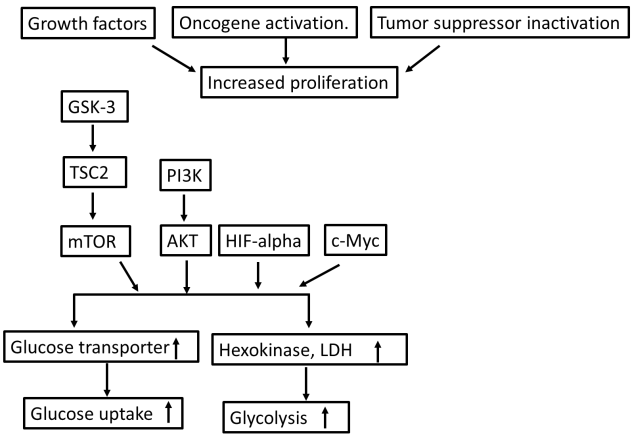

Figure 2: Growth factor, oncogene activation, and tumor suppressor inactivation regulate cancer cell metabolism. The uptake of glucose and glycolysis is controlled by PI3K/AKT, GSK-3/TSC2/mTOR, HIF-1 and cMyc pathways.

1.3. Natural polyphenols inhibiting Glucose transport across the cell membrane

Cancer cells in comparison with normal cells utilize more glucose for various activities. For this Glucose transporters like GLUT1 transporter is always overexpressed in cancer cells.[15,16] Therefore, by targeting glucose transporters is an emerging approach for anticancer therapy. Many natural polyphenols block metabolic processes in cancer cells by inhibiting the glucose transpor (Figure 3). Quercetin upregulates GLUT1 membrane expression in hepatocellular carcinoma.[17] The report also suggests that quercetin inhibits glucose transport by binding to the GLUT1 receptor,[18,19] Cinnamon polyphenol inhibits glucose uptake via down-regulation of GLUT1 expression.[20] Rubusoside (Rub) is a natural sweetener from the Chinese sweet tea plant (Rubus suavissimus) that inhibits (IC_{50} of 4.6 ± 0.3 mM) GLUT1.[21]

Likewise, Graviola, the fruit of *Annona muricata*, reduces glucose uptake and inhibits the expression of many key glycolytic enzymes in pancreatic cell lines.[22] Green tea extracts also known as catechins have an inhibitory effect on glucose transport across the cell membrane. The major active green tea polyphenols are epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) which have suppressing activity against GLUT1 in cancer cells.[23] It also inhibited aerobic glycolysis in several hepatocellular carcinoma cells and treatment of genistein (40 and 80 mg kg^{-1}) reduced tumor volume in xenograft tumor model.[24] Genistein binds to GLUT1 with its outer surface only linked with glucose, whereas green tea polyphenols could bind to this transporter with its internal surface means its cytosolic side is bound by glucose.[25] Resveratrol is a stilbene natural polyphenol found in red grapes, red wine, peanuts, and groundnuts, already proved to have anti-cancer properties and also inhibits glucose transport.[26] Resveratrol blocks GLUT1-mediated glucose transport by directly binding to one of its internal sites in such a way as to reduce glucose uptake in HL-60 and U-937 human leukemic cells.[27,28] Flavonoids such as fisetin, myricetin, quercetin, apigenin, genistein, cyaniding, daidzein, hesperetin, naringenin, and catechin inhibited glucose uptake in U937 cells.[29] Naringenin, a grapefruit flavanone inhibited glucose uptake in MCF-7 breast cancer cells.[2] The compound kaempferol found in various vegetables,[30] inhibited glucose transport in MCF-7 human breast cancer cells.[31] The compound Methyl alpinumiso flavone isolated from Lonchocarpus *glabrescens* inhibits HIF alpha mediated Glut 1 expression in T47D breast cancer cells.[32] Some plant extracts are reported to inhibit glucose transport in cancer cells. The hexane extract of Baeckea frutescens inhibits glucose transport in MCF-7 cells.[33]

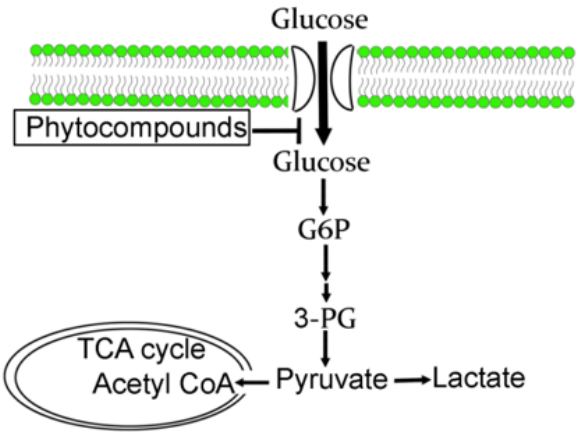

Figure 3: Anticancer activities of phytocompounds by inhibiting glucose transporter

1.4. Phytocompounds modulating expression glycolytic enzymes

Several phytocompounds have been identified those demonstrated inhibitions of glucose transport and glycolysis in cancer cells. Most of the compounds inhibit the enzymes at particular stages of glycolysis (Figure 4).

1.4.1. Hexokinase 2

Hexokinase catalyzes the first committing step of glycolysis. Hexokinase 2 is highly expressed in cancer cells.[34] The PI3K/Akt/PKB/mTOR as well as HIF1signaling play a major role in the regulation of hexokinase 2.[35,36] The natural compound from the fungus Albatrellus confluens, Neoalbaconol induced cell death in nasopharyngeal carcinoma (NPC) nude mouse model and downregulated hexokinase 2 expressions through the PDK1-PI3-K/Akt signaling pathway.[37] Jolkinolide B, a bioactive compound isolated from the plant Euphorbia fischeriana Steud showed cytotoxic activity in A549 and H1299 cells (IC_{50}= 83.67 mM and 60.82 mM) and downregulated hexokinase expression by inactivating Akt/mTOR pathway[38] The compound bavachinin from the Chinese herb Fructus psoraleae showed anticancer activities (5mg/kg body weight) in an in vivo mouse model and inhibited hexokinase 2 by inhibiting HIF-1α activity.[39] The compound limonin suppresses tumor glycolysis by blocking hexokinase 2 phosphorylation in hepatocellular carcinoma.[40] The polyphenol resveratrol inhibited glycolysis by inhibiting hexokinase 2 in non-small cell lung cancer cells.[41] Treatment of Oroxylin A (150 μM), a major active component of the plant Scutellaria baicalensis inhibited hexokinase 2 through sirtuin-3 dependent manner in MDA-MB-231 and MCF-7 cells.[42] Baicalein and Baicalin (20 μM and 40 μM each) promoted apoptosis and senescence in Mel586, SKMEL-2 and A375 cells by inhibiting hexokinase 2.[43] Treatment of Deguelin (1-5μM), a compound from Mundulea sericea (Leguminosae) inhibited Akt-dependent hexokinase 2 expressions in various Non-small cell lung cancer (NSCLC) cells.[44] Lymphoma cells tumor bearing mouse treated with emetine (10 mg/kg body weight), a natural compound from Cephaelis ipecacuanha, inhibited tumor growth and hexokinase 2 expression.[45] The compounds klugine, isocephaeline, and emetine inhibited hypoxia-inducible factor-1 (HIF-1) activation in T47D breast tumor cells.[46] Prosapogenin A derived from the plant Veratrum inhibits hexokinase 2 and induce apoptosis in MCF-7 cells (IC_{50}=9.65 μM).[47] Licochalcone A, showed cytotoxic activities in MKN45 and SGC7901 gastric cancer cells (IC_{50}=63.57 and 55.56 μM) and decreased the activity of HK2 which inhibits both glucose absorption and lactate production.[48] Luteolin inhibits Hexokinase 2 in keratinocytes.

1.4.2. Phosphofructokinase 1& 2

Phospho fructokinase 1 is one of the rate-limiting enzymes for the glycolysis pathway.[49] Knockdown of PFK 1 inhibits metastasis in CNE-2 cells.[50] The PI3K/AKT signaling promotes expression of GLUT1 and activation of phosphofructokinase 2 (PFK2) through phosphorylation thus increased production of fructose-2,6-bisphosphate, which in turn promotes phosphofructokinase 1 activation. The phytocompounds taxodone, taxodione, vernolepin, eupacunin, and euparotin inhibited PFK 1 activity. The phytocompound resveratrol directly inhibited PFK 1 in MCF-7 cells[51] Similarly EGCG inhibited the PFK1 activity and induced apoptosis in hepatocellular carcinoma.[52] Two compounds salicylic acid and acetylsalicylic acid were identified as inhibitors of PFK1.[53]

1.4.3. Phosphoglycerate mutase 1 (PGAM1

PGAM1 is the glycolytic enzyme that catalyzes the conversion of 3-phosphoglycerate to 2-phosphoglycerate. The PGAM1 is over-expressed in several types of cancers.[54] The PGAM1 expression is regulated through mTOR pathways. The natural compound (-)-Epigallocatechin-3-gallate is a potent PGAM1 inhibitor.[55] The compound resveratrol down-regulates the phosphoglycerate mutase B gene and induced apoptosis in prostate cancer cells.[56]

1.4.4. PKM2

Pyruvate kinase regulates the final and rate-limiting step of glycolysis by converting Phosphoenolpyruvate (PEP) to Pyruvate Four isomers (PKL, PKR, PKM1, and PKM2) regulate glucose metabolism in different tissues. The PKM2 regulates tumor cell metabolism towards lactate production.[57] Several phytocompounds were identified to modulate PKM2 activity. In a study, it was observed that Resveratrol (10 μM) blocks the PKM2 activity in Human endothelial cells and as a result, it suppresses the expression of GLUT1, HK2, and PFK which leads to a reduction in aerobic glycolysis.[58] Apigenin is a dietary flavonoid found in green leafy vegetables and has anticancer, anti-inflammatory, antiviral, and antioxidant effects. It blocked glycolysis by regulating PKM2 activity in colon cancer cells.[59] Quercetin is a plant flavonol that significantly decreases the activity of glycolytic enzymes including PKM2 and thus blocked glycolysis in many cancer cells.[60] Shikonin is a natural flavonoid found in a plant commonly known as purple groomwell known for its inhibitory effect of glycolysis via suppressing PKM2 activity in various cancer cell lines. Berberine is the active ingredient available in different species of the family Berberidaceae. It inhibited cell proliferation by inhibiting the Pyruvate Kinase M2.[61] Curcumin is also reported to inhibit the PKM2 expression in H1299, MCF-7, HeLa, and PC3 cells.[62] Polyphenols like neoeriocitrin, (-)-catechin gallate, fisetin, (±)-taxifolin, and (-)-epicatechin inhibited PKM2 activity.[63] The inhibition of pyruvate kinase M2 (PKM2) with suppression of aerobic glycolysis was observed with the treatment of Oleanolic acid in PC-3 and MCF-7 cells.[64]

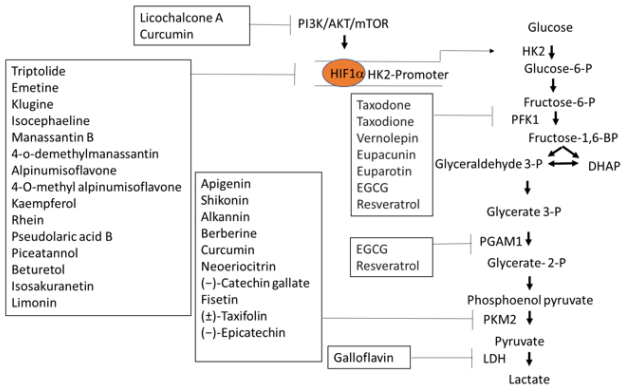

Figure 4: Phytocmpounds and their target in inhibiting glycolysis

1.5. Reversing Warburg effect by decreasing lactate production in cancer cells

Lactate dehydrogenase (LDH) catalyzes the conversion of lactate to pyruvate. Serum LDH levels are a biomarker for the diagnosis of cancer due to tissue destruction caused by tumor growth.[65] pounds have been identified which inhibit lactate production in cancer. We have reported that some phytocompounds like Quercetin, Indole-3-carbinol, Curcumin, Ellagic acid, and Resveratrol inhibit cell proliferation and modulation of lactate and pyruvate level in a cervical cancer cell line (HeLa cells).[66] Betulinic acid decreases lactate levels in breast cancer cells by downregulating proteins involved in aerobic glycolysis.[67] Bitter melon (Momordica charantia) has some bioactive compounds which decreased glucose uptake, inhibit the activity of glycolytic enzymes like LDH-A and lactate production in oral cancer cells.[68] Epigallocatechin, inhibited glucose uptake and lactate production in 4T1 breast cancer cells.[69]

1.6. Effect of ketogenic diet and cancer: A new perspective in modulating Glycolysis

A ketogenic diet is probably based on fats, for their total energy intake. This diet gradually maximizes acetones in the blood and also decreases glucose levels by stimulating fasting. The acetyl-CoA production and beta-oxidation gradually increase at high rates. The low–carb high-fat diet is a current approach that mainly aims at minimizing blood glucose and insulin levels thus approaching the Warburg effect.[77] In cancer therapy, providing a ketogenic diet mainly a high fat and low-carb diet which minimizes the glucose levels in the body and causes acidosis, which exhausts the liveliness of tumor cells, while normal cells

Table 1: A list of phytochemicals and their metabolic target in cancer

Plant-derived compounds	Metabolic Target	Reference
Resveratrol	It inhibits the increased glycolytic activity. It downregulates the activity of PKM2, PFK activity, glucose oxidation, and lactate production	70
Curcumin	It decreases lactate production. It also inhibits PKM2 activity, GLUT1 activity, and HK2 activity, and FAS activity	71
Epigallocatechin,	It inhibits LDH-A activity in both MCF-7 cells and MDA-MB-231 cells in vitro, also inhibiting tumor growth and LDH-A expression in both breast cancer xenografts in vivo	72
Epigallocatechin-gallate	It has anticancer and antioxidant effects, promoting cytotoxicity and inhibiting glycolysis in many cancer cells	73
Genistein	It inhibits glucose uptake and glutamine uptake, it alters sphingolipid metabolism, GLUT1 mRNA level,p-ACC protein level. It downregulates glucose oxidation. It upregulates glucose uptake, GLUT1, and GLUT4 protein levels	31
Gallic acid	In melanoma cancer cells it upregulates glucokinase, α-enolase, aldolase, and PK protein levels	74
Quercetin	It down-regulates glucose uptake and lactate production, lipid synthesis, and FAS activity.	75
Rosmarinic acid	It downregulates glucose consumption and lactate production[56] and also downregulates LDL levels.	76
Silibinin A	In colon cancer, it altered glucose metabolism.	77
Wogonin	Incolon cancer, downregulates HK2, PDK1m, and LDHA protein levels and also downregulates glucose uptake, lactate production.	78
Xanthohumol	In cervical cancer cells (HeLa) it down-regulates mitochondrial complex-I activity and ECAR. In lung cancer, it downregulates mitochondrial complex-I activity and ECAR.	79
Alpha-mangostin	It regulates FASN activity in Breast Cancer.	80
Caffeic acid	It inhibits the activity of the glycolytic enzymes Glucose-6-phosphate dehydrogenase, 6-phosphogluconate Dehydrogenase in many cancer cells.	81
Betulinic acid	It inhibits the activity of the enzyme Stearoyl-CoA desaturase 1 and blocks the AMP-activated kinase pathway in HeLa cells.	82
Emodin	It inhibits FASN activity in Colon cancer cells. It suppresses the activity of Glucose transporter 1, Hexokinase II, and Phosphofructokinase 1 in Pancreatic cancer, inhibits Acetyl-CoA carboxylase activity in Hepatocellular carcinoma.	83
Kaempferol	It inhibits FASN activity in many cancer cells.	40
Rhein	It inhibits HIF alpha mediated Glucose transporter 1, Hexokinase II, and Phosphofructokinase 1 activity in pancreatic cancer.	84
Alkannin	Naphthoquinone, Inhibits the activity of PKM2	76
Apigenin	Flavones, Inhibits glucose uptake in U937 and MC3T3-G2/PA6 cells and inhibits activation of Akt and translocation of GLUT4	73
Berberine	PKM2 inhibitor	77
Fisetin	PKM2 inhibitor	79
4-O-Methyl alpinumisoflavone	HIF-1 inhibitor; inhibits HIF-1 target genes GLUT1	41
Luteolin	HK2 inhibitor	58
Myricetin	Flavonol, Inhibits glucose uptake in human myeloid leukemia cells.	37
Naringenin	Flavanone, Inhibits glucose uptake in human myeloid leukemia cells.	37
Neoalbaconol	Inhibits PI3-K/Akt-HK2 pathway.	46
Oleanolic acid	Induces PKM2/PKM1 switch and suppresses aerobic glycolysis.	80

utilize ketone bodies through metabolism. Minimizing the glucose levels in the blood also decreases the levels of insulin and insulin-like growth factors, which are essential for cancer cell proliferation. Many testing models already observed that the ketogenic diet is related to inhibition of tumor growth either by direct or as an indicator of the effect of maximal insulin inhibition.[76] It was already reported to retard human gastrointestinal cancer cell growth in nude mice and a syngeneic model of prostate cancer. Alteration in gene expression concludes that ketogenic diet can suppress the activity of epidermal growth factor receptor (EGFR) and platelet-derived growth factor (PDGF), signaling pathways.Figure 2

1.7. Natural polyphenols as inhibitors of Pentose Phospate pathways

The pentose phosphate pathway is the main Glucose metabolism pathway for Glucose utilization in cancer cells other than Glycolysis. The PPP supports cell survival, cell proliferation by generating pentose phosphate for nucleic acid synthesis and providing nicotinamide-adenine dinucleotide phosphate (NADPH).[75] Polyphenols like Naringenin, caffeic acid, ellagic acid, ferulic acid, and sinapic acid against two enzymes, hesperidin and polydatin inhibited G6PD activity using isolated enzymes from erythrocytes.[74] Polydatin was also demonstrated to inhibit the activity of Glucose-6-phosphogluconate and cell cycle arrest.[72] Natural compound Physcion which was approved by Food and drug administration is an inhibitor of glycolytic key enzymes like Glucose-6-phosphate dehydrogenase and prevents much cancer like breast and lung cancer.[71]

2. Conclution

Cancer cells exhibit a distinct metabolic phenotype characterized by altered energy metabolism, notably increased glycolysis even in the presence of oxygen, termed the Warburg effect. This metabolic shift is crucial for sustaining rapid proliferation and survival of cancer cells. Here, we discuss the intricate interplay between signaling pathways regulating carbohydrate metabolism and the potential of natural polyphenols to modulate these pathways. Evidence shows that the signaling pathways are deregulated in cancer cells modulating carbohydrate metabolism. Additionally, many natural polyphenols act as inhibitors of glucose transport across the cell membrane, effectively disrupting the energy supply to cancer cells. Moreover, natural polyphenols also inhibits the pentose phosphate pathway, an alternative metabolic pathway crucial for cancer cell survival and proliferation. By targeting this pathway, polyphenols offer a promising avenue for disrupting the metabolic flexibility of cancer cells. Collectively, this review provides insights into the multifaceted approaches for modulating cancer cell metabolism, with a focus on targeting glycolysis and the pentose phosphate pathway using natural polyphenols and ketogenic diets. Further studies are required to increase the bioavailability of such compounds to evaluate the bioavailability with sufficient concentration in the systemic circulation to be used as a drug for cancer therap.

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4. Conflict of Interest

The authors declared that there is no conflict of interest in this work.

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