Flavonoids as modulators of metabolic reprogramming in renal cell carcinoma (Review)

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Abstract. Renal cell carcinoma (RCC) is distinguished by its varied metabolic reprogramming driven by tumor suppressor gene dysregulation and oncogene activation. Tumors can adapt nutrient uptake and metabolism pathways to meet the altered biosynthetic, bioenergetic and redox demands of cancer cells, whereas conventional chemotherapeutics and molecular inhibitors predominantly target individual metabolic pathways without addressing this adaptability. Flavonoids, which are well-known for their antioxidant and anti-inflammatory properties, offer a unique approach by influencing multiple metabolic targets. The present comprehensive review reveals the intricate processes of RCC metabolic reprogramming, encompassing glycolysis, mitochondrial oxidative phosphorylation and fatty acid biosynthesis. The insights derived from the present review may contribute to the understanding of the specific anticancer mechanisms of flavonoids, potentially paving the way for the development of natural antitumor drugs focused on the metabolic reprogramming of RCC.

Contents

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Abbreviations: RCC, renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; GLUT, glucose transporter; ECG, epicatechin gallate; EGCG, epigallocatechin-3-gallate; TCA, tricarboxylic acid; LDH, lactate dehydrogenase; LDHA, LDH A; PKM2, pyruvate kinase M2; HK, hexokinase; PDH, pyruvate dehydrogenase; ETC, electron transport chain; PPP, pentose phosphate pathway; 6PGD, 6-phosphogluconate dehydrogenase; ACC, acetyl CoA carboxylase; FAS, fatty acid synthase; SCD, stearoyl CoA desaturase; LPA, lysophosphatidic acid; COX, cyclooxygenase; GLS, glutaminase; GPX1, glutathione peroxidase 1

Key words: flavonoids, metabolic reprogramming, Warburg effect, RCC, anticancer drug

1. Introduction

Renal cell carcinoma (RCC), also known as renal adenocarcinoma, is a type of kidney cancer that arises from the renal tubule cells, representing 2-3% of all adult cancers (1). Each year, physicians identify an estimated 210,000 new instances of kidney cancer worldwide, making it the seventh most prevalent cancer in men and the ninth most common cancer in women (2). The United States, northern Europe, Canada, Australia, and New Zealand have the highest rates of kidney cancer according to the National Cancer Institute. Thailand, the Philippines, and China have the lowest incidences (3). Clear cell RCC (ccRCC) accounts for 70-80% of RCC cases, while the other subtypes are primarily composed of chromophobe tumors (3-5%) and papillary tumors (10-15%) (4). Furthermore, ~4% of RCCs are hereditary and 96% are sporadic (5). Cancers are characterized by disordered metabolism (6). Tumor growth is facilitated by certain metabolic processes that are necessary for cell transformation or other related biological processes (7). Cancer cells can modify their metabolic systems in various ways to meet their needs for energy and biosynthesis. The first strategy involves increasing the intake and utilization of nutrients and substrates, mainly glucose since the glycolytic rate of some

types of cancer cells is ~30 times higher than that of normal cells (8). The second approach is to use metabolic pathways that are advantageous to biosynthesis when breaking down nutrients (9). The Warburg effect, which refers to the observation that cancer cells tend to use anaerobic glycolysis to utilize glucose even in aerobic environments, is one of the most important examples (10). The third strategy involves the aberrant activation of biosynthetic pathways. Tumor cells actively engage in pathways related to fatty acid production and desaturation to meet the increased demands for their cell membranes and signaling molecules (11,12). Reprogrammed metabolic processes are crucial for the proliferation of cancer cells and are also becoming recognized as a critical factor in determining the outcome of the individual cells (13). Kidney cancer or renal cancer is a prime example of metabolic reprogramming among cancer types due to its distinct reliance on altered metabolic pathways to support tumor growth and adaption (14,15). Researchers have linked numerous altered, inactive, or hyperactivated genes in RCC to the control of several metabolic processes, including glutamine metabolism, glycolysis, and the tricarboxylic acid (TCA) cycle (16,17), ATP synthesis, and the regulation of pathways crucial for the balance of redox and hypoxia reactions. Kidney cancer can also be characterized by its metabolic alterations, as the disease involves marked changes in metabolic pathways that support tumor growth and survival (17,18).

Therapeutic approaches for renal cancer are often hindered by the resistance to multiple drugs exhibited by tumor cells, which is a major cause of chemotherapy failure (19). This resistance arises from metabolic and cellular physiological responses triggered by the tumor, including the evasion of drug-induced apoptosis, activation of detoxification pathways, reduction in drug uptake and activation of DNA repair mechanisms (20). In this context, the utilization of flavonoids in a clinical trial has been instrumental in suppressing resistance mechanisms and inducing reprogramming of cancer cells, and thus, is of utmost importance in the search for novel genotoxic therapeutic approaches against tumors (21). These natural products have facilitated the development of more effective strategic combinations with fewer side effects for the treatment of renal cancer and have enhanced the understanding of metabolic reprogramming, cancer cell defense and resistance mechanisms (22). The alteration of gene expression patterns in ccRCC cells is linked to genetic and epigenetic events (23). Flavonoids have gained prominence in anticancer pharmaceutical studies since they inhibit glycolysis and oxidative phosphorylation (OXPHOS), and modulate key enzymes such as hexokinase (HK) and pyruvate kinase (24,25). A summary of the metabolic reprogramming altered by flavonoids in ccRCC is shown in Fig. 1. Flavonoids possess potent epigenetic properties that regulate DNA methylation, histone modification, and microRNAs in the context of cancer therapy. Specifically, flavonoids exhibit the ability to modulate crucial metabolic pathways by targeting tumor suppressor genes and pivotal catalytic enzymes in cancer cells (24,26). Their efficacy has been demonstrated when combined with chemotherapy drugs or other natural compounds, thus driving extensive research efforts and the development of novel therapeutic strategies for cancer treatment (27).

2. Anticancer drugs targeting metabolic reprogramming

The field of cancer biology has observed a gradual increase in knowledge and comprehension of the numerous targets of metabolic reprogramming as advancements in research occur. These advancements have facilitated the development of customized pharmacological therapies for various components of metabolism (28). Medicines targeting pertinent metabolic pathways may inhibit the growth and proliferation of RCC cells (29). Scientists categorize drugs according to their target metabolic pathways, which include glucose metabolism, glycolysis, tricarboxylic acid cycle, oxidative phosphorylation, pentose phosphate pathway, lactate metabolism, lipid metabolism, and amino acid metabolism. Table SI summarizes these metabolic pathways, detailing the drugs targeting each pathway, the models in which they have been tested, and their current phase of research. While the majority of anticancer medications are still in the preclinical stage, a few have already exhibited significant promise in cancer treatment and have advanced to phase IV studies or clinical trials (30). For example, curcumin derived from *Curcuma longa* has been investigated for its potential to target metabolic reprogramming in cancer cells, including modulation of glycolysis and oxidative stress pathways (31). Resveratrol has shown potential in targeting metabolic pathways such as glucose metabolism and mitochondrial function in cancer cells (32). Regarding treatment options for recurrent colorectal cancer, tumor drug-induced cell drug resistance is considered to be the primary factor for the ineffectiveness of chemotherapy. This occurs because the drug-induced apoptosis decreases drug absorption and activates DNA repair mechanisms (33). Natural molecules have several advantages over synthetic medications or chemicals, including reasonable safety, minimal side effects, and multistep targeting (34-36). Numerous natural substances have been employed as preventative and therapeutic measures against various illnesses, including cancer (37-39). Some molecules from food and beverages, traditional Chinese medicines, and medicinal plants have an impact on the initiation, growth and metastasis of human cancers (40). For example, curcumin has been shown to inhibit cancer cell proliferation, induce apoptosis and reduce metastasis in various cancer types through multiple mechanisms, including modulation of signaling pathways and reduction of inflammation (41). Berberine has shown potential in inhibiting cancer cell growth, and modulating multiple signaling pathways involved in cancer progression (42). Epigallocatechin-3-gallate (EGCG) has demonstrated anticancer effects by inducing apoptosis and blocking angiogenesis (43). Although numerous secondary metabolites, such as flavonoids from medicinal plants, have been utilized for a long time, it is still unclear which molecular mechanism underlies their tumor-suppressive actions and which anticancer properties they have (44).

3. Role of flavonoids in RCC metabolic reprogramming

There are >10,000 known subtypes of bioflavonoids, making them a diverse class of natural compounds. The most prevalent phenolic compounds in the human diet are flavonoids, mostly in cereals. Dried food, nuts, seeds, fruits, vegetables, cereal-like foods, green tea and wine are everyday dietary

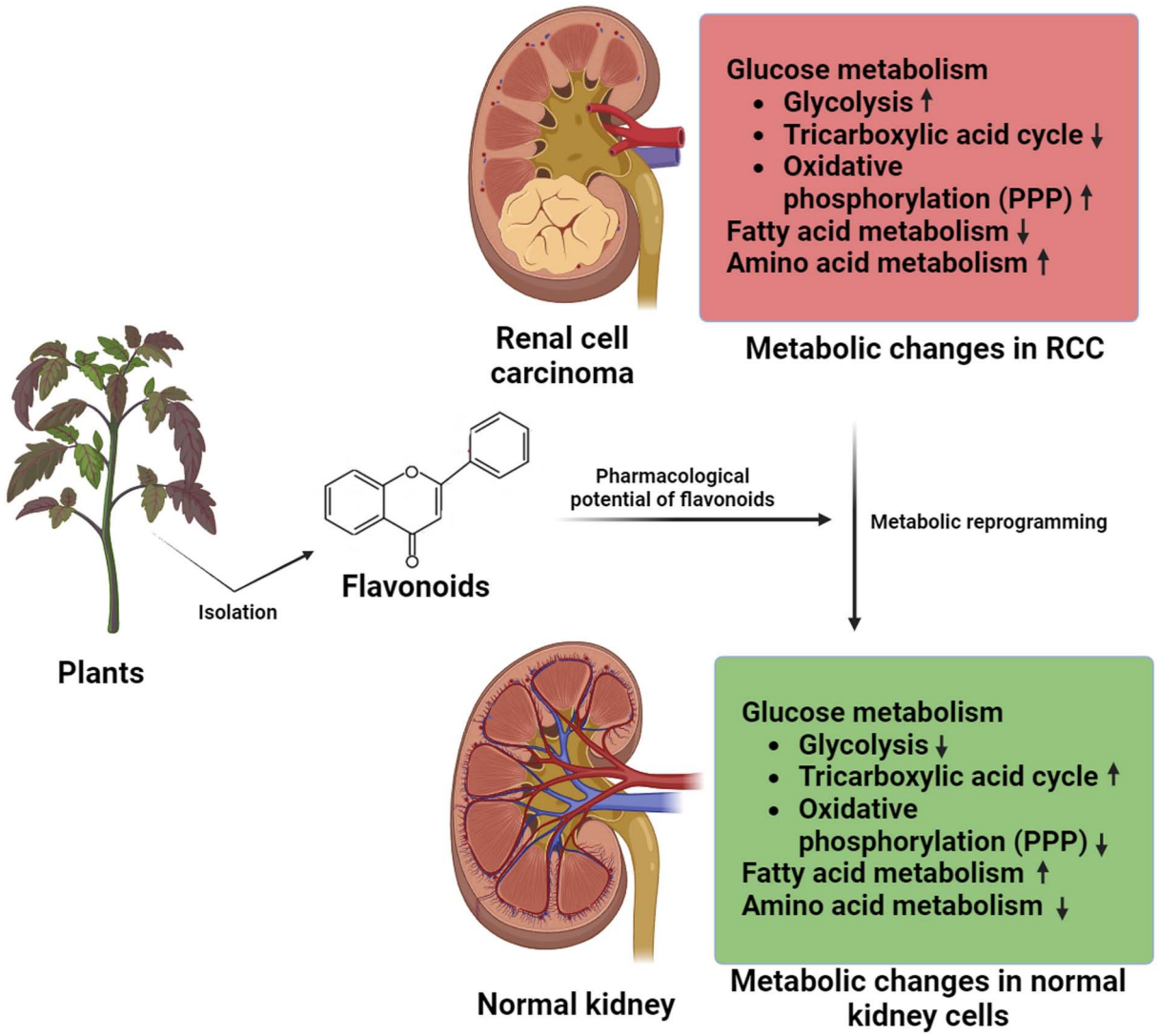

Figure 1. Flavonoids counteracting metabolic reprogramming in clear cell RCC. PPP, pentose phosphate pathway; RCC, renal cell carcinoma.

items that are frequently consumed and can be sources of bioactive compounds, including flavonoids. These compounds have been studied for their potential health benefits, including their anticancer properties. These everyday dietary items are readily available and can be incorporated into a regular diet. Their consumption may contribute to overall health and potentially offer protective effects against cancer through their bioactive compounds (24). Depending on the degree of unsaturation, oxidation of the C ring, and chemical structure, flavonoids can be further classified into six subgroups. These subcategories include isoflavones or chalcones, anthocyanins, flavones, flavonols and flavanones or catechin. Each flavonoid is composed of two benzene rings joined by a heterocyclic pyran ring (2-phenyl-1,4-benzopyran) and has 15 carbons in its chemical structure (C6-C3-C6) (Fig. 2) (45,46). Flavonoids exhibit numerous biological properties, including anti-viral (47), antifungal (48), antibacterial (49), antioxidant (50), anti-inflammatory (51), antidiabetic (52), antimutagenic (53), anti-obesity (54), cardioprotective (55) and anticancer (24) activities. Moderate levels of reactive oxygen species (ROS), generated through mitochondrial activity, function as redox signaling molecules that regulate growth, differentiation, and

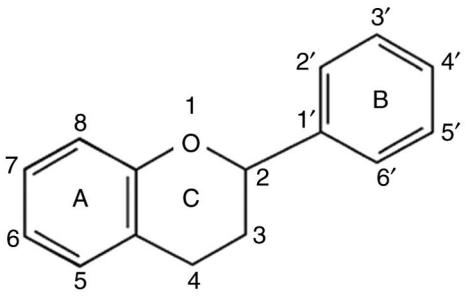

Figure 2. General structure of flavonoid and lettering generated using ChemDraw (12.0.2) with default settings (https://revvitysignals.com/products/research/chemdraw).

cell proliferation pathways. However, excessive ROS can be detrimental to cancer cells, leading to cell death. As a result, tumor cells develop adaptive detoxification mechanisms to counteract high levels of ROS (56). The elevation of ROS can induce apoptosis in cancer cells, and therapeutic strategies that modulate ROS levels have exhibited efficacy as anticancer drugs (57). Flavonoids exhibit dual activity: Antioxidant

effects in non-tumor cells and pro-oxidant effects in cancer cells. In non-tumor cells, flavonoids exert antioxidant effects, reducing oxidative stress by scavenging ROS. Conversely, in cancer cells, flavonoids induce oxidative stress, increasing ROS levels and thereby inhibiting cell proliferation signaling and metabolic reprogramming of cancer cells, suppressing pro-inflammatory cytokines, and promoting apoptosis, necrosis, and autophagy (58). The ability of flavonoids to scavenge ROS is attributed to the presence of a number of phenolic hydroxyl groups in their molecular structure, which facilitate electron exchange and stable compound formation through substitution reactions with free radicals. Therefore, flavonoids with a higher number of hydroxyl groups exhibit greater antioxidant and pro-oxidant capacities (59,60). A study has demonstrated that ovarian cancer cells treated with flavonoids, such as apigenin, luteolin and myricetin, exhibit a dose-dependent increase in intracellular ROS levels compared with untreated control cells. This ROS elevation triggers activation of the intrinsic apoptotic pathway, leading to cell cycle arrest and inhibition of invasion (61). Similarly, quercetin has been reported to induce cancer cell death by positively modulating ROS levels (62).

ccRCC undergoes metabolic reprogramming to sustain excessive cell proliferation, directly influencing the maintenance and aggressiveness of neoplastic cells (63). For instance, glutathione (GSH) metabolism has been extensively investigated in tumor progression and as a targeted therapeutic strategy for cancer (64,65). The upregulation of GSH levels is closely associated with cellular detoxification mechanisms, providing certain types of cancer, including breast cancer, in which elevated GSH levels have been linked to resistance against chemotherapy drugs such as doxorubicin and cisplatin, and non-small cell lung cancer, in which high levels of GSH contribute to resistance against various chemotherapeutic agents such as cisplatin and paclitaxel, with an advantage by eliminating and detoxifying specific chemotherapeutic agents, thus conferring therapeutic resistance (66,67). Additionally, elevated levels of GSH contribute to tumor development and increase the likelihood of metastasis. Depletion of GSH levels can induce various types of cell death, including apoptosis, necroptosis, ferroptosis, and autophagy (68). This serves as the foundation for studies investigating the suppression of GSH levels as a chemo-sensitization approach in cancer therapies, rendering tumor cells more susceptible to the cytotoxic and cytoprotective effects of antineoplastic agents (69,70). In this context, tangeretin has been shown to prevent GSH depletion in cells exposed to tert-butyl hydroperoxide (71). The anticancer properties of flavonoids have been extensively studied, revealing that they mediate antitumor effects through multiple mechanisms. These include promoting autophagy and apoptosis, inhibiting tumor invasion, growth and angiogenesis, as well as modulating ROS levels in tumor cells (24). Additionally, flavonoids can inhibit carcinogens and regulate pro-inflammatory pathways, further contributing to their potential as therapeutic agents (51).

Flavonoids, a group of naturally occurring polyphenolic compounds, exhibit anticancer properties by modulating various key processes involved in carcinogenesis (72). These processes include apoptosis, proliferation, angiogenesis and metastatic progression, which are often driven by dysregulation of tumor suppressor genes and activation of oncogenes (73). Quercetin and genistein have been demonstrated to induce apoptosis in cancer cells through the activation of intrinsic and extrinsic apoptotic pathways. They enhance the expression of pro-apoptotic proteins (Bax and p53) and inhibit anti-apoptotic proteins (Bcl-2) (74). EGCG and lutein inhibit cyclin-dependent kinases (CDKs) and upregulate CDK inhibitors, including p21 and p27, leading to cycle arrest (75,76). Apigenin and kaempferol have been reported to inhibit angiogenesis by downregulating VEGF and its receptors, thereby reducing the supply of nutrients to tumors (77,78). Naringenin and hesperidin have been demonstrated to suppress epithelial-mesenchymal transition markers, including vimentin and N-cadherin, and reduce the activity of MMPs, limiting cancer cell invasion and migration (79). A study has demonstrated that flavonoids exert anticancer effects by regulating cascades that influence the metabolic reprogramming of various pathways, including lipid metabolism, amino acid metabolism and ketogenesis, in both *in vitro* and *in vivo* experiments (80), and they represent a viable strategy to inhibit key stages in the development of cancer (81). Table SII summarizes the findings of research studies investigating the influence of flavonoids on critical metabolic pathway components across various cancer types, with distinctions made where the studies focus specifically on RCC.

Glucose metabolism in RCC. The fundamental and significant source of energy in the biological system is glucose. In RCC cells, glucose deprivation causes oxidative stress and cellular cytotoxicity (82). Several mechanisms, including glucose absorption, glycolysis, glycogenolysis, gluconeogenesis, lactate reabsorption, and lactate excretion, maintain glucose homeostasis (83) (Fig. 3).

Transmembrane glucose transport. Renal carcinoma cells need more glucose than normal cells to function as an energy source and as a resource for the production of various chemicals (84). Several cancer cell types exhibit upregulated expression levels of glucose transporters (GLUTs), particularly GLUT1, to maintain steady glucose uptake. Therefore, targeting GLUTs using various natural substances, such as flavonoids, is an optimal strategy for RCC treatment. Catechins from green tea exhibit inhibitory action against GLUT1 in RCC (85). Other polyphenols, such as epicatechin gallate (ECG) and EGCG, inhibit GLUT1 by directly binding to the transporter (86), which can change how it recognizes its substrates competitively or non-competitively. The connections of the extracellular side of the transporter with ECG and EGCG can competitively prevent glucose from binding to GLUT1 (87). Studies have demonstrated that quercetin exerts non-competitive inhibition by binding to GLUT1. Kinetic analysis has also demonstrated that flavonoids can decrease the Michaelis constant and maximum velocity values of GLUT1 (87,88). Genistein, an iso-flavonoid compound, exerts a preventive effect against prostate and breast cancer by blocking GLUT1 activity and acting as a competitive inhibitor (89). Due to its potent activities, including antioxidant, chemopreventive and anticancer activities, resveratrol might directly inhibit GLUT1 by non-competitively binding to its internal domains, decreasing uptake of glucose in human leukemia cells (90). Flavonoids,

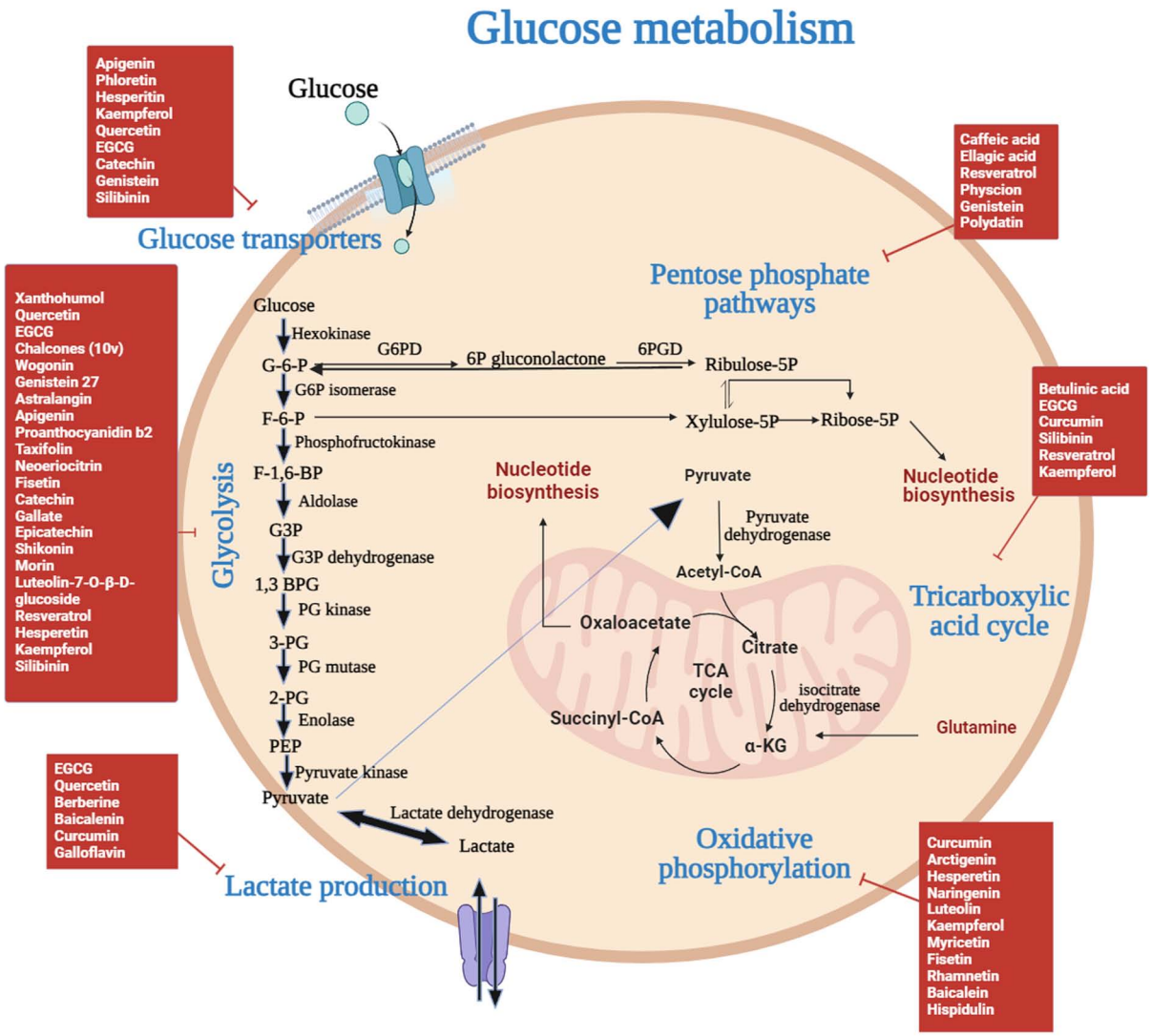

Figure 3. Flavonoids pharmacologically target glucose metabolism in RCC. Glycolysis and the PPP in the cytoplasm, as well as the TCA in the mitochondria, make up glucose metabolism. RCC is associated with increased levels of glycolysis and activation of the PPP. After being transported into the cells by glucose transporters, glucose proceeds through glycolysis to produce pyruvate, which is then converted to ATP via the TCA cycle. The majority of pyruvate in cancer cells enters lactic acid fermentation to produce ATP quickly, whereas the flow of pyruvate into the TCA cycle decreases. Various flavonoids control the metabolism of glucose. α-KG, α-ketoglutaric acid; 1,3 BPG, 1,3-bisphosphoglyceric acid; 2-PG, 2-phosphoglyceric acid; 3-PG, 3-phosphoglyceric acid; 6PGD, 6-phosphogluconate dehydrogenase; EGCG, epigallocatechin-3-gallate; F-1,6-BP, fructose 1,6-bisphosphate; F-6-P, fructose 6-phosphate; G-6-P, glucose 6-phosphate; G3P, glycerol-3-phosphate; G6PD, glucose-6-phosphate dehydrogenase; PEP, phosphoenol pyruvate; PPP, pentose phosphate pathway; RCC, renal cell carcinoma; TCA, tricarboxylic acid cycle.

natural substances in plants with anticancer and antioxidant properties, might affect GLUTs in RCC (91,92). Flavonoids may affect how RCC cells utilize glucose, interfering with their energy metabolism and preventing the formation of tumors (24). More research is required to fully comprehend the mechanism and therapeutic implications of flavonoids in the metabolic reprogramming of RCC. Research on the possible therapeutic effect of flavonoids in targeting glucose metabolism in renal cancer is ongoing.

Glycolysis. In normal cells, glycolysis converts the majority of glucose to pyruvate. The mitochondria undergo this process to participate in the TCA cycle (83). Through OXPHOS, pyruvate causes the synthesis of ATP. Renal cancer cells use the enzyme lactate dehydrogenase (LDH)A to ferment lactic acid to convert pyruvate into lactate (93). This mechanism produces less energy compared with OXPHOS (94). To compensate for this lower energy yield, renal cancer cells require a higher rate of glucose consumption. A complex web of processes, including glucose absorption, glycolysis, glycogenolysis, gluconeogenesis, glucose reabsorption, and glucose excretion, manages glucose homeostasis, which is influenced by kidney function (83). ccRCC cells exhibit increased glycolysis, suppressed pyruvate dehydrogenase (PDH) flux, and decreased TCA cycle activity compared with other tumor cells. A substantial difference is observed when comparing the rate of glycolysis in ccRCC cells with that in adjacent kidney cells (94). Renal cancer cells have been found to exhibit the conventional Warburg effect, which is characterized by increased cellular expression of all glycolysis-related enzymes (93). Fructose-1,6-bisphosphate, the rate-limiting enzyme, is also recognized as a tumor suppressor in RCC tumors (94). Various biological effects, including

antioxidative, antiangiogenic and general antitumor effects, have been attributed to certain phytochemicals (24,47-49). Flavonoids target the modulation of certain glycolysis-related enzyme activities (24); therefore, flavonoids offer a promising therapeutic strategy for cancer-related studies. A common dietary flavonoid, apigenin, inhibits multiple biochemical pathways involved in the formation of tumors and has anti-cancer properties. Apigenin inhibits glycolysis by regulating pyruvate kinase M2 (PKM2) activity in HCT116 colon cancer cells (95). Inhibition by apigenin can result in the maintenance of a low PKM2/pyruvate kinase 1 ratio (96). Proanthocyanidin B2 influences PKM2 activity in hepatocellular carcinoma (97). The first irreversible stage in glycolysis is the phosphorylation of hexoses, carried out by the enzyme HK (98). Since cancer cells mostly exhibit upregulated expression levels of HK, HK may be a promising molecular target for flavonoid-based treatment (99). Xanthohumol is a flavonoid that affects colon cancer by inhibiting HK2, a crucial enzyme involved in glycolysis (98). In hepatocellular carcinoma, quercetin inhibits Akt/mTOR signaling and decreases the activity of HK2 (99). Both *in vitro* and *in vivo*, the synthetic flavonoids Gl-v9 and 10v reduce HK2 expression (100,101). Morin, a flavonoid, may prevent LDH from acting enzymatically in RCC (102). In addition, to efficiently inhibiting the growth and proliferation of several cancer cell lines, quercetin also reduces the levels of enzymes linked to glycolysis, such as LDH and LDHA (103). The flavonoid EGCG decreases the activity of LDH, LDHA and phosphofructokinase in *in vitro* analysis (86,104,105). Quercetin also downregulates the enzymatic activity of aldolase, GAPDH and α-enolase (106). Overall, researchers are currently studying how flavonoids affect glycolysis in the metabolic reprogramming of RCC. Although the preclinical results are encouraging, more thorough research, including clinical trials, is required to determine whether flavonoids can be used to treat RCC by modulating glycolytic pathways.

TCA cycle. Nephrological disorders, such as type 2 diabetes, chronic kidney disease, and kidney damage, can disrupt the TCA cycle by impairing mitochondrial function and reducing levels of key TCA cycle intermediates leading to altered energy metabolism (107,108). The enzyme PDH restores the metabolic flux to the TCA cycle in renal cancer cells, which is often disrupted by downregulation of pathways such as glycolysis, lipid metabolism, and amino acid metabolism (93). These enzymes catalyze the biochemical reactions that generate end products, which either enter the TCA cycle directly or are converted into intermediates that feed into the cycle (94). PDH catalyzes the conversion of pyruvate into acetyl-CoA (109,110). Different flavonoids, such as betulinic acid, can inhibit the activity of PDH in cancer cells, as demonstrated in an *in vitro* study (111). Typically, RCC cells divert glucose for aerobic glycolysis breakdown from the TCA cycle. Thus, glutamine and fatty acids are needed by kidney cancer cells to power the TCA cycle (111,112). Further study is required to fully establish the direct actions of flavonoids against the TCA cycle in the metabolic reprogramming of RCC. Future research is needed to fully understand how flavonoids affect RCC metabolism, particularly given the complex interactions suggested by their potential influence on mitochondrial function, redox balance, and enzyme activity.

OXPHOS. Normal kidney cells filter blood and reabsorb nutrients, which are processes that are heavily dependent on ATP. These cells have high OXPHOS activity, which is supported by the electron transport chain (ETC) (94). In renal cancer cells, decreasing the activity of the TCA cycle also results in diminished ETC activity (94). A study has measured the activity of OXPHOS and the ETC in RCC tissues (93). From the less aggressive to the most aggressive type of RCC, there is an increase in mitochondrial damage. Marked downregulation of OXPHOS complexes, which impairs the overall OXPHOS process, has been observed. This impairment is linked to dysfunction in the ETC, which is responsible for generating the proton gradient required for ATP synthesis (113). Different phytochemicals present in various medicinal plants control the activity of different complexes. Curcumin is a flavonoid that suppresses the activity of ATP synthase (113-116). A study examined the role of metabolic reprogramming in breast cancer, specifically focusing on the targeting of the ATP synthase complex (117). The flavonoid arctigenin also inhibits mitochondrial complexes II and IV, selectively killing only OXPHPOS-dependent pancreatic cancer cells (116). Some flavonoids, including luteolin, myricetin, fisetin, rhammetin, and baicalein, directly inhibit complex I activity by lowering H_2O_2 production in rat heart mitochondria (118). Other flavonoids, such as hispidulin and eupafolin, inhibit complex III by lowering H_2O_2 production (118). Flavonoids may influence mitochondrial processes that could modify cellular energy metabolism, thereby potentially affecting OXPHOS in the metabolic reprogramming of RCC. The therapeutic implications of flavonoids in targeting OXPHOS in RCC require additional investigation, including clinical studies.

Kidney cancer cells, particularly ccRCC cells, exhibit distinct metabolic reprogramming that supports their rapid proliferation and survival under hypoxic conditions. This reprogramming often involves a shift from OXPHOS to glycolysis, even in the presence of oxygen (91). Hypoxia-inducible factor 1 (HIF-1) serves a central role in this metabolic adaptation. HIF-1 is a transcription factor that is stabilized and activated under hypoxic conditions, leading to the upregulation of genes involved in glycolysis, angiogenesis, and cell survival (91,119). Quercetin, resveratrol, and EGCG have been shown to decrease HIF-1α protein levels by promoting its degradation and inhibiting its synthesis (91,120). This effect occurs through the inhibition of the PI3K/Akt/mTOR signaling pathway, which serves a crucial role in the translation and stabilization of HIF-1α (121). Kaempferol influences mitochondrial function and OXPHOS, providing an additional layer of metabolic regulation by activating the AMP-activated protein kinase pathway. This shifts the metabolic balance towards OXPHOS, reducing the reliance on glycolysis and inhibiting cancer cell proliferation (73). Luteolin promotes mitochondrial apoptosis by increasing the production of ROS and disrupting the mitochondrial membrane potential. This leads to the activation of caspase-dependent apoptotic pathways, thereby reducing the survival of cancer cells (122).

Pentose phosphate pathway (PPP). Glycolysis is diverted from glucose 6-phosphate (G-6-P) to fructose 6-phosphate by the PPP. In the context of cellular metabolism, this process provides crucial components for nucleotide synthesis. Specifically, it generates five-carbon sugars (ribose and

deoxyribose) and reduces equivalents in the form of NADPH. The five-carbon sugars are essential for the backbone structure of nucleotides, which are the building blocks of DNA and RNA. NADPH is a key reducing agent that supplies the necessary electrons for various biochemical reactions, including those involved in the synthesis of nucleotides. This synthesis is vital for cell proliferation and repair, making these components critical for maintaining cellular function and integrity (123). The PPP in renal cancer cells acts as a defense against high levels of oxidative stress. This pathway influences kidney diseases by altering key metabolic processes involved in disease progression. For example, in diabetic kidney disease, the pathway can affect the accumulation of advanced glycation end-products and oxidative stress, which are critical in the development of diabetic nephropathy. By modulating these factors, the pathway may help mitigate inflammation, fibrosis, and oxidative damage associated with kidney injury. In cases of kidney damage, the pathway modulation of oxidative stress and cellular repair mechanisms can impact the extent of tissue damage and repair processes, potentially slowing disease progression and improving renal function (12,93). According to a previous study, RCCs may rewire their metabolism to control glucose flow into the PPP (124). G-6-P enters the PPP pathway, which produces precursors for lipids, nucleotides, and NADPH. These molecules provide cells with the energy and substrates required for the creation of macromolecules, which promotes the growth of tumors (125). Two steps in the PPP are often reprogrammed in cancer. First, the oxidative phase, an irreversible step that involves the enzyme G6PD, which catalyzes the conversion of G6P to 6-phosphoglucose lactone. The step is considered rate-limiting and is crucial for generating NADPH, which is essential for counteracting oxidative stress. Second, the non-oxidative phase, the subsequent step involving the enzyme ribulose-5-phosphate epimerase, which converts ribulose-5-phosphate into xylulose-5-phosphate. This step is important for the generation of nucleotides and amino acids, which are often upregulated in cancer cells to support rapid cell proliferation (126).

Renal cancer cells express glucose-6-phosphate dehydrogenase (G6PD), the first and rate-limiting enzyme of the PPP, at high levels (127). Similar to G6PD, other oxidative branch NADPH-generating enzymes, such as 6-phosphogluconate dehydrogenase (6PGD), regulate PPP flux in renal cancer cells (93). Different phytochemicals, including caffeic acid, ellagic acid and physcion, directly downregulate the activity of G6PD and 6PGD in different types of cancer, including lung cancer, leukemia, and breast cancer (124,125,128). Limited research has been performed on the precise impact of flavonoids on the PPP in the metabolic reprogramming of RCC. Flavonoids may indirectly impact the PPP. The PPP is essential to sustain redox equilibrium and supply the building blocks for nucleotide synthesis (129,130). Although further research is required to understand the precise mechanism and clinical implications, the aforementioned information suggests that flavonoids may impact the course of RCC by modulating the PPP.

Fatty acid metabolism in RCC. One of the most prominent metabolic abnormalities found in cancer cells is defective lipid metabolism, which serves a major role in the development and metastasis of cancer cells (131). Dysregulated lipid *de novo* synthesis was observed in tumor cells in the 1950s, and this was found to be a critical metabolic state for cancer cells (132). Obesity is frequently linked to RCC, and patients with ccRCC have been found to exhibit greater levels of cholesterol ester accumulation in their kidneys (93). An outline of the metabolic pathways for fatty acids in ccRCC and how flavonoids alter them is shown in Fig. 4. Metabolomics research has revealed that ccRCC cells exhibit higher levels of fatty acyl-carnitines and carnitine than control cells (16). These differences were shown to be closely linked to the clinical features of patients with kidney cancer. Furthermore, RCC cells have a markedly compromised β-oxidation pathway, which may cause a greater accumulation of fatty acyl-carnitines (133). Since the formation of lipid droplets in the cytoplasm produces the characteristic clear cell phenotype, ccRCC is considered to be characterized by these droplets (134). Additionally, the accumulation of lipid droplets around the endoplasmic reticulum (ER) supports the ER integrity in ccRCC cells (135). It has been demonstrated that, compared with normal kidney cells, ccRCC cells exhibit downregulation of fatty acid oxidation enzymes, such as acetyl CoA carboxylase (ACC), fatty acid synthase (FAS), and stearoyl CoA desaturase (SCD) (136). NADPH oxidation is catalyzed by the β-ketoacyl reductase (KR) and enoyl reductase domains of the multifunctional enzyme FAS (93). EGCG can inhibit the enzymatic activity of FAS *in vitro* by competing with NADPH to bind the KR domain (135,137). Emodin flavonoids can also inhibit FAS activity in breast, liver, prostate, leukemia, and colon cancer (133). SCD1 is the enzyme that is responsible for lipid storage, which is highly expressed in ccRCC and serves an important role in growth and proliferation (138). Flavonoids, such as betulinic acid and platyphylloside, directly inhibit SCD1 in colon cancer (139). Flavonoids reduce the activity of SCD1, which subsequently inhibits RCC growth. FAS is also associated with RCC tumor growth aggressiveness and poor patient survival (140). The activity of FAS can be directly affected by flavonoids such as kaempferol, luteolin, morin, platyphylloside, quercetin, and resveratrol (131,133,135,137,141,142). HIFs are essential for the proliferation of RCC cells (91). Flavonoids such as oroxylin A, resveratrol, methylalpinumisoflavone, and EGCG can also regulate the activity of HIFs, which has been primarily observed in patients with breast cancer (133,143,144). Malonyl CoA is produced by ACC, a rate-limiting enzyme for fatty acid synthesis (145). Soraphen A is a polyketide that inhibits the activity of ACC1, which is upregulated in ccRCC (139). Additionally, quercetin reduces the production of triacylglycerol and fatty acids in rat hepatocytes and inhibits ACC without having any detectable influence on FAS (146). One of the distinctive features of kidney cancer is the reprogramming of the glycerophospholipids and arachidonic acid metabolism (147). The primary constituents of cell membranes are glycerophospholipids, which are also the sources of triacylglycerol, lysophosphatidic acid (LPA), and phosphatidic acid, which are the building blocks of lipid storage. Autotaxin, the enzyme responsible for producing LPA, is highly expressed in the endothelial cells surrounding the tumor, and its activity can be inhibited by several polyphenols (148). Arachidonic acid, a crucial compound in RCC derived from membrane phospholipids, is synthesized through pathways involving

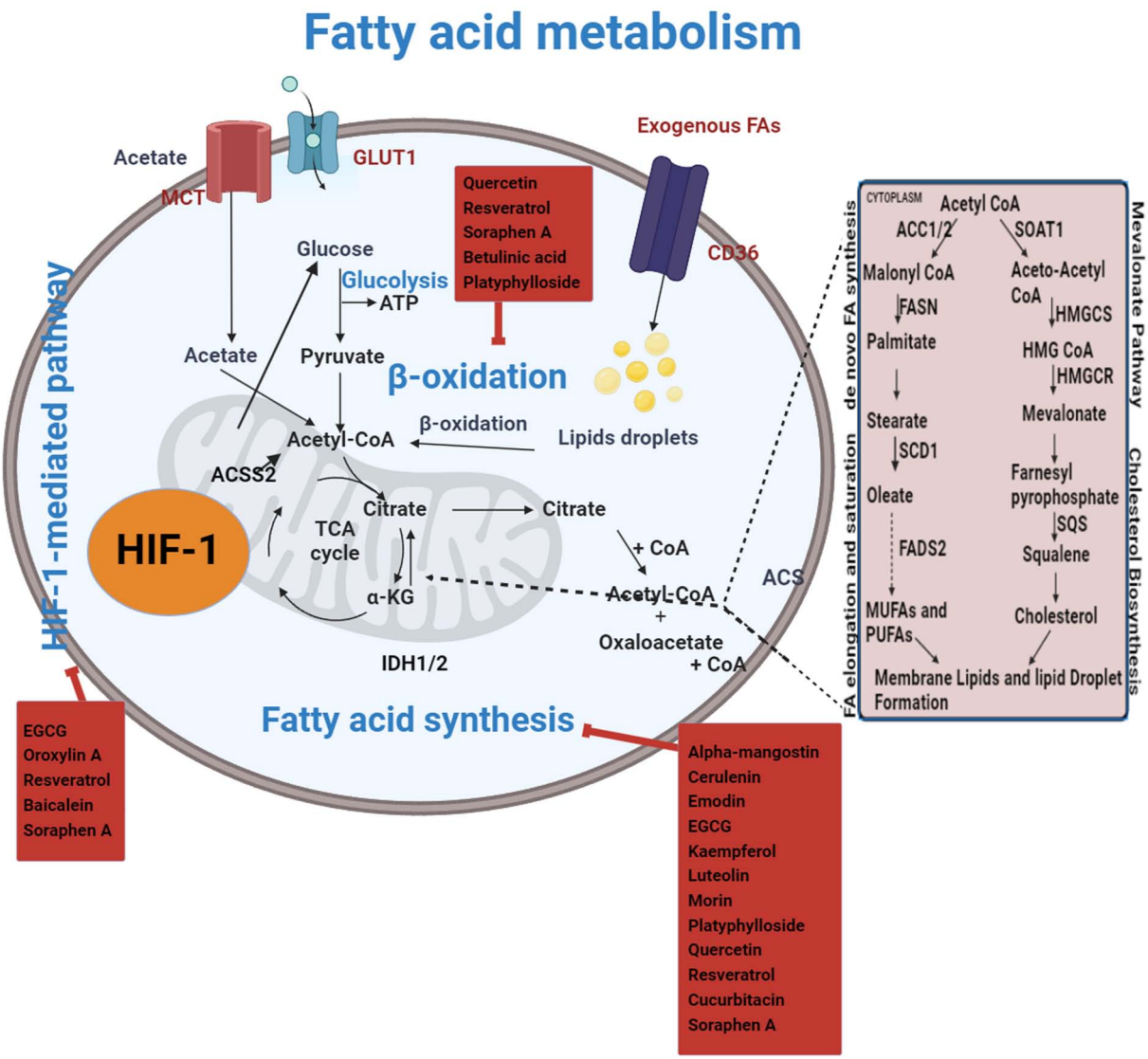

Figure 4. Flavonoids pharmacologically target FA metabolism in RCC. The metabolic pathways for FAs include synthesis, degradation and utilization processes. In RCC, these pathways are altered. Specifically, the balance is shifted towards increased lipid production, which surpasses lipid degradation. In RCC, exogenous FAs (FAs from external sources) contribute to the increased lipid pool, further exacerbating the imbalance between lipid synthesis and degradation. The uptake of these FAs supports enhanced lipid production, which is critical for tumor cell proliferation and metabolic reprogramming. Lipid production surpasses lipid degradation in RCC. The lipid β-oxidation pathway is downregulated in RCC, leading to reduced fatty acid breakdown. Consequently, acetyl-CoA levels are maintained, which continues to support the TCA cycle. This metabolic shift allows cancer cells to utilize acetyl-CoA for energy production and biosynthesis despite the decreased activity of lipid β-oxidation. However, RCC is associated with elevated levels of carnitine, FA synthesis, phospholipid synthesis and cholesterol production. By focusing on metabolism enzymes, flavonoids inhibit the FA production pathway and are considered to be a possible inhibitor for the metabolic reprogramming of RCC. α-KG, α-ketoglutaric acid; ACC, acetyl CoA carboxylase; ACS, acyl CoA synthetase; ACSS2, acyl CoA synthetase short-chain family member 2; EGCG, epigallocatechin-3-gallate; FA, fatty acid; FADS2, fatty acid desaturase-2; FAS, fatty acid synthase; GLUT1, glucose transporter 1; HIF-1, hypoxia-inducible factor 1; IDH1/2, isocitrate dehydrogenase; HMG, hydroxymethylglutaryl; HMGCR, anti-3-hydroxy-3-methylglutaryl-CoA reductase; HMGCS, hydroxymethylglutaryl CoA synthase; MCT, monocarboxylate transporter; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; RCC, renal cell carcinoma; SCD1, stearoyl CoA desaturase-1; SOAT1, sterol O-acyltransferase 1; SQS, squalene synthase; TCA, tricarboxylic acid.

inflammatory enzymes such as cyclooxygenase (COX)-1, COX-2, and lipoxygenases (149). Different flavonoids have a potential effect on these inflammatory enzymes and have exhibited inhibitory effects on them. Quercetin, EGCG, and resveratrol have been reported to inhibit the activity of COX-1 and COX-2 in enzymatic assays (82,135,150). Compared with normal kidney cells, RCC cells express more of these enzymes (82). Numerous investigations have demonstrated that elevated COX-2 levels are linked to tumor size, stage, and grade in RCC. These findings imply that COX-2 may be a target in ccRCC (151,152). Sterol regulatory element binding protein-1 (SREBP-1) is a key regulator of lipid metabolism. Specifically, flavonoids may inhibit SREBP-1 activity, thereby reducing the expression of genes involved in lipogenesis and contributing to the reprogramming of metabolic pathways in ccRCC (153). Recognized antioxidants and anti-inflammatory flavonoids may affect important facets of RCC fatty acid metabolism. According to some research, flavonoids may alter lipid metabolism-related enzymes and pathways, which may have an impact on lipid synthesis, storage, and utilization in

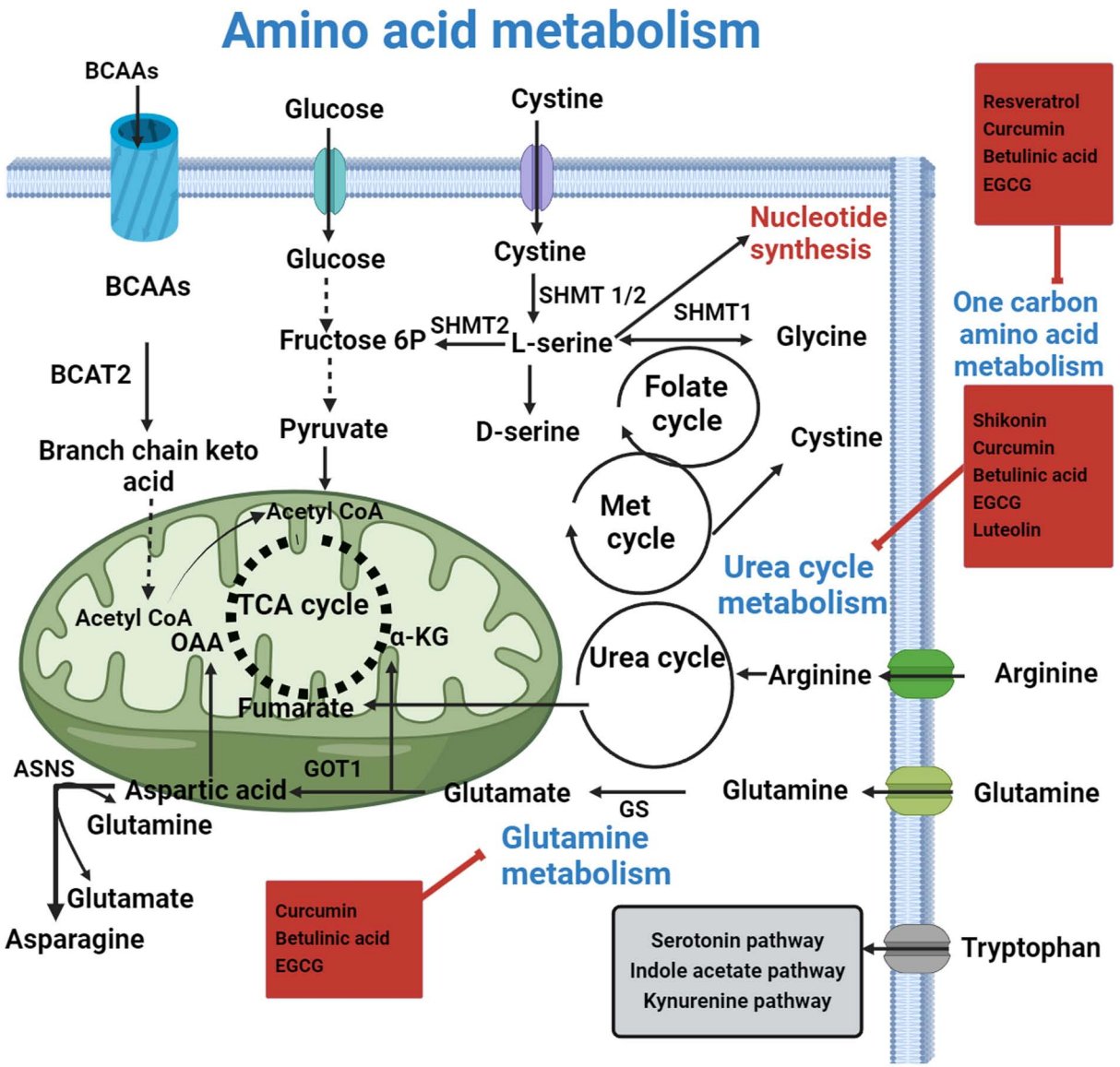

Figure 5. Flavonoids pharmacologically target AA metabolism in RCC. AAs provide metabolic intermediates, such as acetyl CoA, that enable energy generation and lipogenesis, which are necessary for a cell to grow and develop. Both essential and non-essential AAs promote altered metabolism by acting as energy sources. Finding strong and specific inhibitors, as well as practical methods for metabolic reprogramming of RCC might potentially be accomplished by focusing on AA metabolism. To effectively exert their anticancer effects, flavonoids target various metabolic pathways, including amino acid metabolism. They inhibit glutamine metabolism, contributing to their anticancer effects by reducing available glutamine levels. This metabolic adjustment helps counteract oxidative stress and supports cancer cell survival and proliferation. α-KG, α-ketoglutaric acid; AAs, amino acids; ASNS, asparagine synthetase; BCAA, branched-chain amino acid (valine, leucine, isoleucine); BCAT, branched-chain amino acid transaminase; EGCG, epigallocatechin-3-gallate; GOT1, aspartate transaminase; GS, glutamine synthetase; Met, methionine; OAA, oxaloacetic acid; RCC, renal cell carcinoma; SHMT, serine hydroxymethyltransferase; TCA, tricarboxylic acid.

RCC cells. Targeting fatty acid metabolism with flavonoids offers a promising approach to understanding and creating treatment plans for RCC; however, further research is required to fully evaluate their effectiveness.

Amino acid metabolism in RCC. In the context of cancer cell metabolic reprogramming, amino acid metabolism is increasingly recognized for its critical role. Amino acids serve not only as substrates for protein synthesis but also act as essential mediators of redox homeostasis and support various biosynthetic pathways that are upregulated in kidney cells (154) (Fig. 5). Their significance is underscored by the rapid proliferation of renal cancer cells, which depend heavily on amino acids as both metabolites and metabolic regulators to promote growth (94). This underscores the potential of targeting amino acid metabolic pathways as a strategy to manage and inhibit cancer cell proliferation effectively in different ways mentioned below (155).

Glutamine metabolism. Glutamine is one of the primary nutrients that cancer cells use to preserve their biomass and bioenergetics. Furthermore, it serves as a component in the synthesis of lipids and proteins. In the renal cortex, glutamine is employed to keep the pH of the urinary system stable (156). Compared with that in normal kidney tissues, the use of glutamine in ccRCC is increased, and the GSH/GSH

disulfide balance is strictly regulated (156). Increased levels of glutamine are linked to elevated levels of free fatty acids in RCC (93,156). Furthermore, in rapidly proliferating renal cancer cells, one of the predominant metabolic pathways is the reductive carboxylation of glutamine (156). In transgenic mouse models of human RCC, there was an increase in the amounts of glutamate and α-ketoglutarate, alongside upregulation of glutaminase (GLS), which serves a crucial role in glutamine metabolism and supports the metabolic needs of rapidly proliferating cancer cells (156). Based on assessment of the literature, it has been established that HIF expression serves a crucial role in triggering the reductive carboxylation of α-ketoglutarate in RCC cells. Additionally, the reversal of isocitrate dehydrogenase flux to the reductive carboxylation of glutamine to citrate has been predicted (93,156). GSH peroxidase 1 (GPX1) expression is upregulated in ccRCC cells. The activity of GLS and GPX1 can be controlled by the flavonoids present in different medicinal plants (93). Curcumin is a flavonoid that downregulates the activity of GLS in RCC (93). GLS is an important enzyme that converts glutamine into glutamate in the metabolic reprogramming of RCC, which can be directly inhibited by betulinic acid (150,157).

Serine and glycine metabolism. Serine can be obtained through extracellular absorption, with a portion of it derived from glucose metabolism (155). Serine and glycine are two amino acids that are connected during biosynthesis, and function as vital precursors for the formation of proteins, lipids and nucleic acid building blocks, all of which are essential for the growth of cancer (155). Under the catalysis of serine hydroxy methyltransferases, serine, whether synthesized *de novo* from 3-phosphoglycerate or imported from external sources, can be further converted into glycine (158). Threonine dehydrogenase and glycine C-acetyltransferase may also convert threonine into glycine (159). The creation of macromolecules, including lipids, proteins and nucleic acid, requires methyl groups for one-carbon metabolism, which glycine subsequently supplies (160). Serine is also involved in DNA methylation, an important step for the metabolic reprogramming of cancerous cells (161). Various synthetic drugs are currently in clinical trials targeting different metabolic pathways to reprogram renal cancer cells (159). However, synthetic drugs often come with side effects, which makes natural alternatives an appealing option (40). Plant-derived secondary metabolites, such as flavonoids, including quercetin, apigenin, morin and resveratrol, have shown efficacy in reprogramming cancer cells with potentially fewer side effects (162).

Arginine metabolism. Numerous solid tumor cells quickly succumb to growth media without arginine, which is an important amino acid (163). Additionally, it participates in several crucial cellular metabolic processes, including the urea cycle, the manufacture of nitric oxide, proline and glutamate, as well as nucleotide biosynthesis (16). Arginine can also be depleted by catalytically converting arginine to citrulline using the pegylated version of arginine deaminase (163). In addition to catalyzing the synthesis of argininosuccinate from citrulline and aspartic acid, argininosuccinate synthetase (ASS) is an enzyme that limits the pace at which arginine may be synthesized entirely from the beginning (163). Renal and parenchymal cells, which can recycle citrulline back to arginine, are examples of cells with normal expression levels of ASS1 (16). However, cells lacking ASS1, such as ccRCC cells, are unable to convert citrulline into arginine (16). Other enzymes, such as argininosuccinate lyase, catalyze the conversion of argininosuccinate to arginine and fumaric acid, which in turn connects arginine metabolism to the TCA cycle-generated energy metabolism of glucose (163). According to the literature, certain human malignancies, such as hepatocellular carcinoma and malignant melanoma, lack ASS, making them vulnerable to arginine deprivation treatment since they are unable to synthesize arginine (164). The activity of these enzymes may be influenced by the flavonoids present in different medicinal plants (165). During oncogenesis, cells often become dependent on external supplies of arginine due to the loss or absence of the enzyme ASS1. While ASS1 is normally expressed in proximal tubule cells, it is absent or not significantly expressed in ccRCC (16,163-165). In arginine metabolism, the activity of arginase and nitric oxide synthase serves vital roles in cancer cell proliferation and immune response (165). Researchers have investigated flavonoids such as quercetin and genistein for their potential effects on nitric oxide production, which is intricately linked to arginine metabolism (123,166). The specific impact of flavonoids on RCC and arginine metabolism requires further research.

Tryptophan. There are three main downstream pathways of tryptophan. The serotonin, indole acetate and kynurenine pathways are significant in understanding its metabolism (15,94). Indoleamine 2,3-deoxygenase (IDO) catabolizes the majority of tryptophan. Through the kynurenine pathways, it serves as a rate-limiting enzyme in this reaction. Tryptophan levels in ccRCC are lower compared with those in normal kidney cells, indicating higher consumption (167). ccRCC tissues exhibit elevated amounts of quinolinate and kynurenine (168). On the other hand, there is a decrease in the amounts of enzymes that support the kynurenine pathways, such as aldehyde dehydrogenase 2, monoamine oxidase and DOPA decarboxylase, in RCC, which is considered to be related to the serotonin and indole acetate pathways (169). These findings suggest the reduction of tryptophan/kynurenine through IDO enrichment in RCC (170). The approval of PD-1 inhibitors such as nivolumab as second-line treatments for RCC represents an advancement in immunotherapy. These inhibitors work by blocking the PD-1 pathways, which normally help to dampen the immune response and prevent autoimmunity. By inhibiting PD-1, these drugs enhance the activity of cytotoxic T cells against cancer cells, leading to increased tumor cell death. In addition to PD-1 inhibitors, adjuvant therapies that stimulate cytotoxic T-cell activity are employed to further boost the immune response (171). Tryptophan catabolism by IDO and other enzymes can suppress T-cell activity and contribute to immune evasion by tumor (172). These therapies help to optimize the effectiveness of PD-1 inhibitors by promoting a more robust and sustained immune attack on RCC cells (173). The activity of enzymatic pathways can be influenced by flavonoids such as morin, quercetin, EGCG, resveratrol and betulinic acid because tryptophan metabolism is involved in various cellular processes, including immune modulation and the production of metabolites, such as serotonin and kynurenine (174).

4. Toxicity associated with flavonoids

While it is commonly considered that using plant secondary metabolites as an alternative medication is safe or does not cause side effects (175), literature has also demonstrated that extended exposure to large dosages of some flavonoids can be potentially harmful (176). One flavonoid with anticancer properties is resveratrol. A study conducted *in vivo* suggested that consuming it at a higher dosage (3,000 mg/kg body weight) may be harmful to the kidneys (177). Turmeric, a commonly used traditional medicine in the Indian subcontinent, contains a complex mixture of chemical compounds. Among these, there are numerous substances that can be categorized based on their biological effects. Specifically, turmeric has been associated with 136 mutagenic, 153 carcinogenic, and 64 hepatotoxic compounds. Among the active ingredients with anticancer potential is curcumin, which exhibits dose-dependent hepatotoxicity (178). Overdosing and continuous usage of curcumin in rats produces ROS and proinflammatory cytokines. It also gradually reduces antioxidants, such as superoxide dismutase and glutathione S-transferase, which leads to liver damage (179). Genistein neutralizes the protective effect of letrozole, an aromatase inhibitor, against estrogen-dependent breast cancer (180). Although EGCG has numerous health advantages, research has demonstrated that a high dosage of the compound in mice can cause hepatotoxicity, which has been linked to the suppression of antioxidant enzymes (181). Both patients and doctors should be aware of the potential side effects of herbal medicines, as well as how they may interact with other prescription medications. Dietary supplements should be used cautiously, considering both the positive and negative consequences. Before being approved for use in the treatment of any disease, herbal drugs must undergo quality and pharmacological evaluations for toxicity.

5. Dietary bioactive compounds as chemopreventive agents

Considering the global increase in cancer cases, mortality, and treatment limits, cancer prevention must continue to be a focus for improved cancer management (182). Lifestyle changes can postpone the beginning of cancer, with nutrition serving a notable role (183). Additionally, consuming a variety of plant-based foods may help prevent cancer and aid in its treatment (182). Numerous plant-based bioactive compounds, including EGCG from green tea, lycopene from tomatoes, apigenin from parsley, curcumin from turmeric, resveratrol from grapes, genistein from soybeans, and gingerol from ginger, have anti-cancer properties and can be used as an easily accessible and affordable cancer prevention strategy (183,184. The American Cancer Society advises individuals, including patients with cancer, to include a variety of plant-based foods in their diet, as this can contribute to overall health and may lower the risk of developing various types of cancer. These include garlic, oranges, green tea, cereals, beans, soy-based food, peas, and other fruits and vegetables (185). The Food and Agriculture Organization and the World Health Organization jointly organized conferences in Japan in 2004 and 2021 titled 'Fruits and Vegetables for Health', which advocated for consuming 400 g of fruits and vegetables daily to lower the risk of various illnesses, including cancer (186).

6. Combination therapy with bioactive compounds against cancer

Numerous bioactive compounds such as resveratrol, quercetin and curcumin may have distal mechanisms of action to produce anticancer effects (187). Their combined utilization suggests promising treatment techniques. Numerous investigations have demonstrated that the combinations of chemicals, such as co-treatments with emodin and curcumin, might have a synergistic impact in preventing the proliferation and invasion of breast cancer cells (188-190). Additionally, the antitumor activities of paclitaxel against lung cancer are synergistically improved by emodin *in vivo* and *in vitro* (191). Cerulenin and emodin are inhibitors of FAS and have cumulative effects on FAS inhibition in colon cancer cells (133). As a result, combining two or more chemicals can result in stronger anticancer effects. However, this depends on the specific genes or metabolic pathways of each molecule and has to be validated by experiments.

7. Summary

The metabolic reprogramming observed in RCC exhibits heterogeneity, demonstrating varying metabolic preferences and patterns among different cancer types. Unlike molecular inhibitors and traditional chemotherapeutics, which mainly target a single metabolic pathway, flavonoids exhibit a unique mechanism of action by impacting several metabolic pathways to achieve their antitumor effects. The molecular mechanisms by which flavonoids control the reprogrammed metabolic pathways in RCC are described in the present review, with particular attention paid to how they target necessary metabolic rate-limiting enzymes such as HK2, FAS, LDHA and SREBP-1. Most flavonoids affect the metabolic pathways of glucose and fats, but some also affect the metabolic pathways of amino acids in RCC. For example, genistein inhibits both the intake of glucose and the process of glycolysis.

By interfering with metabolic pathways, some flavonoids not only directly lower RCC cell viability but also improve the antitumor effectiveness of traditional chemotherapeutics. For instance, shikonin activates the mitochondria to cause intracellular oxidative stress and inhibits the glycolytic process by lowering PKM2 activity. In contrast to traditional cancer treatments, such as radiation, chemotherapy, and surgery, which focus solely on the illness, the use of flavonoids is intended to enhance the defenses of the body against cancer by promoting the mobilization and regulation of all physiological systems. This holistic approach underscores the potential of flavonoids in directly impacting tumor metabolism but also synergistically enhancing the effectiveness of existing cancer treatments.

Flavonoid therapeutic approaches mainly target enhancing blood flow, supporting overall health, and strengthening the defenses of the body against disease. These approaches aim to provide systemic detoxification, reduce inflammation, and alleviate pain (192). For example, EGCG has the potential to improve the quality of life for patients with cancer by both preventing the growth of cancer and relieving the neuropathic pain caused by paclitaxel (193). Flavonoids exhibit marked advantages in impeding the growth and proliferation of cancer cells *in vivo* by modulating metabolic pathways.

Several studies have validated the inhibitory effects of natural constituents in animal models (194,195); however, it is imperative to note that the quality of some studies requires further systematic investigation. Additionally, it is important to dispel the misconception that flavonoids are inherently gentler or less toxic than synthetic chemical drugs. While flavonoids are natural compounds with potential therapeutic benefits, they can still have adverse effects and interactions, and their safety profile must be carefully evaluated in clinical contexts, just as with synthetic drugs. Certain flavonoids exhibit hepatotoxicity or nephrotoxicity, potentially leading to irreversible impairments in patients (196).

According to the traditional theory of compatibility, toxic herbal medicines, including some flavonoids, could be combined with other appropriate conventional Chinese medicines to mitigate potential toxicity risks (178). Challenges persist in standardizing the production and quality control for flavonoids. Furthermore, evaluating the efficacy of flavonoids in interfering with reprogrammed cell metabolism in RCC necessitates randomized controlled clinical trials. Addressing these aspects is essential to advance the understanding of the therapeutic potential of flavonoids, and ensure their safe and effective application in the context of RCC treatment.

Flavonoids represent a promising class of compounds for the treatment of RCC due to their ability to target multiple metabolic pathways with lower toxicity compared with conventional chemotherapeutics (197). Future research should focus on exploring the synergistic effects of flavonoids with other therapeutic agents. Understanding the long-term outcomes of flavonoid-based interactions with specific metabolic targets is crucial for evaluating their efficacy and safety in cancer treatment. Comprehensive studies are needed to assess how these interactions affect metabolic pathways over extended periods and determine their potential impact on overall patient health and treatment outcomes. These studies could pave the way for the development of more effective and personalized treatment strategies for RCC.

8. Conclusion

Flavonoids hold significant promise as anticancer agents due to their ability to modulate various pathways involved in cancer metabolism. Their natural origin and multifunctional properties make them appealing alternatives to synthetic drugs. Flavonoids exhibit lower toxicity and fewer side effects compared with conventional chemotherapy agents, enhancing patient compliance and quality of life (197). This makes them preferable to other anticancer drugs targeting metabolic reprogramming. Furthermore, the ability of flavonoids to selectively inhibit cancer cell proliferation, induce apoptosis, and prevent metastasis underscores their potential as more effective anticancer agents compared with other phytochemicals and synthetic drugs (197).

Because of the extensive reprogramming of metabolic pathways, extracellular stress and the immune system, renal cancer is frequently recognized as a metabolic disorder. By improving tumor imaging and identifying novel therapeutic targets, all of these programmed metabolic pathways may be used to create a more successful RCC treatment. By controlling the metabolic reprogramming of cancer cells, flavonoids have effective inhibitory effects on tumor cells and may also improve the sensitization of cancer cells to chemotherapy treatments. Due to poly-pharmacological actions, flavonoids may be able to reduce cancer pain and enhance the quality of life of patients with cancer. Flavonoids counteract metabolic reprogramming in RCC through diverse mechanisms, including inhibition of key metabolic pathways, modulation of glucose transporters and reduction of oxidative stress. By targeting multiple signaling pathways and metabolic processes, flavonoids may disrupt the survival advantage conferred by the altered metabolism of cancer cells.

Additionally, their low toxicity profile and accessibility from natural sources make them attractive drug candidates for further clinical investigation. Integrating flavonoid-based interventions into comprehensive therapeutic strategies may offer novel avenues to improve the prognosis and treatment outcomes of individuals with RCC. Continued research in this field is essential to advance the understanding of the molecular mechanisms involved and ultimately translate these findings into effective clinical applications.

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Availability of data and materials

Not applicable.

Authors' contributions

QZ and ZY conceived the study, supervised the research and contributed to the critical revision of the manuscript. AS conceived the study, collected data, wrote the original draft, and reviewed and edited the manuscript. WL, BS and YZ provided resources, contributed to drafting the manuscript, prepared the tables and figures, and reviewed and edited the manuscript. XL, YS, JX and KC provided resources, contributed to the critical revision of the manuscript, and reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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