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Phytochemicals regulate cancer metabolism through modulation of the AMPK/PGC-1α signaling pathway

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Abstract

Background Due to the complex pathophysiological mechanisms involved in cancer progression and metastasis, current therapeutic approaches lack efficacy and have significant adverse effects. Therefore, it is essential to establish novel strategies for combating cancer. Phytochemicals, which possess multiple biological activities, such as antioxidant, anti-inflammatory, antimutagenic, immunomodulatory, antiproliferative, anti-angiogenesis, and antimetastatic properties, can regulate cancer progression and interfere in various stages of cancer development by suppressing various signaling pathways.

Methods The current systematic and comprehensive review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria, using electronic databases, including PubMed, Scopus, and Science Direct, until the end of December 2023. After excluding unrelated articles, 111 related articles were included in this systematic review.

Results In this current review, the major signaling pathways of cancer metabolism are highlighted with the promising anticancer role of phytochemicals. This was through their ability to regulate the AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) signaling pathway. The AMPK/PGC-1α signaling pathway plays a crucial role in cancer cell metabolism via targeting energy homeostasis and mitochondria biogenesis, glucose oxidation, and fatty acid oxidation, thereby generating ATP for cell growth. As a result, targeting this signaling pathway may represent a novel approach to cancer treatment. Accordingly, alkaloids, phenolic compounds, terpene/terpenoids, and miscellaneous phytochemicals have been introduced as promising anticancer agents by regulating the AMPK/PGC-1α signaling pathway. Novel delivery systems of phytochemicals targeting the AMPK/PGC-1α pathway in combating cancer are also highlighted in this review.

Keywords Cancer, Metabolism, Phytochemicals, AMPK, PGC-1α

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Introduction

Cancer is one of the major causes of death worldwide. There are several manifestations of this deadly disease, such as lumps, unusual bleeding, protracted coughing, weight loss, and decreased appetite [1–3]. Factors effective in causing cancer include smoking, obesity, an unhealthy diet, excess alcohol consumption, lack of exercise, sickness, exposure to ionizing radiation and environmental pollutants, or infection with viruses, bacteria, and certain parasites. Cancer occurs due to neoplastic growth in an irregular manner, which often forms a mass of cancer cells [4–6]. Under physiologic conditions, complex signaling pathways are involved in the development of cancer. Oxidative stress, apoptosis, autophagy, and inflammation are the most important pathways that affect cancer, engaging pro-inflammatory cytokines and apoptotic mediators. Therefore, the control of regulatory mechanisms, such as the release of cytokines or chemokines, oxidative stress and the process of apoptosis, has a significant function in the management of cancer [7]. Studies have demonstrated that several signaling pathways have considerable function in cancer pathogenesis. These include the Ras/extracellular signal-regulated protein kinase (ERK), phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways [8]. Several other dysregulated signaling pathways are responsible for cancer metabolism such as carbohydrate, lipid, and protein metabolism. An altered metabolism may advance the proliferation and survival of cancer cells [9].

Cancer treatments include a variety of approaches tailored to improve patient outcomes and effectively manage the disease, depending on the specific type and stage of cancer. These approaches include surgical intervention, chemotherapy, targeted therapy, radiation therapy, hormone therapy, and immunotherapy, as well as complementary and integrated therapies, such as herbal treatments. Healthcare professionals select treatment modalities based on the patient's clinical status, medical history, and potential side effects. The appropriate and judicious combination of these modalities may lead to improved treatment outcomes and reduced adverse effects, ultimately contributing to an enhanced quality of life for the patient. Over the years, more than 300 chemotherapeutic drugs have been used in the treatment of cancer, such as taxol, vincrictine, *cis*-platin, 5-fluorouracil, bevacizumab, erlotinib, nivolumab, ipilimib, santin, and olaparib. However, these drugs are very toxic and may create resistance, which leads to tumor recurrence and metastasis [10]. Therefore, alternative treatment methods, such as the use of bioactive plant secondary metabolites (phytochemicals) should be considered [1, 11].

Phytochemicals, also known as plant secondary metabolites, have been the focus of extensive research in recent years due to their potential health benefits, including their anticancer properties. Phytochemicals may be obtained from various sources, including whole grains, fruits, vegetables, nuts, and spices [12]. Phytochemicals have remarkable chemical diversity and possesses various bioactivities, including, anti-inflammation, antioxidative, antimicrobial, antiviral and antiaging properties, and have been widely investigated for their anticancer potential [13]. Preclinical studies have indicated that phytochemicals are able to modulate various oncogenic and oncosuppressive cell signaling pathways, such as the PI3K/Akt/mTOR/P70S6K [14], peroxisome proliferator-activated receptor (PPARs) [15], nuclear factor erythroid 2-related factor 2 (Nrf2), Janus kinase (JAK)–signal transducer and activator of transcription (STAT) [16], hypoxia-inducible factor-1 (HIF-1), transforming growth factor-beta (TGF-β) [17], toll-like receptors (TLR)/nuclear factor-κB (NF-κB)/Nod-like receptor protein (NLRP), MAPK, ERK, and p38 signaling pathways [18–20]. Phytochemicals also target multiple dysregulated pathways of cancer metabolism, such as carbohydrate, lipid, and protein metabolism. This ability of phytochemicals to target multiple pathways involved in cancer development and progression is one of the key reasons why they may have potential in cancer treatment. Traditional cancer therapies often target specific molecular pathways, but phytochemicals simultaneously modulate multiple signaling pathways, potentially making them more effective in combating the complex nature of cancer. Phytochemicals not only have direct anticancer effects, but also influence the metabolic pathways within cancer cells. For instance, researchers have discovered that several phytochemicals hinder cancer cell growth by disrupting crucial metabolic processes, such as carbohydrate metabolism, lipid metabolism, and protein synthesis [21]. By disrupting these essential pathways, phytochemicals can potentially starve cancer cells of the nutrients they need to survive and proliferate.

The use of phytochemicals has unique advantages for medical applications, providing a novel approach to cancer prevention and improving patient outcomes and treatment efficacy, resulting in more effective treatment strategies. Additionally, studies have demonstrated that phytochemicals are a cost-effective option that mitigates the common adverse side effects of traditional treatments and decreases drug resistance, providing a safer and more patient-friendly alternative. These benefits are crucial in the field of medicine, where personalized and targeted therapies are essential for optimizing patient care and improving overall health outcomes. In this line novel analytical methodologies (e.g., Liquid chromatography-tandem mass spectrometry) is necessary to identify

active phytochemicals of traditional medicine [22]. In addition, novel drug delivery systems will pave the road in combating different diseases [23, 24].

Numerous phytochemicals are being tested in vitro and in vivo experiments. Moreover, various clinical trials also utilize phytochemicals in combination with other approved drugs. These clinical trials involve the rigorous testing and evaluation of phytochemicals in real-world settings, providing valuable insights into the effectiveness and safety of plant ingredients. By integrating plant-based therapeutic appriaches with established treatments, it is possible to enhance the overall efficacy and outcomes of clinical trials, ultimately contributing to the advancement of medical science and patient care.

Cancer metabolism refers to the unique metabolic characteristics and alterations that occur in cancer cells when compared to normal cells. Cancer cells exhibit specific metabolic requirements and mechanisms to maintain their rapid growth and reproduction. Metabolic reprogramming has been established as the hallmark of cancer. Key aspects of cancer metabolism are heightened glucose absorption and glycolysis, regardless of oxygen availability (the Warburg effect), modified lipid processing, elevated glutamine utilization, and alterations in mitochondrial activity. These pathways provide cancer cells with a flexible metabolic characteristic and offer chances for survival for cancer cells under stress. Comprehending cancer metabolism is crucial to developing specific treatments that capitalize on the metabolic defects of cancer cells without damaging normal cells. Researchers are investigating the disrupted metabolic pathways in cancer cells to pinpoint possible drug targets and create novel therapeutic approaches. There are several signaling pathways that play a crucial role in regulating cancer cell metabolism. Some of the key signaling pathways involved in cancer cell metabolism include, PI3K/Akt/mTOR pathway, AMPK, HIF, p53, Wnt/β-catenin, and Nrf2 pathway. These signaling pathways interact with each other and with other cellular processes to coordinate the metabolic reprogramming that occurs in cancer cells. Targeting these pathways with specific inhibitors or modulators holds promise for developing novel therapeutic strategies to selectively target cancer metabolism.

As a critical signaling pathway, 5´-adenosine monophosphate-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), has recently been highlighted as a promising target in combating cancer [25]. The dysregulation of the AMPK/PGC-1α axis is associated with many types of malignancies and may affect tumor development, metastasis, and treatment outcomes. In cancer cells, alterations in AMPK and PGC-1α activity can lead to metabolic reprogramming that supports the high energy demands of rapidly proliferating cells. For example, AMPK activation regulates mTOR signaling and inhibits cell growth, whereas PGC-1α overexpression promotes mitochondrial function and accelerates oxidative metabolism. The modulation of the AMPK and PGC-1α signaling pathways by phytochemicals presents a novel approach to targeting cancer cells and disrupting their metabolic processes. By elucidating the complex processes and mechanisms by which phytochemicals interact with these keys signaling pathways, researchers aim to develop innovative strategies for combating cancer and improving patient outcomes.

The influence of phytochemicals on cancer cell metabolism via altering the AMPK/PGC-1α signaling pathway has not been thoroughly investigated in existing literature, and no previous reviews have been published in this area. The aim of this review is to explore the impact of phytochemicals on the regulation of cancer metabolism through modulation of the AMPK/PGC-1α signaling pathway. By examining the current literature and summarizing the findings from in vitro and in vivo studies, we aim to elucidate the molecular mechanisms underlying the anticancer effects of phytochemicals targeting this key metabolic pathway. Ultimately, this review aims to provide a systematic review of the therapeutic potential of phytochemicals in cancer treatment and highlight their role in modulating cellular metabolism for improved patient outcomes. It's the first systematic review on the promising anticancer role of phytochemicals through the regulation of AMPK/PGC-1α signaling pathway. We have also summarized various novel drug delivery systems for phytochemicals targeting AMPK/PGC-1α pathway and combat cancer.

The core role of AMPK/PGC-1α signaling pathway in cancer metabolism

The AMPK, a type of enzyme called a serine/threonine kinase, has remained similar in various species through evolution. It has a significant function in controlling cellular energy and redox homeostasis and affects all aspects of energy metabolism and mitochondrial biogenesis [26]. The AMPK enzyme has a heterotrimeric structure consisting of three subunits: α, β, and γ. The α subunit plays a catalytic role, the β subunit has a scaffolding function, and the γ subunit is a regulatory component. There are at least 12 known isoforms of AMPK identified in various cells and tissues [27, 28]. The α subunit is present in both the cell membrane and nucleus [29]. The N-terminus of the β subunit binds to carbohydrates and inhibits AMPK signaling, affecting glycogen synthesis in the liver and muscle [28, 30]. The γ subunit connects to the β subunit through its N-terminus and helps activate the enzyme [31]. AMPK gets activated when adenosine triphosphate (ATP) production decreases due to factors

like hypoxia, or low oxygen, or lack of nutrients [32]. This phosphorylation mediates by liver kinase B1 (LKB1), calcium/calmodulin-dependent protein kinase kinase-β (CaMKKβ), and protein phosphatase 2 C and 2 A (PP2C and PP2A) [33, 34]. However, evidence indicates that LKB1 has an important function in AMPK phosphorylation and activation in energetic stress conditions [33].

The activation of AMPK can cause inhibition of the anabolic pathway and stimulation of the catabolic pathway [34, 35]. Adenosine monophosphate (AMP) has a higher affinity for attachment to the γ subunit of AMPK than adenosine diphosphate (ADP) [33]. Furthermore, AMP, in contrast to ADP, can promote LKB1-induced AMPK phosphorylation [33]. In times of abundant energy, enzymes like TGF-β-activated kinase 1 (TAK1), PP2A, PP2C, and dependent protein phosphatase 1E (PPM1E) inactive AMPK through dephosphorylation [36].

Reactive oxygen species (ROS) can active AMPK signaling, through direct and indirect mechanisms. Direct activation takes place via S-glutathionylation of cysteines on the AMPK α and β subunits. While indirect activation is mediated by changes in the cellular ATP/AMP and ATP/ADP ratios [37]. Numerous studies indicate that the activation of AMPK could be a potential treatment for various cancer types by inhibiting cancer promoting metabolic processes, arresting the cell cycle, and acting as a cyclooxygenase-2 (COX-2) inhibitor, decreasing cancer stemness [38]. AMPK increases autophagy and mitophagy by activating UNC-51-like kinase 1 (ULK1) and death-associated protein 1 (DAP1), respectively.

AMPK starts the apoptotic program through the activation of p53, p21, p27 and retinoblastoma protein (pRb) arrests cell cycle through the inhibition of HUR and the concomitant activation of cyclin A, cyclin B1, and cyclin D1 [39–41]. AMPK inhibits metabolic pathways in tumor cells, such as the Warburg effect, depriving cancer cells of energy and fuels [42]. The activation of AMPK signaling results in the reduction of mammalian target of rapamycin complex 1 (mTORC1) via the phosphorylation of tuberous sclerosis complex 2, also known as tuberin (TSC2) and regulatory-associated protein of mTOR (RAPTOR) [43]. This process suppresses oncogenic signaling, thereby restricting the proliferation and migration of cancer cells [44]. Furthermore, AMPK activation induces autophagy, inhibits glycolysis, and promotes mitochondrial oxidative metabolism through mTORC inhibition [45]. AMPK phosphorylates and deactivates oncogenic yes-associated protein (YAP) through Hippo tumor suppressive signal during glucose deprivation [46]. Studies suggest that AMPK phosphorylates and counteracts the oncogenic activity of glioma-associated oncogene 1 (Gli-1), the central transcription factor that regulates cell proliferation and differentiation in the Hedgehog pathway, particularly in medulloblastoma [47]. The LKB1, also called serine/threonine kinase 11 (STK11), is a known activator of AMPK, is tumor suppressor that act via the inhibition of mTORC1, and its deactivation is indicated in various cancers, include lung adenocarcinoma [43].

In epigenetic reprogramming, AMPK affects DNA methylation by phosphorylating and activating the tumor suppressor TET methylcytosine dioxygenase 2 (TET2) at S99 [48]. Metformin, a biguanide antidiabetic drug, activates AMPK, leading to the phosphorylation of checkpoint blocker programmed cell death ligand 1 (PD-L1) at S195. This process causes PD-L1 degradation through endoplasmic reticulum-associated protein degradation (ERAD) and enhances antitumor immunity [49]. Metformin enhances the expression of NF-κB via the AMPK/SIRT1 pathway, ultimately resulting in cellular apoptosis [50]. AMPK-mediated phosphorylation of enhancer of zeste homolog 2 (EZH2) inhibits polycomb repressive complex 2 (PRC2) cancer-promoting function and associated with improved survival outcome in breast and ovarian cancer [51].

Numerous experimental evidence in rats supports the tumor-suppressor action of AMPK. First, the loss of AMPKβ1 in the prostate accelerates the onset of prostate adenocarcinoma [52]. Second, elevated ubiquitin conjugating enzyme E2 (UBE2O) expression in various cancers induced the degradation of AMPKα2, therefore increasing the development and spread of tumors [53]. Third, the loss of AMPKα1 in T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) accelerates the formation of leukemia and lymphoma [54]. Fourth, the inactivation of AMPKα1 promotes MYC (a hallmark of tumorigenesis)-driven lymphomagenesis by inducing HIF-1α-dependent aerobic glycolysis [43]. Fifth, depleting AMPKβ1 accelerates the onset of T-cell lymphoma after the inactivation of the p53 gene [43]. Finally, MAGE-A3/6-TRIM28, a cancer-specific ubiquitin ligase, induces the ubiquitination and degradation of AMPK. This process promotes mTOR signaling and contributes to malignant transformation in lung, breast, and colon tissues [55].

There are conflicting perspectives on whether AMPK actions may function in cancer development. AMPK plays a role in metabolic adaptation by participating in the signaling pathways associated with metabolic stress in tumor microenvironment (TME), which include nutrient starvation, matrix detachment, oxidative stress, and hypoxia [34]. As a result, activating AMPK may enhance the resistance of tumor cells to metabolic stress and maintain ATP levels by reprogramming energy metabolism [25, 34]. One study indicates that in low glucose conditions, the AMPK-p38-PGC-1α pathway induces metabolic homeostasis in cancer cells [56]. AMPK provides the metabolic requirements for cancer cells that are

growing during autophagy, thus promoting cell growth and survival. On the other hand, autophagy causes chemoresistance in cancer cells [25]. AMPK enhances mitochondrial respiration through MYC, resulting in efficient glutamine metabolism for energy production [34]. It has been reported that the effects of AMPK on tumor development may depend on the nutrient levels in the TME. In the absence of nutrients, AMPK may promote tumor growth and support survival, while in the presence of nutrients, AMPK may suppress tumor development [57]. AMPK phosphorylates and deactivates acetyl-CoA carboxylases 1/2 (ACC1/2) to maintain nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) homeostasis, thereby promoting cancer cell survival and breast cancer progression [58].

AMPK is involved in EGF/Akt signaling, a process disrupted in malignant transformation and cancer metastasis through the activation of Akt, leading to oncogenic procedure [59]. AMPK promotes T-ALL cells survive by inhibiting aerobic glycolysis, increasing mitochondrial oxidative metabolism, and decreasing metabolic stress and apoptosis [45]. During metabolic stress, AMPK activation causes resistance to oxidative stress and DNA damage in tumor cells in the bone marrow [60]. Studies indicated that the activation of AMPK-SKP2-Akt axis and AMPK-PDHc cascade is linked to a dismal prognosis in breast cancer [61]. Sirtuin 3 (SIRT3), a mitochondrial protein that removes acetyl groups, increases AMPK expression and leads to increased lymph node metastasis in cervical cancer cells. In colorectal cancer cells, non-muscle myosin IIA (NMIIA) triggers AMPK signaling, promoting the expression of mTOR, which increases growth and invasion [50]. Experimental evidence in rats supports the continuous function of AMPK in cancer advancement. In an acute myeloid leukemia (AML) model, AMPK inactivation decreased leukemia-initiating cells (LIC) and decelerated leukemogenesis [60]. In a lung cancer model, AMPK loss diminished tumor development, underscoring the essential role of AMPK activation in tumorigenesis [62].

One of the key regulators of cell metabolism is a member of the PGC-1 transcriptional co-activator family, known as PGC-1α. The PGC-1 family has three members: PGC-1α, PGC-1β, and PGC-1-related coactivator (PRC) [63]. PGC-1α primarily regulates mitochondrial biogenesis (mitobiogenesis) and function, including oxidative phosphorylation (OXPHOS), fatty acid/lipid metabolism, and the regulation of ROS levels [64]. The activation of PGC-1α in brown adipose tissue and in skeletal muscle contributes to an increase in metabolic activity and heat production as a response to cold exposure, exercise, and fasting [63, 65]. The PGC-1α predominantly localizes within metabolically active tissues, including the liver, heart, muscles, kidneys, adipose tissue, and the brain [66]. PGC1α activity and mitochondrial function decline with age, potentially contributing to age-related cancer. However, exercise and a calorie-limit diet have been shown to enhance PGC1α activity, promoting healthy aging and potentially acting as protective factors against age-related cancer [64].

Numerous studies indicate the expression of PGC-1α is closely associated with cancer progression. PGC-1α has a function in maintaining metabolic homeostasis in microenvironments with high energy demands and restricted nutrition supplies in cancer cells. Overexpression of PGC-1α is identified in various type of cancers [67]. Similar to normal cells, PGC-1α mainly influences mitochondrial respiration, detoxification ROS, fatty acid oxidation (FAO), and glucose- or glutamine-derived lipogenesis in cancer cells [68, 69]. However, literature contains conflicting reports, as both increased and decreased levels of PGC1α expression were related to cancer and a worse prognosis. Even within a specific cancer, include breast cancer, there exist discrepancies in the reported PGC1α levels [64]. Melanoma cells that overexpress PGC-1α demonstrate elevated mitochondrial oxidative metabolism, effective detoxification of ROS, dependence on OXPHOS, and resistance to apoptosis and chemotherapy [63, 70, 71]. In contrast, melanoma cells expressing low levels of PGC-1α, depend on glycolysis to survive, making them more vulnerable to apoptosis induced by ROS [70]. Nevertheless, despite the enhanced proliferation and survival associated with PGC-1α overexpression, it concurrently suppresses the invasive properties of these cells [71]. Furthermore, in melanoma, BRAF and inhibition of mTORC1/2 inhibits the melanocyte lineage factor (MITF), which, in turn, downregulates PGC-1α and increases glycolytic metabolism [72].

Under metabolic stress, the switch from glucose to fatty acid usage helps cells survive and occurs in various cancer types. PGC-1α induces the transactivation of FAO genes via PPARα and sirtuin 1 (SIRT1) [67, 73, 74]. When cells are deprived of glucose, PGC1α breaks down, leading to the aggregation of ROS and apoptosis [75]. In nutrient deprivation conditions, p53 has both cytoprotective and cytotoxic functions, while PGC-1α regulates p53 stress-dependent transcription, enhancing its activation of genes for cell cycle arrest and metabolism [75, 76]. Receptor-interacting protein 1 (RIP1) regulates p53 via PGC-1α signaling. RIP1 inactivation reduces PGC-1α expression and OXPHOS, promoting glycolysis. Excessive glycolysis lowers nicotinamide adenine dinucleotide (NAD) levels, impairing DNA repair and activating p53-mediated cell growth inhibition [77]. MYC regulates glucose and glutamine metabolism, along with mitobiogenesis in cancer cells. C-MYC attaches to the promoter of PGC-1α and inhibits its transcription. The ratios of PGC-1α to MYC are associated with metabolic

phenotypes in tumors, including pancreatic ductal adenocarcinoma, ranging from OXPHOS-based to glycolytic [78, 79].

Pancreatic cancer stem cells express high levels of PGC-1α due to the absence of c-MYC. The strong expression of PGC-1α is implicated in mitochondrial respiration, as well as sensitivity to metformin treatment [78]. This ratio can be controlled by the transcription factor Forkhead box O3a (FOXO3a). Similar to PGC-1α, FoxO3a expression levels are correlated with cancer and adverse outcomes at both high and low levels [64, 80]. Estrogen-related receptor (ERR) and PGC-1α are downstream proteins of kinase suppressor of Ras 1 (KSR1), a molecule that promotes Ras-induced transformation in breast cancer [81]. PGC-1α can mimic the actions of the natural ligands that ERR typically binds to, even though ERRα itself doesn't bind to estrogens. Similar to PGC-1α, ERRα functions in the quick response to metabolic stress [64, 82]. The PGC-1α/ERRα axis can influence glucose, glutamate, and fatty acid metabolism, as well as the TCA cycle, thereby stimulating the proliferation of breast cancer cells, even in conditions of low nutrients or hypoxia. Furthermore, in breast tumors, the PGC-1α/ERRα axis is involved in angiogenesis, metastasis, and resistance to chemotherapy [64, 83]. High level of PGC-1α in mammary tumor cells induces dependence on the folate cycle for nucleotide synthesis and tumor proliferation [84]. Studies indicate that increased levels of PGC-1α, and its associated glutaminolysis genes, forecast a poor prognosis in breast cancer and demonstrate a negative association between the expression of PGC-1α and patient survival [83].

Evidence indicates a mutual influence and activation between androgen receptor (AR) and PGC-1α in prostate cancer. The androgen/AR/AMPK/PGC-1α signaling axis promotes mitochondria biogenesis, glucose oxidation, and FAO, which provides structural units and ATP for cancer cell growth [67, 85]. PGC-1α-mediated tumor suppression primarily occurs through the induction of cell death. In addition, PGC-1α plays a role in tumor suppression by enhancing antioxidant defense via the upregulation of enzymes, including manganese-dependent superoxide dismutase and Nrf2, which can help prevent oxidative DNA damage and the development of cancer [64, 86]. The function of PGC-1α in advanced tumor stages is hypothesized to be shaped by both the microenvironment and the metabolic conditions of the tumor [87]. Evidence indicates that PGC-1α has a function in promoting and inhibiting tumor progression, depending on the microenvironment and the metabolic conditions of the tumor [64]. For instance, one study demonstrated that in melanoma, treatments that inhibit BRAF upregulate PGC-1α and ID-2, its downstream target, leading to the suppression of metastasis-related genes [71]. In contrast, evidence suggests that the downstream effectors of PGC-1α, specifically β-oxidation and fatty acid/lipid metabolism, play an essential role in promoting metastasis [88]. Furthermore, chemoresistant metastatic cells exhibit heightened metabolic patterns involving both glycolysis and increased OXPHOS [64]. Expression of PGC is upregulated by AMPK, ERRα, and p53. In contrast, PGC is downregulated through hypermethylation.

To fully understand the mechanisms underlying PPARGC1A methylation and its possible therapeutic implications, more research is necessary, as the precise significance of this alteration in cancer is currently unclear [64, 67, 89, 90]. Glycogen synthase kinase-3β (GSK-3β) phosphorylates the PGC-1α protein, which is then degraded via the ubiquitin-proteasome pathway. The breakdown of the PGC process is inhibited by the nuclear protein necdin, a tumor suppressor, thus preserving OXPHOS integrity [64, 91]. Inflammatory cytokines, including TGF-β, tumor necrosis factor-α (TNF-α), interleukin- 6 (IL-6), and TNF-related weak inducer of apoptosis (TWEAK), suppress the expression of PGC1α [64, 92, 93]. The E3 ligase Parkin orchestrates the elimination of dysfunctional mitochondria via mitophagy. Deactivating mutations of Parkin result in the accumulation of ZNF746, a transcriptional repressor of PGC-1α. Numerous studies suggest the presence of Parkin deletions in various types of cancers [64, 94].

MicroRNAs (miRNAs or miR)-485, miR-485-3p, and miR-5p, along with miR-23a and miR-217, downregulate PGC-1α. However, these miRNAs are inhibited in certain tumors [95–97]. Finally, in various types of carcinomas, the expression of MYC is upregulated, subsequently inhibiting PGC1 through acetylation by general control non-depressible 5 (GCN5) enzyme. This finding reinforces the inverse relationship between MYC and PGC-1α [64]. Autophagy exhibits tumor-suppressive functions during early tumorigenesis, but it may support the survival of cancer cells in established tumors [64]. Mitophagy has an important function in normal tissue function but is implicated in tumor cell resistance to stress, hypoxia, and DNA damage [98, 99]. Recent studies indicated that melanoma has two types of cells, one with high levels of PGC-1α and the other with very low levels of PGC-1α. In breast cancer, PGC-1α activates PPARα, ERRα, Nrf1, and Nrf2, which leads to development of mitochondrial biogenesis and OXPHOS and can generate large amounts of ATP for tumor growth [100]. The function of PGC-1α in prostate cancer is similar to that of melanoma. It has been demonstrated that c-MYC directly regulates PGC-1α in pancreatic adenocarcinoma. C-MYC binds to the PGC-1α promoter and inhibits its transcription. Further, the ratio of c-MYC/PGC-1α controls the metabolic behavior of pancreatic cancer cells [63].

Methodology of literature search

Based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria, the current systematic and comprehensive review was conducted. Thus, a systematic literature search was performed through electronic databases, including PubMed, Scopus, and Science Direct for articles written in the English language. The last search was performed at the end of December 2023. The systematic search in databases was carried out by applying the following keywords: (tumor OR cancer OR malignant* OR neoplasm OR melanoma OR leukemia) found in title or abstract AND (herb* OR plant* OR natural product OR polyphenol* OR phenolic compound* OR terpene* OR alkaloid* OR flavonoid* OR glucosinolate* OR coumarin*) AND (AMPK OR PGC-1alpha OR PGC-1α) were found in title/abstract. The search process was executed by two independent researchers (S.F. and S.Z.M.). Accordingly, the review process was finalized through discussion with a senior author (A.B.) to resolve disagreements. Initially, 265 articles of the 717 articles, which were obtained from the primary electronic search, were excluded due to duplication. Furthermore, 101 review articles were excluded. To evaluate the results based on the title and full text of the articles, 177 and 61 unrelated articles were exempted, respectively. Finally, after excluding unrelated articles, 111 related articles were included in this systematic review (Fig. 1).

Anticancer phytochemicals targeting AMPK/PGC-1α signaling pathway

Several recent studies have highlighted the modulatory roles of various phytochemicals against AMPK/PGC-1α. Accordingly, alkaloids, phenolic compounds, terpenes/terpenoids, and several miscellaneous compounds have shown potential in the modulation of AMPK/PGC-1α pathway to combat cancer.

Phenolic compounds

The most widespread type of secondary metabolite in plants are phenolic compounds. Phenolic compounds are identified by an aromatic ring with a characteristic hydroxylated structure. There are two main types of phenolic compounds: non-flavonoids and flavonoids.

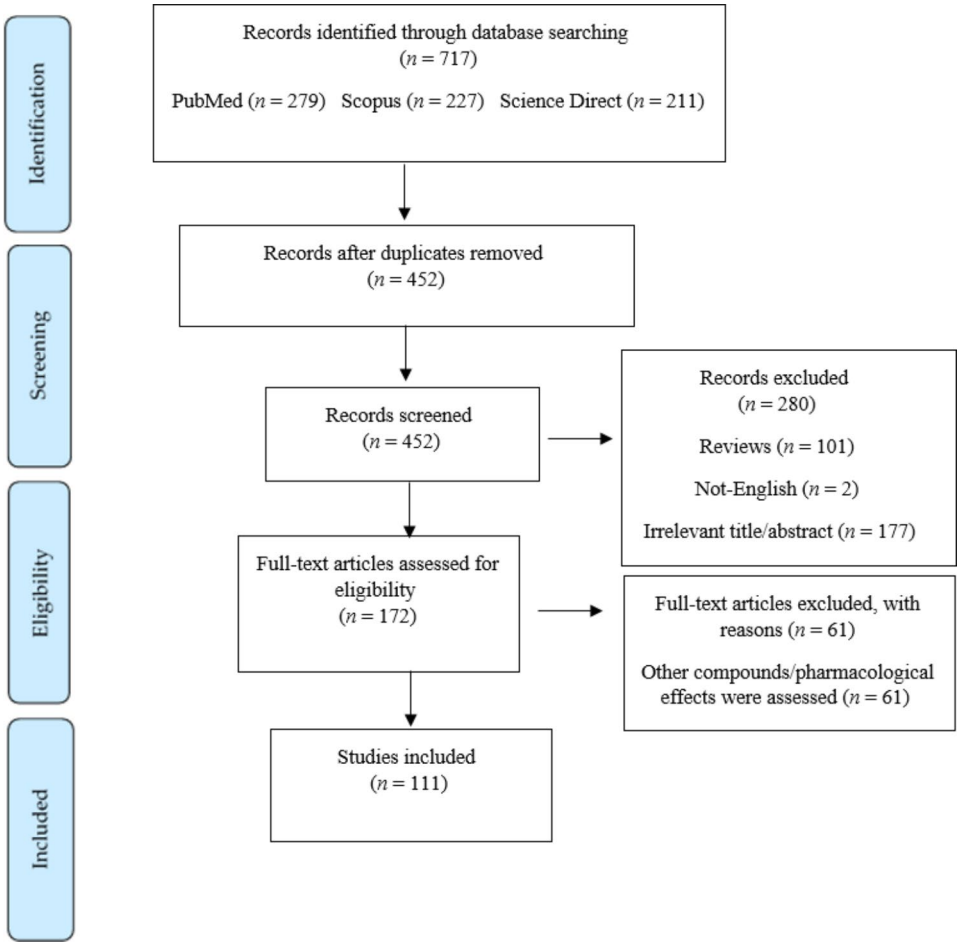

Fig. 1 PRISMA flowchart on the process of literature search and selection of relevant studies

Non-flavonoids include stilbenes, phenolic acids, tannins, coumarins, and lignans [101–104]. Flavonoids include flavanols, flavonols, flavones, flavanones, anthocyanidins, and isoflavonoids. Phenolic compounds display a variety of advantageous traits, such as antibacterial, anticancer, anti-inflammatory, cardioprotective, antiviral, and antimutagenic effects [101–104]. The most notable phenolic substances with anticancer properties are the subject of research presented in the following paragraphs, emphasizing the pathways linked to cancer metabolism, especially AMPK/PGC-1α, that underlie their anticancer action.

Resveratrol

Resveratrol (Fig. 2), an extensively researched polyphenol, possesses a broad range of pharmacological

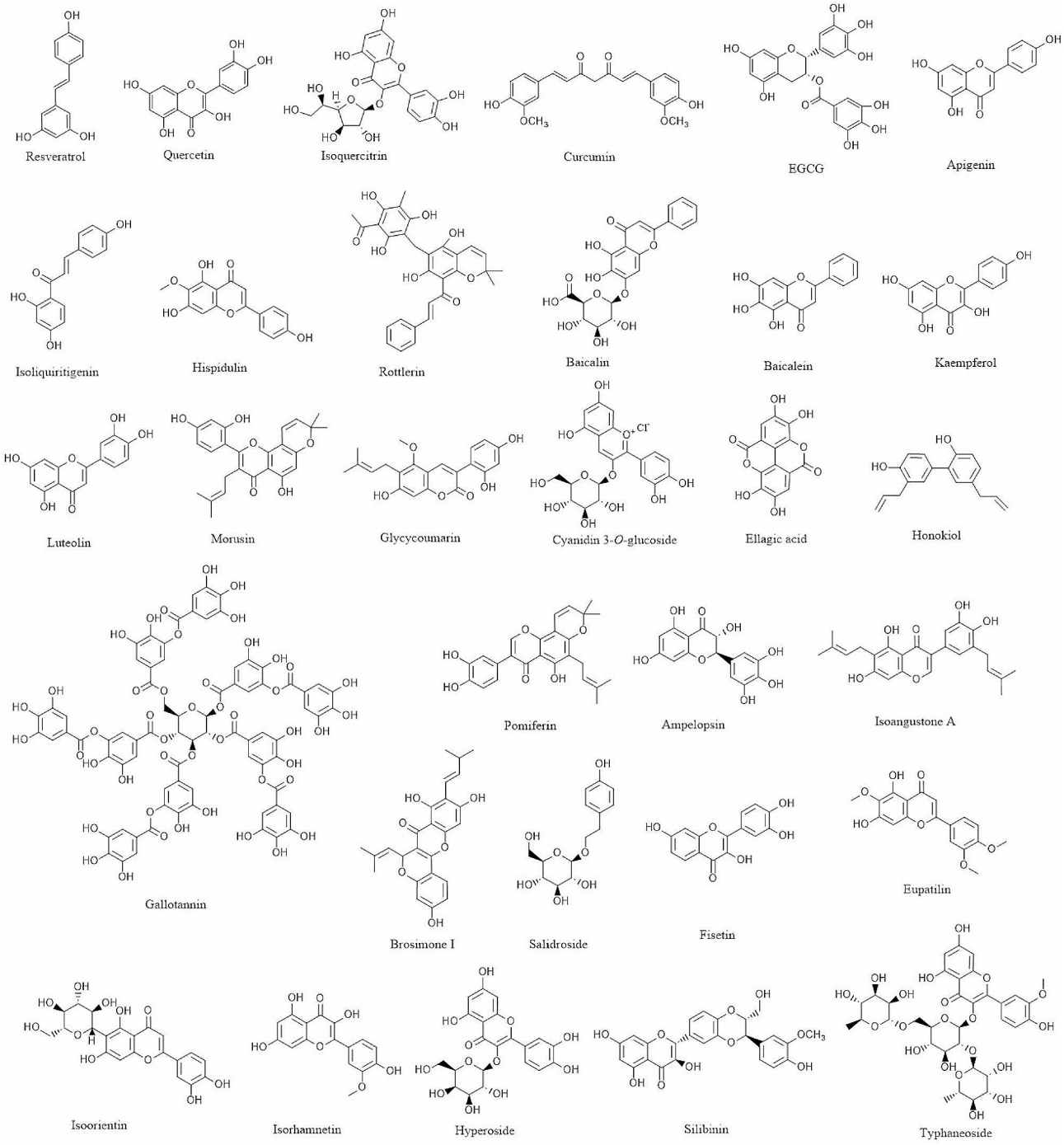

Fig. 2 Chemical structures of common phenolic compounds in the regulation of cancer metabolism AMPK/PGC-1α

properties, including anticarcinogenic, antibacterial, antioxidant, and anti-inflammatory effects [105–108]. Resveratrol induced apoptosis and inhibited the migration, proliferation, and invasion of in vitro and in vivo models of ovarian [109], breast [110], leukemia [111], colon [112, 113], prostate [114], and glioblastoma [115] cell lines via inhibiting glycolysis and fatty acid synthase. Resveratrol also reversed the Warburg effect and downregulating acetyl-CoA carboxylase-α via targeting pyruvate dehydrogenase, AMPK/mTOR, STIM1, NF-κB, AMPK-YAP, and c-Jun NH_2-terminal kinase (JNK)-mediated p62/SQSTM1 signaling pathways.

Quercetin

Quercetin (Fig. 2) is a naturally occurring flavonoid that is prevalent in fruits and vegetables and mechanistically displays antioxidant, anti-inflammatory, and anticancer properties in a variety of cellular and animal models. It has been shown to have biological actions that include anticancer, anti-inflammatory, immunoprotective, and antiviral activities [116–119]. Quercetin induced apoptosis and autophagy and suppressed viability, migration, and proliferation of various human cancer cell lines, such as lung [120], cervical [121], colon [122, 123], and breast [124] cancer. This was due to quercetin's ability to interfere with AMPK, epidermal growth factor receptor (EGFR), Akt/AMPK/mTOR, and SIRT1/AMPK signaling pathways.

Isoquercitrin

It has been reported that isoquercitrin (Fig. 2), a naturally occurring flavonoid found in various plant species, including *Mangifera indica* and *Rheum nobile*, significantly inhibited the proliferation of human liver cancer cells Huh7 and HepG2 [7, 125]. This was achieved through the inhibition of viability and colony growth, activation of the apoptotic pathway, and dysregulation of autophagy via the activation of the AMPK/mTOR/p70S6K pathway [126].

Curcumin

Curcumin (Fig. 2) is a phenol compound that can be extracted from Curcuma *longa* L. (Zingiberaceae family). Curcumin possesses significant biological activities, including antioxidant, anti-inflammatory, antimicrobial, neuroprotective, and anticancer activities [127–130]. It has been reported that curcumin inhibits growth, angiogenesis, and metastasis of 4T1, B16, CT26, A204, RD, SJCRH30, and SMMC-7721 cell lines by inducing apoptosis, fatal energetic impairment, and cell cycle arrest, mainly through the inhibition of NF-κB, suppression of ATP-synthase activity, and the activation of AMPK [131–133].

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) (Fig. 2) is a phenolic compound derived from green tea. It is well-known for its antioxidant, anti-inflammatory, neuroprotective, and antineoplastic properties [134–138]. EGCG exerted significant anticarcinogenic activity in H1299 lung cancer cells in vitro via targeting AMPK, mTOR, and Akt signaling [139]. Moreover, treatment with EGCG leads to apoptosis and suppression of the proliferation of HT-29 cells via interfering with COX-2, AMPK, vascular endothelial growth factor (VEGF), and Glut1-related pathways. In addition, treatment decreased the formation and synthesis of fatty acid, lipid droplets formation, energy metabolism, mitochondrial oxidation/glycolysis, lipolysis, and fatty acid β-oxidation was reported as the main anticancer activities of EGCG in both HCT-116 and HT-29 cancer cells [140, 141].

Apigenin

Apigenin (Fig. 2), a 4′,5,7-trihydroxyflavone, is predominantly found in plants and belongs to the Apium genus, including parsley and Chinese celery. This bioactive molecule exhibits a wide range of biological activities, including antiviral, anti-inflammatory, and antioxidant, and anticancer properties [128–130, 142]. Apigenin promoted autophagy and apoptosis in the H1975 cell line via targeting HIF-1α, c-MYC, glucose metabolism, Glut1, Glut4, monocarboxylate transporter 1 (MCT1), and AMPK [143]. Moreover, apigenin exert significant in vitro and in vivo anti-carcinoma activities in gastric cancer models by interfering with AMPK, ULK1, mTOR, p62, protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), and HIF-1α [144].

Isoliquiritigenin

Isoliquiritigenin (Fig. 2), a chalcone compound from the natural source locorice, has exhibited noteworthy biological activities, such as antitumor, antiviral, anti-inflammatory, antispasmodic, antidiabetic, and antioxidant effects [145, 146]. Treatment with isoliquiritigenin led to the inhibition of growth of colorectal cancer cells via regulating AMPK/mTOR-mediated glycolysis and HIF-1α signaling. Similarly, isoliquiritigenin promoted the suppression of Glut4-mediated glucose uptake by targeting PDHK1/PGC-1α in gastric cancer cells [147, 148].

Hispidulin

Hispidulin (Fig. 2) is a naturally occurring flavone isolated from the Artemisa and Salvia plants, which are widely accepted as traditional medicinal plants. Hispidulin possesses various biological activities, including antioxidant, antifungal, neuroprotective, and antiproliferative properties [105, 106, 149]. Hispidulin suppressed the growth, proliferation, and metastasis of hepatocellular

carcinoma cells by targeting ERK, AMPK, and AMPK/mTOR signaling pathways [150].

Rottlerin

Rottlerin (Fig. 2), a phytoconstituent with vital biological properties, such as anticancer, antibacterial, antifilarial, and anti-inflammatory activities, is found in the pericarp of *Mallotus philippensis*. Its multifaceted pharmacological effects against cancer are promising. Rottlerin promoted apoptosis and autophagy in prostate cancer cells by interfering with the AMPK and PI3K/Akt/mTOR signaling pathways [151]. Moreover, suppression of the Wnt/β-catenin and mTORC1 signaling pathways were noted to be the main antitumor effects of rottlerin in several in vitro models of breast and prostate cancer cells [152].

Baicalin and baicalein

Baicalin (Fig. 2) is a major bioactive glycosyloxyflavone that can be isolated from root of the *Scutellaria baicalensis* plant [153]. Baicalin has anticancer, hepatoprotective, anti-inflammatory, neuroprotective, cardioprotective, antioxidant, renal protective, and antibacterial advantages [154–156]. Baicalin exerts significant anticancer activity against several in vitro models of cancer, including non-small cell lung cancer (NSCLC) via regulating AMPK/Nrf2 and activating SIRT1/AMPK signaling [157, 158]. Baicalin can hydrolyzed to its metabolite and aglycone form, baicalein (Fig. 2), which has garnered significant attention from cosmetic, food, and pharmaceutical industries for its exceptional antioxidant, neuroprotective, anti-inflammatory, cardioprotective, anticancer, hepatoprotective, and antiviral properties [154–156]. Baicalein suppresses the growth of PC-3 and DU145 cells in in vitro models of prostate cancer by activating AMPK/ULK1 and inhibiting mTORC1 signaling [159]. In a similar study, baicalein promoted apoptosis and autophagy in glioblastoma cells (U251) through activation of AMPK [160]. Moreover, baicalein showed meaningful anticarcinoma activities in H1299, A549, PC9, and H1650 cell lines as in vitro models of NSCLC via facilitation of apoptosis and increasing p-ERK1/2, FOXO3a, and RUNX3 [161].

Other phenolic compounds

Kaempfero, (Fig. 2, a natural flavonol found in plants and plant-derived foods) [162], luteolin (Fig. 2, a flavonoid that is known for its antioxidant and anti-inflammatory properties) [163], morusin (Fig. 2, prenylated flavonoid produced from *Morus alba* Linn) [164], glycycoumarin (Fig. 2, a major coumarin in licorice) [165], and cyanidin 3-*O*-glucoside (Fig. 2, an anthocyanidin glycoside found in legumes) [166], are some of the known polyphenolic compounds that inhibit growth and glycolysis in various in vitro and in vivo models of hepatic carcinoma. This was achieved by inducing apoptosis, senescence, and cell cycle arrest through targeting AMPK, NF-κB, Akt, and CDK1/cyclin B. In addition, interfering with AMPK, HIF-1α, AMPK-mTOR, Sirt3/HIF-1α, PI3K/Akt/mTOR, and CaMKKβ-AMPK-mTOR signaling pathways was identified as the primary anticarcinogenic activity of ellagic acid (Fig. 2, a bioactive polyphenolic agent found *Punica granatum* L.) [167], honokiol (Fig. 2, a lignan polyphenol found in several Magnolia species) [168], gallotannin (Fig. 2, a specific type of hydrolyzable tannin present in vegetables) [169], and pomiferin (Fig. 2, a bioactive prenylated flavonoid isolated from *Derris montana*, *Citrus aurantium*) [170] in different in vitro and in vivo lung cancer models. Furthermore, multiple preclinical models of colon carcinoma illustrated the capability of other phenolic compounds to promote apoptosis, inhibit epithelial-mesenchymal transition (EMT), invasion, and growth, and induce cell cycle arrest by targeting several signaling pathways, including AMPK/mTOR, AMPK/MAPK/XAF1, TGF-β1, NF-κB, CaMKKβ-AMPK, and JAK2/STAT3 signaling. Of those phenolics, such as ampelopsin (Fig. 2, a flavanonol flavonoid known as dihydromyricetin) [171], isoangustone A (Fig. 2, a flavonoid obtained from *Glycyrrhiza glabra*) [172], brosimone I (Fig. 2, a flavonoid isolated from jackfruit) [173], and salidroside (Fig. 2, a tyrosol glucoside isolated from *Rhodiola rosea*) [174], have exerted promising antineoplastic potential by targeting AMPK signaling. Moreover, in PANC-1 and MIA-PaCa2 pancreatic cancer cells, fisetin (Fig. 2, a flavonoid found in several fruits and vegetables) [175], eupatilin (Fig. 2, a flavonoid derived from *Artemisia asiatica*) [176], and isoorientin (Fig. 2, a flavone C-glycoside constituent) [177] interfered with AMPK/mTOR, VEGF, and AMPK. Also, isorhamnetin (Fig. 2, a monomethoxyflavonol extracted from leaf of *Ginkgo biloba*) [178, 179], hyperoside (Fig. 2, a flavonol glycoside present in genera Hypericum and Crataegus) [180], silibinin (Fig. 2, a bioactive compound derived from *Silybum marianum* L.) [181], and typhaneoside (Fig. 2, a phenolic component isolated from *Typha angustifolia* L.) [182] are some of the known polyphenolic compounds with variant biological effects that showed significant anticarcinoma potential against in vitro and in vivo models of breast, skin, renal, melanoma, and leukemia cancers by interfering with several metabolism-related pathways, including AMPK/mTOR/p70S6K, PI3K, and Akt signaling pathways (Table 1).

Alkaloids

Alkaloids are naturally occurring organic nitrogen compounds found in various organisms, particularly plants, and are hypothesized to have substantial pharmacological and biological activities. These activities include

Table 1 Phenolic compounds targeting AMPK/PGC-1α in cancer

Compound	Types of study	Cell line(s)/tumor model(s)	Mechanism of action	References
Resveratrol	In vitro and in vivo	Ovarian cancer cells (SKOV3, A2780) Xenograft nude mouse model	↑AMPK/mTOR; ↓glycolysis; ↑apoptosis; ↑AMPK; ↑caspase-3	[109]
	In vitro	Breast cancer cell (BT-474)	↑AMPK; ↓acetyl-CoA carboxylase alpha; ↓fatty acid synthase; ↓mTOR	[110]
	In vitro	Leukemia cells (K562)	↑AMPK; ↓mTOR; ↑JNK; ↑p62	[111]
	In vitro	Colon cancer cells (Caco2, HTC116) Breast cancer cell (MCF-7)	↑CamKKB/AMPK; ↑glucose oxidation; ↓pentose phosphate; ↑ATP; ↓glycolysis; ↑OXPHOS; ↑PDH; ↓Ca2 + flux	[112]
	In vitro	Colorectal cancer cell (HCT-116/L-OHP)	↑p-AMPK; ↓NF-κB; ↓CAMP; ↓MDR1; ↓NF-κB; ↓p-IκBα; ↓MDR1	[113]
	In vitro	Prostate cancer cell (PC-3, DU145)	↑AMPK; ↓Akt/mTOR; ↓STIM1; ↓mTOR; ↑Apoptosis; ↓ER calcium storage; ↓Store operated calcium entry (SOCE); ↑ER stress	[114]
	In vitro	Glioblastoma cells (A172)	↓AMPK-YAP; ↑mitochondrial dysfunction; ↓pak2; ↑apoptosis; ↑caspase-9; ↑ROS; ↑mitochondria-JNK	[115]
Quercetin	In vitro	NSCLC (H1299, A549)	↑pAMPK-AMPK ratio; ↑SIRT1/AMPK; ↑LC3-II; ↑Beclin 1; ↓p62; ↑Atg5; ↑Atg7; ↑SIRT1	[120]
	In vitro	Cervical cancer cell (HeLa)	↑p-AMPK; ↓HSP-70; ↑Caspase-3; ↓EGFR; ↓phosphatases; ↓pP2a; ↓SHP-2	[121]
	In vitro and in vivo	Colorectal cancer cell (HT-29) Nude mice	↑AMPK; ↑apoptosis; ↓cell viability; ⊥G1 phase cell cycle; ↑p53; ↑p21	[122]
	In vitro and in vivo	Colorectal cancer cell (HCT-116) Athymic BALB nu/nu mice	↓AMPK; ↑apoptosis; ↓HIF-1α	[123]
	In vitro and in vivo	Breast cancer cell (MDA-MB-231, MDA-MB-435) SCID mice	↑p-AMPK; ⊥G2/M phase cell cycle; ↑p-Akt; ↑p-mTOR; ↓Akt	[124]
Isoquercitrin	In vitro	Hepatocellular carcinoma cell (HepG2, Huh7)	↑AMPK/mTOR/p70S6K; ↑Apoptosis; ↑Autophagy; ↑Caspase-3; ↑Cleaved PARP; ↑Bax/Bcl-2 ratio	[126]
Curcumin	In vitro and in vivo	Murine lymphocytic leukemia cell (L1210) Murine breast tumor cell (4T1) Murine melanoma cell (B16) Murine colon tumor cell (CT26) B16 Xenograft mouse model	↓ATP-synthase activity; ↑AMPK; ↓NF-κB; ↑Apoptosis; ↑ROS; ↑Malondialdehyde (MDA); ↑Lipid oxidation; ↑Autophagy	[131]
	In vitro	Rhabdomyosarcoma cells (A204, RD, SJCRH30)	↓AMPK; ↓Akt/mTOR; ⊥G2/M phase cell cycle; ↓Akt; ↑MAPK; ↑ERK; ↑JNK; ↑c-Jun; ↓STAT	[132]
	In vitro	Hepatocellular carcinoma cell (SMMC-7721)	↑AMPK; ↓Proliferation; ⊥G1 phase cell cycle; ↓Bcl-2; ↓Survivin; ↑Bax	[133]
EGCG	In vitro	NSCLC (H1299)	↑AMPK; ↓p-AMPK; ↓Colony formation; ↓Migration; ↓Cell invasion; ↓p-mTOR; ↓p-Akt	[139]
	In vitro	Colorectal cancer cell (HT-29)	↑AMPK; ↓Prostaglandin E2; ↓COX-2; ↓VEGF; ↓Glut1; ↑ROS	[140]
	In vitro	Colorectal cancer cell (HCT-116, HT-29)	↑AMPK; ↓Fatty acid de novo synthesis; ↓Lipid droplet formation; ↓Energy metabolism; ↓Mitochondrial oxidation/glycolysis; ↓Lipid uptake; ↓Lipolysis; ↓Fatty acid β oxidation; ↓Thermogenesis	[141]
Apigenin	In vitro	NSCLC (NCI-H1975)	↓AMPK; ↓Glucose metabolism; ↓Glucose uptake; ↓Glut1; ↓Glut3; ↓Glut4; ↑Autophagy; ↑Apoptosis; ↓HIF-1α; ↓c-MYC; ↓EGFR; ↓p-EGFR; ⊥G0/G1 phase cell cycle; ↓pDK1; ↓MCT1	[143]
	In vitro and in vivo	Human gastric carcinoma cell (AGS, SNU-216, NCI-N87, SNU-638, MKN-7, MKN-74) Athymic BALB/c nude mice	↑p-AMPK; ↑ATG5; ↑LC3-II; ↑ULK1; ↓p-mTOR; ↓p62; ↑PERK; ↑ER stress; ↓HIF-1α; ↓Ezh2	[144]
Isoliquiritigenin	In vitro	Colorectal cancer cell (HCT-116)	↓AMPK/mTOR; ↓Glycolysis; ↓Proliferation; ↓Glucose uptake; ↓Lactate; ↓ENO1; ↓ALDOA; ↓ LDHA; ↓MCT4; ↓c-MYC; ↓HIF-1α; ↓AMPK; ↓Akt/mTOR	[147]
	In vitro and in vivo	Human gastric carcinoma cells (MGC803) Nude mice	↓Glut4; ↓Glucose uptake; ↑PDHK1/PGC-1α; ↓Energy metabolic; ↑ROS; ↑Apoptosis; ↓Lactic acid; ↓OXPHOS; ↓Glycolysis; ↓pGC-1α; ↓c-MYC; ↓HIF-1α; ↓Glut4; ↓pDHK1	[148]

Table 1 (continued)

Compound	Types of study	Cell line(s)/tumor model(s)	Mechanism of action	References
Hispidulin	In vitro and in vivo	Hepatocellular carcinoma cell (SMMC-7721, Bel7402) Athymic BALB/c nu/nu mice	↑p-AMPK; ↑Caspase-3; ↑Apoptosis; ↓MMP-2; ↓MMP-9; ↑TIMP-3; ↑PPARγ; ↑p- ERK; ↑p-JNK	[150]
Rottlerin	In vitro	Human prostate tumor stem cells	↑AMPK; ↑Cytoplasmic vacuolation; ↑Autophagy; ↓PI3K/Akt/mTOR; ↑Ratio of Bax/Bcl-2	[151]
	In vitro	Colorectal cancer cell (HEK293) Breast cancer cell (T-47D, MDA-MB-231) Prostate cancer cell (PC-3 and DU145)	↑AMPK; ↑Wnt co-receptor LRP6 degradation; ↓Wnt/β-catenin; ↓mTORC1; ↓LRP6; ↓Wnt/β-catenin; ↓Cyclin D1; ↓Survivin	[152]
Baicalin	In vitro	Intestinal porcine epithelial cell line-J2	↑AMPK; ↓AMPK/Nrf2; ↑ZO-1; ↑Occludin; ↑Claudin1; ↓Ratio of p-AMPK/AMPK	[157]
	In vitro	NSCLC (H1299, A549)	↑SIRT1/AMPK; ↓Proliferation; ↓Migration	[158]
Baicalein	In vitro	Prostate cancer cell (PC-3, DU145) Breast cancer cell (MDA-MB-231)	↑AMPK/ULK1; ↓mTORC1; ↑ULK1; ↓Cdk2; ↓Cdk4; ↓Cyclin D1	[159]
	In vitro	Glioblastoma cells (U251)	↑AMPK; ↑Autophagy; ↑Apoptosis	[160]
	In vitro	NSCLC (H1299, A549, PC9, H1650, H358, H1975)	↓Growth; ↑Apoptosis; ↑p-AMPKα; ↑p-ERK1/2; ↑FOXO3a; ↑RUNX3	[161]
Kaempferol	In vitro	Hepatocellular carcinoma cell (SK-HEP-1)	↓AMPK; ↑p-AMPK; ↑Autophagy; ↑DNA fragmentation; ↑Apoptotic bodies; ↑Caspase-3; ↑LC3-II; ↑Atg 5; ↑Beclin 1; ↓CDK1; ↓Cyclin B; ↓ p-Akt; ↓p-mTOR; ⊥G2/M phase cell cycle; ↓CDK1/cyclin B; ↓p-Akt	[162]
Luteolin	In vitro and in vivo	Hepatocellular carcinoma cells (HepG2) Nude mice	↓AMPK; ↓NF-κB; ↑ROS	[163]
Morusin	In vitro	Hepatocellular carcinoma cells (Hep3B, Huh7)	↓Glycolysis; ↑AMPK; ⊥G1 phase cell cycle; ↓Cyclin D1; ↓Cyclin D3; ↓Cyclin E; ↓CDK2,4, 6; ↑p21; ↑p27; ↑p-AMPK/ACC; ↓p-mTOR; ↓p-Akt; ↓c-MYC; ↓HK2; ↓pKM2	[164]
Glycycoumarin	In vitro and in vivo	Liver cancer cell lines (HepG2, Huh-7, SMMC-7721) Mice	↑p-AMPK; ↑p-ACC; ↓Lipogenesis; ↓Tumor growth; ↓Survivin; ↓TOPK; ↓Lipogenesis	[165]
Cyanidin 3-*O*-glucoside	In vitro and in vivo	Hepatocellular carcinoma cell line (HepG2) C57BL/6J male mice	↓Hepatic gluconeogenesis; ↑AMPK; ↑p-CRTC2; ↑p-HDAC5; ↑Cellular senescence; ↑Apoptosis; ↑Oxidative-stress	[166]
Ellagic acid	In vitro and in vivo	NSCLC (HOP62, H1975) C57 mice	↑AMPK; ↓HIF-1α; ↓Cell proliferation; ↓ATP; ↓Mitochondrial membrane potential; ↓oxygen consumption	[167]
Honokiol	In vitro	NSCLC (A549, H460, H358, H2122, BEAS-2B, NIH3T3, CCD19-Lu)	↓p-Akt; ↓HIF-1α; ↓p-mTOR; ↑Apoptosis; ⊥G1 phase cell cycle; ↑Autophagy; ↑Sirt3; ↑Bax; ↓Bcl-2; ↓C-RAF; ↓ERK	[168]
Gallotannin	In vitro	Colorectal cancer cell (HCT-116, CT26, SW620)	↓AMPK; ↑LC3B; ↑Apoptosis↑Autophagy; ↓CDK2/cyclin A complex; ↑p62; ↓PI3K/Akt/mTOR; ↓Migration; ↓Invasion; ↓MMP-2; ↓MMP-9; ↓EMT; ↓Snail; ↓Twist; ↓vimentin	[169]
Pomiferin	In vitro, in vivo, and *in silico*	C57BL/6 mice Cervical cancer cell (HeLa) Hepatocellular carcinoma cells (Hep3B, HepG2) NSCLC (H1299, A549, LLC-1) Breast cancer cell (MCF-7) Prostate cancer cell (LNcap, RM-1)	↓SERCA; ↑CaMKKβ-AMPK-mTOR; ↓p-gp (MDR1/ABCB1) efflux; ↑Autophagy; ↑Apoptosis	[170]
Ampelopsin	In vitro	Colorectal cancer cell (HCT-116, HCT-8, HT-29)	↑AMPK/MAPK/XAF1; ↑AMPK; ↑ROS; ↑Apoptosis; ↑ER stress; ↑Cleavage caspase-9; ↑PARP; ↑Cleavage caspase-3	[171]
Isoangustone A	In vitro and in vivo	Hepatocellular carcinoma cells (SW480) Balb/c nu/nu mice	↑AMPK; ↓ATP; ↓Akt/mTOR	[172]
Brosimone I	In vitro	Colorectal cancer cell (HCT-116)	↑CaMKKβ-AMPK; ⊥G1 phase cell cycle; ↑Apoptosis; ↑ROS; ↑ER stress; ↑Cytosolic Ca2+	[173]
Salidroside	In vitro	Colorectal cancer cell (HCT-116)	↑AMPK/mTOR; ↑AMPK; ↓p-AMPK; ↑NF-κB; ↑TGFβ1; ↑Apoptosis; ↑LC3B; ↑Becline-1; ↑Autophagy; ↓ p-mTOR; ↓p-NF-κB (p65); ↓ p-JAK2; ↓p-STAT3; ↑JAK2/STAT3	[174]

Table 1 (continued)

Compound	Types of study	Cell line(s)/tumor model(s)	Mechanism of action	References
Fisetin	In vitro and in vivo	BALB/c nude mice Pancreatic cancer cell (PANC-1)	↑AMPK/mTOR; ↑p-PKC-α; ↑Autophagy; ↓Proliferation; ↑ER stress; ↑p53	[175]
Eupatilin	In vitro	Pancreatic cancer cell (MIA-PaCa2)	↓Glucose uptake; ↑AMPK; ↑Cell cycle arrest; ↑p21	[176]
Isoorientin	In vitro	Pancreatic cancer cell (PANC-1)	↑AMPK; ↑Apoptosis; ↓VEGF; ↓MMPs; ↓EMT; ↓N-cadherin; ↓Angiogenesis	[177]
Isorhamnetin	In vitro and in vivo	Breast cancer cell (MCF-7, MDA-MB-231) Xenograft models	↓AMPK/mTOR/p70S6K; ⊥G2/M phase cell cycle; ↑Apoptosis; ↑DNA damage; ↑ROS; ↓ CDK1/Cyclin B1	[178]
	In vitro	Bladder cancer cell lines (T24, 5637, 2531 J, EJ)	↑AMPK; ↓ATP; ↓Mitochondrial function; ↑Apoptosis; ↑ROS; ⊥G2/M phase cell cycle; ↓Wee1; ↓Cyclin B1; ↑$p21^{WAF1/CIP1}$; ↑p21; ↑Fas/Fas ligand; ↓Bcl-2/Bcl-2	[179]
Hyperoside	In vitro and in vivo	Squamous cell carcinoma cell lines (A431, A432, HS-4) Female mice	↑AMPK; ↓Proliferation; ↑Apoptosis; ↑Autophagy; ↓PI3K/Akt/mTOR	[180]
Silibinin	In vitro	Renal cell carcinoma cell (ACHN, 786-O)	↑AMPK; ↑LC3-II; ↑Auto phagolysosome vacuoles; ↓p-mTOR	[181]
Typhaneoside	In vitro	Acute myeloid leukemia cell (AML)	↑AMPK; ↑Ferroptosis; ↑Ferritin degradation; ↓Proliferation; ⊥G2/M phase cell cycle; ↑Autophagy; ↑Caspase-3; ↑ROS; ↑Ferroptotic cell death	[182]

neuroprotective, antibacterial, antifungal, and antitumor properties [129, 153, 183, 184]. The following section presents information on how various alkaloids target the AMPK/PGC-1α signaling pathway, which ultimately regulates cancer metabolism.

Berberine

Berberine (Fig. 3) is a phytocompound extracted from *Berberis vulgaris* and *Berberis aristata* plants. It is classified as an isoquinoline alkaloid and has a variety of pharmacological properties, including anti-inflammatory, immunomodulatory, antidepressant, and antineoplastic effects [185–187]. Berberine led to the suppression of growth, migration, and invasion of a colorectal cancer cell line via suppressing fatty acid synthesis and downregulating the activities of AMPK, NF-κB, and integrin β1 signaling [188–190]. Similarly, berberine attenuated the growth and proliferation of U87MG [191], HepG2 [192], PANC-1 [193], B16F10 [194], and AGS [195] cells in in vitro models of glioblastoma, hepatocellular, pancreatic, melanoma, and gastric cancer, respectively. This was done by inhibiting DNA synthesis, AMPK/mTOR/ULK1, mTORC1, COX-2, ERK, and the AMPK/HNF4α/WNT5A pathway.

Chaetocochin J and neferine

Chaetocochin J (Fig. 3) and neferine (Fig. 3) are natural alkaloids with significant antimetastatic, antiproliferative, and neuroprotective properties. These alkaloids play a crucial role against HCT-116 and SW480 in vitro colorectal cancer cell models via interfering with Ulk-1-PERK, AMPK, AMPK-mTOR, and PI3K/Akt/mTOR pathways [196].

Stachydrine

Targeting the LIF/AMPK and PI3K/Akt/mTOR axis was reported to be the main anticarcinoma activity of stachydrine (Fig. 3, an active constituent obtained from of *Castanea sativa* Mill.) and coptisine (Fig. 3, an isoquinoline alkaloid present in Chinese goldthread) in several in vitro models of hepatocellular carcinoma [197, 198].

Other alkaloids

Fangchinoline (Fig. 3), a miscellaneous alkaloid extracted from *Stephania tetrandra*, exerted anticancer effects on lung and colorectal cancer via promoting apoptosis, autophagy, suppression of metastasis, and EMT through regulation of the AMPK/mTOR/ULK1 and Akt-mTOR pathways [199, 200]. Aloperine (Fig. 3, a quinolizidine alkaloid isolated from *Sophora alopecuroides* L.) [201], hydroxycamptothecin (Fig. 3, an active ingredient found in *Nothapodytes nimmoniana*) [202], hernandezine (Fig. 3, a bisbenzylisoquinoline alkaloid derived from *Thalictrum glandulosissimum*) [203], ethoxysanguinarine (Fig. 3, a benzophenanthridine alkaloid obtained from *Macleaya cordata*) [204], cryptolepine (Fig. 3, an alkaloid that can be found in *Cryptolepis sanguinolenta*) [205], angustoline (Fig. 3, an active ingredient of *Camptotheca acuminata*) [206], and 11-methoxytabersonine (Fig. 3, an active ingredient isolated from *M. cochinchinensis*) [207], are some of the valuable alkaloids found in several vegetables and fruits. They have been shown to possess crucial antimetastatic potential against various in vitro

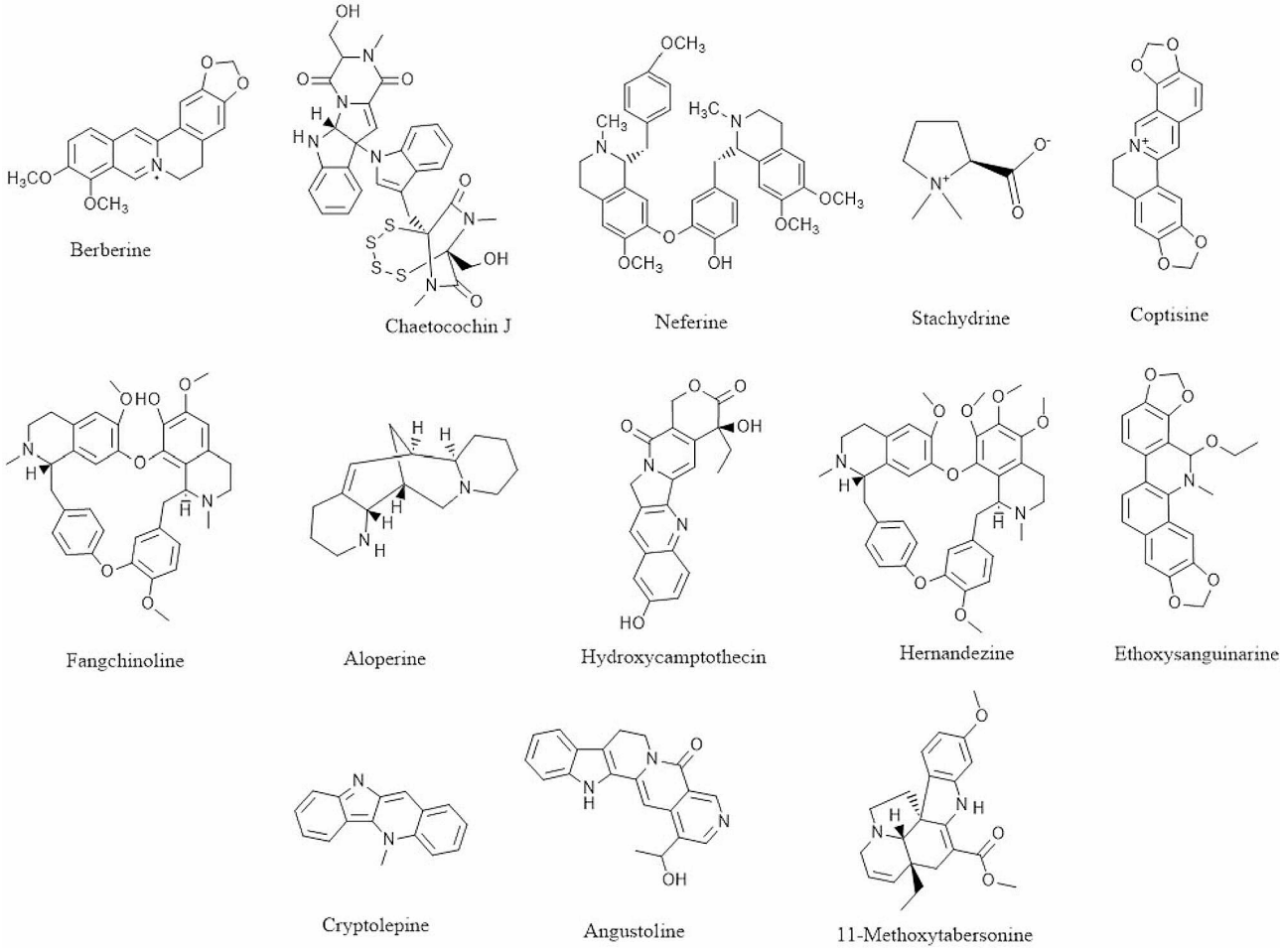

Fig. 3 Chemical structures of common alkaloids in the regulation of cancer metabolism through AMPK/PGC-1α

and in vivo cancer models, including thyroid, bladder, pancreatic, breast, melanoma, esophageal, and lung cancers. They do so by targeting AMPK, Akt, AMPK-mTOR-ULK1, ERK, ROS/AMPK, AMPKα1/2-LKB1, JNK, LKB1/AMPK/ELAVL1/LPACT2, and AMPK/mTOR signaling pathways (Table 2).

Terpenes/terpenoids

Terpenes, a hydrocarbon, and terpenoids, which are terpenoids that contain oxygen, are potent organic compounds obtained from plants that provide a wide variety of therapeutic benefits. Terpenes and terpenoids consist of a structure made of isoprene units, which are five-carbon unit components. The bonds between various isoprene units form the main structure of these compounds. Terpenes and terpenoids possess significant anticancer activities against variant types of carcinomas via interaction with apoptosis, autophagy, and metabolism-related signaling pathways [208–210]. In the following section, we provide an overview of research carried out on the most notable terpenes and terpenoid substances that possess substantial anticancer properties via modulation of the AMPK/PGC-1α signaling pathway.

Furanodiene and β-elemene

Furanodiene (Fig. 4) and β-elemene (Fig. 4) are two bioactive sesquiterpenes that exert significant anticancer activity against MCF-7, breast cancer [211], and A549, lung cancer [212], cells by alteration of mitochondrial function, suppression of DNA methyltransferase 1 expression, and activation of the AMPKα and ERK1/2 signaling pathways.

Ursolic acid

Ursolic acid (Fig. 4) is a naturally occurring pentacyclic triterpenoid carboxylic acid that is present in many fruits and vegetables, such as oregano, apples, peppermint, cranberries, lavender, bilberries, and elder flower. Ursolic acid possesses a wide spectrum of pharmacological activities such as antibacterial, cardioprotective, hepatoprotective, anti-inflammatory, and antiproliferative effects [213]. It can inhibit tumor growth and is increasingly being recognized as a promising molecule for both

Table 2 Alkaloids targeting AMPK/PGC-1α in cancer

Compound	Types of study	Cell line(s)/tumor model(s)	Mechanism of action	References
Berberine	In vitro	Colorectal cancer cell (HCT-116) Cervical cancer cell (HeLa)	↑AMPK; ↓Fatty acid; ↓Biogenesis of extracellular vesicles; ⊥G1 phase cell cycle	[188]
	In vitro	Colorectal cancer cell (HCT-116, SW480)	↑AMPK; ↓Ki-67; ↓COX-2; ↑Apoptosis; ↓mTOR; ↓NF-κB; ↓Cyclin D1; ↓Survivin; ↑phosphorylation of p53; ↑Caspase-3 cleavage	[189]
	In vitro	Colorectal cancer cell (HCT-116, SW480)	↑AMPK; ↓Integrin β1; ↓Migration; ↓phospho-Src; ↓FAK	[190]
	In vitro and in vivo	Glioblastoma cells (U87, U251) Athymic mice	↑AMPK/mTOR/ULK1; ↑Autophagy flux; ↓Glycolytic capacity; ↑Apoptosis; ↑Bax; ↑Cytochrome C; ↑Cleaved caspase-3; ↓Bcl-2; ↑Mitochondrial dysfunction	[191]
	In vitro	Hepatocellular carcinoma cells (HepG2, SMMC-7721, Bel-7402)	↑p-AMPK; ↑p-Akt; ↑AMPK; ↑Apoptosis; ↑Cytochrome c; ↑Caspase-9, ↑Caspase-3; ↑Bax/Bcl-2; ↑Caspase-3	[192]
	In vitro	Pancreatic cancer cell (PANC-1, MiaPaCa-2)	↓ATP; ↑AMPK; ↑p-AMPK α subunit; ⊥G1 phase cell cycle; ↓mTORC1; ↓ERK; ↓DNA synthesis; ↓Proliferation; ↓Mitochondrial membrane potential	[193]
	In vitro and in vivo	Human melanoma cell (A375) Mouse melanoma cell (B16F10) C57BL/6J mice	↑AMPK; ↓ERK; ↓COX-2; ↓Metastases	[194]
	In vitro and in vivo	Gastric carcinoma cells (SGC7901, AGS) Xenograft mouse model	↓AMPK/HNF4a; ⊥G0/G1 phase cell cycle; ↓Migration; ↑AMPK; ↑p-AMPK; ↓MMP-3; ↓HNF4a; ↓WNT5A; ↓Cytoplasmic β-catenin	[195]
Chaetocochin J	In vitro	NSCLC (A549) Hepatocellular carcinoma cell (SMMC-7721, SW480) Breast cancer cell (MCF-7)	↑AMPK; ↑Apoptosis; ↑Autophagy; ↓Proliferation; ↓PI3K/Akt/mTOR	[196]
Neferine	In vitro, in vivo, and *in silico*	Cervical cancer cell (HeLa) Breast cancer cell (MCF-7) Hepatocellular carcinoma cells (HepG2, Hep3B) NSCLC (H1299, A549)	↑AMPK-mTOR; ↑Cytosolic [Ca2+]; ↑Apoptosis; ↑Autophagy; ↑ULK-1; ↑Pancreatic ER kinase	[267]
Stachydrine	In vitro, in vivo, and *in silico*	NSG mice Hepatocellular carcinoma cells (HepG2, SMMC-7721)	↑p-AMPK; ⊥G0/G1 phase cell cycle ↑Autophagy; ↑Senescence; ↑p62; ↑LC-3B; ↓Cyclin D1; ↑p27; ↓LIF	[197]
Coptisine	In vitro	Hepatocellular carcinoma cells (Hep3B)	↑Mitochondrial dysfunction; ↑p-AMPK; ↑Autophagy; ↓PI3K/Akt/mTOR; ↑ROS	[198]
Fangchinoline	In vitro and in vivo	Colorectal cancer cell (HCT-116, RKO, SW620, HT29) BALB/C nude mice	↓AMPK/mTOR/ULK1; ⊥G0/G1 phase cell cycle; ↑AMPK; ↑Autophagy	[199]
	In vitro, in vivo, and *in silico*	Mice xenograft NSCLC cells	↓Akt-mTOR; ↓NOX4; ↓Metastasis; ↓EMT; ↓ROS	[200]
Aloperine	In vitro	Thyroid cancer cell (KMH-2, 8505c, IHH-4)	↓AMPK; ↑Cell cycle arrest; ↑Apoptosis; ↓Tumorigenesis; ↑Autophagy; ↓p70S6K; ↓mTOR; ↓phospho-p38; ↓phospho-Erk; ↓Akt/mTOR; ↓Erk; ↓p38	[201]
Hydroxycamptothecin	In vitro	Bladder cancer line (T24, 5637)	↑AMPK-mTOR-ULK1; ↑autophagy; ↑Apoptosis	[202]
Hernandezine	In vitro	Pancreatic cancer cells (Capan-1, SW1990)	↑ROS/AMPK; ↑p-AMPK; ↓phosphorylation of mTOR/p70S6K; ↑autophagy	[203]
Ethoxysanguinarine	In vitro, in vivo, and *in silico*	Nude mice Breast cancer cell (MCF-7, MDA-MB-231, DMA-MB-436, SK-BR3, MDA-MB-468, MDA-MB-453, and MDA-MB-435 S) Nude immunodeficient mice (nu/nu)	↑AMPK; ↑Autophagy; ↑p- mTORC1	[204]

Table 2 (continued)

Compound	Types of study	Cell line(s)/tumor model(s)	Mechanism of action	References
Cryptolepine	In vitro	Melanoma cell lines (A375, Hs294t, SK-Mel28, SK-Mel119)	↓ATP; ↓mitochondrial mass; ↑AMPKα1/2-LKB1; ↓mitochondrial membrane potential; ↓mitochondrial biogenesis; ↑mitochondria depletion; ↓Mfn1; ↓Mfn2; ↓Opa1; ↓p-Drp1; ↓mitochondrial dynamics; ↓MTOR; ↓SDH-A; ↓COX-I; ↑LKB1	[205]
Angustoline	In vitro and in vivo	Esophageal cancer cell (KYSE450) Bearing mouse model	↓LKB1/AMPK/ELAVL1/LPACT2; ↓phospholipid remodeling; ↑LKB1/AMPK; ↓ELAVL1/LPCAT2	[206]
11-Methoxytabersonine	In vitro	NSCLC (H157, A549)	↑AMPK/mTOR; ↑necroptosis; ↑autophagy; ↑JNK	[207]

Abbreviations: AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2; COX-2, cyclooxygenase-2; Drp1, dynamin-related protein 1; EMT, epithelial-mesenchymal transition; ERK1/2, extracellular signal-regulated protein kinase; HNF4a, hepatocyte nuclear factor 4α; JNK, c-Jun NH_2-terminal kinase; LKB1, liver kinase B1; MMPs, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; Opa1, optic atrophy 1; ROS, reactive oxygen species; SHH, sonic hedgehog

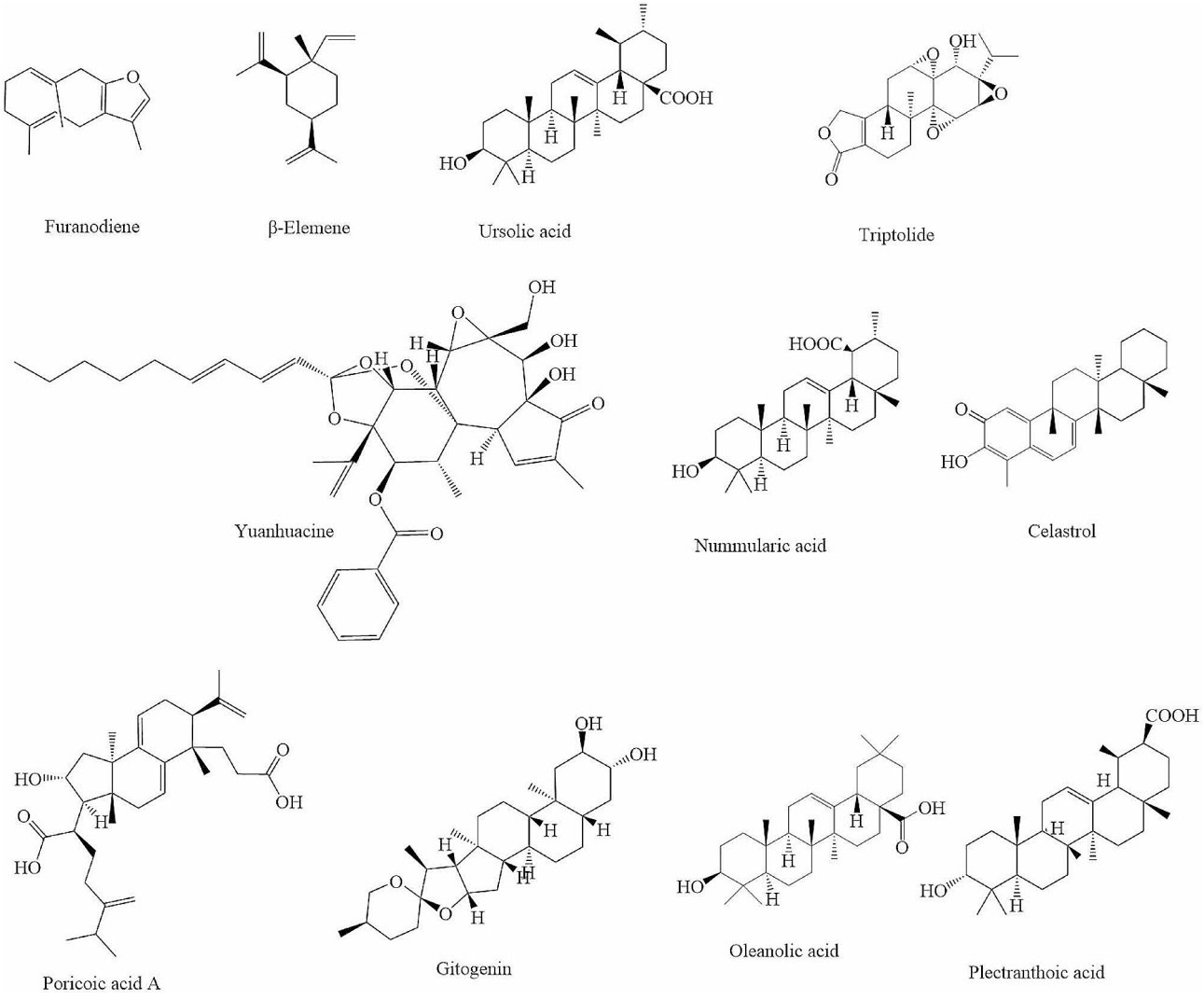

Fig. 4 Chemical structures of common terpenes/terpenoids in the regulation of cancer metabolism through AMPK/PGC-1α

preventing and treating cancer. Ursolic acid suppresses the growth of hepatocellular carcinoma cells through the alteration of the glycolytic pathway, AMPKα, and pERK1/2 signaling pathways [214]. Moreover, treatment with ursolic acid leads to the induction of apoptosis and the suppression of the proliferation in MCF-7 and MDA-MB-231 cells by interfering with Akt, ERK, ROS, and AMPK pathways [215].

Triptolide

Triptolide (Fig. 4) is a primary active ingredient isolated from *Tripterygium wilfordii* Hook F. with notable anticancer potential. This phytocompounds can promote apoptosis and autophagy in lung and prostate cancer cells via activation of the CaMKKβ-AMPK and regulation of AMPK/mTORC2 signaling pathways [216, 217].

Yuanhuacine

Yuanhuacine (Fig. 4) is another diterpene terpenoid that showed antitumor activity in the A549 cell line via regulating AMPK/mTOR axis [218].

Other terpenoids

Nummularic acid (Fig. 4, a triterpenoid derived from the *Fraxinus xanthoxyloides*) [219], celastrol (Fig. 4, an active ingredients isolated from *Tripterygium wilfordii*) [220, 221], gitogenin (Fig. 4, a natural component extracted from *Allium rotundum* and *Yucca gloriosa*) [222], oleanolic acid (Fig. 4, a pentacyclic triterpenoid derived from *Phytolacca americana*) [223], poricoic acid A (Fig. 4, a tricyclic triterpenoid isolated from Poria cocos) [224], and plectranthoic acid (Fig. 4, a pentacyclic triterpenoid in *Ficus microcarpa*) [225] are some of the other triterpenoid components that possess considerable anticarcinoma activities in several in vitro and in vivo models of prostate, colorectal, lung, leukemia, and breast cancer via inducing cycle arrest and apoptosis and interfering with numerous signaling pathways, including mTOR/S6K, AMPK/mTOR, and AMPK signaling (Table 3).

Miscellaneous phytochemicals

Research on the most important miscellaneous phytocompounds with notable anticancer activities are summarized in the following section, with an emphasis on the cancer metabolic pathways that underlie their anticancer action. Osthole (Fig. 5) is a natural coumarin agent with several pharmacological activities that can be isolated from *Cnidium* spp. Osthole suppressed the growth of various malignant phenotypes by promoting ferroptosis and apoptosis and suppressing glycolysis, AMPK/Akt, and the GSK-3β/AMPK/mTOR signaling pathway [226–228]. Targeting of AMPK/miR-299-5p/ATF2, AMPK, E-cadherin/AMPK/mTOR, and ROS/AMPK/mTOR axes was described as the major anticancer mechanism of numerous miscellaneous phytocompounds, such as 6′-O-galloylpaeoniflorin (Fig. 5, an active ingredients extracted from paeoniflorin) [229], gambogic acid (Fig. 5, a xanthonoid compound isolated from brownish) [230], gracillin (Fig. 5, a steroidal saponin that can be extracted from *Dracaena draco*) [231], aspiletrein A (Fig. 5, a steroidal saponin found in *Aspidistra letreae*) [232], and schizandrin A (Fig. 5, a dibenzocyclooctadiene lignan) [233], against several in vitro and in vivo models of lung carcinoma. In addition, ginkgolic acid (Fig. 5, an active ingredient in *Ginkgo biloba* L.) and periplocin (Fig. 5, a plant-derived glycoside) diminished the growth and development of PANC-1 and BxPC-3 cell lines in vitro models of pancreatic cancer by suppressing lipogenesis, promoting apoptosis, and activating AMPK-mTOR signaling [234, 235]. In similar studies, panduratin A (Fig. 5, a major active ingredient isolated from *Boesenbergia rotunda*) [236], bixin (Fig. 5, an apocarotenoid extracted from *Bixa orellana*) [237], β-sitosterol (Fig. 5, an active phytosterol) [238], physciosporin (Fig. 5, a natural constituent obtained from *Pseudocyphellaria faveolata*) [239], hydroxycitric acid (Fig. 5, a derivative of citric acid in *Garcinia cambogia*) [240], and isogambogenic acid (Fig. 5, an active component from *Garcinia hanburyi*) [241], showed remarkable antineoplastic effects against numerous in vitro models of cancer, including melanoma, glioma, colorectal, breast, leukemia, and gastric adenocarcinoma, by diminishing metastasis, mitochondrial respiration, aerobic glycolysis, EMT, cancer metabolism, and cell proliferation by disrupting AMPK/PGC-1α, mTOR, and AMPK and interconnected signaling pathways. Table 4 presents miscellaneous phytochemicals targeting AMPK/PGC-1α in cancer.

Novel delivery systems of phytochemicals in cancer

Novel delivery systems and formulations of phytochemicals play a crucial role in enhancing the bioavailability, stability, and efficacy of these natural compounds. Phytochemicals obtained from plants have favorable health effects such as anti-inflammatory, antioxidant, and anticancer characteristics. However, their poor solubility, low stability, and limited absorption in the body can hinder their therapeutic potential. By developing innovative delivery systems, such as nanoparticles, liposomes, micelles, and nanoemulsions, researchers can overcome these challenges and improve the targeted delivery of phytochemicals to specific tissues or cells [242, 243]. This progress improves the therapeutic impact of phytochemicals and introduces new opportunities for personalized medicine and disease therapy.

The effectiveness of many phytochemicals is limited due to rapid metabolism, low bioavailability, poor water solubility, and systemic elimination. To address these challenges, scientists have investigated novel drug

Table 3 Terpenes/terpenoids targeting AMPK/PGC-1α in cancer

Compound	Types of study	Cell line(s)/tumor model(s)	Mechanism of action	References
Furanodiene	In vitro	Breast cancer cell (MCF-7)	↓Mitochondrial function; ↓ATP; ↑AMPK	[211]
β-Elemene	In vitro	NSCLC (H1299, A549, PC9, H1650, H358, H1975)	↑AMPKα; ↑p-ERK1/2; ↑p-Akt; ↓DNMT1; ↑ERK1/2; ↓Sp1 protein expression	[212]
Triptolide	In vitro and in vivo	Prostate cancer cells (PC-3, LNCaP, C4–2) Nude mice	↑CaMKKβ-AMPK; ↓mTORC1; ↑AMPK; ↑ER; ↑ULK complex; ↑Class III PI3K complex; ↑Autophagy	[216]
	In vitro	NSCLC (H1395, A549)	↑p-AMPK; ↑CaMKKβ/AMPK; ↑Apoptosis; ↓p-Akt; ↑cleaved PARP; ↑Caspase-3/7; ↑Ca2 + influx	[217]
Vuanhuacine	In vitro and in vivo	Xenograft nude mouse model NSCLC (H358, H460, Calu-1, H1299, A549, H199)	↑AMPK; ↓mTORC2; ↓p-Akt; ↓pKCα; ↓Invasion; ↓Migration	[218]
Ursolic acid	In vitro	Hepatocellular carcinoma cells (HepG2)	↑p- AMPKα; ↓ DNMT1; ↓Sp1; ↑Apoptosis	[214]
	In vitro	Breast cancer cells (SK-BR-3, MCF-7, MDA-MB-231)	↑AMPK; ⊥G0/G1 cell cycle; ↑DNA damage; ↑DDR; ↓p-Akt; ↓ERK; ↑ROS	[215]
Nummularic acid	In vitro	Prostate cancer cell (PC-3, DU145, C4-2)	↑AMPK; ↑acetyl CoA carboxylase phosphorylation; ↑ADP/ATP ratio; ↓glycolytic rate; ↓migratory properties; ↓invasive properties; ↑apoptosis; ↓pS6 phosphorylation	[219]
Celastrol	In vitro and in vivo	Colorectal cancer cell (HCT-116, HEK293, SW480) BALB/c nude mice	↑AMPKα; ↑β-catenin degradation; ↑LKB1–AMPKα; ↑HSF1; ↑p-YAP; ↑LKB1	[220]
	In vitro	Breast cancer cell (MCF-7)	↑p-AMPK; ↑phosphorylation p53; ⊥sub G1 phase cell cycle; ↑PLK-2; ↑ROS	[221]
Gitogenin	In vitro	NSCLC (H1299, A549)	↑AMPK; ↑apoptosis; ↑autophagy; ↓proliferation; ↑cleaved caspase-3; ↑PARPs; ↑ROS	[222]
Oleanolic acid	In vitro	Breast cancer cells (SK-BR-3, MCF-7, MDA-MB-231)	↑AMPK; ⊥G0/G1 cell cycle; ↑DNA damage; ↑DDR; ↓p-Akt; ↓ERK; ↑ROS	[223]
Poricoic acid A	In vitro and in vivo	Nude mice Human T-cell acute lymphoblastic leukemia cell lines (JURKAT, MOLT-3, ALL-SIL ADN RPMI-8402)	↓AMPK/mTOR; ↓GSH; ↑MDA; ⊥G2 cell cycle; ↑ferroptosis; ↑apoptosis; ↑ROS; ↑autophagy; ↓proliferation	[224]
Plectranthoic acid	In vitro	Human non-tumorigenic cells (RWPE-1, NHEK) Melanoma cells (A375) Prostate cancer cell (PC-3 and DU145)	↑AMPK; ⊥G0/G1 phase cell cycle; ↓mTOR/S6K; ↑p21/CIP1 and p27/KIP1	[225]

Abbreviations: ADP, adenosine diphosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; CaMKKβ, Ca2+/calmodulin-dependent protein kinase kinase-β; DDR, DNA damage response; DHTMF, 5;3′-dihydroxy-6;7;4′-trimethoxyflavanone; DNMTs, DNA methyltransferases; ERK1/2, extracellular signal-regulated protein kinase; GSH, glutathione; HSF1, heat-shock factor 1; LKB1, liver kinase B1; MDA, malondialdehyde; PARP, poly (ADP ribose) polymerase; PI3K, phosphatidylinositol 3 kinase; PKC, protein kinase C; PLK-2, polo-like kinase 2; ROS, reactive oxygen species; YAP, yes-associated protein 1

delivery systems, including lipid-based nanoparticles, polymeric nanoparticles, micelles, exosomes, nanogels, and mesoporous silica nanoparticles [130, 244–246]. In the following section, novel delivery systems of phytochemicals, with their anticancer potentials, are reviewed.

Curcumin

Liposomal curcumin has demonstrated potential in cancer treatment through in vitro, in vivo, and clinical studies. Other novel delivery systems for curcumin against cancer include graphene oxide, poly(glycerol subcategory) nanoparticles, and nanodelivery systems, such as polymer nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, niosomes, and nanoemulsions. These delivery systems have enhanced the therapeutic effectiveness of curcumin against various types of cancer, primarily because of its antiproliferative and proapoptotic effects on tumor cells. However, potentially serious side effects, including interactions with other drugs and the toxic aspects of nanoparticles, may occur. More high-quality studies are needed to determine clinical efficacy [247–250]. The potential of curcumin-loaded nanoparticles to reduce oxidative stress and apoptosis in various conditions, including cancer, through the AMPK pathway, has been analyzed. A study on curcumin nanoparticles demonstrated their ability to reduce palmitate-induced oxidative stress in the heart and protect it from apoptosis by activating the AMPK pathway [251]. Curcumin phytosomes combine curcumin with phospholipids to enhance this phytochemical's bioavailability. Curcumin has been extensively studied for its potential health benefits, including its effects in fighting cancer. Research has shown that phytosome curcumin can inhibit thrombin-induced cell growth and migration through AMPK in breast cancer [252]. Curcumin's phytosome formulation, such as Meriva® Phytosome®

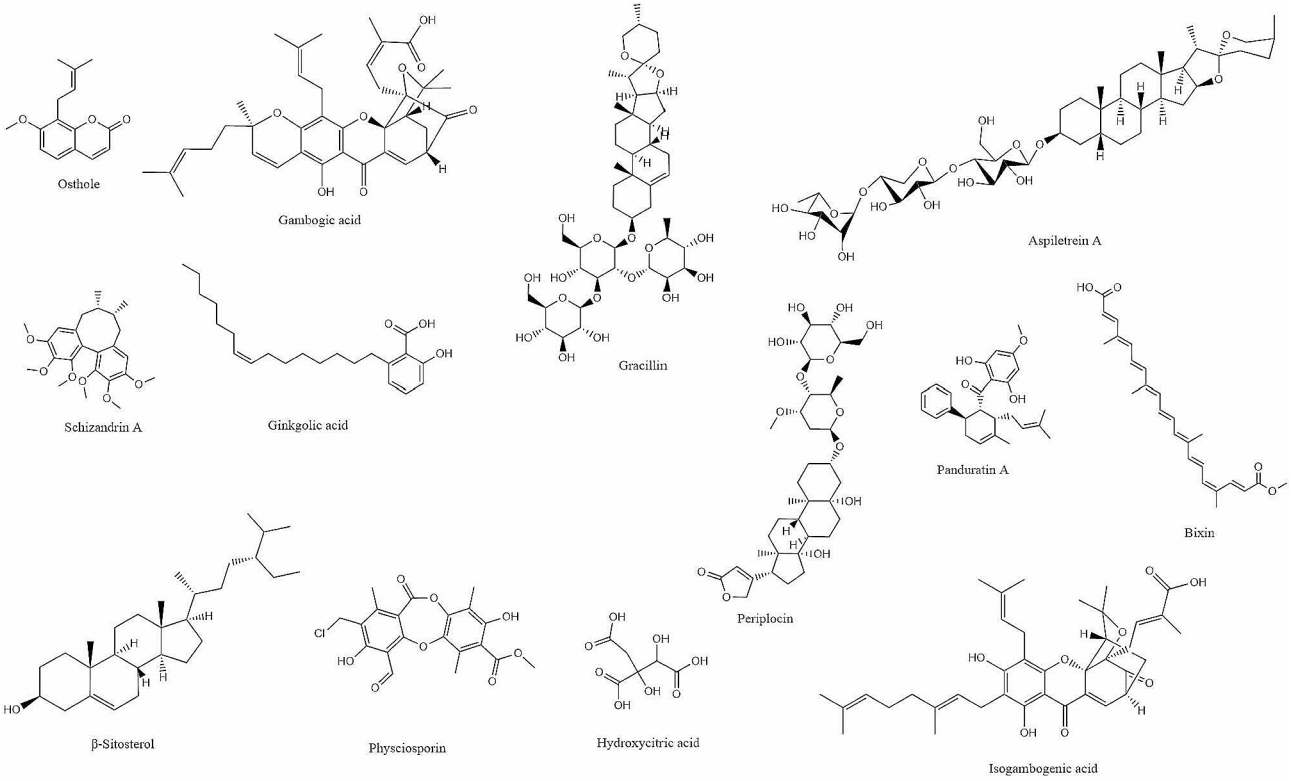

Fig. 5 Chemical structures of miscellaneous phytochemicals in the regulation of cancer metabolism through AMPK/PGC-1α

technology, enhanced the bioavailability of curcuminoids and ensured optimal absorption in the body [253]. Phytosome curcumin has demonstrated potential effects on cancer, especially in relation to breast cancer. Research has shown that phytosome curcumin can inhibit thrombin-induced cell growth and migration through AMPK in breast cancer [252].

EGCG

Several nanodelivery systems have been developed to enhance the effectiveness of EGCG in cancer treatment. It has been shown that liposomal co-delivery systems, including EGCG and paclitaxel, induce apoptosis in cancer cells more effectively than either of these compounds alone [254]. Gold and lipid-based nanoparticles have also been investigated as delivery systems for EGCG [255, 256].

A recent study demonstrated that delivering EGCG in nanoparticles increased cytotoxicity in breast cancer cell lines. Furthermore, a co-delivery nanosystem of EGCG and rutin has been suggested for their potential anticancer and antibacterial effects [257]. These studies suggest that nanodelivery systems may enhance the potential of EGCG in cancer treatment. The anticancer effects of EGCG nanoemulsion on lung cancer have been analyzed, and the results indicate that nano EGCG may inhibit lung cancer cell proliferation, colony formation, migration, and invasion by activating protein signaling pathways and inhibiting AMPK [139].

Resveratrol

In one study, resveratrol was bioconjugated with gold nanoparticles using polyvinylpyrrolidone as a crosslinker. This led to improved delivery performance and enhanced the antitumor effects of resveratrol [258]. Another study investigated the targeted delivery of resveratrol to mitochondria by conjugating it to triphenylphosphonium (TPP), resulting in the potentiation and induction of mitochondrial-mediated apoptosis. Similarly, nanocarrier-based delivery systems have also been investigated to enhance the bioavailability and therapeutic potential of resveratrol [259].

Ginsenosides

Ginsenosides are important bioactive compounds that can be found in ginseng roots. These compounds have been studied for their potential health benefits, such as anticarcinoma, antioxidant, neuroprotective, and anti-inflammatory properties. Ginsenosides have demonstrated therapeutic potential in triggering apoptosis in tumor cells, decreasing proliferation, invasion, and metastasis, as well as reversing multidrug resistance [260]. These ginsenosides have been encapsulated or modified in various nanodelivery systems, such as

Table 4 Miscellaneous phytochemicals targeting AMPK/PGC-1α in cancer

Compound	Types of study	Cell line(s)/tumor model(s)	Mechanism of action	References
Osthole	In vitro and in vivo	Colorectal cancer cell (HCT-116, SW480) Nude mice	↑Ferroptosis; ↓AMPK/Akt; ↓proliferation; ↓tumor growth; ↑autophagy; ↓p-AMPK; ↓p-Akt; ↓p-mTOR; ↑AMPK; ↓AMPK/Akt/mTOR	[226]
	In vitro	Hepatocellular carcinoma cell (SK-HEP-1, HCC-LM3)	↓GSK-3β/AMPK/mTOR; ↓glycolysis; ↓colony formation; ↓DNA damage repair; ↓lactic acid; ↓p-GSK-3β/GSK-3β; ↓p-mTOR/mTOR; ↓Glut-1/3; ↓pKM2; ↑p-AMPK/AMPK	[227]
	In vitro and in vivo	Nude mice Hepatocellular carcinoma cell (SK-HEP-1, HCC-LM3)	↓GSK-3β/AMPK/mTOR; ↓glycolysis; ↓tumor volume; ↓tumor weight; ↓lactic acid	[228]
6′-O-galloylpaeoniflorin	In vitro and in vivo	NSCLC (H1299, A549) BALB/C-nu/nu nude mice	↑AMPK; ↓clonality; ↓ invasion; ↓metastasis; ↓miR-299-5p; ↓ATF2 mRNA; ↓miR-299-5p/ATF2	[229]
Gambogic acid	In vitro and in vivo	NSCLC (H1299, Calu-1, H358, H460, A427, A549) Athymic BALB/c nude mice	↑p-AMPK; ↑E-cadherin; ↓ZEB1; ↓mTOR	[230]
Gracillin	In vitro and in vivo	NSCLC (A549) Athymic nude mice	↑AMPK; ↓mTOR; ↑Beclin-1; ↑LC3-II; ↓p62; ↑WIPI1	[231]
Aspiletrein A	In vitro	NSCLC (A549, H460, H23)	↑AMPK; ↓p-mTOR; ↓p-Bcl-2; ↓p-AMPK; ↑apoptosis; ↑ROS; ↑cleaved caspase-3; ↑cleaved PARP	[232]
Schizandrin A	In vitro	NSCLC (H1299, A549, H1975)	↓ATP; ↑AMPK; ⊥G1/S phase cell cycle; ⊥G2/M phase cell cycle; ↑apoptosis; ↑autophagy; ↑p53; ↑SOX4; ↑p21; ↑Bim; ↑BimL; ↑BimS; ↑p62; ↑cyclin E2; ↑CDK2; ↓cyclin D1; ↓CDK4; ↓CDK6; ↓cyclin E1; ↓mitochondrial membrane potential	[233]
Ginkgolic acid	In vitro and in vivo	Pancreatic cancer cell (PANC-1, BxPC-3) Hepatocellular carcinoma cells (HepG2) BALb/c nude mice	↓Lipogenic genes; ↑AMPK; ↑apoptosis; ↓acetyl-CoA carboxylase; ↓FASN	[234]
Periplocin	In vitro and in vivo	Pancreatic cancer cell (PANC-1, cfpac1) Balb/c nude mice	↑AMPK/mTOR; ↓p70 S6K; ↑p-AMPK; ↓p-mTOR; ↑AMPK; ↓mTOR; ↓p-S6K; ↓growth; ↑apoptosis	[235]
Panduratin A	In vitro	Human melanoma cell (A375)	↑AMPK; ↑mTOR; ↑autophagy	[236]
Bixin	In vitro and in vivo	Colon cancer cells (Caco2, SW480) Athymic nude mice	↑AMPK/PERK/eIF-2α; ↑ER Stress; ↑p-ERK; ↑p-eIF2α; ↑apoptosis; ↑PERK/eIF-2α	[237]
Beta-sitosterol	In vitro and in vivo	BALB/c nude mice Gastric cancer cell (SNU216, SNU601, AGS cells)	↑AMPK/PTEN/HSP90; ↑p-AMPK; ↑p-PTEN; ↑AMPK; ↑PTEN	[238]
Physciosporin	In vitro and in vivo	Breast cancer cell (MCF-7, MDA-MB-231, iRFP-4T1) BALB/c mice	↓ATP; ↓glycolysis capacity; ↑apoptosis; ↓Bcl-xL; ↑Bax; ↑cleaved caspase-7; ↑PARP; ↓mitochondrial respiration; ↓pGC-1α; ↓aerobic glycolysis; ↓Glut1; ↓HK2; ↓pKM2; ↓LDHA; ↓β-catenin; ↓cyclin D1; ↓c-MYC; ↓HIF-1α; ↓p-NF-κB	[239]
Hydroxycitric acid	In vitro and in vivo	Leukemia cells (K562, CML-T1, SKH-1, MEG-01, KYO-1) NSG mice	↑AMPK; ↑mTOR; ↑EIF2α/ATF4; ↑DNA fragmentation; ↑p-AMPK; ⊥G2/M phase cell cycle	[240]
Isogambogenic acid	In vitro and in vivo	Glioblastoma cells (U87, U251) BALB/c nude mice	↑AMPK/mTOR; ↑autophagy; ↑AMPK; ↓mTOR; ↓4E-BP1; ⊥G0/G1 phase cell cycle	[241]

Abbreviations: AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2; CDK2, cyclin-dependent kinase 2; DNA methyltransferases; EIF2α, eukaryotic initiation factor 2α; ERK1/2, extracellular signal-regulated protein kinase; FASN, fatty acid synthase; Glut, glucose transporter; GSK-3β, glycogen synthase kinase-3β; HIF-1α, hypoxia-inducible factor-1α; HK2, hexokinase 2; LDHA, lactate dehydrogenase A; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; PARP, poly (ADP ribose) polymerase; PGC-1α, peroxisome proliferator-activated receptors-1α; ROS, reactive oxygen species; SOX4, sex-determining region Y-related high mobility group-BOX gene 4

polymeric nanoparticles, liposomes, micelles, and biomimetic nanoparticles, to enhance drug bioavailability and targeting ability [261]. In addition, ginsenosides serve as chemotherapeutic adjuvants and membrane stabilizers in a novel multifunctional liposome system that demonstrates antitumor efficacy and active targeting abilities [262]. Ginsenosides have been reported to activate the AMPK pathway, which can regulate metabolic reprogramming and reverse the Warburg effect in breast cancer [263]. New ginsenoside delivery systems have been developed to effectively target the AMPK pathway for cancer therapy, according to recent findings [264–266].

Conclusion, challenges/pitfalls, and future perspectives

As a major area of extensive attention, cancer metabolism has been an emerging hallmark of cancer. Targeting the major dysregulated metabolic pathways by multi-targeting phytochemicals could be a promising strategy to combat cancer cells. Despite the benefits behind targeted therapies, many cancer cells cannot be treated using just one type of treatment. Furthermore, considering the complexity of cancer metabolism, it is necessary to find new treatments that can target multiple dysregulated pathways. Accordingly, phytocompounds have indicated potential in combating cancer dysregulated pathways, but with fewer side effects than other commonly used treatments. Such potentials have introduced phytochemicals as promising compounds for prevention and treatment of cancer through regulating different signaling pathways.

Amongst those dysregulated pathways, AMPK/PGC-1α and interconnected pathways plays critical roles in cancer metabolism. In this line, alkaloids, phenolic compounds, terpenes/terpenoids, and several miscellaneous phytochemicals, represent major candidates in modulating cancer metabolism (Fig. 6). Phytochemicals have also demonstrated potential in the regulation of downstream signaling pathways of AMPK/PGC-1α, including angiogenesis, apoptosis, inflammation, and oxidative stress (Fig. 7).

The instability, low solubility/selectivity, poor bioavailability, rapid metabolism, and chemical degradation of phytochemicals limit their therapeutic applications in cancer. Employing novel delivery systems kindly overwhelmed such pharmacokinetic limitations by increasing bioavailability. Accordingly, lipid-based nanoparticles, polymeric nanoparticles, micelles, nanogels, cyclodextrin, gold, and mesoporous silica nanoparticles, have been critically employed to drawback the pharmacokinetic limitations of phytochemicals in targeting the AMPK/PGC-1α signaling pathway. Several phytochemicals have demonstrated notable antitumor effects by regulating cancer metabolism via influencing different signaling pathways, such as AMPK/PGC-1α, NF-κB, PI3K/Akt/mTOR, HIF-1α, ERK1/2, and the AMPK/mTORC2 axis. As a result, they suppress cancer metabolism, cell growth, invasion, and EMT. Phytocompounds are recognized as excellent and promising substances for the treatment of cancer.

Phytochemicals targeting AMPK/PGC-1α in cancer treatment face several challenges and limitations. One major challenge is the limited bioavailability of phytochemicals due to poor absorption and quick metabolism in the body. This can lead to decreased levels and lower concentrations of the phytochemicals when reaching their targeted tissues, diminishing their efficacy. It can also be difficult to determine how a certain

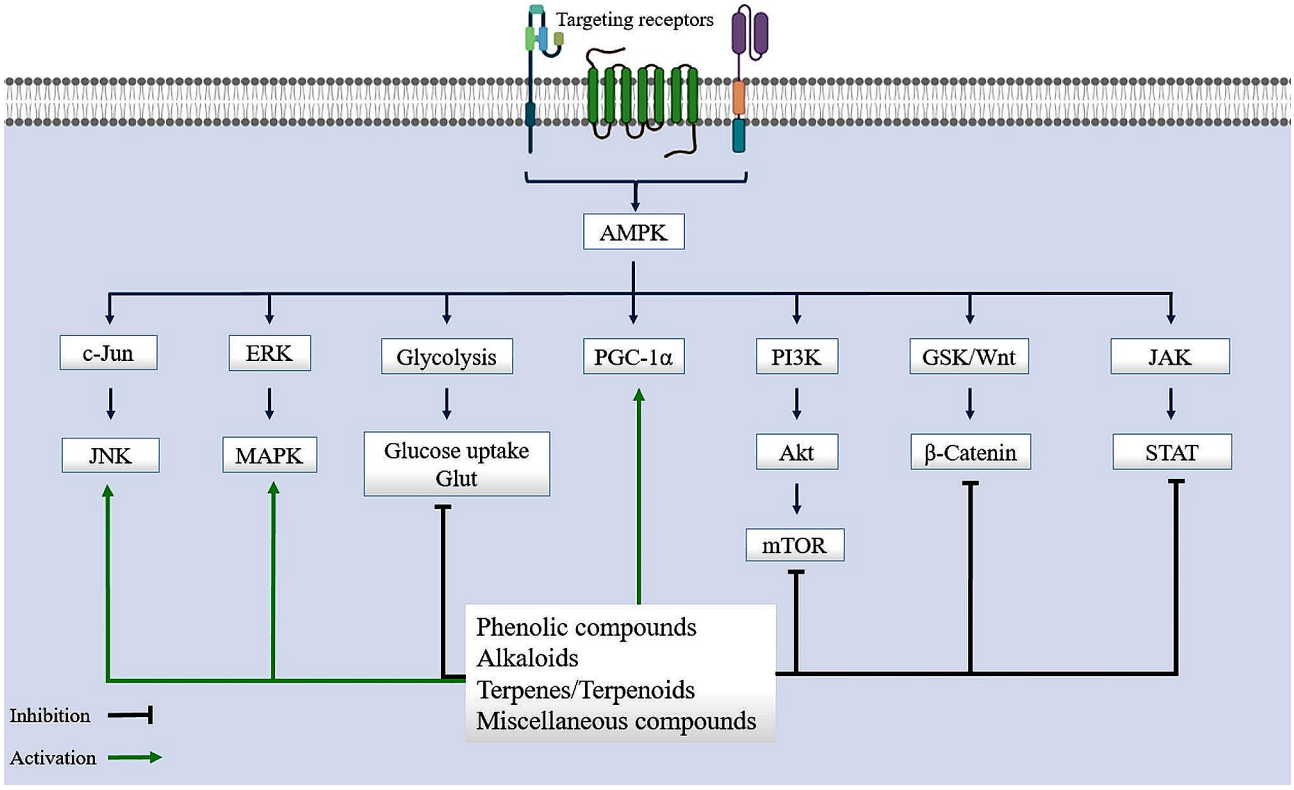

Fig. 6 Targeting AMPK/PGC-1α and interconnected signaling pathways by phytochemicals in cancer

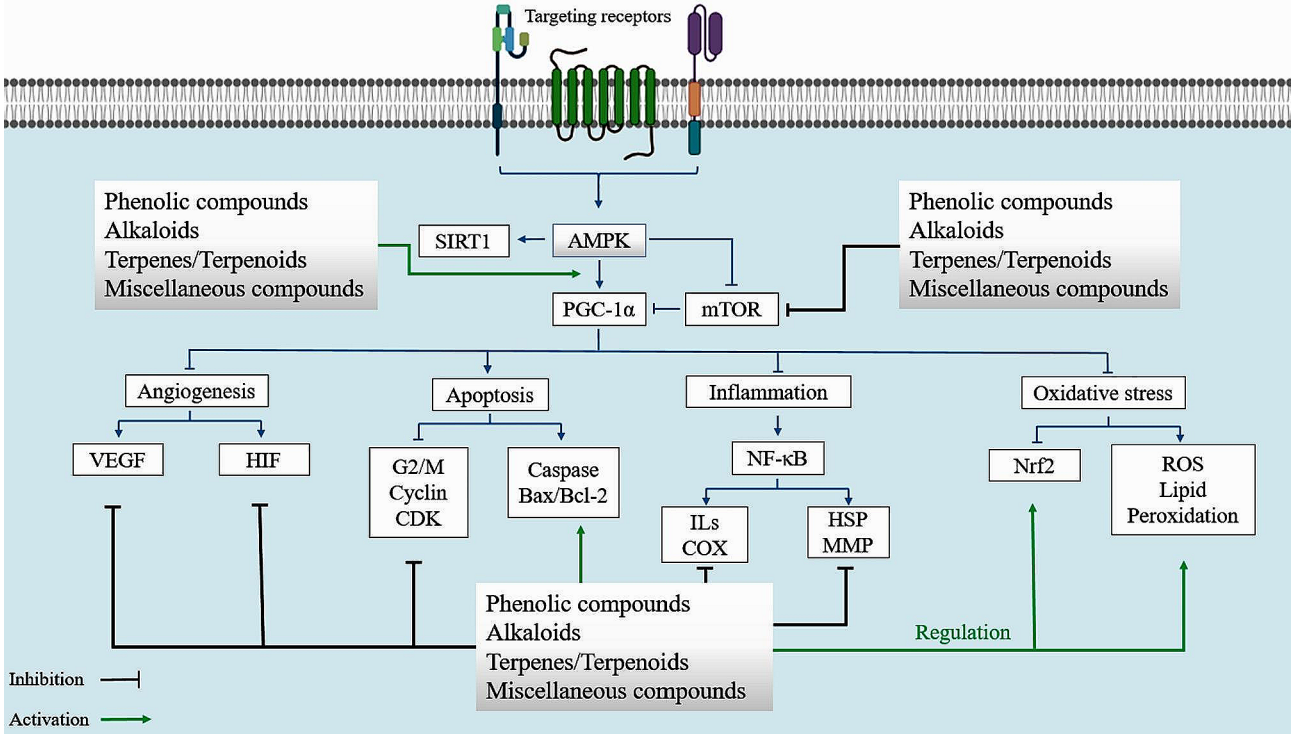

Fig. 7 Targeting the downstream signaling pathways of AMPK/PGC-1α by phytochemicals including angiogenesis, apoptosis, inflammation, and oxidative stress

phytochemical will interact with AMPK/PGC-1α signaling pathways in various types of cancer due to cancer biology being very complicated and cancer cells differing greatly from one another. Furthermore, the potential for off-target effects and interactions with other medications or treatments can pose as a risk. Another significant challenge and limitation in the use of phytochemicals targeting AMPK/PGC-1α in cancer treatment is the lack of extensive clinical studies to confirm and validate their effectiveness and safety. Promising outcomes in cell cultures and animal models require accurate clinical trials before being used in clinical practice. Insufficient clinical evidence makes it difficult to safely endorse the use of phytochemicals as a conventional therapy for cancer patients. Therefore, more well-designed clinical trials are needed to bridge the gap between preclinical research and the clinical application of phytochemicals targeting AMPK/PGC-1α in cancer therapy. While phytochemicals show promise as potential therapeutic agents in cancer treatment, further research is needed to address these challenges and optimize their use in clinical settings.

In summary, the current systematic review underlines the significance of targeting the AMPK/PGC-1α signaling pathway in cancer metabolism by multi-targeted phytochemicals. Future studies should focus on evaluating the effects of phytochemicals during well-controlled clinical trials in combating cancer.

Abbreviations

ACC1/2	Acetyl-CoA carboxylases 1/2
Akt	Protein kinase B
AML	Acute myeloid leukemia
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate-activated protein kinase
AR	Androgen receptor
ATP	Adenosine triphosphate
CaMKKβ	Calcium/calmodulin-dependent protein kinase kinase-β
COX-2	Cyclooxygenase-2
DAP1	Death-associated protein 1
EGCG	Epigallocatechin gallate
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
ERAD	Endoplasmic reticulum-associated protein degradation
ERK	Extracellular signal-regulated protein kinase
ERR	Estrogen-related receptor
EZH2	Enhancer of zeste homolog 2
FAO	Fatty acid oxidation
FAS	Fatty acid synthase
FOXO3a	Forkhead box O3a
GCN5	General control non-depressible 5
Gli-1	Glioma-associated oncogene 1
GSK-3β	Glycogen synthase kinase-3β
HIF-1	Hypoxia-inducible factor-1
IL-6	Interleukin- 6
JAK	Janus kinase
JNK	c-Jun NH2-terminal kinase
KSR1	Kinase suppressor of Ras 1
LIC	Leukemia-initiating cells
LKB1	Liver kinase B1
MAPK	Mitogen-activated protein kinase
MCT1	Monocarboxylate transporter 1
miRNAs or miR	MicroRNAs
mTOR	Mammalian target of rapamycin
mTORC1	Mammalian target of rapamycin complex 1
NAD	Nicotinamide adenine dinucleotide

NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NF-κB	Nuclear factor-κB
NLRP	Nod-like receptor protein
NMIIA	Non-muscle myosin IIA
Nrf2	Nuclear factor erythroid 2-related factor 2
NSCLC	Non-small cell lung cancer
OXPHOS	Oxidative phosphorylation
PD-L1	Programmed cell death ligand 1
PERK	Protein kinase R (PKR)-like endoplasmic reticulum kinase
PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator-1α
PI3K	Phosphoinositide 3-kinase
PP2A	Protein phosphatase 2 A
PP2C	Protein phosphatase 2 C
PPM1E	Protein phosphatase 1E
pRb	Retinoblastoma protein
PRC	PGC-1-related coactivator
PRC2	Polycomb repressive complex 2
RAPTOR	Regulatory-associated protein of mTOR
RIP1	Receptor-interacting protein 1
ROS	Reactive oxygen species
SIRT3	Sirtuin 3
STAT	Signal transducer and activator of transcription
STK11	Serine/threonine kinase 11
TAK1	TGF-β-activated kinase 1
T-ALL	T-cell acute lymphoblastic leukemia/lymphoma
TET2	TET methylcytosine dioxygenase 2
TGF-β	Transforming growth factor-beta
TLR	Toll-like receptors
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-α
TPP	Triphenylphosphonium
TSC2	Tuberous sclerosis complex 2, also known as Tuberin
TWEAK	TNF-related weak inducer of apoptosis
UBE2O	Ubiquitin conjugating enzyme E2
ULK1	UNC-51- like kinase 1
VEGF	Vascular endothelial growth factor
YAP	Yes-associated protein

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