Phytochemicals targeting metabolic reprogramming in cancer: an assessment of role, mechanisms, pathways and therapeutic relevance

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Abstract

The metabolism of cancer is remarkably different from that of normal cells and confers variety of benefits including the promotion of other cancer hallmarks. As the rewired metabolism is a near-universal property of cancer cells, efforts are underway to exploit metabolic vulnerabilities for therapeutic benefit. In the continued search for a safer and effective ways of cancer treatment, structurally diverse plant-based compounds have gained substantial attention. Here, we present an extensive assessment of the role of phytocompounds in modulating cancer metabolism and make a case for the use of plant-based compounds in targeting metabolic vulnerabilities of cancer. We discuss the interactions of phytocompounds with major metabolic pathways and evaluate the role of phytochemicals in the regulation of growth signaling and transcriptional programs involved in metabolic transformation of cancer. Lastly, we examine the potential of these compounds in clinical management of cancer along with limitations and challenges

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Abstract: The metabolism of cancer is remarkably different from that of normal cells and confers variety of benefits including the promotion of other cancer hallmarks. As the rewired metabolism is a near-universal property of cancer cells, efforts are underway to exploit metabolic vulnerabilities for therapeutic benefit. In the continued search for a safer and effective ways of cancer treatment, structurally diverse plant-based compounds have gained substantial attention. Here, we present an extensive assessment of the role of phytocompounds in modulating cancer metabolism and make a case for the use of plant-based compounds in

targeting metabolic vulnerabilities of cancer. We discuss the pharmacological interactions of phytocompounds with major metabolic pathways and evaluate the role of phytochemicals in the regulation of growth signaling and transcriptional programs involved in metabolic transformation of cancer. Lastly, we examine the potential of these compounds in clinical management of cancer along with limitations and challenges.

Keywords: Cancer metabolism; Phytocompounds; Warburg effect; Cancer therapy; Metabolic reprogramming; Growth signaling

Cancer metabolism: An emerging hallmark of therapeutic relevance

Nearly a century ago, Otto Warburg described for the first time that cancer cells produce large amount of lactate even in the presence of oxygen, a phenomenon later termed as Warburg effect or Aerobic glycolysis [1]. This unusual metabolic activity of cancer cells is exploited by FDG-PET scan for clinical detection of cancer [2]. It is now appreciated that metabolic hallmarks of cancer extend beyond glycolysis which involves deregulated uptake of various nutrients, use of glycolysis/tricarboxylic acid cycle (TCA) intermediates for biosynthesis, $NADPH+H^+$ production, elevated nitrogen requirement, metabolite-driven epigenetic regulation, and interactions of metabolites with the micro-environment [3]. Besides, the metabolic rewiring confers a variety of non-metabolic benefits such as immune escape, transcriptional regulation, epigenetic modifications, metabolite-mediated autocrine and paracrine signaling [4-7]. Proliferating cells need energy and building blocks to divide. In order to meet the metabolic requirements of cell division, targeted changes in key metabolic pathways must take place in tumor cells. The changes in the metabolic flux are in turn regulated by signal cascades, which are frequently mutated in tumor cells at different sites [8].

The altered metabolic properties of cancer cells can be correlated with mutations in the growth signaling pathways [9, 10]. Different driver mutations in growth signaling pathways may result in differential metabolic addictions, thus, highlighting the complex regulation of cancer metabolism [8, 11].

The preclinical and clinical evidence suggest that metabolism-targeting drugs can efficiently influence tumor progression and made this approach a promising field of research for the development of new anti-cancer strategies [12, 13]. However, the clinical success of targeting metabolism is limited due to variety of reasons that include metabolic heterogeneity of different tumors even within the same entity, metabolic plasticity, drug resistance, unwanted side-effects, and systemic toxicity.

2. Phytochemicals inhibiting major metabolic pathways

Phytochemicals are biologically active and diverse chemical compounds that are found in plants as secondary metabolites. For a long time, they have traditionally been associated with protection of humans from various diseases and recently have gained much attention to be used in the treatment of cancer as well [14-16]. Hitherto chemotherapy and surgery are the two conventional approaches majorly used to treat cancer but their undesirable side effects such as immune suppression, regional and systemic toxicity, organ damage, etc. limit their use in the clinical settings [17-19]. To overcome these challenges, structurally diverse phytocompounds with chemically novel entities can be used in the development of drugs to combat cancer due to their ideal chemo-preventive properties such as immune-modulatory activity, selective toxicity for cancer cells, oral route of administration, synergistic effects in combination with other drugs, ease of availability, low cost, easy acceptance by people, etc. [20, 21]. Numerous phytocompounds can be obtained from diet sources which makes their usage cost efficient, easily available and lower the risk of cancer as well. Recognizing these array of benefits offered by phytochemicals, they are gradually being added to the list of drugs effective in cancer treatment [22, 23].

Distinct metabolic changes allow cancer cells to adapt to metabolism that enables them to support unchecked proliferation. Pathways of central metabolism play a vital role by acting as feeders of other metabolic pathways engaged by cancer cells. Accumulating evidence suggests that inhibition of the altered metabolic activities results in impaired tumor growth [24, 25]. With this perspective, we discuss below key pathways of central metabolism that are targeted by phytocompounds with their effect on tumor growth. All the phytochemicals reviewed below are listed in Table 1 with their exact botanical names, investigated cell

models as well as references in which they have been investigated.

2.1. Glycolysis

Upregulated glycolysis is an almost universal property of all cancers as it supports macromolecular synthesis, bioenergetics, and provides tumors flexibility to grow regardless of oxygen availability [26, 27]. In order to support upregulated glycolytic flux, cancer cells overexpress glucose transporters (GLUTs) for continuous uptake of glucose. Compare to normal cells, cancer cells express 10 to 12 times the amounts of GLUTs on their membranes allowing them to mobilize more glucose inside the cell to meet bioenergetic and biosynthetic demands [28, 29]. Thus, inhibition of GLUTs may represent an attractive way of attacking cancer by blocking the uptake of glucose, thus, leading to the reduction in glycolytic flux, ultimately resulting in cell growth inhibition [30]. In fact, a number of phytochemicals were identified that reduced tumor growth in different cell cultures and animal models by inhibiting their glucose uptake (Table 1). Apigenin and hesperetin inhibit mRNA and protein expression of GLUT1 in several cell lines and mice, resulting in growth retardation and apoptosis [31-34]. Naringenin and hesperetin downregulate the translocation of GLUT4 (insulin-regulated GLUT) to the plasma membrane [34, 35]. Silibinin and its derivative dehydrosilybin inhibit GLUT4 activity by directly blocking its glucose binding site [36]. Galbanic acid inhibits the mRNA expression of GLUT1 through HIF1α [37]. Another compound, bavachinin is reported to inhibit GLUT1 and hexokinase 2 (HK2) both at transcriptional and translational levels via downregulating the activity of its transcriptional regulator-HIF1α [38]. N-methylhemeanthidine chloride decreases protein expression of GLUT1 via downregulating Akt [39].

After the entry of glucose inside the cell, the rate-limiting enzyme hexokinase (HK) catalyzes the first step of glycolysis converting glucose to glucose-6-phosphate (G6P). The latter can be further metabolized through glycolysis or pentose phosphate pathway (PPP) to produce ATP and macromolecules respectively (Figure 1). Out of all HK isoforms, HK2 is the predominant isoform expressed in various tumors and plays a key role in trapping glucose inside the cell for further utilization in anabolic and catabolic pathways [40, 41]. Oroxylin A, chrysin, deguelin and curcumin repress glycolytic conversion rates and tumor cell proliferation by downregulation of HK2 expression and/or activity (Table 1 and Figure 1) [42-46].

The next rate-limiting enzyme in glycolysis is 6-phosphofructo 1-kinase (PFK1) which catalyzes the irreversible conversion of fructose-6-phosphate (F6P) to fructose-1,6-bisphosphate (FBP), ensuring the commitment towards glycolysis. Thus, targeting PFK may block downstream glycolysis leading to reduced ATP and lactate production [47]. Resveratrol and berberine attenuate the expression and activity of PFK1 resulting in suppressed cell viability, proliferation, and induction of apoptosis [48, 49]. Epigallocatechin-3-gallate (EGCG) directly suppresses the mRNA/protein expression and activity of PFK thereby inducing apoptosis [50].

Likewise, for the three subsequent enzymes of glycolysis aldolase (ALDO), phosphoglycerate mutase (PGAM) and enolase (ENO), inhibiting phytochemicals found in nature are described [51-55]. ALDO reversibly cleaves FBP into glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP). Vitexin displays anti-metastatic property as well as reduces the expression of ALDOA and ENO1 via HIF1α inhibition [56]. PGAM1 controls the intracellular level of 3-phosphoglycerate (3PG) thereby coordinating glycolysis and anabolic pathways [57, 58]. PGAM1 has an important role in cancer cell metabolism and its over-expression PGAM1 lead to immortalization and indefinite proliferation of mouse embryonic fibroblasts [59, 60]. These observations drove the development of PGAM1 inhibitors for anticancer applications. Proteomic analysis reveals that tetrandrine downregulates PGAM1 protein expression [61]. In silico and *in vitro*studies reveals EGCG as another potent inhibitor of PGAM1 activity [62]. ENO converts 2-phosphoglycerate (2PG) to phosphoenolpyruvate (PEP) in the payoff phase of glycolysis. It has been reported that ENO1 isozyme is frequently upregulated in some cancer types [63, 64]. Galbanic acid and berberine reduce the mRNA and protein expression of ENO1/α-Enolase in cancer cells respectively [37, 65].

The final and rate-limiting step of glycolysis is the conversion of PEP to pyruvate, catalyzed by pyruvate kinase (PK). Tumor cells overexpress a certain isozyme of PK, termed pyruvate kinase M2 (PKM2 or

M2-PK) [66, 67]. PKM2 is a multifunctional enzyme having glycolytic as well as non-glycolytic roles in cancer such as protein kinase activity, gene transcription, redox balance and post-translational modifications [68-71]. Targeting PKM2 by different drugs inhibition is associated with a decrease in glycolysis, pentose phosphate pathway (PPP), serine and lipid metabolism resulting in reduced cancer cells proliferation and tumor growth as well [72, 73]. Curcumin and resveratrol downregulate PKM2 expression via inhibition of mammalian target of rapamycin (mTOR)-HIF1α pathway [74, 75]. Shikonin, apigenin and berberine decrease glycolysis by inhibiting PKM2 activity [76-79], wherein apigenin also inhibits the transcription of PKM2 via the blockade of the β-catenin/c-Myc/PTBP1 signal pathway [78]. Treatment of pancreatic cancer cells with thymoquinone and gemcitabine synergistically resulted in the reduction of PKM2 protein level, cell proliferation and induction of apoptosis [80].

Glycolysis ends up with the production of pyruvate. The latter is converted to lactate or alanine. Alternatively, pyruvate can be infiltrated into the mitochondrial TCA cycle after decarboxylation to acetyl CoA. To evade pyruvate entry into mitochondria, cancer cells over-express the enzyme-lactate dehydrogenase isozyme type A (LDHA, LDH M4 or LDH5) which is characterized by high affinity to pyruvate. Baicalein inhibits LDHA expression via blockade of PI3K/Akt/PTEN signal cascade [81]. Galloflavin, EGCG, crocetin and gossypol directly inhibit LDHA activity. In all cases targeting of LDHA induced an inhibition of glycolysis and cell proliferation. Additionally, I*n vivo* application of ECCG in mice was not associated with toxic side effects [82-85].

High conversion rates of glucose to lactic acids may lead to an acidification of the cytosol with severe consequences on cellular functions [86]. In order to get rid of intracellular lactic acid cancer cell overexpress monocarboxylate transporter (MCT). The release of lactate promotes metastasis and angiogenesis and protects tumor cells from immune cell attacks [87, 88]. Among different isoforms of MCTs, MCT1 and MCT4 are found to be highly expressed in different types of cancer [89]. In hypoxic regions of tumors, activation of HIF1α stimulates increased production and export of lactate by MCT4. The extracellular lactate is taken up by other cancer cells and cancer associated fibroblasts via MCT1 and converted back to pyruvate for further oxidation to yield energy. This kind of lactate recycling within the tumor is an effective mechanism to reserve glucose for the cancer cells in hypoxic areas [90, 91]. However, MCT1 and MCT4 both are capable of importing as well as exporting lactate from the cell [92], MCT1 predominantly induces an increased import of lactate inside the cell. MCT1 activity is inhibited by phytochemicals of different origins such as Silybin (silibinin), naringenin and kaempferol [93, 94]. In melanoma cells, α-cyano-4-hydroxycinnamate inhibits MCT1 activity which induces cytosolic acidification accompanied by a higher sensitivity to hyperthermia [95].

2.2. Pentose phosphate pathway

Besides rapid generation of ATP, cancer cell glycolysis channels glucose carbons into the pentose phosphate pathway (PPP), a key anabolic pathway that generates $NADPH+H^+$ and ribose sugar (the sugar component of nucleotides) [96]. $NADPH+H^+$ is necessary for fatty acid synthesis and serves as an antioxidant to handle oxidative stress, a common challenge faced by cancer cells [97]. In the first step of the oxidative PPP, glycolytic intermediate glucose-6-phosphate (G6P) is irreversibly converted to 6-phosphogluconolactone catalyzed by glucose-6-phosphate dehydrogenase (G6PD) [98]. This committed step of PPP makes G6PD an attractive metabolic target for inhibition of anabolism in cancer cells as it contributes to cancer growth and survival by determining the flux of glycolytic intermediates into PPP for biosynthetic purpose as well as $NADPH+H^+$production (which maintains redox homeostasis and prevents oxidative stress). An upregulation of the enzymes involved in the oxidative PPP (such as G6PD) has been reported in many cancer types with poor prognosis [99, 100]. In the non-oxidative branch of the PPP, a series of reversible reactions links glycolysis and PPP in a context-dependent manner. To meet anabolic requirements of a proliferating cells, glycolytic G6P and fructose 6-P are converted to ribose 5-P (R5P) while during energy depletion/oxidative stress, ribose 5-P (originally generated by oxidative branch of PPP) is converted to G3P and fructose 6-Phosphate in order to re-infiltrate the ribose carbons into glycolysis which can also be further utilized into oxidative PPP for $NADPH+H^+$ production [96]. Key enzymes of the non-oxidative PPP are transaldolase

(TALDO1) and transketolase (TKT) [101]. Higher expression of TKT has been reported as a poor prognosticator in esophageal and ovarian cancer. Silencing of TKT reduces migration and invasion of esophageal cancer cells [102, 103].

Genistein has been shown to attenuate tumor cell proliferation by inhibiting the incorporation of glucose carbons into non-oxidative PPP required for the production of nucleic acid [104]. Polydatin inhibits G6PD activity in breast cancer [105]. Epicatechin gallate and resveratrol are described to show anti-proliferative effects by inhibiting specific enzyme activities of two important enzymes i.e. G6PD and TKT in human colon cancer [106, 107]. Inhibition of G6PD and TKT activity by resveratrol results in the inhibition of cell proliferation and induction of apoptosis [107]. Targeting of TKT and TALDO may result in decreased nucleic acid biosynthesis. However, inhibition of TKT and TALDO can also lead to reduced recovery of R5P carbon atoms in glycolysis. As a consequence, oxidative PPP gets fewer substrates and oxidative stress increases due to NADPH+H^+ deficiency. TALDO1 shows sensitivity towards tetrandrine treatment. Tetrandrine downregulates the expression of TALDO1 and may play a role in inducing apoptosis [61]. Apart from resulting in reduced nucleotide biosynthesis, targeting TKT and TALDO can also block the recycling of R5P into glycolysis. This may prevent the refilling of the oxidative arm of PPP for sufficient NADPH+H^+synthesis, subsequently resulting in elevation of oxidative stress (Figure 1) [96].

2.3. Targeting amino acid metabolism

Amino acids are the substrates of protein synthesis as well as of anabolic and catabolic metabolic pathways. Cancer cells display increased demand for essential and non-essential amino acids which provide an alternative source to fulfill their bioenergetic and biosynthetic demands. Therefore, cancer cells modulate the amino acid metabolism in their favor, adapting it to the available nutrient conditions and thus supporting their growth and survival.

2.3.1. Glutaminolysis and serine biosynthesis

Besides glucose, the amino acid glutamine, is the second most important nutrient required by tumors [108]. Although glutamine can be synthesized as a non-essential amino acid by the cells themselves, many cancer cells depend on exogenous glutamine to support their growth and are termed as 'glutamine addicted' [109-111]. Exogenously obtained glutamine can undergo glutaminolysis-a process that breaks glutamine into anaplerotic intermediates that replenish TCA cycle intermediates through α-ketoglutarate (α-KG), and maintains mitochondrial metabolism, synthesis of amino acids, nucleic acids and fatty acids for cellular division as well as synthesis of glutathione synthesis - an important ROS scavenger [109, 110, 112].

Evidence do also suggest an epigenetic role of glutamine-derived metabolites such as α-KG [113, 114]. In transformed mammalian cells, OXPHOS is driven by TCA carbons derived from glutamine serving as a major source of ATP both in normoxia as well as in hypoxia [115]. For the first time, Harry Eagle highlighted the excessive consumption of glutamine by cancer cells (*in vitro*), which was ten-folds higher than the consumption rate of other amino acids [116]. The increased glutamine uptake by cancer cells is mediated by the amino acid transporters in which solute carrier family 1 member 5 (SLC1A5)-a high-affinity L-glutamine transporter, also known as ASCT2 has been studied well and reported to be upregulated in many cancer types [109, 117]. Phytocompounds such as morin and esculetin inhibit the expression of ASCT2 in colon of rats [25]. Resveratrol, in combination with cisplatin shows synergistic effects on decreasing glutamine uptake by downregulating ASCT2 in human hepatoma cells [118]. After glutamine enters the cells, it is first converted to glutamate by glutaminase (GLS), thus, glutaminase is considered to be a 'gate-keeper' enzyme of glutaminolysis [119, 120]. The GLS1 isozyme (kidney-type glutaminase) is a downstream effector of Myc and highly upregulated isoform of GLS in many cancers associated with poor prognosis [119, 121, 122]. Brachyantheraoside A8 blocks glutamine metabolism by inhibiting the enzymatic activity of GLS1 in breast cancer [123]. Physapubescin k inhibits GLS1 activity and tumor growth both *in vitro* and*in vivo.* Whereas, in combination with benserazide (HK2 inhibitor) and erlotinib (EGFR inhibitor) it showed a synergistic inhibitory effect on the growth of cancer cell lines [124, 125]. Glutamine uptake is significantly restricted by genistein and daidzein in a concentration-dependent manner, leading to alterations in protein synthesis

[126]. Morin and esculetin inhibit c-Myc driven glutaminolysis by downregulating GLS1 in colon cancer [25]. However, the effectiveness of glutaminase inhibition is highly dependent on factors like-tumor cell origin and microenvironment. Therefore, these factors should also be considered while targeting glutamine metabolism in tumors [127]. Another enzyme involved in glutaminolysis is glutamate dehydrogenase (GLUD) which converts glutamate to α-ketoglutarate which is further used for TCA anaplerosis. EGCG- a glutamate dehydrogenase (GLUD) inhibitor is currently being evaluated as adjuvant therapy for colorectal cancer in phase I clinical trial [128]. Glutaminolysis not only aids in energy production but also assists in various biosynthetic reactions critical for cancer. Due to its clear importance, targeting glutamine metabolism may prove beneficial in limiting the alterative nutrient supply of tumors affecting their growth and proliferation.

In addition to glutamine, serine is another non-essential amino acid required by cancer cells for protein biosynthesis, synthesis of glycine, cysteine, phospholipids, sphingolipids, nucleotides, glutathione as well as regeneration of $NADPH+H^+$ (via one carbon metabolism) [129-134]. Accordingly inhibition of *de novo* serine synthesis inhibits a variety of debranching synthetic processes [135, 136]. Phosphoglycerate dehydrogenase (PHGDH) is the first important enzyme of *de novo* serine biosynthesis that catalyzes the rate-limiting oxidation of 3PG to phosphohydroxypyruvate (3-PPyr) (Figure 1). Increased expression of PHGDH has been associated with poor prognosis in many cancer types [137-140]. Non-competitive inhibition of PHGDH by ixocarpalactone A results in suppression of proliferation in tumor cells with high PHGDH-expression [141]. The observed cellular consequences of PHGDH inhibition suggest a potential role of serine metabolism in tumor therapy. Future experiments may raise the question whether inhibition of the other enzymes within the serine synthesis such as phosphoserine aminotransferase 1 (PSAT1), serine hydroxy methyltransferase (SHMT) by phytochemicals could also prove beneficial in tumor therapy.

2.4. Lipid metabolism

Lipid metabolism and fatty acid synthesis (FAs) in particular is required for various cellular pathways and processes such as membrane biosynthesis, signaling transduction, lipidation reaction, and energy regeneration via β-oxidation [142]. Several studies have demonstrated that the activation of *de novo*fatty acid synthesis contributes to tumor progression and metastasis cancer [143-145].

FAs chiefly requires acetyl-CoA and $NADPH+H^+$. In addition to glucose, glutamine can produce acetyl-CoA via the TCA cycle or by reductive carboxylation of α-KG (Figure 1). $NADPH+H^+$ is produced within the glutaminolytic malic enzyme reaction as well as the oxidative PPP. The first enzyme involved in fatty acid synthesis is ATP Citrate lyase (ACLY) which converts citrate into cytosolic acetyl-CoA, thus channeling citrate into lipid biosynthesis. ACLY also facilitates histone acetylation by providing excess of acetyl CoA [146]. Expression and activity of ACLY are found to be upregulated in different types of tumors [146, 147]. Inhibiting ACLY consequentially diverts citrate from being utilized for lipogenesis and favors citrate oxidation in the TCA cycle which together suppress tumor cell proliferation and induces apoptosis [148]. Furanodiene, inhibits ACLY activity in AMP-activated protein kinase (AMPK) dependent manner. In doxorubicin-resistant cells this inhibition decreased tumor cell proliferation by mitochondrial function. [149]. Another strategy to reduce lipid synthesis is by targeting acetyl CoA carboxylase (ACC) the pace-setting enzyme within FAs that carboxylates cytosolic acetyl-CoA to malonyl-CoA. Several studies confirm that targeting ACC significantly decreases cancer cell proliferation [150, 151]. In prostate cancer, treatment with silibinin shows remarkable efficacy in decreasing proliferation both *in vitro* and *in vivo* by inhibiting HIF1α -mediated ACC expression [152]. Demethoxycurcumin (DMC) (natural curcumin derivative) and pomolic acid significantly reduce ACC expression and activity through activation of AMPK in different cancers [153-155]. Along with inhibition of FAs, targeting ACC stimulates β-oxidation of fatty acids resulting in lipid depletion which further limits cell proliferation [151, 156]. Fatty acid synthase (FASN) is the main biosynthetic enzyme that connects both acetyl-CoA and malonyl-CoA to predominantly produce palmitate, which is the first fatty acid to be produced by *de novo* FAs [157]. FASN is found to be upregulated in variety of human cancers such as breast, colorectal and endometrial cancer. High FASN expression is also associated with poor survival [158, 159]. Considering the clear importance of fatty acid synthesis and FASN in cancer, there are several clinical trials studying the efficacy of FASN inhibitors on lung, breast, colon and

other resectable cancers (NCT03808558, NCT03179904, NCT02980029)

In plants, range of phytochemicals have been identified that inhibit FASN expression thereby suppressing tumor cell proliferation or inducing apoptosis. These phytochemicals include: Resveratrol, which induces apoptosis in the cancer stem-like cells through suppression of fatty acid synthesis by modulating the expression of FASN [160]. Amentoflavone and catechin gallate derivatives (including EGCG, epicatechin gallate, and catechin gallate)- have also proven their effect as FASN inhibitors both *in vivo* and *in vitro* [161-166]. Osthole and amentaflavone downregulate FASN and human epidermal growth factor receptor 2 (HER2) protein expression in HER2 overexpressing cancer cell lines [166, 167]. Capsaicin, curcumin, tannic acid and primisterin inhibit FASN expression and its activity in different cancers [168-172]. EGCG inhibits FASN activity and induce apoptosis in breast tumor via targeting growth signaling without inducing weight loss in animal models, which limits the use of FASN inhibitors due to stimulation of β-oxidation [173]. Likewise, several flavonoids such as luteolin, quercetin, kaempferol, taxifolin as well as baicalein were identified as inhibitors of FASN activity, with the first three compounds being the most potent effectors [174]. Another flavonoid, morin inhibits FASN by binding to the β-ketoacyl synthase (highly conserved domain in FASN) which is responsible for the condensation of malonyl CoA and acetyl-CoA and thus attenuates the elongation of the fatty acid chain [175]. In addition, inhibition of FASN has been reported to improve the sensitivity of breast and pancreatic cancer cells towards docetaxel and gemcitabine [176, 177]. Recently, berberine has been reported to decrease the expression of all three important lipogenic enzymes FASN, ACC, ACLY through SREBP1 modulation in colon cancer [178]. Since $NADPH+H^+$ is required for reductive fatty acid biosynthesis, inhibition of oxidative arm of PPP may inhibit FAs as well.

Apart from FAs, several compounds also target other enzymes of lipid metabolism (Table 1). For instance, cyclooxygenase-2 (COX-2) that catalyzes the conversion of arachidonic acid to prostaglandins is known to promote angiogenesis, tumor invasion and resistance to apoptosis in tumor cells [179, 180]. In addition, COX-2-dependent prostaglandins benefit cancer cells by suppressing antigen presentation and immune activation [181]. Genistein and ECGC downregulate COX-2 expression via activating AMPK pathway in different cancer cells there by inducing apoptosis. Genistein along with 5-Flourouracil display synergistic effects in inducing apoptosis in chemo-resistant colon cancer cells [182, 183]. Genistein reduces proliferation in breast cancer cells in a dose-dependent manner by inhibiting various enzymes involved in sphingolipid metabolism (Sphingosine-1-Phosphate Kinase 2 and SIP lyase) [184].

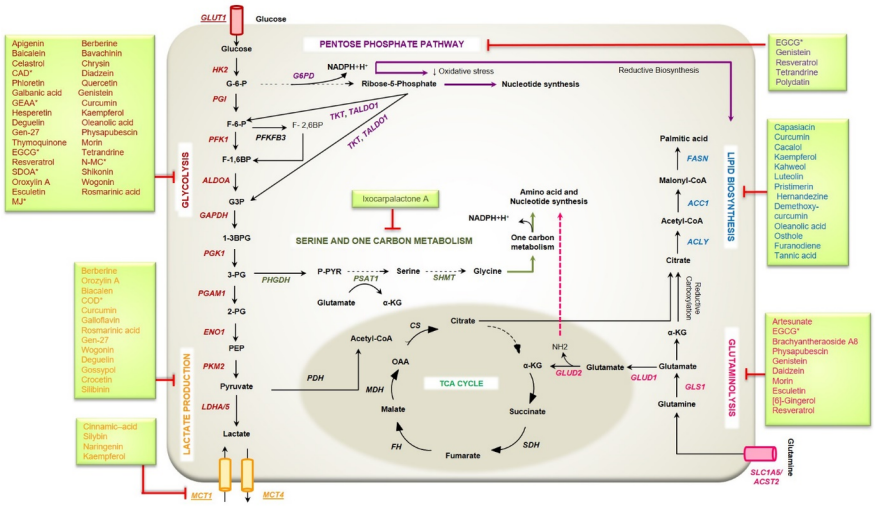

Figure 1. Overview of important metabolic targets of phytocompounds (listed in Table 1). Interaction of key metabolic pathways shown along with important phytochemicals targeting oncogenic isoforms of enzymes involved in these pathways. Red arrows represent inhibition of metabolic enzyme/pathway.

Black arrows represent steps involved in metabolic pathways. Dashed arrows represent multiple steps. GEAA: Graviola extract and its annonaceous acetogenins, CAD; Cinnamic acid derivatives SDOA: Secoiridoid decarboxymethyl oleuropein aglycone, DMC; Demethoxy-Curcumin, EGCG: epigallocatechin gallate; N-MC: N-methylhemeanthidine chloride; MJ: Methyl- jasmonate.

Growth signaling and transcriptional regulation of cancer metabolism: interaction with phytochemicals

Normal cell growth depends upon extracellular growth factors and nutrient supply. Under adequate nutrient supply, growth factor-induced signaling cascade triggers the transcriptional program that promotes metabolism of the nutrients to provide energy and building blocks necessary for regulated cell division (Figure 2A) [26, 185]. However, in the absence of enough nutrients or growth factors normal proliferating cells may undergo apoptosis (Figure 2B). In tumor cells, mutations within the growth factor receptors or the downstream components of the growth factor signaling cascades may lead to constitutive activation of signaling cascade, even in the absence of growth factors (Figure 2C). The aberrant signaling may disrupt their nutrient uptake ability as well as the regulation of the associated metabolic genes/pathways. Phytochemicals against signaling pathways are being used to indirectly target the impaired tumor metabolism by blocking their upstream regulatory cascade. Therefore, below we discuss the phytocompounds with their known mode of action on signaling pathways involved in the metabolic transformation of cancer with their effect on tumor growth.

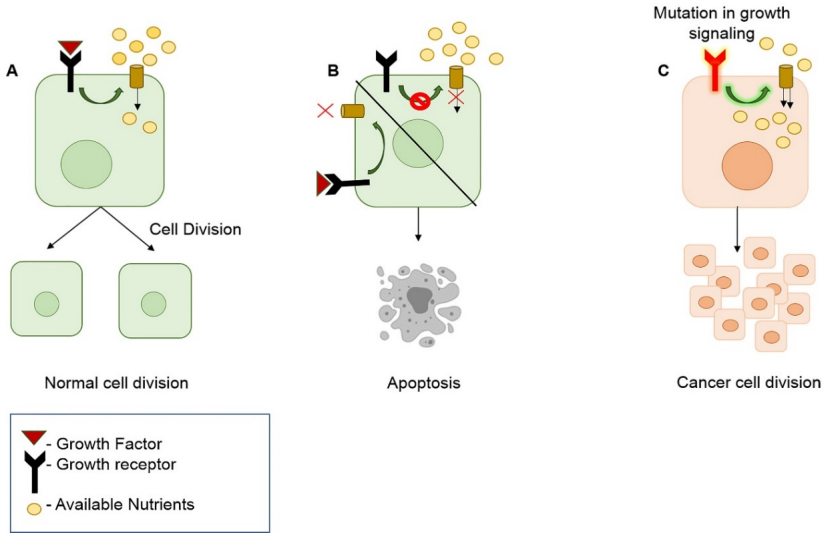

Figure 2. Effect of nutrient availability and growth signaling on cell proliferation. Regulation of cell division by growth factors and nutrients (A and B) in normal proliferating cells and C) in cancer cells.

3.1. Growth factor signaling

Major signaling axes regulating cancer metabolism are PI3K/Akt/mTOR, Ras/MAPK and LKB1/AMPK which are observed to be frequently mutated in variety of cancers [9, 186, 187]. Downstream to these pathways, transcription regulators like hypoxia inducible factor-1α (HIF1-α) and Myc are key players involved in reprogramming cancer metabolism [188]. Various therapeutic strategies target these signaling pathways and transcriptional regulators for anticancer therapy [189-191].

Downstream to epidermal growth factor receptor (EGFR)/receptor tyrosine kinase (RTK) there are two important signaling cascades i.e. PI3K/AKT/mTOR and Ras/MAPK that promotes cell growth and survival. PI3K phosphorylates Akt that regulates cell proliferation, invasion, angiogenesis, genome stability and response to nutrient availability. It is also an important driver of tumor glycolysis [192, 193]. Further, p-Akt

activates mTOR which serves as a metabolic integration point, linking growth signals to nutrient availability (Figure 3). mTOR regulates the expression of various transcription factors (TFs) such as HIF1α, Myc and SREBP1. HIF1α is activated under hypoxic conditions and induces the expression of genes which are important for the regulation of metabolism and cell survival at low oxygen supply. HIF1α regulates the expression of several glycolytic genes including GLUT1, HK2, PKM2, LDHA, PDK1 suggesting that inhibition of PI3K/mTOR signaling may result in decreased glycolysis, which in turn limits the supply of glycolytic intermediates important for anabolism, i.e. nucleic acids, lipids, and amino acids synthesis [194, 195]. Myc- a regulator of protein synthesis, is found to be overexpressed in human cancer [196]. Its activation results in the expression of pro-proliferative genes as well as increases genome instability and cell survival [197-199]. Myc upregulates downstream glycolytic genes such as glucose transporter (GLUT1), hexokinase 2 (HK2), phosphofructokinase (PFKM), enolase 1 (ENO1) and lactate dehydrogenase A (LDHA) [200]. Another transcription factor-Sterol regulatory element-binding proteins (SREBPs)-which binds to sterol regulatory elements (SRE) and target wide range of genes involved in lipid metabolism [201]. SREBP1, a predominant isoform in cancer, not only regulates enzymes involved in FAs but also enzymes of other pathways that are integrated with lipid metabolism (i.e. PPP and glutamine metabolism) [202].

Among the downstream molecules of RTK, Ras (a GTPase family member) is well-known to transduce cell proliferative signals [203]. This pathway also known as the Ras-Raf-MEK-MAP pathway is a chain of proteins in the cell that communicates an external stimulus through RTK to the nucleus of the cell for the activation of various transcriptional factors involved in regulating cancer cell metabolism [204]. Hyperactivation of Ras triggers MAPK to phosphorylate TFs such as Myc, that has been correlated with increased cell growth and survival in many cancer types [205, 206]. Phytochemicals of different origin and chemical structures are described to inhibit cancer cell proliferation by downregulation of these signaling cascades in different cancer cells.

Few compounds such as phloretin and resveratrol have been reported to downregulate the PI3K signaling via increasing the expression of phosphatase and tensin homolog (PTEN-a negative regulator of PI3K) [207, 208]. Oroxylin A induces PTEN-mediated negative regulation of mouse double minute 2 homolog (MDM2) and suppressed the expression of p53-regulated glycolytic enzymes to exert an anti-cancerous effect [209]. Wogonin and betulinic acid obstruct PI3K/Akt signaling and downregulate protein expression of HIF1α-induced glycolytic genes [210, 211]. Betulinic acid seems to be a very effective chemosensitizer for anticancer drug treatment in chemoresistant cell lines [212, 213]. Curcumin and esculetin induce apoptosis by inhibiting EGFR-directed signaling of PI3K pathway [214, 215]. Dioscin has been shown to induce autophagy by diminishing PI3K/Akt/mTOR pathway [216]. Fisetin, paeonol, quercetin, and silibinin have been found to downregulate PI3K/Akt/mTOR signaling axis both *in vitro* as well as *in vivo* models [217-220]. Ruthenium-baicalein complex elevates p53 levels while decreasing the protein expression of Akt/ mTOR and vascular endothelial growth factor (VEGF) which makes this complex capable of preventing angiogenesis and undergo p53 dependent apoptosis both *in vivo* and *in vitro*[221]. Rosmarinic acid and auraptene inhibit proliferation of cancer cells via downregulating HIF1α and its downstream regulated metabolic pathways [222-224]. Amentoflavone suppresses FASN expression by downregulating the translocation of SREBP1. It also inhibits HER2 oncogene and its related pathways such as PI3K/mTOR [225]. Cacalol inhibits lipid biosynthesis and impairs tumor growth both *in vivo* and *in vitro* by downregulating FASN via Akt/SREBP pathway [226]. Piperine and kahweol have been reported to inhibit FASN activity and SREBP1c, by interfering with Akt/mTOR signaling in HER2 overexpressing cells resulting in reduced cell growth via induction of apoptosis [227, 228]. [6]-Gingerol-an active component of ginger inhibits ERK1/2 and JNK MAP kinases and induces caspase-dependent apoptosis [229]. Naringenin inhibits cancer cell proliferation via inhibiting PI3K and MAPK activation thus reducing glucose uptake [35].

In addition, the cellular energy status plays an important role in regulating metabolism through signaling pathway. In response to the changing environment, the energy status is sensed by AMPK. Liver kinase B1 (LKB1) encoded by *STK11* , is the upstream kinase activating AMPK in response to an increase in AMP (Figure 3). At lower energy level, AMPK limits energy consumption by inhibiting energy-demanding processes like protein synthesis (via mTOR inhibition) and FAs while stimulating ATP-generating processes such

as glycolysis, fatty acid oxidation [230]. Thus, APMK acts in a tumor-suppressive manner and its inhibition increases mTOR which promotes cancer cell survival [231]. Activation of AMPK leads to phosphorylation of ACC, thus reducing the level of malonyl-CoA and lipogenesis [232]. Activated AMPK also induces the expression of p53- a transcriptional factor that plays tumor suppressive role by tightly regulating biological processes like cell cycle, DNA replication, apoptosis and metabolism [233]. p53 is mutated in most of the human cancers and its mutation is known to drive metabolic reprogramming by deregulating glycolysis, glutamine metabolism and mitochondrial metabolism [233-236]. Curcumin induces AMPK-mediated down-regulation of several glycolytic enzymes [237]. Honokiol has been recognized as an effective phytocompound in inhibiting cell proliferation, invasion, and migration via activation of LKB1/AMPK pathway resulting in inhibition of mTOR and its downstream effector molecules (4EBP1 and pS6K) [238]. Magnolol, plectranthoic acid, tanshinone IIA, widdrol, cryptotashinone, and flavokawain B activate the AMPK pathway in several cancer types [239-243]. The combination of docetaxel and capsaicin shows a synergistic effect in inhibiting the growth of prostate cancer by activation of AMPK and inhibition of the Akt and mTOR signaling axis [244]. Together the described growth inhibitory effects of phytochemicals that target oncogenic signaling cascades confirm the high anticancer potential of this therapeutic strategy. All phytochemicals and their mode of action are summarized in Table 1.

Yet another signaling regulating the cancer metabolism is Wingless (Wnt)/β-catenin signaling, which is an evolutionarily conserved pathway with its role in cell fate determination, proliferation, differentiation, and various pathological processes including cancer [245, 246]. Aberrant Wnt signaling caused by mutation/epigenetic changes has been reported in many type of cancers such as colon rectal cancer, breast cancer, hepatocellular carcinoma, leukemia etc. [247-251]. Regulation of Wnt signaling has been associated with cancer stem cells, tumor microenvironment and anti-cancer immune response [252, 253]. Recently, it has been linked with metabolic reprogramming of tumors, altering various metabolic pathways such as glycolysis, glutaminolysis, and lipogenesis [254, 255].

In canonical wnt signaling, binding of Wnt (ligand) with Frizzled (FZL) and low-density lipoprotein receptor-related protein (LRP) activates a downstream molecule known as Dishevelled protein (Dvl) which further blocks β-catenin destructive complex consisting of axin, casein kinase 1(CK1), glycogen synthase kinase-3 (GSK-3β), and adenomatous polyposis coli (APC). This prevents the degradation of β-catenin which translocates into the nucleus where it interacts with other transcription factors (TCF/LEF) to transcribe target genes [245]. β-catenin can either directly upregulate the expression of metabolic enzymes (e.g. PDK1, MCT1, COX2) or through metabolic regulators (such as c-Myc, c-jun) that promote glycolysis (via GLUT1, PDH, PFK1, HK2, PKM2) and glutaminolysis (via ASCT2) (Figure 3). Non-canonical Wnt signaling can also modulate the cellular metabolism through PI3K/Akt pathway leading to the activation of mTOR, further affecting various metabolic pathways (Figure 3) [256]. Wnt signaling is also known to promote metabolic plasticity by switching mitochondrial respiration to aerobic glycolysis via upregulation of various enzymes like PDK1 which prevents the access of pyruvate into TCA and MCT1 that promotes Warburg effect [257].

Many natural compounds have been found to target Wnt signaling. In vivo as well as in vitro studies shows that Physalis peruviana-Derived 4-Hydroxywithanolide E-a natural withanolide and umbelliprenin alters the Wnt signaling by reducing the protein expression of Wnt-2, β-catenin, GSK-3β, p-GSK-3β, Survivin and c-myc. It also inhibits the translocation of β-catenin into the nucleus in colorectal and gastric cancer respectively [258]. Silibinin also inhibits the β-catenin levels and its translocation inside the nucleus in colorectal cancer [259]. Flavonoids such as Genistein, kaempferol, isorhamnetin, and baicalein (Table 1) inhibit Wnt/β-catenin signaling by decreasing the expression of β-catenin and its binding with consensus DNA in colon and kidney cancer [260]. Wnt pathway makes a good therapeutic target due to its multifunctional role in cancer, whereas its in-depth molecular understanding in metabolic reprogramming will expand the clinical implications of this pathway in treating cancer. Berberine decreases lipogenic enzymes FASN, ACC, ACLY and lipogenesis through SREBP1 resulting in inhibition of β-catenin levels (Wnt pathway) in colon cancer [178].

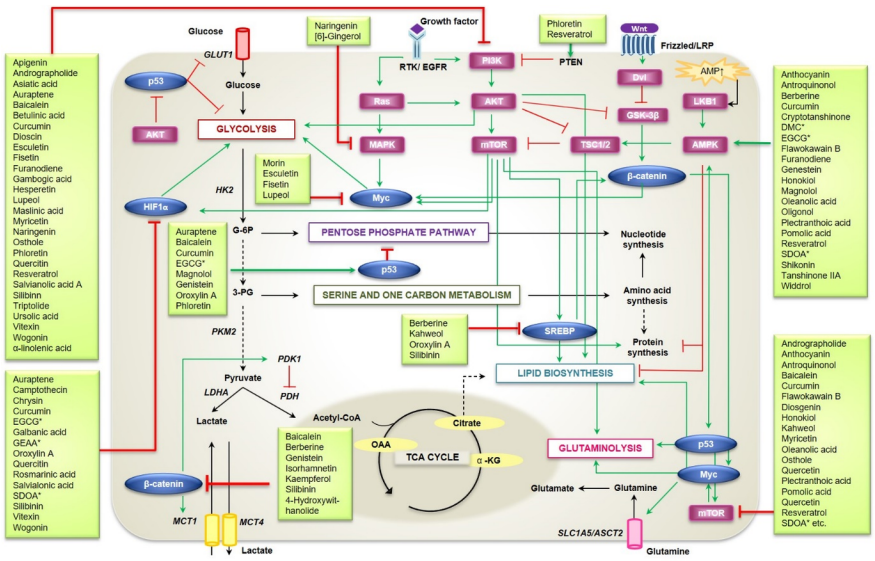

Figure 3. Overview of signaling pathways targeted by phytochemicals . Green and red arrows represent activation and inhibition of effector molecules, respectively. Black arrows represent steps involved in metabolic pathways. Dashed arrows represent multiple steps. RTK-receptor tyrosine kinase; PTEN-phosphate and tensin homolog; PI3K-phosphatidylinositol-3-phosphate kinase; LKB1-liver kinase B1; AMPK-AMP activated protein kinase; mTOR-mammalian target of rapamycin; SREBP-sterol regulatory element-binding protein; HIF1α -hypoxia-inducible factor-1α

Clinical relevance of phytocompounds

Evidently, phytocompounds interfere with the process of metabolic transformation in cancer by direct inhibition of metabolic pathways and also via modulation of regulators of cancer metabolism. As growing evidence highlights the therapeutic significance of metabolic addictions of cancer, the ability of phytochemical to target cancer metabolism further endorses their clinical relevance. For compounds already known to have anti-cancer properties, their ability to target metabolism should be evaluated and could be used as a criterion for inclusion of compounds for further clinical evaluation. For a perspective, we discuss below few plant-based compounds, known to inhibit cancer metabolism, that are already in various stages of clinical trials.

In recent phase I/II clinical study, It has also been shown to be effective against human non-melanoma skin cancer [261]. Curcumin- an anticancer compound derived from turmeric which is a traditionally used spice in Chinese and Indian medicines [262]. A study showed that curcumin administration in patients with colorectal cancer (360 mg/thrice a day) increased body weight, upregulated p53 expression and decreased TNF-alpha levels [263]. The clinical translation of curcumin has been significantly hampered due to improper metabolization, poor absorption and systemic bioavailability, which mandates the high oral consumption of free curcumin (up to 8–10 gram/day) for its detectable levels in the circulation [264].Curcumin has also been reported to act as chemosensitizer for some anticancer drugs (e.g., gemcitabine, paclitaxel, 5-fluorouracil and doxorubicin) and exhibit a synergistic effect in combination with other natural compounds (e.g., resveratrol, honokiol, epigallocatechin-3-gallate, licochalcone and omega-3) [265-267].Curcumin can also be combined with pepper (piperine as its active constituents) which enhances its bioavailability up to 2000% [268]. EGCG is a powerful antioxidant found in green tea which is a popularly consumed beverage throughout the world. It has also been studied for its anticancer activity as well as its effectiveness for treating premalignant lesions. In a study to determine the effect of EGCG in prostate cancer development, subjects treated with 600 mg/day showed reduced incidences of developing prostate cancer (3%) as compared to placebo (30%) [269]. Genistein has also shown encouraging anticancer effects in treating breast cancer (NCT00244933,

NCT00290758), prostate cancer (NCT00058266, NCT01126879) and pancreatic cancer (NCT00376948). In a phase I clinical study, (S)-camptothecin and 20-(S)-9-nitrocamptothecin-derivatives of Camptothecin (a natural alkaloid) exhibited antitumor effects in a number of patients with refractory breast cancer, prostate cancer and melanoma [270]. Lycopene is a natural antioxidant that gives red color to different fruits and is abundantly found in tomatoes [271]. In a phase II randomized clinical trial, supplementation of lycopene before radical prostatectomy suggested that its supplementation may decrease the growth of prostate cancer (NCT00450749).

Phytochemicals targeting cancer are still in their infancy as relatively fewer phytocompounds (such as paclitaxel, docetaxel, vinblastine) have been approved to be used in clinical practices. This highlights the need for a better pipeline of clinical assessment of phytochemicals. A meticulous approach that encompasses the drug optimization, efficacy evaluation, tissue toxicity and distribution, chemical accessibility, pharmacokinetics, absorption and most importantly the bioavailability, should be designed for an improved evaluation of phytochemicals. Use of stable synthetic analogues, chemically modified derivatives, coating of drugs with materials using micelles, liposomal conjugates, phospholipid complexes, adjuvants, nano particles are few way to improve the stability and availability of compounds in blood [272-276]. Also, approaches like structure–activity relationship-directed optimization and pharmacophore-oriented molecular design can be adopted to increase the potency of plant-based drugs [274].

Conclusion

Cancer metabolism is highly discriminatory between normal and tumor cells and thus holds immense potential for anticancer strategies. The ability of phytocompounds to inhibit metabolic preprogramming in cancer makes them attractive contender in therapeutic interventions. Off-course, further research into molecular, biochemical, and pharmacokinetic aspects combined with systematic preclinical and clinical evaluation of phytochemicals is required to unravel the potential of plant-based targeting of metabolism in cancer. Expanding our knowledge of plant-based compounds in cancer therapeutics along with the identification of critical tumor-specific metabolic characteristics may pave a way for improved clinical inhibition of cancer. Dietary phytochemicals (as highlighted in the Table 1) may provide an inexpensive way of chemoprevention and thus improving health by scaling down cancer incidence worldwide. In summary, this review attempts to spotlight the potential of natural compounds in targeting metabolic vulnerabilities of cancer and highlights prospective therapeutic benefit that can be extracted by improving our understanding in this field.

Table 1. Phytocompounds targeting different metabolic and signaling pathways in cancer cells.

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Berberine*	*Coptis and Hydrastis canadensis* commonly known as Goldenseal, Yellow Root, Orangeroot (Ranunculaceae)	Breast cancer cells (MCF-7) Breast cancer cells (MCF-7) Colon cancer cells (HCT-116) Cervical cancer cells (HeLa) Colon cancer cells (DLD-1 and Caco-2) and *in vivo*	Decreases TPI, ALDO A and ENO-α protein expression Decreases glucose consumption, PFKP expression and citrate content Decreases glucose consumption, PFKP expression and citrate content Inhibits PKM2 activity. Inhibits lipogenic enzymes FASN, ACC, ACLY Inhibits SREBP1 activation	[65] [49] [79] [178]
Brucine	Seeds of *Strychnos nux-vomica Linn.* Commonly known as Poison nut (Loganiaceae)	Hepatocellular carcinoma cells (HCC)	Inhibits HIF1α pathway	[277]
Camptothecin	Stem and bark of *Camptotheca acuminate* (Nyssaceae)	Human embryonic kidney cells (HEK293)	Inhibits HIF1α protein synthesis	[278]
Capsaicin*	Isolated from genus *Capsicum* (Solanaceae)	Hepatocellular carcinoma cells (HepG2) Pancreatic cancer cells (AsPC-1, BxPC-3)	Decreases FASN protein and *de novo* fatty acid synthesis Decreases mitochondrial ETC complex I, III activity.	[168] [279]
Hernandezine	From genus *Thalictrum* (Ranunculaceae)	Cervical cancer cells (HeLa)	Increases p-ACC protein level	[280]
N-methylhemeanthidine chloride	*Zephyranthes candida* commonly known as Autumn zephyrlily, White windflower and Peruvian swamp lily (Amaryllidaceae)	Pancreatic cancer cells (AsPC-1, BxPC-3, Mia PaCa-2)	Downregulates GLUT1, PGK1, LDHA, PKM2 protein expression Decreases glucose uptake, lactate production	[39]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Piperine *	*Piper nigrum Linn* commonly known as Black pepper (Piperaceae)	Breast cancer cells (SKBR3)	Decreases SREBP1 and FASN expression	[228]
Tetrandrine	*Stephenia tetrandra S Moore* commonly known as Han Fang ji/ Fan Fang ji (Menispermaceae)	Hepatocellular carcinoma cells (HepG2)	Decreases PGAM1, TALDO1 protein level	[61]
Phytochemicals (Phenols)	**Sources**	**Cancer cell lines/Model**	**Metabolic targets**	**References**
Acetoxypinoresinol *	*Olea europaea* (Oleaceae) Virgin olive oil	Breast cancer cells (SKBR3 and MCF-7)	Decreases FASN protein level	[281]
Amentoflavone	*Selaginella tamariscina* (Selaginellaceae)	Breast cancer cells (SKBR3) Breast cancer cells (SKBR3)	Decreases FASN expression Suppresses FASN expression by downregulating HER2 pathways and SREBP-1 translocation	[166] [225]
Anthocyanin*	Fruit of *Vitis coignetiae Pulliat* commonly known as Crimson Glory Vine (Vitaceae)	Colon cancer cells (HT-29)	Stimulates AMPK phosphorylation Inhibits mTOR and Akt phosphorylation	[282]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Apigenin*	*Olea europea* (Oleaceae) *Apium graveolens, Petroselinum crispum* (Apiaceae) And widely extracted from fruits, vegetables (especially celery), beans, and tea	Adenoid cystic carcinoma (ACC2) Breast cancer cells (SKBR3, MCF-7) Cisplatin-resistant colon cancer cell line (HT-29) and xenograft mice model Colon cancer cells (HCT 116, HT29, DLD-1) Lung cancer cells (H1299, H460) and *in vivo* Pancreatic cancer cells (S2-013 and CD18) Breast (MDA-MB-231) and prostate cancer cells (LNCaP)	Decreases GLUT1 mRNA and protein levels Decreases FASN protein level Inhibits mTOR/PI3K/Akt pathway Allosterically inhibits PKM2 activity Decreases PKM2 expression by blocking β-catenin/c-Myc/PTBP1 signal pathway. Downregulates glucose uptake, lactate production, ATP generation. Downregulates expression of GLUT1 Decreases glucose/glutamine utilization, lactate production, ATP, and NADPH+H^+ generation Decreases GLUT1 mRNA and protein levels Decreases lipid synthesis, FASN activity, synthesis of phospholipids, triglycerides and cholesterol levels	[31] [281] [283] [78] [284] [33] [174]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Baicalein	Root of *Scutellaria baicalensis* commonly known as Baikal skullcap, Chinese skullcap (Lamiaceae)	Gastric cancer cells (AGS cells) Colon cancer cells (HT-29 cells) Human embryonic kidney cells (HEK293) and colon cancer cells (SW480)	Decreases HK2, LDHA and PDK1 mRNA and protein levels Decreases glucose uptake and lactate production Downregulates Akt, mTOR, VEGF protein expression Increases p53 expression. Suppress β-catenin/tcf transcriptional activity. Inhibits formation of β-catenin/Tcf–DNA complex	[81] [221] [260]
Bavachinin	*Psoralea corylifolia* commonly known as Bakuchi (Leguminosae)	HeLa derivative (KB)	Decreases GLUT1, HK2 mRNA and protein levels (under hypoxia)	[38]
Chrysin	*Passiflora caerulea* commonly known as Blue passionflower (Passifloraceae)	Hepatocellular carcinoma cells (LM-3, SMMC-7721, Bel-7402) and *in vivo* Prostate cancer cells (DU145)	Inhibits HK2 protein expression Decreases HIF1α expression	[45] [285]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Curcumin*	Rhizomes of *Curcuma longa* commonly known as Turmeric (Zingiberaceae)	Breast cancer cells (MCF-7) Breast cancer cells (MDA-MB-231) Breast cancer cells (SKBR3) Esophageal cancer cells (Ec109) Hepatocellular carcinoma cells (HepG2) H1299, MCF-7, HeLa and PC3 cell lines. Human umbilical vein endothelial (HUVECs), lung cancer cells (A549 and PC-9) and *in vivo*	Decreases GLUT1 mRNA and protein levels in TNF-α stimulated cell Restored glycolysis to basal levels Decreases HK2 mRNA and protein level Decreases FASN expression and activity Decreases AMPK mediated expression of glycolytic enzymes GLUT4, HK2, PFKFP3 and PKM2. Decreases FASN activity, mRNA levels Downregulates PKM2 protein via mTOR-HIF1α Inhibits c-Met induced PI3K/Akt/mTOR pathway	[286] [287] [169] [237] [170] [74] [288]
Demethoxycurcumin (DMC)*	Rhizomes of *Curcuma longa* commonly known as Turmeric (Zingiberaceae)	Prostate cancer cells (LNCaP, DU145, PC-3) Breast cancer cells (MDA-MB-231)	Decreases FASN and p-ACC protein expression Decreases FASN and ACC protein expression via activation of AMPK signaling	[154] [153]
Daidzein*	Leaves of *Glycine max* commonly known as Soyabean (Fabaceae)	Breast cancer cells (MCF-7, MDA-MB-231)	Increases PPP Decreases glucose and glutamine uptake.	[126]
Deguelin	*Mundulea sericea* commonly known as Cork Busk, Silver Leaf, Silver Bush (Leguminosae)	Non-small cell lung cancer (NSCLC) cell (H460, H1650, H1299, H520, HCC827, H1975, H358)	Inhibits Akt dependent HK2 expression, glucose uptake, lactate production	[46]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Esculetin*	Coumarin derivative isolated from-*Atremisia capillaries* commonly known as Oriental wormwood (Asteraceae), *Citrus limonia* commonly known as Rangpur lime or Nagpur lime (Rutaceae) and *Euphorbia lathyris* commonly known as Caper spurge or Paper spurge (Euphorbiaceae)	Human oral squamous HN22 and HSC2 Colon of experimental rat (*in vivo*)	Inhibits EGFR/PI3K/Akt signaling pathway Decreases expression of GLUT1, HK2, PKM2, LDHA, ASCT2 and GLS1	[215] [25]
Epigallocatechin-3- Gallate (EGCG)*	*Camellia sinensis* commonly known as Tea (Theaceae)	NCI-H1299 and MDA-MB-231 cells Colon cancer cells (HT-29) Breast cancer cells (MCF-7) Colon cancer cells (HT-29) Hepatocellular carcinoma cells (HCCLM3, HepG2) Breast cancer cells (MCF-7 and MDA-MB-231) Breast (MDA-MB-231) and prostate cancer cells (LNCaP)	Inhibits PGAM1 activity Increases ROS, AMPK signaling, p53 protein levels Decreases COX-2, GLUT1 expression Decreases FASN mRNA and protein expression Decreases glutamate production Inhibits TKT and G6PD activity Decreases mRNA/protein expression and activity of PFK Inhibits glucose uptake, lactate production Inhibits LDHA activity Decreases lipid synthesis, FASN activity, synthesis of phospholipids, triglycerides and cholesterol levels	[62] [182] [164] [106] [50] [82] [174]

Phytochemicals (Alkaloids)	Sources	Cancer cell lines/Model	Target	References
Fisetin*	*Acacia greggii* commonly known as Devil's Claw Acacia and *Acacia berlandieri* commonly known as Guajillo (Fabaceae)	Breast cancer cells (4T1, MCF-7, MDA-MB-231) and *in vivo* Pancreatic cancer cells (MiaPaca-2)	Inhibits PI3K/Akt/mTOR pathway Downregulates ERK-MYC signaling	[217] [289]
Gallic acid*	Extracted from gallnut tannins of oaks under the genus (*Quercus),* Fagaceae seeds and skin of *Vitis vinifera* commonly known as Grapes (Vitaceae), leaves of *Camellia sinensis* commonly known as Tea or Green tea (Theaceae)	Human Acute myeloid leukemia cell lines (THP-1 and MV411) and in vivo	Suppress Akt/mTOR pathway Inhibits mitochondrial respiration, ATP production and induces oxidative stress	[290]
Galloflavin	Derived from gallic acid	Hepatocellular carcinoma cell line (PLC/PRF/5)	Inhibits LDHA and LDHB activity	[85]
Gambogic acid	Isolated from *Garcinia hanburyi* commonly known as Siam gamboge, Hanburyi's garcinia *(Clusiaceae)*	Human colon carcinoma cell lines (HCT116, SW620) and *in vivo*	Dysregulates lipid metabolism Inhibits Akt-mTOR signaling	[291]
Genistein*	*Genista tinctoria, Glycine max* commonly known as Soybean (Fabaceae) form roots of L*inum usitatissimum* commonly known as Flax or Linseed (Linaceae)	Breast cancer cells (MCF-7, MDA-MB-231) Breast cancer cells (MCF-7) Colon cancer cells (HT29) Pancreatic cancer cell (MIA PaCa-2) Human embryonic kidney cells (HEK293) and colon cancer cells (SW480)	Decreases glycolysis and glutamine uptake Inhibits Sphingolipid metabolism Downregulates COX-2 expression, Elevates p53, p21, AMPK level Decreases TCA cycle, non-oxidative PPP. Suppress β-catenin/tcf transcriptional activity Inhibits formation of β-catenin/Tcf–DNA complex Inhibits phosphorylation of Akt and GSK-3β	[126] [184] [183] [104] [260]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Gen-27 (Genistein derivative)	Genistein derivative	Breast cancer cells (MDA-MB-231, MCF-7, MDA-MB-468)	Decreases HK2, PKM2 and LDHA protein levels Downregulates glucose uptake, lactate production and ATP generation.	[292]
Gossypol	*Gossypium hirsutum* commonly known as Cotton (Malvaceae)	Human tumor cell lines (glioma melanoma, colon, and adrenocortical carcinoma)	Non-selectively inhibits LDH5 and LDHA activity	[83]
Hesperetin*	Fruit peel of *Citrus aurantium L.* commonly known as Bergamot orange (Rutaceae)	Breast cancer cells (MDA-MB-231) Human umbilical vascular endothelial cells (HUVECs)	Decreases GLUT1 mRNA and protein level and translocation of GLUT4 Inhibits VEGF via downregulating PI3K/Akt/ERK pathway	[34] [293]
Honokiol	Root and stem bark of *Magnolia grandiflora* commonly known as Southern Magnolia or bull bay, (Magnoliaceae)	Breast cancer cells (MCF7 and MDA-MB-231) .	Increases LKB1, p-AMPK, p-ACC Inhibits mTOR	[238]
Hydroxytyrosol*	Fruit oil of *Olea europaea* commonly known as Olives (Oleaceae)	Colon cancer cells (SW620)	Decreases FASN activity and mRNA level	[294]
Isorhamnetin*	From roots of *Scutellaria baicalensis* commonly known as Baikal skullcap, Chinese skullcap (Lamiaceae)	Human embryonic kidney cells (HEK293) and colon cancer cells (SW480)	Suppress β-catenin/tcf transcriptional activity Inhibits formation of β-catenin/Tcf–DNA complex	[260]

Phytochemicals (Alkaloids)	Sources	Cancer cell lines/Model	Target	References
Kaempferol*	*Cuscuta chinensis* (Convolvulaceae), *Euphorbia pekinensis* commonly known as Peking spurge (Euphorbiaceae), Glycine max commonly known as Soybean (Fabaceae)	Breast cancer cells (MCF-7) Breast (MDA-MB-231) and prostate cancer cells (LNCaP) Human embryonic kidney cells (HEK293) and colon cancer cells (SW480)	Decreases glucose uptake by inhibiting MCT4, GLUT1 mRNA expression Decreases lipid synthesis, FASN activity, synthesis of phospholipids, triglycerides and cholesterol levels Suppress β-catenin/Tcf transcriptional activity Inhibits formation of β-catenin/Tcf–DNA complex	[94] [174] [260]
Lichochalcone E	*Glycyrrhiza inflata* commonly known as Chinese licorice (Fabaceae)	Breast cancer cells (MDA-MB-231 cells)	Decreases expression of HIF1α, VEGF and COX2	[295]
Luteolin*	Fruit oil of *Olea europaea* commonly known as Olives (Oleaceae)	Breast cancer cells (MCF-7 and SKBR3) Breast cancer cells (MDA-MB-231) and prostate cancer cells (LNCaP) Pancreatic cancer cells (MIA PaCa-2)	Decreases FASN protein level Decreases lipid synthesis, FASN activity, synthesis of phospholipids, triglycerides and cholesterol level Decreases *de novo* fatty acid synthesis	[281] [174] [296]
Magnolol	*Magnolia officinalis* commonly known as Hu-bak or Magnolia bark (Magnoliaceae)	Colon cancer cells (HCT-116)	Activates p53 and AMPK signaling pathway	[239]
Morin*	*Ficus carica* commonly known as Common fig (Moraceae)	Colon of experimental rat (*in vivo*)	Decreases expression GLUT1, HK2, PKM2, LDHA, ASCT2 and GLS1	[25]
Myricetin*	*Camellia sinensis* commonly known as Tea (Theaceae), petals of *Rosadamascene* (Rosaceae) etc	Hepatocellular carcinoma cells (HepG2) Glioblastoma multiforme cells (DBTRG-05MG)	Inhibits mTOR activation Upregulated expression of SIRT3 mediated PI3K/Akt pathway.	[297] [298]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Naringenin*	*Citrus paradise* commonly known as Grapefruit (Rutaceae)	Breast cancer cells (MCF-7) Colorectal adenocarcinoma cells (Caco-2)	Inhibits PI3K/Akt and MAPK pathway Decreases glucose uptake by GLUT4 Inhibits MCT1 activity	[35] [93]
Oligonol*	*Litchi chinensis* commonly known as Lychee (Sapindaceae)	Hepatocellular carcinoma cells (HepG2)	Downregulates lipogenesis and lipid accumulation Enhances lipolysis Increases AMPK phosphorylation	[299]
Osthole	*Cnidium monnieri (L.)* commonly known as Shechuangzi, Osthole, Jashoshi, Cnidii Fructus (Apiaceae)	Ovarian cancer cells (SKOV3)	Decreases FASN protein level Decreases p-Akt, p-mTOR	[167]
Oroxylin A	*Scutellaria baicalensis* commonly known as Baikal skullcap or Chinese skullcap (Lamiaceae) *Oroxylum indicum* commonly known as Midnight horror, Oroxylum, Indian trumpet flower, broken bones, Indian caper, or Tree of Damocles. (Bignoniaceae,)	Breast cancer cells (MDA-MB-231, MCF-7) Breast cancer cells (MDA-MB-231) Breast and colon cancer cells (MCF-7, HCT116) Colon cancer cells (HCT116) and *in vivo* NSCLC (A549)	Dissociation of HK2 from the mitochondria Downregulates HIF1α regulated HK2 mRNA and protein expression Decreases glucose uptake, lactate production (under hypoxia) Decreases glucose uptake and lactate production. Inhibits p53 mediated 23inctorial of GLUT1,4 and PGAM. Decreases ADRP, SREBP-1, FASN mRNA and protein expression Decreases HK2 protein expression and dissociates from mitochondria Downregulates glucose uptake, lactate production and ATP generation	[300] [42] [209] [301] [43]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Paeonol	Root bark of *Paeonia suffruticosa* commonly known as Mŭdān (Paeoniaceae)	Ovarian cancer cells (A2780, SKOV3) and *in vivo*	Induces autophagy via inhibiting Akt/mTOR pathway	[218]
Phloretin*	Fruit of *Malus domestica* commonly known as Orchard Apple *(*Rosaceae)	Breast cancer cells (MDA-MB-231) and *in vivo* Glioblastoma cells (U87 and U251 cell)	Inhibits GLUT2 protein expression Inhibits PI3K/Akt/mTOR pathway Increases PTEN expression	[302] [207]
Polydatin	*Polygonum cuspidatum* commonly known as Japanese knotweed (Polygonaceae)	Breast cancer cells (MCF-7)	Inhibits G6PD activity Increases ROS levels	[105]
Quercetin*	From Brassicaceae family such as *Brassica oleracea* also known as Kale, *Malus domestica* commonly known as Apple (Rosaceae), *Camellia sinensis* commonly known as Tea or Green tea (Theaceae)	Breast cancer cells (MCF-7) and *in vivo* B cell lymphoma Breast cancer cells (MCF-7, MDA-MB-231) Breast (MDA-MB-231) and prostate cancer cells (LNCaP) Neuroblastoma cells (SK-N-MC)	Blocked mTOR pathway Blocked PI3K-Akt, NF-kB and STAT3 Suppresses glycolysis via Akt/mTOR pathway Decreases lipid synthesis, FASN activity, synthesis of phospholipids, triglycerides and cholesterol levels Decreases HIF1α mRNA and protein expression	[219] [303] [304] [174] [305]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Resveratrol*	Fruit of *Vitis vinifera* (Vitaceae)	Breast cancer cells (MCF-7) HeLa, HepG2 and MCF-7 cell lines Breast cancer cells (MCF-7) Breast cancer cells (MCF-7, MDA-MB-231) Colon cancer cells (HT-29) Human hepatoma cells C3A and SMCC7721 Human acute promyelocytic leukemia (APL) cell line NB-4 and HL-60 Human diffuse large B-cell (LY18)	Directly inhibits PFK1 activity Inhibition of glycolysis Decreases expression of PKM2 via mTOR pathway Decreases lactate production and increases glucose oxidation Increases *de novo* ceramide synthesis SPT, nSMase activity Inhibits lipogenesis by downregulating FASN in cancer stem-like cells Decreases G6PD, TKT activity Inhibits glutamine uptake by downregulating ASCT2 (synergistically with cisplatin) Induces PTEN expression and Inhibits PI3K/Akt signaling Decreases PFK activity, glucose consumption and intracellular ATP content Increases AMPK activity	[48] [75] [306] [160] [107] [118] [208] [307]
Rosmarinic acid	*Rosmarinus officinalis* commonly known as Rosemary, *Melissa officinalis also known as Lemon balm or Balm mint and Prunella vulgaris L.* commonly known as Self-heal, Heal-all, woundwort, Heart-of-the-earth (Lamiaceae)	Colon cancer cells (HCT-8, HCT116)	Decreases glucose consumption, lactate production via inhibiting HIF1 α	[222]

Phytochemicals (Alkaloids)	Sources	Cancer cell lines/Model	Target	References
Salvianolic acid	*Salvia miltiorrhiza* commonly known as Red sage, Chinese sage, Tan shen, or Danshen, (Lamiaceae)	Human AML cells (THP-1, KG-1, and Kasumi-1) Human umbilical endothelial cells (HUVECs)	Inhibits PI3K/Akt pathway Inhibits hypoxia induced-expression of very-low-density lipoprotein receptor (VLDLR)	[308] [309]
Silibinin*	Seeds of s*ilybum marianum* (Asteraceae)	Prostate cancer cells (LNCaP, 22Rv1) and *in vivo* Rhabdoid tumor (G401 cell line) Endometrial carcinoma cells (EC) 3T3-L1 fibroblasts and CHO-K1 cells Colorectal adenocarcinoma cells (Caco-2) Colorectal cancer cell (SW480) and *in vivo* Pancreatic ductal adenocarcinoma (S2-013, T3M4)	Inhibits HIF1α induced lipogenesis Inactivates PI3K/Akt signaling pathway Inhibits STAT3 activation and lipid synthesis via SREBP1 Directly inhibits GLUT4 and GLUT1 transporters, decrease glucose uptake Inhibits MCT1 activity Decreases β-catenin-dependent T-cell factor-4 (TCF-4) transcriptional activity and protein expression c-Myc, cyclin D1 and cyclin-dependent kinase 8 (CDK8) Reduces mRNA and protein expression of GLUT1, HK2 and LDHA	[152] [220] [310] [36] [93] [259] [311]
Scutellarein	*Scutellaria lateriflora* (Lamiaceae)	Breast cancer cells (MDA-MB-231)	Decreases ECAR and oxygen consumption rate (OCR)	[312]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Tannic acid*	*Caesalpinia spinosa* commonly known as Spiny Holdback or Tara pods (Fabaceae), Gallnuts of *Rhus semialata* commonly known as Chinese sumac or nutgall tree, leaves Rhus coriaria commonly known as Sicilian Sumac (Anacardiaceae)	Breast cancer cells (MDA-MB-231 and MCF-7)	Inhibits FASN expression and activity	[171]
Taxifolin*	*Pinus* roxburghii commonly known as Chir pine, Cedrus *deodara* commonly known as Deodar (Pinaceae), *Silybum marianum* commonly known as Milk thistle (Asteraceae) etc.	Breast cancer cells (MDA-MB-231) and prostate cancer cells (LNCaP)	Decreases lipid synthesis, FASN activity, synthesis of phospholipids, triglycerides, and cholesterol levels	[174]
Vitexin	*Crataegus pinnatifida* commonly known as Mountain hawthorn, Chinese haw, Chinese hawthorn or Chinese hawberry, (Rosaceae)	NSCLC (A549) Rat pheochromacytoma (PC12)	Inactivates PI3K/AKT/mTOR pathway Inhibits mRNA expression of HIF1α, ADLOA, ENO1	[313] [56]
Wogonin	*Scutellaria baicalensis* commonly known as Baikal skullcap or Chinese skullcap (Lamiaceae)	Colon cancer cells (HCT-116)	Downregulates HIF1α, HK2, PDK1 and LDHA protein level Downregulates glucose uptake, lactate production via inhibiting PI3K/AKT signaling pathway (under hypoxia)	[210]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Xanthohumol	*Humulus lupulus* commonly known as Common hop or Hops (Cannabaceae)	Cervical cancer (HeLa) and lung cancer cells (A549)	Decreases mitochondrial complex I activity and ECAR	[314]
Phytochemicals (Steroids)	**Sources**	**Cancer cell lines/Model**	**Metabolic targets**	**References**
Dioscin	*Dioscorea nipponica* and *Dioscorea zingiberensis* commonly known as Yam (Dioscoreaceae)	Gall bladder cancer cells (NOZ and SGC996)	Inhibits ROS mediated PI3K/AKT signaling	[315]
Diosgenin	*Dioscorea rotundata* commonly known as Yam (Dioscoreaceae)	Myeloid leukemia cells (BaF3-WT and K562)	Inhibits mTOR pathway	[316]
Physalis peruviana-Derived 4-Hydroxywithanolide E	From *Physalis peruviana* commonly known as golden berry	Colorectal cancer cells (HCT116, SW480, and HT-29) and *in vivo*	Blocked Wnt/β-catenin signaling pathway	[258]
Withaferin A*	*Withania somnifera* commonly known as Ashwagandha, Indian ginseng, Poison gooseberry or Winter cherry (Solanaceae)	Human neuroblastoma cell lines IMR 32 and GOTO	Inhibits Akt/mTOR/NF-ϰB activation and down regulate N-Myc	[317]
Phytochemicals (Terpenoids)	**Sources**	**Cancer cell lines/Model**	**Metabolic targets**	**References**
Andrographolide	*Andrographis paniculate commonly known as Green chireta* (Acanthaceae)	T-cell acute lymphoblastic leukemia (T-ALL Jurkat cells)	Inhibits PI3K/Akt and increases p38 MAPK pathways	[318]

Phytochemicals (Alkaloids)	Sources	Cancer cell lines/Model	Target	References
Artesunate	Derivative of artemisinin i.e. from *Artemisia annua* commonly known as Sweet wormwood, Sweet annie, Sweet sagewort, Annual mugwort or Annual wormwood (Asteraceae)	Colorectal carcinoma cells (HCT116)	Downregulates Acyl-CoA synthetase 5 (ACSL5), hydroxyacyl-coenzyme A dehydrogenase (HADH), and FASN.	[319]
Asiatic acid	*Centella asiatica* commonly known as Gotu Kola, Indian pennywort, Asiatic pennywort (Apiaceae)	Ovarian cancer cells (SKOV3 and OVCAR-3)	Suppresses PI3K, Akt and mTOR signaling	[320]
Auraptene*	*Citrus hassaku Hort ex Tanaka* commonly known as Hassaku orange (Rutaceae)	Renal cell carcinoma (RCC4) Gastric cancer cells (SNU-1)	Degrades HIF1α protein. Downregulates mTOR signaling via PI3K/Akt pathway Activates p53 signaling.	[224] [321]
Betulinic acid	Bark of *Betula papyrifera* commonly known as Canoe Birch, Paper Birch (Betulaceae)	Bladder cancer cells (KU7 and 253JB-V) Cervical cancer cells (HeLa) Breast cancer cells (MCF-7, MDA MB-231) and *in vivo* breast cancer xenograft models	Decreases EGFR and Akt protein expression Downregulates PI3K/Akt pathway Generated ROS Decreases the expression of LDHA, PDK1 and c-myc Suppresses aerobic glycolysis via Cav-1/NF-ϰB/c-Myc pathway	[214] [211] [322]
Brachyantheraoside A8	*Stauntonia brachyanthera* commonly known as Huang la guo (Lardizabalaceae)	Breast cancer cells (HCC1806)	Inhibits GLS1 activity	[123]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Cacalol	*Cacalia delphiniifolia* commonly known as Momijigasa (Asteraceae) and from the roots of *Psacalium decompositum* commonly known as Indian bush (Asteraceae)	Breast cancer cells (MCF-7, MDA-MB-231) and *in vivo*	Blocks FASN mRNA expression and FASN protein level by downregulating AKT-SREBP pathway	[226]
Celastrol	*Trypterygium wilfordii Hook F.* commonly known as Thunder God Vine or Thunder Duke Vine (Celastraceae)	Cervical cancer cells (HeLa)	Decreases glycolysis, TCA cycle, amino acid metabolism protein biosynthesis	[323]
Crocetin*	Flower of *Crocus sativus* commonly known as Saffron (Iridaceae)	Lung (A549) cervical cancer cells (HeLa)	Inhibits LDH5 and LDHA activity	[84]
Cryptotanshinone	Salvia miltiorrhiza commonly known as red sage, Chinese sage, tan shen, or danshen (Lamiaceae)	Colon cancer cells (HepG2) and *in vivo*	Induces autophagic cell death by AMPK/mTOR	[243]
Galbanic acid	Rhizome of *Ferula ovina Boiss.* (Apiaceae)	Lung (A549) and ovarian cancer cells (NIH: OVCAR-3)	Downregulates EGFR/HIF1α mediated GLUT1 and ENO1 mRNA expression	[37]
Ingenol Mebutate*	*Euphorbia peplus* commonly known as milkweed (Euphorbiaceae)	Colon cancer cells (Colo205)	Activates PKC d and reduces PKCa Decreases PI3K signaling	[324]
Kahweol*	*Coffea arabica* commonly known as Arabian coffee (Rubiaceae)	Breast cancer cells (BT-549, MDA-MB-231, HER2 positive MDA-MB-453 and SKBR3)	Downregulates FASN and SREBP-1c activity Downregulates p-Akt and mTOR Decreases HER2 mRNA, protein levels and activity in SKBR3 cells.	[227]

Phytochemicals (Alkaloids)	Sources	Cancer cell lines/Model	Target	References
Lupeol*	*Abronia villosa* commonly known as Desert sand-verbena or Chaparral sand-verbena (Nyctaginaceae), *Acacia visco* (Fabaceae)	Hepatocellular carcinoma cells (HCCLM3, HepG2)	Reduces expression of Akt1, PI3K, β-catenin, c-Myc and cyclin D1 mRNA Decreases BDNF and GSK-3β mRNA expression.	[325]
Maslinic acid*	Wax-like coatings of fruit-*Olea europaea* commonly known as Olives (Oleaceae)	ApcMin/+ mouse model of colon cancer	Decreases Akt 1 and glycogen synthase kinase 3β (GSK3b) involved in Wnt/β-catenin signaling	[326]
Oleanolic acid*	Fruit of *Olea europaea* commonly known as Olives (Oleaceae), *Phytolacca americana* commonly known as American pokeweed, Poke sallet, or Poke salad, (Phytolaccaceae)	Prostate carcinoma (PC-3) and breast cancer cells (MCF-7) and *in vivo*	Activates AMPK Inhibits mTOR Inhibits protein synthesis, aerobic glycolysis, and lipogenesis	[327]
Oridonin	*Rabdosia rebescens* (lamiaceae)	Colorectal cancer cells (SW480) Melanoma cell (OCM-1 and MUM2B)	Downregulates GLUT1 and MCT1 expression Downregulates FASN expression and increases Bcl-2 expression	[328] [329]
Pristimerin	*Maytenus ilicifolia* commonly known as Espinheira Santa (Celastraceae)	Breast cancer cells (SKBR3)	Decreases FASN protein level and FASN activity	[172]
Pseudolaric acid B	Root and stem bark of *Pseudolarix kaempferi* commonly known as Golden larch (Pinaceae)	Gastric adenocarcinoma cells (SGC7901), drug resistant cells (SGC7901/ADR) and *in vivo*	Downregulates COX-2/PKC- α /p-Gp/MDR-1 signaling pathway	[330]

Phytochemicals (Alkaloids)	**Sources**	**Cancer cell lines/Model**	**Target**	**References**
Plectranthoic acid	*Ficus microcarpa* commonly known as Chinese banyan, Malayan banyan, (Moraceae)	Prostate cancer cells (DU145, PC3 and NB26)	Activates AMPK Inhibits mTOR and 70S6K	[240]
Pomolic acid	Leaves of *Cecropia pachystachya* (Urticaceae)	Breast cancer cells (MCF-7)	Activates AMPK pathway, Decreases expression of FASN, ACC Inhibits mTOR and p70S6K	[155]
Tanshinone IIA	*Salviae miltiorrhizae* commonly known as Chinese sage, tan shen (Lamiaceae)	Leukemia cells (KBM-5)	Induces autophagic cell death by AMPK/mTOR/p70S6kinase	[241]
Triptolide	*Tripterygium wilfordii Hook.f* commonly known as Thunder God Vine (Celastraceae)	Breast cancer cells (MCF-7 and MDA-MB-468)	Downregulates Akt pathway via MDM2/REST pathway	[331]
Thymoquinone*	Seed oil of *Nigella sativa* commonly known as Black caraway, Black cumin or Kalonji (Ranunculaceae)	Pancreatic cancer cells (MIA PaCa-2 and PANC-1)	Downregulates PKM2 expression	[80]
Ursolic acid	Leaves of *Eriobotrya japonica* commonly known as Japanese MedlarJapanese or Plum Loquat (Rosaceae)	Breast cancer cells (MCF-7, MDA-MBA-231)	Inhibits PI3K/Akt /mTOR and STAT3 Downregulates the expression of JNK, MMPP-2, c-Fos, C-Jun, NF-kBp65	[332]
Widdrol	*Juniperus sp* (Cupressaceae)	Colon cancer cells (HT-29)	Induces apoptosis via AMPK pathway activation	[242]
Phytochemicals (Miscellaneous)	**Sources**	**Cancer cell lines/Model**	**Metabolic targets**	**References**
Cinnamic acid derivatives (e.g., α–cyano-4-hydroxy cinnamic acid)*	Stem bark of genus *Cinnamomum* (Lauraceae)	Human melanoma cell line DB-1	Inhibits MCT1 activity	[95]

Phytochemicals (Alkaloids)	Sources	Cancer cell lines/Model	Target	References
Flavokawain B	*Piper methysticum* commonly known as Ava, Ava Pepper, Intoxicating Pepper, Kawa Awa, Kawa Kawa, Wati, Yogona, Waka (Piperaceae)	Human thyroid cancer cells (TCa)	Activates AMPK and Inhibits mTOR pathway	[333]
Furanodiene	*Curcuma wenyujin* commonly known as Curcuma Rhizome, Zedoary rhizome, Zedoaria (Zingiberaceae)	Breast Doxorubicin resistant cells (MCF-7) Breast cancer cells (MDA-MB-231)	Induces the expression of p-AMPK and decreases downstream intermediates ACLY, GSK-3β and ATP level Inhibits PI3K/Akt pathway and MMP-9	[149] [334]
Graviola extract and its annonaceous acetogenins (Annona Muricata)	*Annona muricata* commonly known as Soursop (Annonaceae)	Pancreatic cancer cells (FG/COLO357 and CD18/HPAF)	Inhibits glucose uptake Decreases expression of HIF1α, NF-ϰB, GLUT1, GLUT4, HK2, LDHA, Akt and ERK	[335]
Ixocarpalactone A*	*Physalis ixocarpa* commonly known as Tomatillo (Solanaceae)	Colon cancer (SW1990), breast cancer (MCF-7) and cervical cancer (HeLa) cells	Inhibits PHGDH activity	[141]
Methyl jasmonate	Derived from jasmonic acid as found in many plants	Colon cancer (CT-36), B-cell leukemia (BCL1), acute human T-lymphoblastic leukemia cells (Molt-4)	Inhibits HK1 and HK2 by detachment from mitochondria. Inhibits Aldo-keto reductase 1 (AKR1) and 5-lipoxygenase (5-LOX), ATP synthesis, blocks OXPHOS	[336]
Phenethyl isothiocyanate (PEITC)	Found in Brassicaceae family	NSCLC (L9981)	Induces apoptosis via MAPK pathway	[337]
Physapubescin	From the genus *Physalis* (Solanaceae)	HCC827-ER HT1080 SW1990 and HCC827-ER	Inhibits GLS1 activity Inhibits GLS1 activity	[124] [125]

Phytochemicals (Alkaloids)	Sources	Cancer cell lines/Model	Target	References
Secoiridoid decarboxymethyl* oleuropein aglycone (SDOA)*	Fruit of *Olea europaea* (Oleaceae)	Breast cancer cells (SUM159) Glioma cancer cells (U251 A172) Colorectal cancer cells (HT-29)	Inhibits mTOR by blocking its ATP domain Inhibits p-Akt and Decreases MMP-9 Inhibits HIF1α protein expression	[338] [339] [340]
Shikonin and its enantiomeric isomer alkannin (Arnebia sp., Alkanna tinctoria)	*Lithospermum erythrorhizo* commonly known as Purple gromwell, Red gromwell, Red-root gromwell or Redroot lithospermum (Boraginaceae)	MCF-7, MCF-7/Adr, MCF-7/Bcl-2, MCF-7/Bcl-x(L) and A549 cell lines Skin epidermal cells (JB6 P+)	Inhibits PKM2 activity Inactivates PKM2 via activation of AMPK	[76] [77]
Sulforaphane*	*Glycine max* (Fabaceae)	Ovarian cancer cells (A2780 and OVCAR)	Inhibits Akt and c-Myc	[341]
α-λινολενις αςιδ (φρομ φλαξσεεδ) *	Seeds of *Linum usitatissimum* commonly known as Flax or Linseed (Linaceae)	Mice with MCF-7 tumors	Reduction of Akt	[342]
α-μονγοστειν*	*Garcinia mangostana* commonly known as Mangosteen (Clusiaceae)	BxPc-3, Panc-1, and hTERT-HPNE cells	Suppresses FASN activity and expression	[343]
[6]-Gingerol*	*Zingiber officinale* commonly known as Ginger (Zingiberaceae)	SW-480 and HCT116	Inhibits ERK1/2/JNK/AP-1 pathway	[229]

* Dietary phytocompounds

Abbreviations

TCA: tricarboxylic acid cycle; OXPHOS: oxidative phosphorylation; GSH: reduced state of glutathione; ROS: reactive oxygen species; PPP: pentose phosphate pathway; NAPH+H^+: nicotinamide adenine dinucleotide phosphate hydrogen; R5P: ribose-5-phophate; NAD: nicotinamide adenine dinucleotide; G6P: glucose 6-phosphate; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; PGAM1: phosphoglycerate mutase 1; 3PG: 3-phosphoglycerate; 3-Ppyr: phosphohydroxypyruvate; 2PG: 2-phosphoglycerate; mTORC1: mammalian target of rapamycin complex 1; Ru-5-P: ribulose 5-phosphate; PGK: phosphoglycerate kinaseLDH: lactate dehydrogenase; TKT: transketolase; TALDO: transaldolase; F6P: fructose-6-phosphate; HK: hexokinase; HIF1α: hypoxia-induced factor 1; GLUT : glucose transporter ; PGK1: phosphoglycerate kinase 1; F6P: fructose-6-phosphate; G3P: glyceraldehyde-3-phosphate; PEP: phosphoenolpyruvate; 6-PG: 6-phosphoglucolactone; R-5-P: Ribose-5-phosphate; PGI: phosphoglucose isomerase; PFK1: phophofructokinase-1, FBP1: fructose-1,6-bisphosphatase, PK: pyruvate kinase, G6PD: glucose-6-phosphate

dehydrogenase; 6-PGD: 6-phosphogluconate dehydrogenase, PFKFB: 6-phosphofructo-2-kiase/fructose-2,6-biphosphatase; NSCLC: non-small cell lung cancer cell line; CML: chronic myeloid leukemia; NADPH+H^+: nicotinamide adenine dinucleotide phosphate hydrogen; GLUT : glucose transporter ; HIF1α : hypoxia-inducible factor 1- α HK: hexokinase; G6P: glucose-6-phosphate; PPP: pentose phosphate pathway; PFK1: phophofructokinase1; F6P: fructose-6-phosphate; PFKP : phophofructokinase platelets; EGCG : epigallocatechin gallate; ALDO : aldolase; PGAM: phosphoglycerate mutase; ENO : enolase; G3P: glyceraldehyde-3-phosphate; 3PG: 3-phosphoglycerate; 2PG: 2-phosphoglycerate; PEP: phosphoenolpyruvate; PKM2: pyruvate kinase-2; TCA: tricarboxylic cycle; mTOR: mammalian target of rapamycin; LDH: lactate dehydrogenase; MCT: monocarboxylate transporter; G6PD: glucose-6-phosphate dehydrogenase; TKT: transketolase; F6P: fructose-6-phosphate; TALDO: transaldolase; Ru-5-P: ribulose 5-phosphate; PGK1: phosphoglycerate kinase 1; OXPHOS: oxidative phosphorylation; SLC1A5: solute carrier family 1 member 5; GLS: glutaminase; αK: α-ketoglutarate; GLUD: glutamate dehydrogenase; PHGDH: phosphoglycerate dehydrogenase; 3-PPyr: phosphohydroxypyruvate; PSAT1: phosphoserine aminotransferase 1; SHMT: serine hydroxymethyltransferase; FAs: fatty acid synthesis; ACLY: ATP citrate lyase; AMPK: AMP-activated protein kinase; ACC: acetyl CoA carboxylase; FASN: fatty acid synthase; HER2: human epidermal growth factor receptor 2; SREBP-1c: sterol regulatory element-binding protein-1c; ERK: extracellular signal-regulated kinase; PI3K: phosphoinositide 3-kinase; COX-2: cyclooxygenase-2; RTK: receptor tyrosine kinase: EGFR: epidermal growth factor receptor; PTEN: phosphatase and tensin homolog; VEGF: vascular endothelial growth factor; TFs: transcription factors; MDM2: mouse double minute 2 homolog; LKB1: liver kinase B1.

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