Cancer Biol Med 2025. doi: 10.20892/j.issn.2095-3941.2025.0246

REVIEW

Current status of traditional Chinese medicine in modulating mitochondrial metabolic abnormalities in tumors

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ABSTRACT Tumor cells undergo metabolic reprogramming to adapt to rapid proliferation and harsh microenvironments, as evidenced by aerobic glycolysis. Mitochondria serve as key coordinators of this process. Under internal and environmental stress in tumors, mitochondria reprogram metabolism by balancing energy dynamics, redirecting metabolic routes, communicating *via* metabolites, and preserving the quality of mitochondria, thus supporting tumor cell survival. Traditional Chinese medicine (TCM) has a key role in modulating mitochondrial reprogramming in tumor cells, possibly disrupting metabolic pathways that are necessary for survival and proliferation. However, the underlying molecular signaling and cellular biological mechanisms need to be elucidated. In this review, we focused on the Key functions of mitochondria in adapting to tumor metabolic reprogramming are the focus of this review and recent advances in and regulatory mechanisms of TCM and nano-pharmaceutical formulations in maintaining mitochondrial homeostasis are discussed. These insights may help understand the role of mitochondria in the pathogenesis of metabolic diseases, such as cancer, and identify therapeutic targets.

KEYWORDS Mitochondria; traditional Chinese medicine; cancer; mitochondrial homeostasis; mitochondria metabolism

Introduction

Metabolic reprogramming, an important hallmark of neoplastic transformation, is a focus of contemporary oncology research[1]. Metabolic reprogramming refers to the adaptive remodeling of metabolic pathways and the redistribution of metabolic substrates by neoplastic cells to overcome environmental challenges and fulfill biosynthetic demands for proliferation and differentiation[2]. Cancer cells do not rely solely on glycolysis. Oxidative phosphorylation (OXPHOS), lactylation, and amino acid metabolism (represented by glutamine) with lipid metabolism may also have roles in the development of various tumors[3]. In some cases these metabolic processes may even be more critical for the survival of tumors than aerobic glycolysis[4,5].

Mitochondria are important sites for catabolism and biosynthesis in tumor cells. Reprogramming of the mitochondria-associated metabolic network, which involves glucose metabolism, fatty acid oxidation (FAO), and glutamine metabolism, represents a key strategy by which cancer cells adapt to fluctuations in nutrient availability and the microenvironment[6]. For example, when nutrients are scarce, particularly under hypoxic conditions, tumor cells preferentially utilize glucose for aerobic glycolysis to generate sufficient adenosine triphosphate (ATP) and biomolecules (nucleotides, lipids, and amino acids) to support the energetic and biosynthetic demands of proliferation[7]. In contrast, in several persistent cancer cell types, such as BRAFV600E-mutated persistent human melanoma cells and KRAS-inhibited, KRASG12D-mutated mouse pancreatic ductal adenocarcinoma (PDAC), these cells often decrease reliance on glucose and switch to alternative energy substrates, such as fatty acids, to fulfill energetic requirements *via* enhanced mitochondrial OXPHOS[8]. Mitochondria also serve as central regulators of tumor metabolic reprogramming. The production of mitochondrial metabolites, aberrant regulation

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Received May 8, 2025; accepted August 13, 2025;
published online September 23, 2025.
Available at www.cancerbiomed.org

of mitochondrial quality control, and mutations in mitochondrial DNA (mtDNA) can collectively drive the reorganization of biological processes in tumor cells, including energy production, metabolic pathways, and signal transduction.

The plasticity of mitochondrial structure and function allows tumor cells to adapt to the dynamic demands at every stage of oncogenesis. This adaptability makes mitochondria highly promising targets for cancer therapy. Several drugs that target

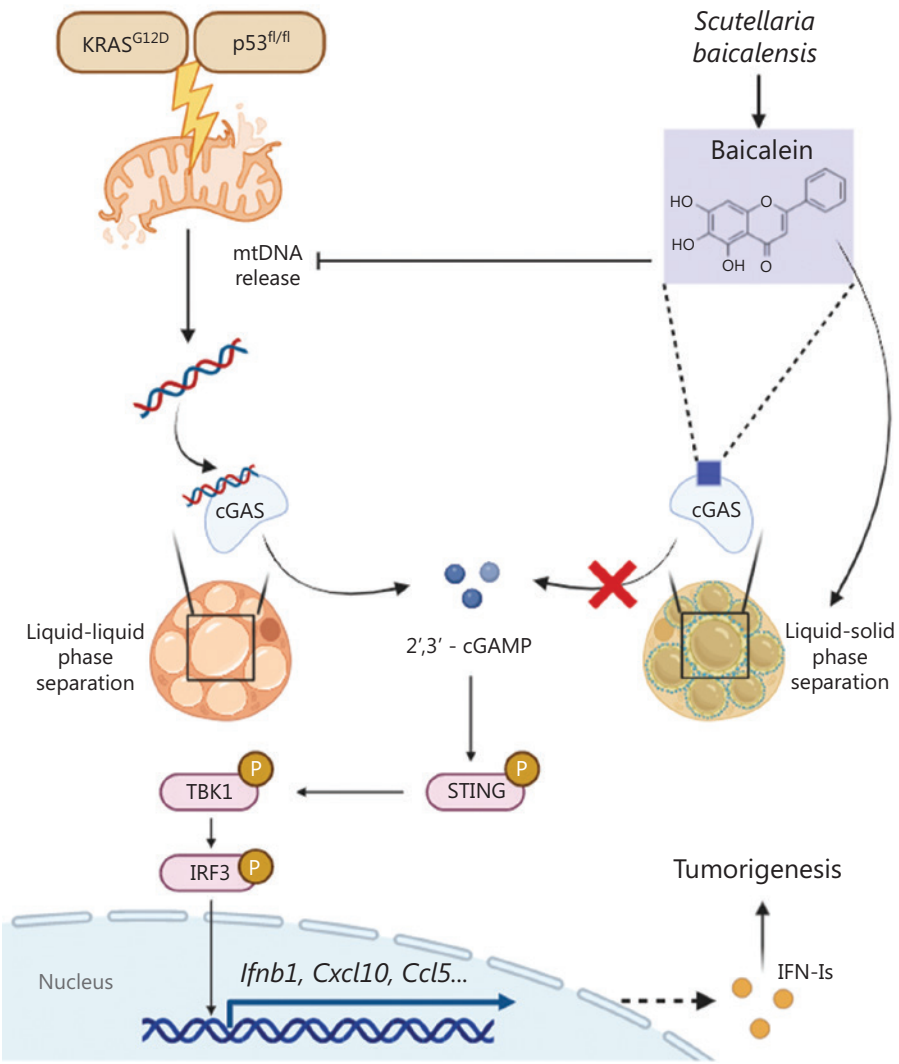

Figure 1 Baicalein induces cGAS phase transition from liquid-to-solid to suppress lung tumorigenesis[10]. KRAS^{G12D}/p53$^{fl/fl}$ mutation induces mitochondrial dysfunction and increases the release of mtDNA. The persistent stimulation of mtDNA is recognized by cGAS and results in the excessive aggregation of cGAS protein liquid condensates. The activated cGAS protein catalyzes the synthesis of 2′,3′-cGAMP. 2′,3′-cGAMP subsequently binds to STING and induces oligomerization, which recruits TBK1 and promotes TBK1 autophosphorylation. Activated TBK1 then phosphorylates STING and IRF3. Phosphorylated IRF3 translocates to the nucleus, initiating the transcription of IFN-Is and other pro-inflammatory cytokines (Cxcl10 and Ccl5), ultimately leading to the formation of lung cancer. Baicalein, extracted from the traditional Chinese medicinal herb *Scutellaria baicalensis*, is able to inhibit the release of mtDNA by preventing mitochondrial dysfunction. In addition, baicalein binds to cGAS and promotes the liquid-solid separation of cGAS protein, thereby terminating the activation of cGAS-STING induced by mtDNA. Ccl5, C-C motif chemokine ligand 5; Cxcl10, C-X-C motif chemokine ligand 10; 2′,3′-cGAMP, 2′,3′-cyclic guanosine monophosphate-adenosine monophosphate; cGAS, cyclic GMP-AMP synthase; IFN-Is, type I interferons; Ifnb1, interferon beta-1; IRF3, interferon regulatory factor 3; mtDNA, mitochondrial DNA; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1.

mitochondrial reprogramming, such as metformin, dichloroacetate, and FV-429, exhibit antitumor activity[9]. Traditional Chinese medicine (TCM) represents a valuable source of mitochondrial reprogramming modulators. Our previous study showed that baicalein, a bioactive compound from *Scutellaria baicalensis* Georgi, prevents the release of mtDNA by restoring mitochondrial function and promotes liquid-solid phase separation in cyclic GMP-AMP synthase (cGAS), thereby terminating activation of the cGAS-STING pathway and suppressing KRAS/p53-driven lung tumorigenesis[10] (**Figure 1**). TCM has promising effects in modulating mitochondrial metabolism, bioenergetics, redox reactions, mitochondrial quality control, and mtDNA in tumor cells. TCM also has unique advantages, such as good biocompatibility, low toxicity, multitarget bioactivity, and favorable long-term tolerability, which have garnered significant interest in testing TCM as mitochondrial modulators[11-13]. In this review how mitochondria contribute to the metabolic reprogramming of cancer to accommodate the survival needs of tumor cells for unrestricted proliferation and progression is described in detail. The research progress and mechanisms of action underlying TCM monomers, compound formulae, and nano-pharmaceutical formulations in regulating metabolic reprogramming are elucidated.

Mitochondrial metabolism and cancer

Mitochondrial alterations are a hallmark of tumor metabolic reprogramming. Key mitochondrial pathways, such as the tricarboxylic acid cycle (TCA) cycle, OXPHOS, FAO, and glutamine metabolism, provide energy and precursors for macromolecule synthesis. Mitochondrial quality and mtDNA are dynamically altered to adapt to different metabolic requirements in response to specific stimuli within the tumor microenvironment.

Glycolysis and OXPHOS

Metabolic reprogramming in tumors is characterized by an increase in glycolysis, which is the central feature of the Warburg effect. This metabolic adaptation provides rapid ATP flux (~100 × faster than OXPHOS) and biosynthetic precursors for macromolecules (nucleotides and fatty acids)[14]. Tumor cells have evolved various regulatory mechanisms to actively increase glycolytic activity, including the activation of oncogenes, stabilization of hypoxia-inducible factors, inactivation of tumor suppressors, activation of signaling pathways, and alteration of metabolic enzymes[15]. For example, aldehyde dehydrogenase 3A1 (ALDH3A1) promotes glycolysis, while restraining OXPHOS to support the survival of non-small cell lung cancer (NSCLC) cells through activation of the HIF-1α/LDHA pathway[16]. AKT1, a member of the AGC kinase family, strongly influences cellular signaling pathways by phosphorylating downstream target proteins. Aberrant activation of AKT1 frequently occurs in various tumors and can induce glycolysis by phosphorylating cytosolic malic enzyme 2 (ME2), thereby facilitating tumorigenesis *in vitro* and *in vivo*[17]. DEPDC1 is a metabolic target that modulates glycolysis in renal cell carcinoma (RCC) through the AKT/mTOR/HIF-1α pathway, which contributes to the malignancy and chemoresistance of RCC[18]. Even though glycolysis dominates cancer metabolism, respiration is not always suppressed but may vary depending on the tumor type and microenvironment. For example, prostate cancer relies more on OXPHOS, while ovarian cancer (OC) engages in vigorous aerobic glycolysis[19]. This difference is also observed among different cellular subpopulations of the same tumor[20]. Specifically, cancer stem and therapy-resistant cells selectively depend on OXPHOS for energy production, including taxane-resistant triple-negative breast cancer (TNBC), temozolomide-resistant glioblastoma multiforme (GBM), and cisplatin-resistant NSCLC cells[5,21,22]. Studies have confirmed that upregulation of OXPHOS-related genes in these tumor cells is crucial for maintaining tumor stemness, acquiring therapeutic resistance, and achieving distant metastasis. Even in cancer types that are highly dependent on glycolysis, subpopulations with high OXPHOS activity have a decisive role in tumor resistance and metastasis with strategies that include continuous ATP supply, the double-edged sword effect of ROS, signaling regulation of metabolic intermediates, and maintenance of NAD^+/NADH balance[20]. A representative study conducted at the MD Anderson Cancer Center revealed that SWI/SNF-mutant lung adenocarcinomas undergoes substantial metabolic reprogramming, characterized by increased OXPHOS dependency, decreased glycolytic capacity, and marked vulnerability to the novel OXPHOS inhibitor, IACS-010759[23]. Therefore, antitumor drugs targeting OXPHOS may represent a promising therapeutic strategy for treating drug-resistant and recurrent cancers[24,25].

mtROS signaling

Tumor cells often exhibit unusually high ROS levels that serve as key catalysts in the onset of cancer[26]. Mitochondria serve as a major source of ROS in cancer cells. A small fraction (0.2%–2%) of O_2 binds to electrons in the electron transport

chain (ETC) that escape the respiratory pathway instead of reaching terminal oxidases, forming $O_2^{\bullet-}$ and resulting in ROS production[27]. Then, $O_2^{\bullet-}$ can be converted to H_2O_2 by superoxide dismutase (SOD). Many tumor-inducing factors, such as oncogene activation, alterations in mitochondrial function, and an increase in hypoxia levels, contribute to ROS generation[28]. However, an increase in ROS production has highly diverse outcomes. Indeed, ROS may promote or inhibit cancer development. Elevated ROS levels in cancer cells may reverse the oxidation of cysteine residues in proteins, thus activating various signaling pathways to promote the survival, proliferation, invasion, and metastasis of cancer cells[29]. For example, ROS oxidize the active-site Cys124 residue of the phosphatase, PTEN, leading to inactivation. This oxidation event relieves the PTEN-driven suppression of PI3K, resulting in sustained activation of the AKT/mTOR signaling pathway, which is closely involved in breast cancer progression and resistance to treatment[30]. Some studies have reported that overproduction of ROS in cancer cells can induce tumor invasion and angiogenesis through NF-κB-mediated activation of MMP-9[31]. In contrast, while ROS can promote tumors, an increase in oxidative damage and ROS-mediated cell death may also hinder tumor initiation. Tetraarsenic hexoxide suppresses mitochondrial STAT3 phosphorylation in triple-negative breast cancer (TNBC) cells to increase ROS production and amplify proptosis *via* the caspase-3/GSDME pathway[32].

Lactate metabolism

Some researchers have challenged the outdated view of lactate as a byproduct of glucose metabolism under anaerobic conditions[33]. Isotope tracing techniques have revealed that lactate can serve as an additional carbon source for the TCA cycle[34]. Lactic acid not only serves as a substrate for cellular respiration and gluconeogenesis but also functions as a signaling molecule that harmonizes metabolic reprogramming. First, in the tumor microenvironment (TME), high lactate concentrations can induce lactylation modifications by targeting lysine residues on histones[35]. Mao et al.[36] reported that mitochondrial protein lactylation inhibits OXPHOS under hypoxia, whereas this effect can be reversed by sirtuin 3 (SIRT3) to promote OXPHOS. And they elucidated the lactylation regulatory mechanisms on mitochondrial function under hypoxic conditions. Lactate can also function as an antioxidant to scavenge excessive ROS in cells and counteract ROS-induced DNA/RNA damage, thereby contributing to treatment resistance and metastasis[37]. Moreover, lactic acid significantly affects the TME by manipulating macrophage polarization toward M2-tumor-associated macrophages (TAMs), promoting angiogenesis and immune evasion, which are hallmark traits of cancer cell[38].

Glutamine metabolism

Glutamine catabolism is another pathway by which malignant tumors acquire nutrients and energy. Glutaminolysis is approximately 10-fold greater in malignant cells than other amino acids. In certain types of cancer, such as melanoma, survival is associated with glutamine addiction[39]. When exogenous glutamine deprivation occurs, cancer cells stagnate and even die. Glutaminolysis provides precursors for nucleotide, protein, and amino acid biosynthesis and substrates for the TCA cycle in mitochondria[40]. Glutaminase 1 (GLS1) serves as a primary target for transcriptional regulators and signaling molecules across different biological conditions. GLS1 is frequently overexpressed in multiple aggressive cancers, such as lung, colorectal (CRC), and head and neck cancer[41-43]. For example, miR-335, a small non-coding RNA, suppresses glutamine-mediated PCa metastasis by targeting GLS[44]. Moreover, c-Myc strongly regulates glutamine metabolism in cells, promoting glutamine transport *via* solute carrier family 1 member 5 (SLC1A5), thereby affecting tumorigenesis[45]. Hu et al.[46] reported that KRAS-mutant CRC has downregulated solute carrier 25 member 21 (SLC25A21), leading to inhibited Gln-derived α-KG efflux, increased glutaminolysis for TCA cycle replenishment, and increased GTP availability, sustaining KRAS activation.

Fatty acid metabolism

Lipid metabolic reprogramming, particularly fatty acid metabolism, is one of the most prominent metabolic abnormalities in cancer. The expression of sterol regulatory element binding protein 1 (SREBP1), a key transcription factor that regulates lipid metabolism, is elevated across multiple malignancies, notably in hepatocellular carcinoma, breast cancer, prostate cancer (PCa), and bladder cancer[47,48]. The tumor suppressor, TIP30, can decrease the expression of SREBP1 and its target genes (*SCD* and *FASN*) *via* the AKT/mTOR signaling pathway, thus inhibiting lipid metabolism in hepatocellular carcinoma (HCC) cells[49].

Fatty acids cross the outer mitochondrial membrane to enter the mitochondrial matrix, where fatty acids undergo β-oxidation to generate acetyl-CoA, which then enters the TCA cycle to produce ATP *via* OXPHOS; this process is known as FAO. Under glucose-deprived conditions, elevated

phosphorylation of PFKL promotes lipid droplet-mitochondria interactions, stimulating lipolysis and enhancing β-oxidation to maintain tumor cell energy homeostasis[50]. FAO has a central role in the TME. Jiang et al.[51] revealed the molecular mechanism underlying FAO-mediated immune evasion in tumor cells. Acetyl-CoA, derived from FAO, promotes the transcription of CD47 through acetylation of NF-κB/RelA, thereby enabling GBM to evade macrophage phagocytosis and drive tumor progression.

Mitochondrial quality control in cancer

Mitochondrial fusion and fission

Mitochondria are highly plastic organelles that exhibit continuous and regulated cycles of membrane fusion and fission, an important homeostatic process collectively referred to as mitochondrial dynamics[52]. Mitochondrial fusion allows for the exchange of materials and information, whereas mitochondrial fission removes aged or damaged mitochondria to maintain morphology and function[53]. Changes in mitochondrial morphology are synergistically regulated by mitochondrial fusion (*OPA1*, *MFN1*, and *MFN2*) and fission genes (*DRP1*), which are necessary for metabolism, apoptosis, and autophagy[54]. Studies have reported that an imbalance in mitochondrial fission and fusion is central to the occurrence of some fundamental cancer cell metabolic features. Salt-inducible kinase 2 (SIK2) activates mitochondrial fission by phosphorylating Drp1 at the Ser616 site, which inhibits mitochondrial oxidative phosphorylation and subsequently contributes to progression of OC[55]. Enhanced mitochondrial fission drives lipid metabolism reprogramming in HCC by inhibiting SIRT1, leading to the transcriptional upregulation of SREBP1 and PGC-1α/PPARα[56]. This regulatory axis facilitates HCC cell proliferation, metastatic progression, and tumor growth *in vivo*. Additionally, mitochondrial dynamics modulate cell death pathways with network remodeling occurring under stress, such as hypoxia or drug exposure, and in disease. Elongated mitochondria effectively counteract the propagation of apoptotic signals, whereas fragmented mitochondria sensitize cells to apoptosis[57,58].

Mitophagy

The accumulation of ROS or nutrient deprivation in tumor cells induces mitochondrial damage, thereby promoting the initiation of mitophagy. Mitophagy is a highly conserved cellular process in which damaged mitochondria are selectively engulfed by autophagosomes, subsequently fusing with lysosomes for degradation and recycling of mitochondrial components. The PINK1/Parkin pathway serves as a key regulator of mitophagy. Parkin gene deletions or mutations can be detected in various tumors, such as glioblastoma, OC, and even breast cancer. Mitophagy progresses and the level of mitochondrial ROS increases when Parkin is not effective[59]. ROS can activate glycolysis by increasing the stability of HIF-1α, thereby contributing to the Warburg effect. Several studies have reported that mitochondrial fusion proteins are required for modulating mitophagy. Dysregulation or aberrant splicing of OPA1 can impair mitochondrial fusion, thereby affecting mitophagy. Following Parkin/PINK1-mediated mitophagy, Parkin ubiquitinates MFN1 and MFN2, causing MFN1 and MFN2 degradation and promoting mitochondrial fission[60-62]. However, the precise functions of these proteins in mitochondrial dynamics have not been established and further studies are needed to elucidate the molecular roles.

mtDNA mutations

mtDNA mutations are among the most common genetic events in tumors and directly affect metabolic homeostasis[63]. Accumulated mutations in mtDNA disrupt the integrity of the ETC, impairing OXPHOS and decreasing the cellular ATP output. In response to bioenergetic stress, adaptive compensatory pathways are activated in neoplastic cells, whereby metabolic rewiring promotes tumorigenic proliferation and survival. For example, Smith et al.[64] established that age-associated accrual of mtDNA mutations elicits progressive deterioration in OXPHOS efficiency through integrated analyses of murine models and human clinical specimens. This bioenergetic compromise drives neoplastic progression in the intestinal epithelium by activating the serine biosynthetic axis, as indicated by significant upregulation of the serine synthesis pathway (SSP). Mahmood et al.[65] inserted mtDNA-encoded mutations into melanoma mice, which induced the Warburg effect, altered the TME, and elicited an antitumor immune reaction marked by a decrease in resident neutrophils. Another study revealed that heterozygous mutants of the mtDNA polymerase (PolgD257A) exhibited greater leukemogenic potential in leukemia models with NMYC proto-oncogene overexpression than the homozygous counterparts[66]. NMYC-driven upregulation of OXPHOS created a metabolic dependency that was accommodated by the PolgD257A heterozygous state, which revealed the interplay between mtDNA mutagenesis and metabolic plasticity in leukemogenesis.

TCM role and mechanisms in targeting mitochondrial reprogramming for cancer therapy

The modulation of mitochondria and associated metabolic pathways has received significant attention in the field of cancer therapy because this strategy represents an important approach with the ability to revolutionize treatment modalities. Several studies have reported that natural products can regulate mitochondrial metabolism, bioenergetics, and redox reactions in tumor cells at non-toxic concentrations, as summarized in **Tables 1–3**. Therefore, we focused on the efficacy and applications of these natural products in mitochondrial reprogramming and elucidated the underlying molecular mechanisms (**Figure 2**).

TCM single compounds

Flavonoids

Flavonoids are widely distributed in the plant kingdom and are composed of two aromatic rings (A and B) connected by a three-carbon chain (C). Emerging studies have revealed that compounds known as flavonoids and their derivatives are effective in treating various cancers, including lung cancer, HCC, CRC, and OC, by modulating the way tumors process nutrients. For example, baicalein, a natural flavonoid extracted from the herb, *S. baicalensis Georgi*, has garnered significant attention as a promising anticancer agent[103]. Baicalein can induce apoptosis in lung cancer cells by suppressing the mTOR pathway by downregulating the expression of glutamine transporters (ASCT2 and LAT1), as well as the glutaminase, GLS1[67]. Additionally, oroxylin A (OA), which is derived from *S. baicalensis*, has been recognized as a prospective mitophagy inhibitor. OA directly inhibits the activity of CDK9, thereby suppressing PINK1-PRKN-mediated mitophagy through inactivation of the SIRT1-FOXO3-BNIP3 axis, leading to disruption of mitochondrial homeostasis and apoptosis of HCC cells[68]. Moreover, *in vivo* studies have demonstrated that OA can augment the therapeutic efficacy of chemotherapeutics, like sorafenib and doxorubicin, by suppressing mitochondrial autophagy and can also surmount drug resistance. Icaritin (ICA), which is derived from *Epimedium* spp., was authorized by the China NMPA for advanced HCC treatment in 2022. ICA suppresses proliferation of HCC cells by inducing mitophagy and apoptosis *via* the PINK1-Parkin/pSer65-Ub signaling pathway[69] and the inhibitory effect can be intensified by mitochondria-targeted OPDEA-PCL nanocarriers[104]. Chrysin inhibits glycolysis in HCC by silencing the expression of hexokinase-2 (HK-2), diminishing HK-2/VDAC connection and activating Bax-mediated apoptosis[70].

Alkaloids

Berberine (BBR), an isoquinoline alkaloid derived from *Coptis chinensis*, has exhibited anticancer potential in preclinical and clinical studies[98]. Yan et al.[71] reported that overexpression of LINC01123 is associated with an unfavorable prognosis based on the TCGA database. BBR modulates the Warburg effect and the formation of autophagosomes in ovarian malignancies *via* the LINC00123/P65/MAPK10 axis, thereby inhibiting the proliferation and metastasis of OC cells. Oxymatrine, an extract from *Radix sophorae tonkinensis*, inhibits the proliferation and spread of CRC cells by triggering mitophagy through LRPPRC downregulation, which in turn inactivates the NLRP3 inflammasome[72]. Corynoxine (Cory) is an indole alkaloid extracted from the plant, *Uncaria macrophylla* Wall. Cory suppresses the AKT-mTOR-GSK3β axis through activation of PP2A, thereby modulating mitochondrial dynamics and glucose metabolism in NSCLC[73]. Tetrandrine (TET) is a natural bisbenzylisoquinoline alkaloid isolated from *Stephania tetrandra* S. Moore that has antitumor potential for treating melanoma. TET directly targets SIRT5 and promotes SIRT5 degradation, which subsequently leads to mitochondrial dysfunction and the accumulation of ROS, thereby impeding the growth of melanoma[74]. Cyclovirobuxine D (CVB-D), which is extracted from *Buxus microphylla*, binds to LIF at Val145 and suppresses HCC *via* the LIF/p38MAPK/p62-regulated mitophagy[75].

Sterides

Steroidal compounds possess diverse biological activities as a natural product and have the potential to be developed into novel anti-tumor agents. Ginsenoside Rh2 (G-Rh2) facilitates the transition from glycolysis to OXPHOS in NSCLC by targeting the HIF-1α/PDK4 axis, thereby inducing apoptosis in tumor cells[76]. G-Rh2 notably enhances the anti-tumor effect of sodium dichloroacetate (DCA) when used in combination and mitigates the toxicity. Ginsenoside CK (CK), a metabolite derived from ginsenosides Rb1 and Rb2, effectively inhibits the progression of TNBC associated with glutamine addiction. CK suppresses the expression of GLS1 in TNBC, decreasing cellular ATP synthesis, reducing glutamine amino acid levels, depleting GSH, increasing ROS accumulation, and finally inducing the apoptosis of TNBC cells[77]. Formosanin

Table 1 Representative natural herbal ingredients that target mitochondrial reprogramming

Active ingredient	Origin	Cancer types	Cell lines	Animal models	Mediated pathways	Ref.
Baicalein	*Scutellaria baicalensis*	LC	H1299, A549, LLC, BEAS-2B	Xenograft model of mice	Inhibiting the glutamine-mTOR metabolic pathway	67
Oroxylin A	*Scutellaria baicalensis*	HCC	HLE, HepG 2/ADR	OTM of mice, PDX of mice	Downregulating PINK1-PRKN-mediated mitophagy	68
Icaritin	*Epimedium* spp.	HCC	SK-Hep1, Huh-7	Xenograft model of mice	Inducing PINK1/Parkin-dependent mitophagy	69
Chrysin	Blue passion flower, propolis, and honey	HCC	Hepatic cell LO2, HepG2, Hep3B, Huh-7, HCC-LM3, Bel-7402, SMMC 7721	Xenograft model of mice	Decreasing the expression of hexokinase-2	70
Berberine	*Coptis chinensis*	OC	SKOV3, HEY,	Xenograft model of mice	Inhibiting LINC00123/P65/MAPK10 signaling pathway	71
Oxymatrine	*Radix sophorae tonkinensis*	CRC	SW620, HCT 116	Xenograft model of mice, Liver metastasis model	Triggering mitophagy through the suppression of LRPPRC, then inhibiting NLRP3	72
Corynoxine	*Uncaria macrophylla* Wall	NSCLC	A549, H1975	Xenograft model of mice	Activating PP2A and regulating AKT-mTOR/GSK3β axes	73
Tetrandrine	*Stephania tetrandra* S. Moore	Melanoma	A375, K-MEL-28, HEK293T	Xenograft model of mice	Targeting SIRT5 and promoting its degradation	74
Cyclovirobuxine-D	*Buxus microphylla*	HCC	HCC	PDX of mice, OTM of mice	Inhibiting LIF, then activating p38MAPK/p62-modulated mitophagy	75
Ginsenoside Rh2	Ginsenosides	NSCLC	A549, PC9	Xenograft model of mice, Tail vein metastasis model, Lymphatic metastasis model	Downregulating the HIF-1α/PDK4 axis	76
Ginsenoside CK	Ginsenosides	BC	MCF-7, MDA-MB-231, SUM159	Xenograft model of mice	Suppressing the expression of GLS1	77
Formosanin C	*Paris polyphylla* var. *yunnanensis*	NSCLC	NCI-H1299, NCI-H1975, A549	ATM of mice	Blocking MCT4/CD147-mediated lactate transport and mitochondrial dysfunction	78
Gracillin	Diosgenin glycoside	NSCLC	HBE, BEAS-2B	PDX, Xenograft model of micef, KRAS transgenic mice	Suppressing mitochondrial complex II	79
Artesunate	*Artemisia annua*	CRC	SW480, HCT116, CT26	ATM of mice	Leading to mitochondrial dysfunction, promoting mtROS generation	80
Tanshinone IIA	Salviae Miltiorrhizae Radix	CRC	SW837, SW480 c	–	Activating INF2-associated mitochondrial fission and the Mst1-Hippo axis	81
Demethylzeylasteral	*Tripterygium wilfordii* Hook. f.	LC	A549, H1299	Xenograft model of mice	Inhibited LRPPRC interaction with mt-mRNA	82
Compound 2	*Rubia cordifolia*	CRC	SW480, HT29, RKO, SW620	Xenograft model of mice	Attenuating AKT/mTOR/P70S6K axis and NF-κB by inhibiting DCTPP	83

Table 1 Continued

Active ingredient	Origin	Cancer types	Cell lines	Animal models	Mediated pathways	Ref.
Ursolic acid	Apples	BC	MDA-MB-231, MCF-7, DOX-resistant MCF-7/ADR	Xenograft model of mice	Inhibiting the AMPK/mTOR/PGC-1α axis	84
Curcumin	Curcuma longa	RCC, LC, BC, CC, PCa	HEK293, H1299, MCF-7, HeLa, PC3	–	Inhibiting the mTOR/HIF-1α axis and downregulating the expression of PKM2 and GLUT1	85
		GC	SGC-7901, BGC-823	Xenograft model of mice	Generating excessive ROS, which depletes POLG and mtDNA	86

LC, lung cancer; HCC, hepatocellular carcinoma; OC, ovarian cancer; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; BC, breast cancer; RCC, renal cell carcinoma; CC, cervical cancer; PCa, prostate cancer; GC, gastric cancer; GLM, glioma; OTM, orthotopic transplantation tumor model; PDX, patient-derived xenograft tumor model; ATM, allogeneic transplantation tumor model.

Table 2 Representative TCM compound formulae that target mitochondrial reprogramming

TCM compound formulae	Ingredients	Cancer types	Cell lines	Animal models	Phases	Mediated pathways	Ref.
QiDongNing	Astragalus, Radix Ophiopogonis, *Paris polyphylla*, Glossy Privet Fruit, and *Fiveleaf Gynostemma*.	NSCLC	A549, NCI-H460, LLC	Xenograft model of mice	None	Inducing p53/DRP1-mediated mitochondrial fission	87
Zuojin pill	*Astragalus mongholicus* Bunge, *Citrus reticulata* Blanco, and *Panax notoginseng*	GPL	GES-1	Xenograft model of rat	None	Inhibiting HIF-1α	88
Xingxiao Pill	Realgar, musk, myrrh, and frankincense	LUAD	A549, H441, LLC	Xenograft model of mice	None	Inhibiting PLA2G4A (cPLA2), lowering AA release, and disrupting SMO/GLI1/SOX2 signaling	89
Shuang-Huang-Sheng-Bai	Astragali Radix, Polygonati Rhizoma, Ligustri Lucidi Fructus, Epimedii Folium, Dry nariae Rhizoma, and Trichosanthis Radix.	LC	LLC, CMT-167	Lung metastasis model of mice, Xenograft model of mice	II	Downregulates ACLY to prevent the production of acetyl-CoA	90
Wenxia Changfu Formula	Araliaceae, Ranunculaceae, and Polygonaceae	LLC	RAW264.7, LLC-Luc	Lung metastasis model of mice	None	Inhibiting the PPAR-γ/CD36 pathway	91
Huachansu	Bufadienolides, alkaloids, and amino acids	CRC	HCT116, DLD1	PDO, OTM of mice	None	Inhibiting PI3K/AKT and glycolysis	92

NSCLC, non-small cell lung cancer; GPL, gastric precancerous lesions; LUAD, lung adenocarcinoma; LC, lung cancer; LLC, Lewis lung cancer; CRC, colorectal cancer; patient-derived organoids, PDO; OTM, orthotopic transplantation tumor model.

C (FC), a *Paris polyphylla* var. *yunnanensis* extract, stimulates apoptosis induced through mitochondrial dysfunction in lung cancer cells by impairing mitochondrial function and disrupting lactate transport *via* MCT4/CD147 inhibition[78]. Gracillin, a natural steroidal saponin, inhibits the function of mitochondrial complex II (CII) by abolishing succinate dehydrogenase (SDH) activity, thereby suppressing ATP synthesis and ROS generation in lung cancer cells[79].

Terpenoids

Terpenoids constitute a large and structurally diverse class of natural products built from five-carbon isoprene units.

Table 3 Multifunctional nanoformulations containing natural herbal ingredients in the field of intervening in tumor metabolic reprogramming

Nanocarrier	Therapeutic agent/s	Cancer types	Cell lines	Animal model	Delivery strategy	Ref.
(Gen + Cur)@FOS	Curcumin	CC	HeLa, A549, H1299, HaCaT, LO2, HCT116	Xenograft model of mice	GLUT1 inhibitor induce starvation of tumor cells	93
Oleanolic tertiary amine	Oleanolic acid	GBM	GL261	Xenograft model of mice	Tertiary amine modification target the mitochondria through interaction with TOM70	94
Glucose-PEG-peptide-triphenylphosponium-PAMAM-paclitaxel	Paclitaxel	BC	MCF-7, L02, MCF-7/ADR	Xenograft model of mice	Targeting GLUT 1 for tumor enrichment, PEG detachment, and TPP-mediated mitochondrial targeting	95
Glu-PEG-Azo/Mito-Cel808 complex	Celastol	LC	A549	Xenograft model of mice	Targeting GLUT 1 for tumor enrichment and using hypoxia-activated TPP for mitochondrial targeting.	96
GO-HA/Cou-DHA/Apt	Dihydroartemisinin	BC	MDA-MB-231	Xenograft model of mice	Cou targets mitochondria	97

CC, cervical cancer; GBM, glioblastoma; BC, breast cancer; LC, lung cancer.

These compounds exhibit diverse and important pharmacologic properties, highlighting the role in drug discovery and advances. For example, artesunate impairs mitochondrial function in CRC cells, causing mtROS overproduction, which subsequently activates p16/p21-dependent cellular senescence and autophagy[80]. Qian et al.[81] demonstrated that tanshinone IIA (Tan IIA) treatment induces mitochondrial oxidative damage and mitochondria-mediated apoptosis in SW480 cells by activating INF2-associated mitochondrial fission and the Mst1-Hippo axis, thereby enhancing the antitumor efficacy of IL-2 therapy. Wang et al.[82] identified demethylzeylasteral (T-96) based on a high-throughput drug screening system and proposed the anti-lung cancer potential. T-96 directly targets LRPPRC, an RNA-binding protein, inhibits the interaction of LRPPRC with mt-mRNAs, induces defects in the synthesis of OXPHOS complexes, and suppresses mitochondrial OXPHOS and ATP synthesis. Compound 2, extracted from the stem of *Rubia cordifolia*, facilitates amino acid reprogramming by inhibiting DCTPP, elevating ROS levels, and attenuating the NF-κB and AKT/mTOR/P70S6K signaling pathways in colon cancer cells[83]. Compound 2 demonstrates equivalent anti-colon cancer activity *in vivo* to fluorouracil, along with acceptable pharmacokinetic characteristics. The $t_{1/2}$ value of Compound 2 in mice is 246.818 ± 161.955 min (i.p.) and 35.576 ± 3.067 min (i.v.). The C_{max} value and t_{max} was 5050 ± 341 ng/mL (i.p.) for 264 min and 15776 ± 3750 ng/mL (i.v.) for 6 min. Ursolic acid (UA) elicits mitochondrial dysfunction by inhibiting the AMPK/mTOR/PGC-1α axis, further activating intrinsic apoptotic pathways, and enhances the chemosensitivity of DOX-resistant BC cells to DOX[84]. To enhance the efficacy of combination therapy, Guo et al.[99] introduced TDTD@UA/HA micelles to target mitochondria, which possesses antitumor activity with good biosafety on the multidrug resistance (MDR) tumor-bearing mice model. Overall, this new therapeutic paradigm held great promise in overcoming MDR-related cancer.

Others

Curcumin, an inhibitor of various hallmarks of cancer, exerts anticancer effects through an influence on tumor metabolism. Curcumin attenuates the Warburg effect across multiple cancer cell lines through targeted silencing of PKM2 with the mTOR/HIF-1α signaling pathway likely playing a regulatory role in this process[85]. Another study revealed that curcumin can suppress gastric tumor growth by generating excessive ROS, which depletes POLG and mtDNA, and ultimately causing cellular bioenergetic dysfunction[86]. However, it should be noted that clinical evidence has indicated that long-term, high-dose supplementation with curcumin may elevate levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), potentially resulting in hepatic injury[100]. Gossypol, a natural compound derived from cottonseed, promotes tumor cell apoptosis by inhibiting anti-apoptotic proteins of the Bcl-2 family[101]. Additionally, gossypol can reverse

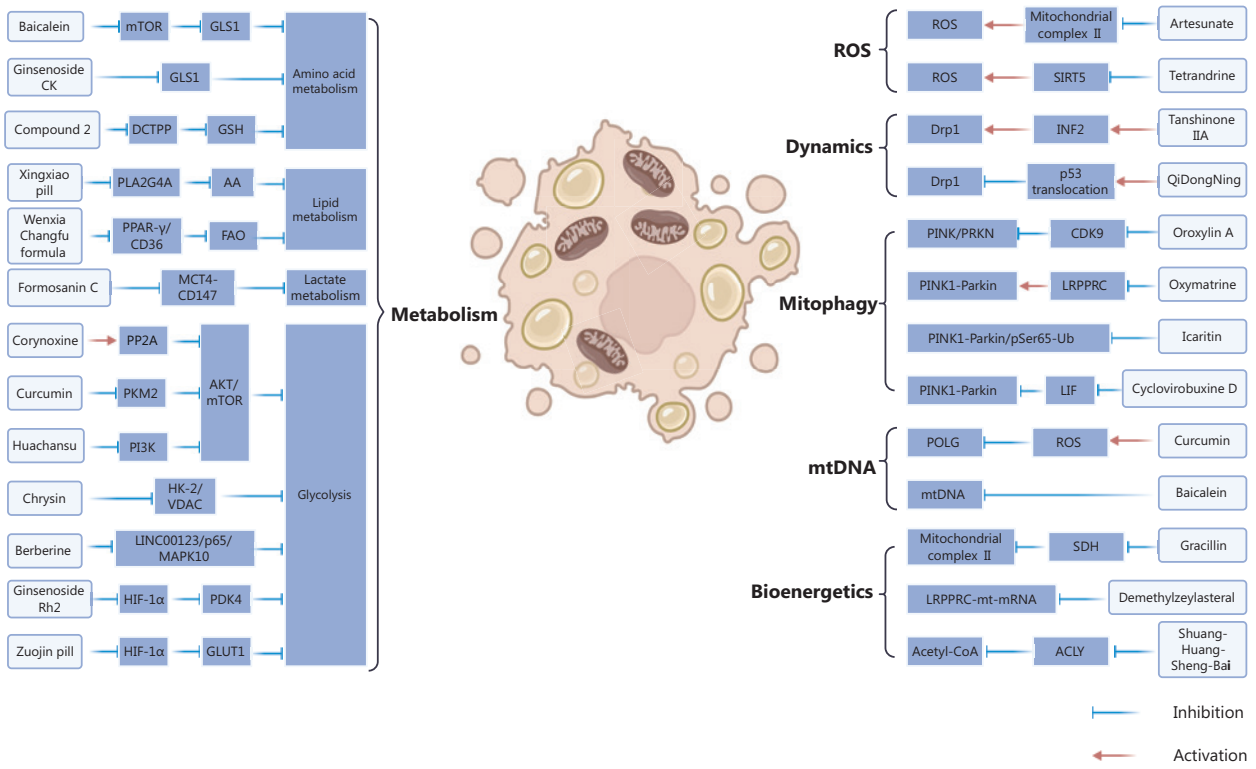

Figure 2 Mechanisms of TCM in suppressing tumor progression *via* mitochondria. **Modulation in metabolism pathways: Baicalein** downregulates GLS1 expression by inhibiting mTOR; **Ginsenoside CK** inhibits GLS1 to reduce glutamine levels; **Compound 2** depletes GSH by inhibiting DCTPP; **Xingxiao pill (XXP)** reduces AA release by inhibiting PLA2G4A (cPLA2); **Wenxia Changfu formula (WCF)** inhibits FAO by downregulating the PPAR-γ/CD36 pathway; **Formosanin C (FC)** disrupts lactate transport by blocking the interaction between MCT4 and CD147; **Corynoxine** regulates glucose metabolism by activating PP2A to inhibit the AKT-mTOR-GSK3β axis; **Curcumin** weakens the Warburg effect by silencing PKM2 to inhibit the mTOR/HIF-1α pathway; **Huachansu (HCS)** inhibits tumor glycolysis through the PI3K/AKT/mTOR pathway; **Chrysin** inhibits glycolysis by inhibiting the interaction between HK-2 and VDAC; **Berberine** regulates the Warburg effect by inhibiting the LINC00123/P65/MAPK10 axis; **Ginsenoside Rh2 (G-Rh2)** promotes the conversion of glycolysis to OXPHOS by targeting the HIF-1α/PDK4 axis; **Zuojin pill (SQQT)** affects the activity of glycolytic enzymes by downregulating HIF-1α. **Modulation in ROS pathways: Artesunate** damages the function of mitochondrial complex II, leading to the massive production of ROS; **Tetrandrine (TET)** targets SIRT5 and promotes its degradation, resulting in ROS accumulation. **Modulation in mitochondrial dynamics: Tanshinone IIA (Tan IIA)** induces tumor cell apoptosis by activating INF2-related mitochondrial fission; **QiDongNing (QDN)** induces mitochondrial fission and promotes tumor cell apoptosis through the P53/DRP1 pathway. **Modulation of mitophagy**: **Oroxylin A (OA)** suppresses CDK9 activity, which inhibits PINK1-PRKN-mediated mitophage formation; **Oxymatrine** triggers mitophagy and apoptosis by downregulating LRPPRC expression; **Icaritin (ICA)** induces mitophagy and apoptosis by inhibiting the PINK1/Parkin/pSer65-Ub axis; **Cyclovirobuxine D (CVB-D)** inhibits PINK1/Parkin-mediated autophagy by binding to LIF. **Modulation of mitochondrial DNA**: **Curcumin** promotes ROS over-production which depletes Polg and mtDNA; **Baicalein** may also inhibit the release of mtDNA by preventing mitochondrial dysfunction. **Modulation of mitochondrial bioenergetics: Gracillin** inhibits the function of mitochondrial complex II (CII) by eliminating SDH activity, resulting in bioenergetic dysfunction; **Demethylzeylasteral (T-96)** directly targets LRPPRC and inhibits its interaction with mt-mRNAs, leading to energy impairment; **Shuang-Huang-Sheng-Bai (SHSB)** inhibits ACLY activity and blocks acetyl-CoA synthesis, impairing ATP production. AA, arachidonic acid; ACLY, ATP citrate lyase; AKT, protein kinase B; ATP, adenosine triphosphate; CD147, cluster of differentiation 147; CD36, cluster of differentiation 36; CDK9, cyclin-dependent kinase 9; cPLA2α, cytosolic phospholipase A2-alpha; DCTPP1, dCTP pyrophosphatase 1; Drp1, dynamin-related protein 1; FAO, fatty acid oxidation; GLS1, glutaminase 1; GSH, glutathione; GSK3β, glycogen synthase kinase-3 beta; HIF-1α, hypoxia-inducible factor 1-alpha; HK-2, hexokinase-2; INF2, inverted formin 2; LIF, leukemia inhibitory factor; LINC00123, long intergenic non-coding RNA 00123; LRPPRC, leucine-rich pentatricopeptide repeat-containing protein; MAPK10, mitogen-activated protein kinase 10; MCT4, monocarboxylate transporter 4; mt-mRNAs, mitochondrial messenger ribonucleic acids; mTOR, mechanistic/mammalian target of rapamycin; OXPHOS, oxidative phosphorylation; Parkin, Parkin RBR E3 ubiquitin-protein ligase; PDK4, pyruvate dehydrogenase kinase 4; PI3K, phosphatidylinositol-3-kinase; PINK1, PTEN-induced

kinase 1; PKM2, pyruvate kinase M2; PLA2G4A, phospholipase A2, group IVA; Polg, DNA polymerase gamma; PP2A, protein phosphatase 2A; PPAR-γ, peroxisome proliferator-activated receptor γ; PRKN, parkin RBR E3 ubiquitin protein ligase; pSer65-Ub, phospho-ubiquitin, Ser65-phosphorylated ubiquitin; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SIRT5, sirtuin 5; VDAC-1, voltage-dependent anion channel 1.

irinotecan resistance in NSCLC cells by inhibiting mitochondrial OXPHOS[102]. However, severe off-target toxicity and insufficient efficacy forced withdrawal from clinical trials. Venetoclax, a highly selective Bcl-2 inhibitor designed based on gossypol, selectively targets cancer cells dependent on Bcl-2 protein for survival without inhibiting Bcl-xL or Mcl-1 proteins and has shown promising results in the clinical treatment of acute myeloid leukemia[105]. Concurrently, venetoclax attenuates OXPHOS in lymphoid malignancies, thereby facilitating mitochondria-mediated apoptotic execution in malignant lymphocytes[106]. Notably, enhancing target selectivity through structural optimization or delivery system compatibility is essential for precision cancer therapy.

Compounds in TCM

TCM compound prescriptions are a common form of clinical application of TCM. Many studies have confirmed the influence of compound prescriptions on tumor metabolism. QiDongNing (QDN), a refined compound preparation, is developed from the anticancer traditional medicine, Jinffu Kuang. Mechanically, QDN induces mitochondrial fission through the P53/DRP1 pathway, thereby triggering programmed cell death in lung cancer cells[87]. The modified Zuojin pill (SQQT) is a Chinese medicine formula used for treating gastric precancerous lesions. SQQT may regulate the expression of HIF-1α, which in turn influences the activity of downstream glycolytic enzymes and inhibits abnormal metabolism and proliferation of precancerous gastric cells[88]. The Xingxiao pill (XXP), a traditional formulation containing myrrh, frankincense, musk, and realgar, has advanced to phase II clinical trials for treating lung adenocarcinoma (LUAD) (ChiCTR2300075712). Recent findings by Fang et al.[89] demonstrated that XXP functions through the bidirectional modulation of lipid metabolism. Specifically, XXP inhibits the production of unsaturated fatty acids and the breakdown of glycerophospholipids (GPLs), while promoting the metabolism of arachidonic acid (AA) through the action of cyclooxygenase. Notably, XXP targets the PLA2G4A-AA-GLI1/SOX2 axis, diminishing cancer stem cell stemness, offering a hopeful therapeutic approach. Additionally, analysis of TCGA indicates that patients with high expression of PLA2G4A may potentially benefit from XXP as an adjuvant therapy. The Shuang-Huang-Sheng-Bai (SHSB) formula is clinically utilized as an adjuvant therapy for cancer patients following chemotherapy. The key mechanism involves inhibition of ACLY enzyme activity and blocking acetyl-CoA biosynthesis[90]. A pilot clinical study showed that lung cancer patients with high ACLY expression often have a poorer prognosis, indicating that SHSB could potentially serve as a novel adjuvant therapeutic strategy targeting ACLY regulation. Wenxia Changfu Formula (WCF) reduces lipid accumulation and inhibits FAO by downregulating the PPAR-γ/CD36 pathway, thereby blocking the transformation of TAMs into a tumor-promoting phenotype[91]. The active components of WCF, 20(S)-ginsenoside Rg3 and ginsenoside Rg5, likely have a key role. Huachansu (HCS), a bioactive compound from toad skin, demonstrates significant antitumor effects in patient-derived organoids (PDO) and orthotopic CRC models by inhibiting tumor glycolysis *via* the PI3K/AKT pathway, downregulating enzymes, like GLUT3, HK2, PKM2, and LDHA[92]. However, the PI3K/AKT pathway in normal cardiomyocytes may be inadvertently blocked by high-dose or long-term use of HCS, which is a potential off-target effect that could induce cardiotoxicity. Thus, establishing tumor-targeted carriers for precise intervention and assessing multi-organ toxicity is urgently needed.

Nanocarrier-based drug delivery systems

With in-depth research on TCM, the design of innovative drug delivery systems with targeting capabilities, improved drug bioavailability, and reduced side effects holds importance for enhancing the TCM efficacy, achieving precise release and strengthening TCM intervention in tumors. Nanocarrier-based drug delivery systems are particularly promising. Li et al.[93] proposed a novel "valve-closing" starvation strategy to increase the anticancer efficacy of curcumin, which involved eliminating the "valve" of glucose transport into tumor cells. This strategy is related to the packaging of genistein, a GLUT1 inhibitor, and curcumin into a stable

nanocarrier, (Gen + Cur)@FOS, which is a novel organosilica hybrid micelle. *In vitro* and *in vivo* results have shown that (Gen + Cur)@FOS can significantly decrease glucose and ATP levels in cancer cells by suppressing GLUT1 expression, a process akin to "valve-closing," thereby triggering a state of starvation in tumor cells. This approach decreased the resistance of cancer cells to chemotherapy-induced apoptosis. Moreover, the incorporation of triphenylphosphonium (TPP) ligands into nanocarriers can achieve more precise mitochondrial release and reduce off-target effects. For example, by tweaking OA with a tertiary amine, OA can be guided to the mitochondria. Triterpene nanoparticles mixed with mitochondria trigger pyroptosis, effectively eliminating glioblastoma cells[94]. Notably, OA nanoparticles are relatively large, which may not be optimal for penetrating brain tumors. Glucose-PEG-peptide-TPP-PAMAM-Paclitaxel was developed to address the issue of chemotherapy failure due to MDR in paclitaxel treatment[95]. The nanomedicine can be actively transported by tumor cells overexpressing GLUT1 and the PEG layer detaches from PAMAM after being cleaved by the upregulated MMP-2. The conjugate directly targets mitochondria *via* TPP, which facilitates the rapid release of paclitaxel. The high concentration of paclitaxel counteracts the efflux function of P-gp and acts on mitochondria to cut off the energy supply for P-gp, thereby overcoming MDR in cancer cells. A study has reported a synergistic therapeutic strategy targeting mitochondrial dysfunction in combination with hyperthermia, which enhances tumor ablation and inhibits tumor metastasis. The GLUT1-targeting and hypoxia-activated mitochondria-targeting PAMAM-based complex (Glu-PEG-Azo/Mito-Cel 808) targets tumor cells by utilizing GLUT1 as a ligand for active targeting[96]. PEG detaches from PAMAM once inside the hypoxic tumor environment, kicking off mitochondrial targeting. This process triggers a rapid release of celastrol into the mitochondrial matrix, while IR 808 generates intense heat under laser exposure, effectively curbing tumor growth and metastasis. Han et al.[97] developed a multifunctional nanosensor (GO-HA/Cou-DHA/Apt) that can monitor the real-time translocation of Cyt c from mitochondria in living cells to evaluate the antitumor effect of DHA. The emission of green fluorescence demonstrated the release of the drug (Cou–DHA) and the mitochondrial targeting by this drug. Subsequently, Cyt c translocates from mitochondria to the cytosol, interacts with Apt to form an Apt-Cyt c complex, and triggers the release of Apt from GO and the emission of red fluorescence from Apt, indicating apoptosis.

Conclusions and prospects

Over the past few years the pivotal role of mitochondria in tumor metabolic reprogramming has been widely recognized[107,108]. Tumor cells continuously allocate the contributions of glycolysis and mitochondrial respiration under the stress of the microenvironment, dynamically adjust the availability of metabolic substrates, and utilize the signaling of metabolic products to regulate the metabolic network to meet the demands of rapid proliferation. In addition, the communication between mtDNA and the nucleus, as well as mitochondrial quality control, contribute to reshaping this process and are core mechanisms for maintaining tumor cell energy homeostasis and survival[109]. Targeting mitochondrial reprogramming is considered an important approach for treating malignant tumors. TCM exhibits good bioactivity and multi-target anti-tumor mechanisms in regulating mitochondrial energy production, catabolism, and mitochondrial quality control. For example, TCM components, such as berberine, curcumin, and baicalein, can simultaneously intervene in multiple pathways or targets, inhibiting the growth, proliferation, and metastasis of tumor cells[67,71,86,110]. Moreover, TCM often serves as an adjuvant in clinical treatment, not only enhancing the effects of other anti-tumor drugs but also counteracting the drug resistance of tumor cells. The application of nanotechnology in encapsulating and delivering TCM can significantly enhance the therapeutic effects and reduce side effects, providing strong support for the clinical translation of TCM.

Although research on anti-tumor TCM based on mitochondrial reprogramming shows promising prospects, with some drugs entering clinical studies, many challenges remain in the process of converting natural compounds into therapeutic agents. First, the complex composition of TCM and the unclear multi-pathway coordination mechanisms require further basic and clinical research for confirmation. Second, tumors of different tissue origins exhibit distinct metabolic characteristics due to the metabolic features of cells and differences in the TME, significantly affecting drug responsiveness. Therefore, precision TCM based on metabolic typing is essential for breaking through the treatment of cross-cancer metabolic reprogramming. Moreover, with the increasing market demand and diversification of herbal sources, quality control of TCM has become an

issue that cannot be ignored. Chinese scholars have constructed the TCM Plant Genome Integrated Database (TCMPG), which has significantly advanced the study of medicinal plants through multi-high-throughput sequencing technologies, which has an important role in the development of TCM. Finally, TCM, which has both traditional Chinese medicine attributes and pharmaceutical properties, has a low degree of standardization and urgently needs to establish a sound evaluation and regulatory system that meets the characteristics of TCM.

Grant support

This work was supported by the National Natural Science Foundation of China (Grant no. 81922030), International Cooperation Project of the Belt and Road (Grant no. 20400750600), Construction Project of Shanghai TCM-Integrated Innovative Flagship Hospital [Grant nos. ZY (2021-2023)-0205-05 and ZXXT-202203], and Shanghai Municipal Commission of Health and Family Plan (Grant no. 201840056).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Siyi Ma, Jiarong Li, Bingjie Hao and Lihong Fan.
Wrote the paper: Siyi Ma.
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References

1. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov. 2022; 12: 31-46.
2. Ohshima K, Morii E. Metabolic reprogramming of cancer cells during tumor progression and metastasis. Metabolites. 2021; 11: 28.
3. Sainero-Alcolado L, Liaño-Pons J, Ruiz-Pérez MV, Arsenian-Henriksson M. Targeting mitochondrial metabolism for precision medicine in cancer. Cell Death Differ. 2022; 29: 1304-17.
4. Chen L, Huang L, Gu Y, Cang W, Sun P, Xiang Y. Lactate-lactylation hands between metabolic reprogramming and immunosuppression. Int J Mol Sci. 2022; 23: 11943.
5. Evans KW, Yuca E, Scott SS, Zhao M, Paez Arango N, Cruz Pico CX, et al. Oxidative phosphorylation is a metabolic vulnerability in chemotherapy-resistant triple-negative breast cancer. Cancer Res. 2021; 81: 5572-81.
6. Anderson RG, Ghiraldeli LP, Pardee TS. Mitochondria in cancer metabolism, an organelle whose time has come? Biochim Biophys Acta Rev Cancer. 2018; 1870: 96-102.
7. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009; 324: 1029-33.
8. Shen S, Vagner S, Robert C. Persistent cancer cells: the deadly survivors. Cell. 2020; 183: 860-74.
9. Dong L, Gopalan V, Holland O, Neuzil J. Mitocans revisited: mitochondrial targeting as efficient anti-cancer therapy. Int J Mol Sci. 2020; 21: 7941.
10. Zheng T, Liu H, Hong Y, Cao Y, Xia Q, Qin C, et al. Promotion of liquid-to-solid phase transition of cGAS by Baicalein suppresses lung tumorigenesis. Signal Transduct Target Ther. 2023; 8: 133.
11. Sheng N, Zhang Z, Zheng H, Ma C, Li M, Wang Z, et al. Scutellarin rescued mitochondrial damage through ameliorating mitochondrial glucose oxidation via the Pdk-Pdc Axis. Adv Sci (Weinh). 2023; 10: e2303584.
12. Zhang C, Chang X, Zhao D, He Y, Dong G, Gao L. Mitochondria and myocardial ischemia/reperfusion injury: effects of Chinese herbal medicine and the underlying mechanisms. J Pharm Anal. 2025; 15: 101051.
13. Lai W, He Y, Zhou B, Wu Q, Wu H, Chen J, et al. Salidroside facilitates neuroprotective effects in ischemic stroke by promoting axonal sprouting through promoting autophagy. Phytomedicine. 2024; 135: 156208.
14. Zheng J. Energy metabolism of cancer: glycolysis versus oxidative phosphorylation (Review). Oncol Lett. 2012; 4: 1151-7.
15. Tang Q, Wu S, Zhao B, Li Z, Zhou Q, Yu Y, et al. Reprogramming of glucose metabolism: the hallmark of malignant transformation and target for advanced diagnostics and treatments. Biomed Pharmacother. 2024; 178: 117257.
16. Chen Y, Yan H, Yan L, Wang X, Che X, Hou K, et al. Hypoxia-induced ALDH3A1 promotes the proliferation of non-small-cell lung cancer by regulating energy metabolism reprogramming. Cell Death Dis. 2023; 14: 617.
17. Chen T, Xie S, Cheng J, Zhao Q, Wu H, Jiang P, et al. AKT1 phosphorylation of cytoplasmic ME2 induces a metabolic switch to glycolysis for tumorigenesis. Nat Commun. 2024; 15: 686.
18. Di SC, Chen WJ, Yang W, Zhang XM, Dong KQ, Tian YJ, et al. DEPDC1 as a metabolic target regulates glycolysis in renal cell carcinoma through AKT/mTOR/HIF1α pathway. Cell Death Dis. 2024; 15: 533.
19. Ashton TM, Mckenna WG, Kunz-Schughart LA, Higgins GS. Oxidative phosphorylation as an emerging target in cancer therapy. Clin Cancer Res. 2018; 24: 2482-90.
20. Uslu C, Kapan E, Lyakhovich A. Cancer resistance and metastasis are maintained through oxidative phosphorylation. Cancer Lett. 2024; 587: 216705.
21. Cruz-Bermudez A, Laza-Briviesca R, Vicente-Blanco RJ, García-Grande A, Coronado MJ, Laine-Menéndez S, et al. Cisplatin resistance involves a metabolic reprogramming through ROS and PGC-1alpha in NSCLC which can be overcome by OXPHOS inhibition. Free Radic Biol Med. 2019; 135: 167-81.

22. Wang N, Huang R, Yang K, He Y, Gao Y, Dong D. Interfering with mitochondrial dynamics sensitizes glioblastoma multiforme to temozolomide chemotherapy. J Cell Mol Med. 2022; 26: 893-912.
23. Lissanu Deribe Y, Sun Y, Terranova C, Khan F, Martinez-Ledesma J, Gay J, et al. Mutations in the SWI/SNF complex induce a targetable dependence on oxidative phosphorylation in lung cancer. Nat Med. 2018; 24: 1047-57.
24. Jiang S, Li W, Zhang Y, Lin J, Huang P. Oxygen-regulated enzymatic nanoplatform for synchronous intervention in glycolysis and oxidative phosphorylation to augment antitumor therapy. J Control Release. 2025; 381: 113594.
25. Qiu X, Li Y, Zhang Z. Crosstalk between oxidative phosphorylation and immune escape in cancer: a new concept of therapeutic targets selection. Cell Oncol (Dordr). 2023; 46: 847-65.
26. Mani S, Swargiary G, Ralph SJ. Targeting the redox imbalance in mitochondria: a novel mode for cancer therapy. Mitochondrion. 2022; 62: 50-73.
27. Gaude E, Frezza C. Defects in mitochondrial metabolism and cancer. Cancer Metab. 2014; 2: 10.
28. Cheung EC, Vousden KH. The role of ROS in tumour development and progression. Nat Rev Cancer. 2022; 22: 280-97.
29. Oberley LW, Oberley TD, Buettner GR. Cell division in normal and transformed cells: the possible role of superoxide and hydrogen peroxide. Med Hypotheses. 1981; 7: 21-42.
30. Jang H, Smith IN, Eng C, Nussinov R. The mechanism of full activation of tumor suppressor PTEN at the phosphoinositide-enriched membrane. iScience. 2021; 24: 102438.
31. Kim A, Im M, Yim NH, Jung YP, Ma JY. Aqueous extract of Bambusae Caulis in Taeniam inhibits PMA-induced tumor cell invasion and pulmonary metastasis: suppression of NF-κB activation through ROS signaling. PLoS One. 2013; 8: e78061.
32. An H, Heo JS, Kim P, Lian Z, Lee S, Park J, et al. Tetraarsenic hexoxide enhances generation of mitochondrial ROS to promote pyroptosis by inducing the activation of caspase-3/GSDME in triple-negative breast cancer cells. Cell Death Dis. 2021; 12: 159.
33. Li J, Ma P, Liu Z, Xie J. L- and D-Lactate: unveiling their hidden functions in disease and health. Cell Commun Signal. 2025; 23: 134.
34. Brooks GA, Curl CC, Leija RG, Osmond AD, Duong JJ, Arevalo JA. Tracing the lactate shuttle to the mitochondrial reticulum. Exp Mol Med. 2022; 54: 1332-7.
35. Ren H, Tang Y, Zhang D. The emerging role of protein L-lactylation in metabolic regulation and cell signalling. Nat Metab. 2025; 7: 647-64.
36. Mao Y, Zhang J, Zhou Q, He X, Zheng Z, Wei Y, et al. Hypoxia induces mitochondrial protein lactylation to limit oxidative phosphorylation. Cell Res. 2024; 34: 13-30.
37. Iatsenko I, Boquete JP, Lemaitre B. Microbiota-derived lactate activates production of reactive oxygen species by the intestinal NADPH oxidase Nox and shortens Drosophila lifespan. Immunity. 2018; 49: 929-42.e5.
38. Ajam-Hosseini M, Heydari R, Rasouli M, Akhoondi F, Asadi Hanjani N, Bekeschus S, et al. Lactic acid in macrophage polarization: a factor in carcinogenesis and a promising target for cancer therapy. Biochem Pharmacol. 2024; 222: 116098.
39. Scott DA, Richardson AD, Filipp FV, Knutzen CA, Chiang GG, Ronai ZA, et al. Comparative metabolic flux profiling of melanoma cell lines: beyond the Warburg effect. J Biol Chem. 2011; 286: 42626-34.
40. Cluntun AA, Lukey MJ, Cerione RA, Locasale JW. Glutamine metabolism in cancer: understanding the heterogeneity. Trends Cancer. 2017; 3: 169-80.
41. Yang C, Wu S, Mou Z, Zhou Q, Dai X, Ou Y, et al. Exosome-derived circTRPS1 promotes malignant phenotype and CD8+ T cell exhaustion in bladder cancer microenvironments. Mol Ther. 2022; 30: 1054-70.
42. Ou D, Wu Y, Liu J, Lao X, Zhang S, Liao G. miRNA-335 and miRNA-182 affect the occurrence of tongue squamous cell carcinoma by targeting survivin. Oncol Lett. 2016; 12: 2531-7.
43. Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, et al. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature. 2009; 458: 762-5.
44. Chen Z, Ding H, Zhu Y, Sun S, Song Z, Zhang L, et al. MicroRNA-335 inhibits invasion and metastasis of prostate cancer by inhibiting glutamine metabolism pathway. J Pharmacol Exp Ther. 2025; 392: 100530.
45. Yue M, Jiang J, Gao P, Liu H, Qing G. Oncogenic MYC activates a feedforward regulatory loop promoting essential amino acid metabolism and tumorigenesis. Cell Rep. 2017; 21: 3819-32.
46. Hu SS, Han Y, Tan TY, Chen H, Gao JW, Wang L, et al. SLC25A21 downregulation promotes KRAS-mutant colorectal cancer progression by increasing glutamine anaplerosis. JCI Insight. 2023; 8: e167874.
47. Li J, Ping P, Li Y, Xu X. Fatty acid metabolism: a new target for nasopharyngeal carcinoma therapy. Chin J Cancer Res. 2024; 36: 652-68.
48. He Y, Qi S, Chen L, Zhu J, Liang L, Chen X, et al. The roles and mechanisms of SREBP1 in cancer development and drug response. Genes Dis. 2024; 11: 100987.
49. Yin F, Sharen G, Yuan F, Peng Y, Chen R, Zhou X, et al. TIP30 regulates lipid metabolism in hepatocellular carcinoma by regulating SREBP1 through the Akt/mTOR signaling pathway. Oncogenesis. 2017; 6: e347.
50. Meng Y, Guo D, Lin L, Zhao H, Xu W, Luo S, et al. Glycolytic enzyme PFKL governs lipolysis by promoting lipid droplet-mitochondria tethering to enhance β-oxidation and tumor cell proliferation. Nat Metab. 2024; 6: 1092-107.
51. Jiang N, Xie B, Xiao W, Fan M, Xu S, Duan Y, et al. Fatty acid oxidation fuels glioblastoma radioresistance with CD47-mediated immune evasion. Nat Commun. 2022; 13: 1511.
52. Pernas L, Scorrano L. Mito-Morphosis: mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function. Annu Rev Physiol. 2016; 78: 505-31.
53. Westermann B. Bioenergetic role of mitochondrial fusion and fission. Biochim Biophys Acta. 2012; 1817: 1833-8.

54. Zacharioudakis E, Gavathiotis E. Mitochondrial dynamics proteins as emerging drug targets. Trends Pharmacol Sci. 2023; 44: 112-27.
55. Gao T, Zhang X, Zhao J, Zhou F, Wang Y, Zhao Z, et al. SIK2 promotes reprogramming of glucose metabolism through PI3K/AKT/HIF-1α pathway and Drp1-mediated mitochondrial fission in ovarian cancer. Cancer Lett. 2020; 469: 89-101.
56. Wu D, Yang Y, Hou Y, Zhao Z, Liang N, Yuan P, et al. Increased mitochondrial fission drives the reprogramming of fatty acid metabolism in hepatocellular carcinoma cells through suppression of Sirtuin 1. Cancer Commun (Lond). 2022; 42: 37-55.
57. Suen DF, Norris KL, Youle RJ. Mitochondrial dynamics and apoptosis. Genes Dev. 2008; 22: 1577-90.
58. Otera H, Mihara K. Mitochondrial dynamics: functional link with apoptosis. Int J Cell Biol. 2012; 2012: 821676.
59. Denison SR, Wang F, Becker NA, Schüle B, Kock N, Phillips LA, et al. Alterations in the common fragile site gene Parkin in ovarian and other cancers. Oncogene. 2003; 22: 8370-8.
60. Liao C, Ashley N, Diot A, Morten K, Phadwal K, Williams A, et al. Dysregulated mitophagy and mitochondrial organization in optic atrophy due to OPA1 mutations. Neurology. 2017; 88: 131-42.
61. Macvicar TD, Lane JD. Impaired OMA1-dependent cleavage of OPA1 and reduced DRP1 fission activity combine to prevent mitophagy in cells that are dependent on oxidative phosphorylation. J Cell Sci. 2014; 127: 2313-25.
62. Gegg ME, Cooper JM, Chau KY, Rojo M, Schapira AH, Taanman JW. Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. Hum Mol Genet. 2010; 19: 4861-70.
63. Kim M, Mahmood M, Reznik E, Gammage PA. Mitochondrial DNA is a major source of driver mutations in cancer. Trends Cancer. 2022; 8: 1046-59.
64. Smith AL, Whitehall JC, Bradshaw C, Gay D, Robertson F, Blain AP, et al. Age-associated mitochondrial DNA mutations cause metabolic remodelling that contributes to accelerated intestinal tumorigenesis. Nat Cancer. 2020; 1: 976-89.
65. Mahmood M, Liu EM, Shergold AL, Tolla E, Tait-Mulder J, Huerta-Uribe A, et al. Mitochondrial DNA mutations drive aerobic glycolysis to enhance checkpoint blockade response in melanoma. Nat Cancer. 2024; 5: 659-72.
66. Li-Harms X, Lu J, Fukuda Y, Lynch J, Sheth A, Pareek G, et al. Somatic mtDNA mutation burden shapes metabolic plasticity in leukemogenesis. Sci Adv. 2025; 11: eads8489.
67. Li J, Zhang D, Wang S, Yu P, Sun J, Zhang Y, et al. Baicalein induces apoptosis by inhibiting the glutamine-mTOR metabolic pathway in lung cancer. J Adv Res. 2025; 68: 341-57.
68. Yao J, Wang J, Xu Y, Guo Q, Sun Y, Liu J, et al. CDK9 inhibition blocks the initiation of PINK1-PRKN-mediated mitophagy by regulating the SIRT1-FOXO3-BNIP3 axis and enhances the therapeutic effects involving mitochondrial dysfunction in hepatocellular carcinoma. Autophagy. 2022; 18: 1879-97.
69. Luo P, An Y, He J, Xing X, Zhang Q, Liu X, et al. Icaritin with autophagy/mitophagy inhibitors synergistically enhances anticancer efficacy and apoptotic effects through PINK1/Parkin-mediated mitophagy in hepatocellular carcinoma. Cancer Lett. 2024; 587: 216621.
70. Xu D, Jin J, Yu H, Zhao Z, Ma D, Zhang C, et al. Chrysin inhibited tumor glycolysis and induced apoptosis in hepatocellular carcinoma by targeting hexokinase-2. J Exp Clin Cancer Res. 2017; 36: 44.
71. Yan X, Yuan C, Wang Z, Xu Z, Wu Z, Wang M, et al. Berberine modulates ovarian cancer autophagy and glycolysis through the LINC01123/P65/MAPK10 signaling axis. Phytomedicine. 2024; 135: 156121.
72. Liang L, Sun W, Wei X, Wang L, Ruan H, Zhang J, et al. Oxymatrine suppresses colorectal cancer progression by inhibiting NLRP3 inflammasome activation through mitophagy induction in vitro and in vivo. Phytother Res. 2023; 37: 3342-62.
73. Hou G, Hu W, Sang Y, Gan X, Xu H, Hu Q, et al. Corynoxine triggers cell death via activating PP2A and regulating AKT-mTOR/GSK3β axes in NSCLC. Biochem Pharmacol. 2024; 222: 116110.
74. Ji Y, Li C, Wan S, Dong Z, Liu C, Guo L, et al. Tetrandrine targeting SIRT5 exerts anti-melanoma properties via inducing ROS, ER stress, and blocked autophagy. J Pharm Anal. 2024; 14: 101036.
75. Shao Y, Lu D, Jin W, Chen S, Han L, Wang T, et al. Targeting LIF with cyclovirobuxine D to suppress tumor progression via LIF/p38MAPK/p62-modulated mitophagy in hepatocellular carcinoma. MedComm (2020). 2025; 6: e70227.
76. Liu X, Li J, Huang Q, Jin M, Huang G. Ginsenoside Rh2 shifts tumor metabolism from aerobic glycolysis to oxidative phosphorylation through regulating the HIF1-α/PDK4 axis in non-small cell lung cancer. Mol Med. 2024; 30: 56.
77. Zhang B, Fu R, Duan Z, Shen S, Zhu C, Fan D. Ginsenoside CK induces apoptosis in triple-negative breast cancer cells by targeting glutamine metabolism. Biochem Pharmacol. 2022; 202: 115101.
78. Li J, Wu Z, Chen G, Wang X, Zhu X, Zhang Y, et al. Formosanin C inhibits non-small-cell lung cancer progression by blocking MCT4/CD147-mediated lactate export. Phytomedicine. 2023; 109: 154618.
79. Min HY, Jang HJ, Park KH, Hyun SY, Park SJ, Kim JH, et al. The natural compound gracillin exerts potent antitumor activity by targeting mitochondrial complex II. Cell Death Dis. 2019; 10: 810.
80. Huang Z, Gan S, Zhuang X, Chen Y, Lu L, Wang Y, et al. Artesunate inhibits the cell growth in colorectal cancer by promoting ROS-dependent cell senescence and autophagy. Cells. 2022; 11: 2472.
81. Qian J, Fang D, Lu H, Cao Y, Zhang J, Ding R, et al. Tanshinone IIA promotes IL2-mediated SW480 colorectal cancer cell apoptosis by triggering INF2-related mitochondrial fission and activating the Mst1-Hippo pathway. Biomed Pharmacother. 2018; 108: 1658-69.
82. Wang L, Zhou W, Wang W, Liang Y, Xue Q, Zhang Z, et al. Demethylzeylasteral inhibits oxidative phosphorylation complex biogenesis by targeting LRPPRC in lung cancer. J Cancer. 2025; 16: 227-40.
83. Feng L, Wang X, Guo X, Shi L, Su S, Li X, et al. Identification of novel target DCTPP1 for colorectal cancer therapy with the natural

small-molecule inhibitors regulating metabolic reprogramming. Angew Chem Int Ed Engl. 2024; 63: e202402543.
84. Luo F, Zhao J, Liu S, Xue Y, Tang D, Yang J, et al. Ursolic acid augments the chemosensitivity of drug-resistant breast cancer cells to doxorubicin by AMPK-mediated mitochondrial dysfunction. Biochem Pharmacol. 2022; 205: 115278.
85. Siddiqui FA, Prakasam G, Chattopadhyay S, Rehman AU, Padder RA, Ansari MA, et al. Curcumin decreases Warburg effect in cancer cells by down-regulating pyruvate kinase M2 via mTOR-HIF1α inhibition. Sci Rep. 2018; 8: 8323.
86. Wang L, Chen X, Du Z, Li G, Chen M, Chen X, et al. Curcumin suppresses gastric tumor cell growth via ROS-mediated DNA polymerase γ depletion disrupting cellular bioenergetics. J Exp Clin Cancer Res. 2017; 36: 47.
87. Ding R, Wang Y, Xu L, Sang S, Wu G, Yang W, et al. QiDongNing induces lung cancer cell apoptosis via triggering P53/DRP1-mediated mitochondrial fission. J Cell Mol Med. 2024; 28: e18353.
88. Liu S, Ji H, Zhang T, Huang J, Yin X, Zhang J, et al. Modified Zuojin pill alleviates gastric precancerous lesions by inhibiting glycolysis through the HIF-1α pathway. Phytomedicine. 2025; 136: 156255.
89. Fang X, Li J, Pang H, Zheng H, Shi X, Feng L, et al. Xingxiao pills suppresses lung adenocarcinoma progression by modulating lipid metabolism and inhibiting the PLA2G4A-GLI1-SOX2 Axis. Phytomedicine. 2025; 143: 156826.
90. Liu D, Dong C, Wang F, Liu W, Jin X, Qi SL, et al. Active post-transcriptional regulation and ACLY-mediated acetyl-CoA synthesis as a pivotal target of Shuang-Huang-Sheng-Bai formula for lung adenocarcinoma treatment. Phytomedicine. 2023; 113: 154732.
91. Yin X, Sun X, Li A, Ruan J, Niu H, Zhou Y, et al. Wenxia Changfu formula inhibits Lewis lung cancer metastasis by reprogramming tumor-associated macrophages through the PPAR-gamma/CD36 pathway. J Ethnopharmacol. 2025; 351: 120103.
92. Yang H, Chen Y, Dai C, Xing Y, Qiu Z, Zhao J, et al. Huachansu suppresses colorectal cancer via inhibiting PI3K/AKT and glycolysis signaling pathways: systems biology and network pharmacology. J Ethnopharmacol. 2025; 343: 119479.
93. Li X, Jiang C, Wang Q, Yang S, Cao Y, Hao JN, et al. A "valve-closing" starvation strategy for amplification of tumor-specific chemotherapy. Adv Sci (Weinh). 2022; 9: e2104671.
94. Gao X, Tang X, Tu Z, Yu J, Bao Y, Long G, et al. Tertiary amine modification enables triterpene nanoparticles to target the mitochondria and treat glioblastoma via pyroptosis induction. Biomaterials. 2025; 317: 123035.
95. Ma P, Chen J, Bi X, Li Z, Gao X, Li H, et al. Overcoming multidrug resistance through the GLUT1-mediated and enzyme-triggered mitochondrial targeting conjugate with redox-sensitive paclitaxel release. ACS Appl Mater Interfaces. 2018; 10: 12351-63.
96. Wei G, Chen J, Jing Z, Li Y, Li Z, Zheng W, et al. Glucose transporter 1 (GLUT1)-targeting and hypoxia-activated mitochondria-specific chemo-thermal therapy via a glycosylated poly(amido amine)/celastrol (PAMAM/Cel) complex. J Colloid Interface Sci. 2022; 608: 1355-65.
97. Han C, Xu X, Zhang C, Yan D, Liao S, Zhang C, et al. Cytochrome c light-up graphene oxide nanosensor for the targeted self-monitoring of mitochondria-mediated tumor cell death. Biosens Bioelectron. 2021; 173: 112791.
98. Wang S, Fu JL, Hao HF, Jiao YN, Li PP, Han SY. Metabolic reprogramming by traditional Chinese medicine and its role in effective cancer therapy. Pharmacol Res. 2021; 170: 105728.
99. Guo Y, Yang X, Zhang Y, Luo F, Yang J, Zhang X, et al. Hyaluronic acid/dextran-based polymeric micelles co-delivering ursolic acid and doxorubicin to mitochondria for potentiating chemotherapy in MDR cancer. Carbohydr Polym. 2024; 332: 121897.
100. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J. 2013; 15: 195-218.
101. Elkattan HH, Elsisi AE, El-Lakkany NM. Gossypol enhances ponatinib's cytotoxicity against human hepatocellular carcinoma cells by involving cell cycle arrest, p-AKT/LC3II/p62, and Bcl2/caspase-3 pathways. Toxicol Rep. 2025; 14: 101856.
102. Lee S, Lee JS, Seo J, Lee SH, Kang JH, Song J, et al. Targeting mitochondrial oxidative phosphorylation abrogated irinotecan resistance in NSCLC. Sci Rep. 2018; 8: 15707.
103. Hao B, Lin S, Liu H, Xu J, Chen L, Zheng T, et al. Baicalein tethers CD274/PD-L1 for autophagic degradation to boost antitumor immunity. Autophagy. 2025; 21: 917-33.
104. Chen S, Sun Y, Xie Y, Liu Y, Hu H, Xie C, et al. Mitochondria-targeted icaritin nanoparticles induce immunogenic cell death in hepatocellular carcinoma. ACS Appl Mater Interfaces. 2025; 17: 2899-910.
105. Gong X, He X, Wang L, Yu T, Liu W, Xu H, et al. Venetoclax-based therapy for relapsed or refractory acute myeloid leukemia: latest updates from the 2023 ASH annual meeting. Exp Hematol Oncol. 2024; 13: 17.
106. Roca-Portoles A, Rodriguez-Blanco G, Sumpton D, Cloix C, Mullin M, Mackay GM, et al. Venetoclax causes metabolic reprogramming independent of BCL-2 inhibition. Cell Death Dis. 2020; 11: 616.
107. Di Gregorio J, Petricca S, Iorio R, Toniato E, Flati V. Mitochondrial and metabolic alterations in cancer cells. Eur J Cell Biol. 2022; 101: 151225.
108. Li M, Hao B, Zhang M, Reiter RJ, Lin S, Zheng T, et al. Melatonin enhances radiofrequency-induced NK antitumor immunity, causing cancer metabolism reprogramming and inhibition of multiple pulmonary tumor development. Signal Transduct Target Ther. 2021; 6: 330.
109. Fulda S, Galluzzi L, Kroemer G. Targeting mitochondria for cancer therapy. Nat Rev Drug Discov. 2010; 9: 447-64.
110. Yan SH, Hu LM, Hao XH, Liu J, Tan XY, Geng ZR, et al. Chemoproteomics reveals berberine directly binds to PKM2 to inhibit the progression of colorectal cancer. iScience. 2022; 25: 104773.

Cite this article as: Ma S, Li J, Hao B, Fan L. Current status of traditional Chinese medicine in modulating mitochondrial metabolic abnormalities in tumors. Cancer Biol Med. 2025; 22: 1439-1454. doi: 10.20892/j.issn.2095-3941.2025.0246