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REVIEW

Traditional Chinese Medicine Monomers and Their Derivatives as a Promising Therapeutic Tool for Hepatocellular Carcinoma by Activation of Mitophagy

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Abstract: Hepatocellular carcinoma (HCC) is a malignant tumor of the liver. Treatment programs according to its physiological and pathological characteristics have reduced the number of new cases and deaths of HCC, but the morbidity and mortality are still high, posing a significant threat to human health. In recent years, the importance of mitophagy in the treatment of HCC has gradually been recognized. The activation of mitophagy inhibits the survival, proliferation and migration of HCC cells through a variety of pathways, promotes cell apoptosis, and can also reduce drug resistance, providing a new direction for the treatment of HCC. Studies have shown that Traditional Chinese medicine (TCM) monomers and their derivatives can improve the therapeutic efficacy of HCC and slow down disease progression by regulating mitophagy. This article summarizes the potential mechanism of mitophagy in the progression of HCC and comprehensively explores the potential of TCM monomers and their derivatives in the treatment of HCC, providing new perspectives and strategies for clinical treatment.

Keywords: hepatocellular carcinoma, mitophagy, traditional Chinese medicine monomers, derivatives

Introduction

According to data from the Global Cancer Observatory 2022, primary liver cancer was the 6th most common cancer in incidence and the third mortality rate, with a whopping 88%.[1] It is estimated that, by 2025, >1 million individuals will be affected by liver cancer annually.[2] HCC is the most common primary liver cancer, accounting for more than 90% of cases, and its five-year survival rate is only 18%.[3] With the advancement of targeted therapy and immunotherapy technology, the therapeutic efficacy has been dramatically improved. However, HCC remains a global health challenge due to its high recurrence rate, high metastasis rate, and chemoresistance.

Mitochondria is a dynamically changing organelle with a bilayer membrane structure, which produces Adenosine Triphosphate (ATP) through the oxidative phosphorylation pathway and plays a central role in cellular energy metabolism.[4] Mitophagy is a specific autophagic process that plays a key role in maintaining cellular homeostasis by selectively identifying and removing damaged or dysfunctional mitochondria.[5] Mitophagy is a specific autophagic process that plays a key role in maintaining cellular homeostasis by selectively identifying and removing damaged or dysfunctional mitochondria.[6] A large number of studies have shown that mitophagy plays a dual role in promoting and inhibiting the occurrence and development of HCC, which may be related to the heterogeneity of HCC.[7] Under conditions of hypoxia and insufficient nutrients, HCC cells can provide energy through mitophagy to ensure their own

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growth and proliferation. At the same time, autophagy can also improve the resistance of cancer cells to chemotherapy drugs and increase the emergence of drug resistance.[8] On the other hand, mitophagy can lead to apoptosis of HCC cells through oxidative stress, especially the accumulation of reactive oxygen species (ROS).[9] Studies have shown a strong link between HCC and mitochondrial abnormalities. Many HCC cells contain dysfunctional mitochondria, and mitophagy selectively removes them, preventing their breakdown products from providing energy for HCC cells to grow.[10]

Traditional Chinese medicinal (TCM) herbs, as a precious treasure of the Chinese nation, have been passed down and developed over thousands of years and continue to play an irreplaceable role in the field of modern medicine. In recent years, these herbs have garnered increasing attention from scholars due to their unique advantages of multiple components, multiple targets, and multiple pathways. Particularly in the field of tumor therapy, TCM herbs and their active components have demonstrated significant clinical value in the treatment of HCC and other malignant tumors.[11] Pharmacological studies have shown that the alkaloids, triterpenoid saponins, flavonoids, and other active components contained in TCM herbs possess diverse pharmacological activities, such as anti-inflammatory, antioxidant, and immune-modulating effects. TCM monomers are chemical substances with explicit chemical structures and pharmacological activities.[12] In the treatment of HCC, these monomers have multiple functions. They can not only inhibit tumor progression and reduce recurrence and metastasis but also improve patients' immune function and quality of life and enhance the sensitivity to chemotherapeutic drugs, showing unique therapeutic potential. With the continuous in-depth research on mitophagy, an increasing number of scholars have begun to focus on the regulatory mechanisms of TCM monomers on mitophagy.[13] However, there are currently few studies that systematically integrate and summarize this field. This study deeply explores the complex pathological mechanisms of mitophagy in HCC and provides a comprehensive review of the research progress of TCM monomers and their derivatives in the treatment of HCC through the regulation of mitophagy. It aims to provide new theoretical basis and therapeutic strategies for the future targeted treatment of HCC and to promote the innovative development of the modernization of TCM.

Review Methodology

We conducted a systematic literature search in databases such as PubMed, Web of Science and Google Scholar to identify the latest research on TCM monomers and its derivatives. The search formula is: TS = ("Carcinoma*Hepatocellular" OR "Hepatocellular Carcinoma*" OR "Hepatoma*" OR "Liver Cancer*" OR "Cancer*Adult Liver" OR "Cell Carcinoma*" OR "Carcinoma, Liver Cell") AND ("Mitophagy") AND ("Traditional Chinese Medicine" OR "Chinese herbal medicine" OR "Chinese medicinal herb" OR "natural product" OR "active compounds"). Our selection of publications is not time-limited and excludes those of low relevance and non-English languages. To minimize selection bias, two authors independently screened the literature, and the results were cross-validated. Additionally, we manually searched the reference lists of relevant reviews to ensure that no significant studies were overlooked. The search strategy spanned multiple databases and followed the PRISMA guidelines (PRISMA Citation 2020). The retrieval process is shown in Figure 1.

The Pathogenesis of Mitophagy

PINK 1/Parkin Signaling Pathway

The PINK1/Parkin pathway is a signature signaling pathway in mitophagy. PTEN-induced kinase 1 (PINK1) is a protein kinase located in the inner mitochondrial membrane; Parkin is an E3 ubiquitin ligase specializing in ubiquitination of proteins on the outer mitochondrial membrane, and both participate in the regulation of mitophagy. When mitochondria are damaged, PINK1 protein accumulates on the outer membrane of the damaged mitochondria. It activates Parkin, promoting the ubiquitination of mitochondrial proteins, tagging the damaged mitochondria for subsequent clearance.[14,15] P62 serves as an adaptor protein between autophagic bodies and substrates; it specifically binds to microtubule-associated protein 1 light chain 3 (LC3) on the membrane of autophagic bodies through its LC3 interaction region (LIR). During Parkin-mediated mitophagy, P62 binds to ubiquitinated mitochondrial substrates to form a P62-ubiquitin complex, which is then transported to the autophagosome via the LIR-LC3 interaction.[16] Optineurin (OPTN) is an autophagy adaptor protein that can recruit LC3 to the autophagosome. Autophagy receptors guide the damaged mitochondria to

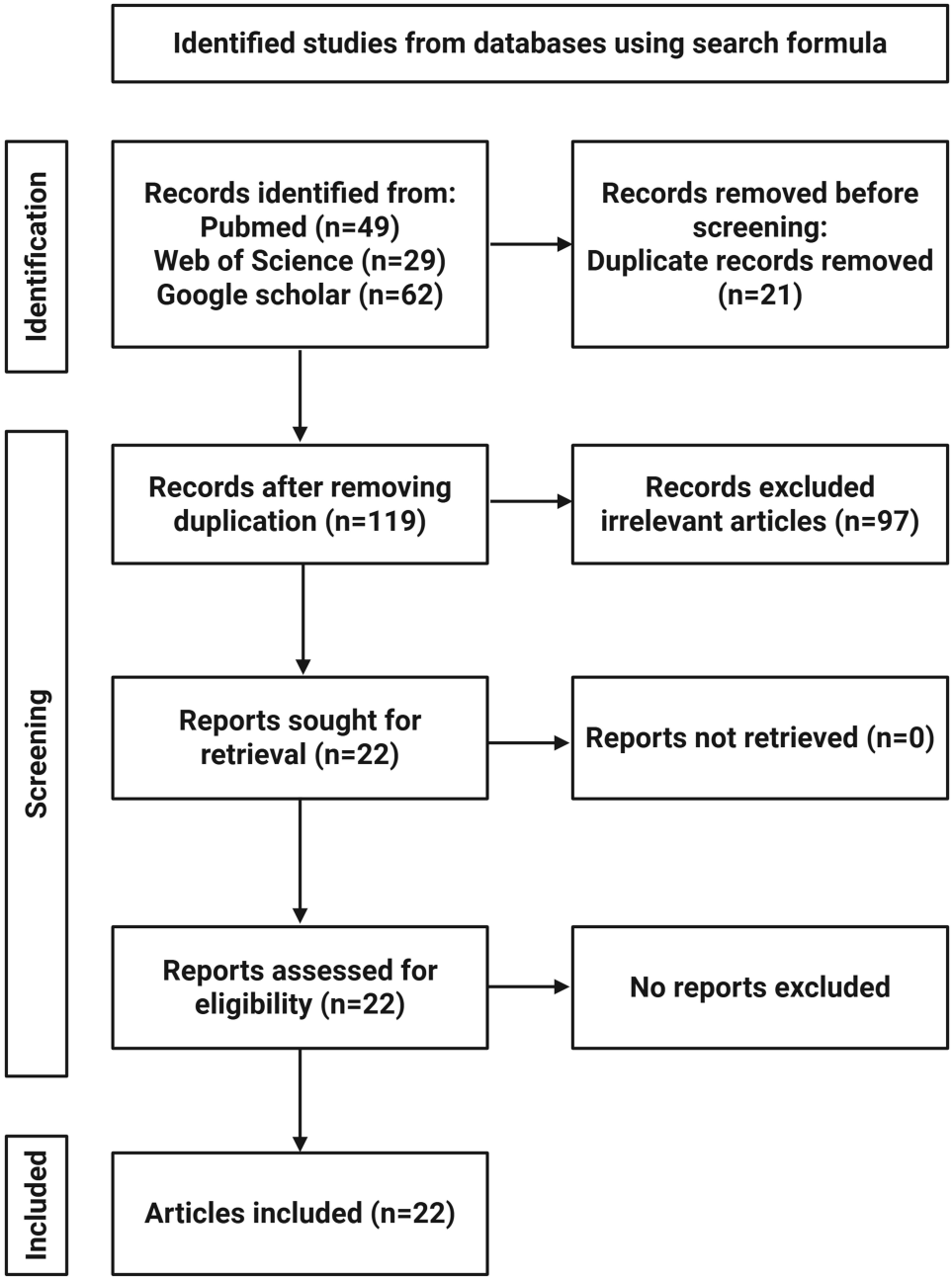

Figure 1 The detailed process of literature screening. Conduct a literature search using search formula in the PubMed, Web of Science, and Google Scholar databases, remove duplicates and irrelevant literature to the research topic, and conduct an in-depth study of the included literature. The search formula is: TS = ("Carcinoma*, Hepatocellular" OR "Hepatocellular Carcinoma*" OR "Hepatoma*" OR "Liver Cancer*" OR 'Cancer*, Adult Liver' OR "Cell Carcinoma*" OR "Carcinoma, Liver Cell") AND ("Mitophagy") AND ("Traditional Chinese Medicine" OR "Chinese herbal medicine" OR "Chinese medicinal herb" OR "natural product" OR "active compounds").

autophagosomes by binding to LC3.[17] The damaged mitochondria are then enclosed by the autophagosome membrane, forming mitophagosomes. Mitophagosomes fuse with lysosomes to form autolysosomes. Within the autolysosomes, the damaged mitochondria are degraded by hydrolases, releasing metabolites that can be reused by the cell.[15,18] Li Zhezhu et al found that PINK1 expression is low in HCC and plays a protective role in the stratified prognosis of liver cancer patients by interacting with immune cells infiltrated in the tumor microenvironment.[19] At the same time, the lack of PINK1 can interfere with the mitophagy process, which may lead to the accumulation of damaged mitochondria, the reduction of oxidative phosphorylation efficiency, the increase of ROS production, and the intensification of glycolysis, which in turn activates the Warburg effect and increases the proliferation and migration of tumor cells.[20,21] Nicotinamide

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Adenine Dinucleotide Phosphate - reduced form (NADPH) oxidase is one of the main sources of ROS.[22] NOX 4 localizes to mitochondria and triggers the production of mitochondrial reactive oxygen species (mtROS). This short-term ROS surge induces PINK1-dependent mitophagy, which in turn eliminates damaged mitochondria by increasing Nrf2 expression and protects cells from apoptosis.[23] These findings reveal a key role for NOX4 in mtROS production and mitophagy. Some studies have found that Parkin can induce the ubiquitination and degradation of PD-1 in HCC, thereby regulating the immune microenvironment through the PD-1/PD-L1 signaling pathway. When Parkin is deficient, the level of mitophagy in hepatocytes is reduced, creating an immunosuppressive microenvironment that promotes the development of HCC. Therefore, reintroducing Parkin or enhancing mitophagy to reshape the tumor microenvironment can activate antitumor immune responses and improve the efficacy of immunotherapy.[24]

AMPK Signaling Pathway

AMP-activated protein kinase (AMPK) is an evolutionarily conserved serine/threonine protein kinase that is activated when cells are under energy stress, such as low energy levels, hypoxia, or nutrient deprivation.[25] Once activated, AMPK regulates cellular metabolism and autophagy by phosphorylating multiple downstream targets. Under glucose starvation, AMPK can directly phosphorylate key sites such as Ser317 and Ser777 on Unc-51 like autophagy activating kinase 1 (ULK1), activating ULK1 and enabling it to form the autophagy initiation complex with proteins like FAK-family interacting protein of 200 kDa (FIP200), Autophagy-related (ATG) protein 13 (ATG13), and ATG101.[26] The formation of this complex is a critical step in autophagy initiation. Subsequently, the ULK1 complex phosphorylates downstream proteins such as Beclin-1 and Vacuolar Protein Sorting 34 (VPS34), activating the Phosphatidylinositol 3-kinase (PI3K) complex, which promotes the formation of phagophores and the maturation of autophagosomes.[27] Additionally, the ULK1 complex regulates the functions of other ATG proteins (eg, ATG5, ATG7, and LC3) to facilitate autophagosome elongation and closure.[28] Ultimately, mature autophagosomes fuse with lysosomes, completing the autophagy process. AMPK can activate ULK1 by inhibiting the mammalian Target of Rapamycin Complex 1 (mTORC1) signaling pathway. Tuberous Sclerosis Complex 2 (TSC2), an upstream inhibitor of mTORC1, forms a complex with Tuberous Sclerosis Complex 1 (TSC1) and acts as a GTPase-activating protein (GAP) to convert Ras homolog enriched in brain (Rheb) from its active GTP-bound state to its inactive GDP-bound state, thereby suppressing mTORC1 activity.[29] Under nutrient deprivation, AMPK enhances this GAP activity by phosphorylating TSC2 at Thr1227 and Ser1345. Additionally, AMPK directly phosphorylates Regulatory-Associated Protein of mTOR (RAPTOR), a subunit of mTORC1, at Ser722 and Ser792, further inhibiting mTORC1 activity.[30,31] Under nutrient-rich conditions, mTORC1 phosphorylates ULK1 at Ser757, inhibiting its kinase activity and thus suppressing autophagy. However, when AMPK inhibits mTORC1, ULK1 is dephosphorylated at Ser757, thereby relieving this inhibition.[26] Meanwhile, AMPK also directly phosphorylates multiple sites on ULK1, such as Ser317 and Ser555, further activating ULK1 and initiating the autophagy process.[32] AMPK phosphorylates PINK1 to enhance its stability on the outer mitochondrial membrane and promote its accumulation, thereby driving the recruitment and activation of Parkin.[33] Recent studies have indicated that certain drugs can induce mitophagy and exert their biological effects by modulating the AMPK/PINK1/Parkin pathway.[34–36] Additionally, ULK1 activated by AMPK can further phosphorylate PINK1 and Parkin, enhancing their activities and thereby synergistically promoting mitophagy.[32] Metformin is an AMPK activator that reduces ATP production, thereby increasing the intracellular Adenosine Monophosphate (AMP)/ATP ratio and directly activating AMPK.[37] It exerts neuroprotective effects by regulating mitophagy mediated through the AMPK/ULK1/PINK1/Parkin pathway.[38] Studies have shown that metformin inhibits protein synthesis and cell growth in hepatocytes by suppressing the mTORC1 signaling pathway, thereby exerting its anti-tumor effects.[39,40] La Hu et al found that metformin can inhibit tumor development by activating AMPK, which helps regulate cellular energy balance and suppress the mTOR signaling pathway, ultimately reducing cell proliferation.[41] Additionally, in terms of combination therapy, the use of metformin in combination with low-dose sorafenib can significantly inhibit the growth, proliferation, migration, and invasion capabilities of HCC cells.[42]

B56γ-p-Drp1^{Ser616}-Rab7 Signaling Axis

Dynamin-related Protein 1 (Drp1) is a GTPase primarily localized in the cytoplasm, and it plays a crucial role in regulating mitochondrial fission. Drp1 is activated through phosphorylation at the serine 616 site (p-Drp1^{Ser616}),

transferring to the mitochondrial outer membrane and promoting mitochondrial fission through the formation of spiral structures.[43] This process can work in concert with the PINK1/Parkin pathway to accelerate the clearance of damaged mitochondria, thereby maintaining intracellular homeostasis.[44] Mitochondrial p-Drp1^{Ser616} is a novel inter-organelle connector protein that is localized at mitochondrial and lysosomal membrane contact sites (MCSs). By interacting with Rab7, it triggers increased mitochondrial-lysosomal crosstalk, leading to PINK1-Parkin dependent mitophagy. Protein Phosphatase 2A B subunit isoform γ (B56γ) is a subunit of protein phosphatase 2A (PP2A). Research has found that in HCC cells, the activation of B56γ dephosphorylates p-Drp1^{Ser616}, blocking the interaction between p-Drp1^{Ser616} and Rab7, reducing mitophagy and increasing apoptosis. This process inhibits the proliferation and metastasis of HCC cells, thereby improving patient prognosis.[45,46] Therefore, the regulatory mechanism of the B56γ-p-Drp1^{Ser616}-Rab7 signaling axis provides a new potential target for targeted therapy in HCC.

NIX Protein

Nip3-like protein X (NIX), also known as Bcl-2/adenovirus E1B 19 kDa-interacting protein 3-like (BNIP3L), is a protein located on the mitochondrial outer membrane and belongs to the Bcl-2 family. NIX can bind to the autophagy-related protein LC3 through its LIR, thereby guiding damaged mitochondria to autophagosomes for degradation.[47] NIX also contains a minimal essential region (MER) that can further enhance the efficiency of mitophagy by interacting with WD Repeat Domain, Phosphoinositide Interacting 2 (WIPI2).[48] In the hypoxic tumor microenvironment of HCC, the expression of NIX protein is upregulated, and it induces autophagic cell death in cancer cells through excessive activation of mitophagy. NIX is a key protein for Apoptin-induced mitophagy. Apoptin is a protein that can induce specific apoptosis in tumor cells. Yiquan Li and his team found that Apoptin triggers apoptosis and mitophagy by weakening the interaction between mitochondrial outer membrane fusion proteins (MFN1 and MFN2), leading to mitochondrial damage and ROS accumulation, which results in the loss of mitochondrial transmembrane potential in HCC cells.[49]

FUNDC1 Protein

FUN14 Domain Containing 1 (FUNDC1) is a receptor protein located on the outer mitochondrial membrane that can bind to the autophagy-related protein LC3, thereby regulating mitophagy.[50] Under normoxic conditions, the tyrosine kinase Src phosphorylates the Tyr-18 site of FUNDC1, inhibiting its binding to LC3 and thus blocking mitophagy.[51] Under hypoxic conditions or when mitochondrial membrane potential decreases, phosphoglycerate mutase 5 (PGAM5) acts as a dephosphorylase to remove the phosphorylation of the Ser-13 site on FUNDC1, enhancing its binding capacity with LC3 and thereby activating mitophagy.[52] Additionally, ULK1 can also promote mitophagy by phosphorylating the Ser-17 site of FUNDC1.[53] Studies have shown that in the initial stage of HCC, FUNDC1 can regulate mitophagy to reduce inflammasome activation, thereby exerting an anti-tumor effect.[54]

BNIP3 Protein

BCL2/Adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) is a protein located on the outer membrane of mitochondria. Under hypoxic conditions, Hypoxia-inducible factor 1 alpha (HIF-1α) is activated, leading to an increase in BNIP3 expression within the cell, a change that is crucial for cellular adaptation to hypoxic environments. BNIP3 binds to LC3 via an LIR, promoting hypoxia-induced mitophagy, which helps cells maintain energy metabolism and survival under hypoxic stress.[55] Sizhe Liu et al have discovered that the HIF-1α/BNIP3 signaling pathway plays a significant role in the recurrence of HCC. In HCC, autophagy in tumor cells and hypoxia are the main driving factors for recurrence. The HIF-1α/BNIP3 signaling pathway promotes mitophagy under hypoxic conditions, which not only supplies energy to tumor cells but also enhances their migration and adhesion capabilities. Furthermore, this signaling pathway induces the epithelial-mesenchymal transition (EMT), which aids in tumor angiogenesis and consequently leads to the recurrence of HCC.[56] Research has shown that sorafenib resistance is closely related to the HIF-1α/BNIP3 signaling pathway.[57]

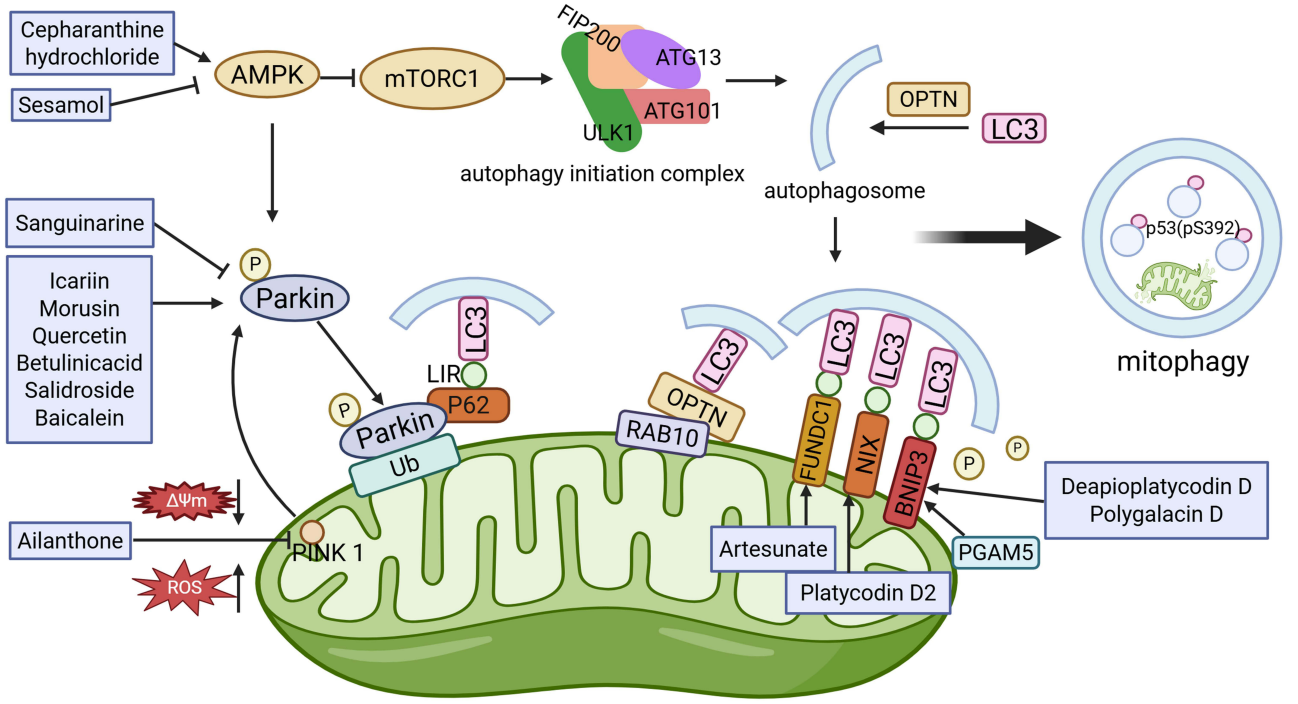


Figure 2 Diagram of mitophagy mechanism. AMPK activates ULK1 by inhibiting the mTORC1 signaling pathway, which then associates with proteins such as FIP200, ATG13, and ATG101 to form the autophagy initiation complex. With the aid of OPTN, LC3 is recruited to the autophagosome, directing the damaged mitochondria into it. Upon mitochondrial damage, PINK1 accumulates on the outer membrane of the damaged mitochondria and activates Parkin, facilitating the ubiquitination of mitochondrial proteins. The ubiquitinated mitochondrial proteins bind to P62 to form a p62-ubiquitin complex, which interacts with LC3 via LIR to promote the formation of autolysosomes, thereby accelerating mitophagy. Furthermore, proteins such as BNIP3, NIX, and FUNDC1 can directly engage in mitophagy by binding to LC3 through their LIR domains. Created in BioRender. shengping, l. (2025) https://BioRender.com/ e38s341.

RAB Protein

The Ras superfamily of small GTPases (RAB) protein family plays an important role in the regulation of mitophagy.[58] Under the action of guanine nucleotide exchange factors (GEFs), they switch from an inactive GDP-bound form to an active GTP-bound form, thereby regulating multiple steps of vesicle transport.[59] RAB10 is a small GTPase that remains in an inactive state under normal physiological conditions. When mitochondria are damaged, the PINK1/Parkin pathway is activated, allowing RAB10 to translocate to depolarized mitochondria and recruit OPTN to promote mitophagy.[60] RAB interacting factor (RABIF) is one of the earliest identified RAB GEFs and directly affects the efficiency of mitophagy by regulating the activity of RAB10.[61,62] Research by Feng Ning et al has shown that RABIF is highly expressed in HCC patients. RABIF interacts with STOML2 (Stomatin-like protein 2) to regulate the activity of PARL (Presenilin-associated rhomboid-like protease) and PGAM5, thereby influencing mitophagy. When the function of RABIF is inhibited, not only is mitophagy blocked, but HCC cell growth is also suppressed, and sensitivity to sorafenib is enhanced.[63] These findings provide new potential therapeutic targets for the treatment of HCC. The mechanisms of mitophagy is shown in Figure 2.

The Roles of Mitophagy in HCC

Mitophagy Has Dual Roles in HCC

Mitophagy can maintain the quality and quantity of mitochondria within cells, thereby preserving cellular homeostasis and contributing to the survival of HCC cells under stress conditions.[64] In the early stages of HCC, mitophagy exerts a protective role by clearing damaged mitochondria, reducing the production of ROS, maintaining intracellular redox balance, and preventing cellular stress and genomic damage.[65] Additionally, the reduction in ROS can inhibit the activation of the NLRP3 inflammasome, decrease the secretion of inflammatory cytokines such as IL-1β and IL-18, prevent excessive activation of the inflammatory response, and thereby reduce hepatocyte injury and death, ultimately

suppressing the initiation and progression of liver cancer. In the advanced stages of HCC, tumor cells are exposed to a harsh microenvironment characterized by hypoxia and low nutrient availability. Under hypoxic conditions, mitochondria generate excessive ROS, leading to mitochondrial dysfunction and reduced efficiency of mitochondrial oxidative phosphorylation. This drives HCC cells to increasingly rely on glycolysis for energy production, thereby promoting the Warburg effect.[66] This means that even in the presence of oxygen, these cancer cells engage in high levels of glycolysis. Although glycolysis produces less ATP compared to mitochondrial oxidative phosphorylation, its rapid reaction rate allows it to quickly supply the energy needed for the rapid proliferation of tumor cells.[67] Meanwhile, the overproduction of ROS can activate mitophagy, leading to increased iron content in mitochondria and subsequent mitochondrial iron overload. The additional ROS generated by iron overload further promotes the Warburg effect.[68] In a nutrient-poor environment, mitophagy degrades mitochondrial components to produce metabolic intermediates such as amino acids, nucleotides, and lipids. These intermediates can enter the glycolytic pathway to provide a rapid energy supply for the cells, thereby sustaining the survival and proliferation of tumor cells under low-nutrient conditions.

The Latest Research on Mitophagy in HCC

The treatment of HCC remains a challenging issue. Although targeted therapies have significantly improved treatment efficacy, drug resistance often emerges, which is partly related to mitophagy. Mitophagy maintains mitochondrial membrane potential, reduces mitochondrial damage, and decreases the production of intracellular ROS. This helps to alleviate oxidative stress damage caused by chemotherapeutic drugs, enabling HCC cells to better adapt to the treatment environment and thereby enhancing their drug resistance.[69] Human menstrual blood-derived stem cells (MenSCs) can be isolated directly from the discharged menstrual fluid and are a novel type of mesenchymal stem cell with strong potential for proliferation, self-renewal, differentiation, and immunosuppression.[70] Studies have shown that MenSCs can modify the expression of sorafenib resistance (SR) -associated genes in HCC cells, achieving the purpose of reversing sorafenib resistance. MenSCs upregulated the expression of tumor suppressor genes BNIP3 and BNIP 3L in HCC-SR cells through active demethylation mediated by tet methylcytosine dioxygenase 2 (TET 2), overactivating mitophagy and eventually leading to autophagic death of HCC-SR cells, consequently decreasing the prevalence of chemoresistance in cancer cells.[71]

Additionally, studies have shown that the acquisition of stem cell-like properties by cancer cells is associated with mitochondrial dysfunction.[72] Mitophagy can selectively eliminate dysfunctional mitochondria, thereby maintaining the stemness of tumor cells.[73] Meanwhile, mitochondrial metabolism can provide energy substrates for tumor stem cells, thereby promoting tumor recurrence and metastasis.[74] Cancer stem cells (CSC) are a subgroup of tumor cells with the ability to differentiate into various types of cells, self-renew, and cause cancer. Due to their unique biological characteristics, CSCs exhibit significant drug resistance in tumor treatment and enhance their invasive ability through epithelial-mesenchymal transition, which is one of the key factors leading to tumor recurrence.[75] P53 is a tumor suppressor that plays an important role in regulating stem cell homeostasis, restricting stem cell self-renewal and symmetrical division, and blocking the reprogramming process of somatic or progenitor cells to the stem cell state, maintaining the normal function of tissues and organs.[76] Under normal conditions, mitophagy can cause p53 to bind to mitochondria and be lost from the nucleus. When mitophagy is impaired, p53 cannot be cleared but is rapidly transferred to the nucleus by PINK1 after phosphorylation at the serine 392 checkpoint, binding to the promoter of the NANOG gene, thereby inhibiting the expression of NANOG, thereby reducing the stemness and the self-renewal ability of hepatic CSCs, inhibiting the occurrence and development of liver cancer.[77]

Studies show that mitophagy promotes cancer by letting cancer cells degrade damaged or excess mitochondria. This maintains ATP levels and provides nutrients when glucose is scarce. In human HCC, tumors with low glucose uptake and high Kirsten rat sarcoma viral oncogene (K-Ras) expression have enhanced mitophagy. This suggests that K-Ras may drive mitophagy to help cancer cells survive in low-glucose conditions, promoting tumor growth.[78] The absence of FUNDC1 leads to the accumulation of damaged mitochondria in the liver and the release of large amounts of mitochondrial DNA (mtDNA) from the mitochondrial matrix into the cytoplasm, which activates the inflammasome. Overactivation of the inflammasome triggers excessive production of inflammatory cytokines, such as IL-1, stimulating macrophages to induce a cytokine storm, including TNF and IL-6. This subsequently activates downstream signaling

pathways, including JAK/STAT and NF-κB, promoting excessive proliferation of hepatocytes and ultimately driving the development of HCC.[79,80] Thioredoxin-related transmembrane protein 2 (TMX2) is highly expressed in HCC tissues and is closely associated with poor patient prognosis. As a critical driver of HCC cell survival, TMX2 interacts with karyopherin subunit beta-1 (KPNB1) to promote the nuclear export of KPNB1, thereby maintaining its nucleocytoplasmic concentration gradient. This regulation facilitates the nuclear entry of transcription factor EB (TFEB), which activates the expression of autophagy-related genes, promoting the initiation of mitophagy. Under oxidative stress conditions, TMX2 further enhances its role by interacting with mitochondrial outer membrane proteins, recruiting Parkin to damaged mitochondria. This process triggers the ubiquitination of mitochondrial proteins, not only amplifying mitophagy but also preserving mitochondrial quality and function through the clearance of damaged mitochondria. Consequently, TMX2 strengthens the tolerance of HCC cells to oxidative stress, driving their proliferation and tumor progression.[81] Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a long non-coding RNA (lncRNA) that plays a critical role in regulating autophagy in HCC cells.[82] Zhao Yijing and her team discovered that MALAT1, encoded by the nuclear genome, is highly enriched in the mitochondria of HepG2 cells and regulates mitochondrial energy metabolism, mitophagy, and the coordination of nuclear and mitochondrial functions. When MALAT1 expression is suppressed, it leads to the activation of mitochondrial apoptosis and the inhibition of mitophagy. These changes may be associated with reduced sensitivity of HCC to anticancer therapies and poor patient prognosis.[83] These findings not only elucidate the role of mitophagy in the development and progression of HCC, but also provide a solid theoretical basis for identifying potential drug targets and the subsequent development of clinical drugs.

Traditional Chinese Medicine Monomers and Their Derivatives Treat HCC by Targeting Mitophagy

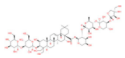
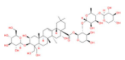
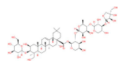
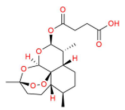
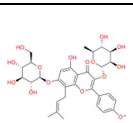
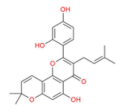
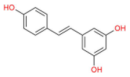
In recent years, more and more attention has been paid to the study of natural compounds. Traditional medicine-derived natural products and extracts are regarded as the most potential new anticancer drugs due to their unique biological activities and reduced side effects.[84] According to relevant statistical data, from 1940 to 2014, about half of the small-molecule drugs approved for cancer treatment were natural compounds or their derivatives.[85] This article systematically summarizes the latest advancements in in vitro and in vivo experimental research on TCM monomers and their derivatives, and delves into the molecular mechanisms by which they exert anti-tumor effects through the regulation of mitophagy (Tables 1 and 2), aiming to provide new perspectives and ideas for future related research.

Monomers and Their Derivatives Promoting Mitophagy for HCC

Platycodon grandiflorus (Jacq). A.DC. (PG) is not only a widely consumed plant but also a common medicinal plant.[102] Platycodin D2 (PD2), a triterpenoid saponin extracted from Platycodon grandiflorus A.DC., is the main bioactive component of PG, which has been shown to have significant anti-tumor activity.[103,104] It can induce HCC cell cycle arrest and cell senescence, thereby inhibiting the proliferation of HCC cells while showing low toxicity to normal hepatocytes. In addition, PD2 activates NIX-mediated mitophagy, causing mitochondrial damage and the release of ROS, thereby enhancing P21/CyclinA2 pathway-mediated hepatoma cell senescence and exerting its anti-tumor effect.[86] Deapioplatycodin D (DPD) is a triterpene saponin with various pharmacological properties. Yiquan Li and his team found that DPD can cause mitochondrial damage and promote the production of ROS, which in turn triggers HCC cell senescence by promoting BNIP3L-induced incomplete mitophagy. At the same time, it can significantly activate β-galactosidase, induce G2 phase arrest of HCC cells, and eventually lead to inhibition of HCC cell proliferation.[87] Polygalacin D (PGD) is also a triterpenoid saponin.[105] Studies have shown that PGD has a significant inhibitory effect on HCC cells, and this inhibitory effect is enhanced with the increase of PGD concentration. In vitro and in vivo experiments, it was found that PGD promotes mitophagy and endogenous apoptosis by increasing the level of BCL2-interacting protein 3-like (BNIP3L), thereby inducing HCC cell death and exerting anti-liver cancer activity.[88]

Artesunate (ART) is a semi-synthetic water-soluble Artemisia annua L. derivative,[106] which has been shown to significantly enhance the cytotoxicity of sorafenib on HCC cells in vitro.[107–109] In sorafenib-resistant HCC cells and tissues, the expression level of AFAP1L2 tends to increase, which activates the downstream of the SRC/FUNDC1

Table 1 Monomers and Their Derivatives Promoting Mitophagy for HCC

Monomers/ Decoctions	Source	Structure	Molecular Formula	Description	In vivo/ In vitro	Model	Autophagy-Related Targets	References
Platycodin D2	*Platycodon grandiflorus* (Jacq). A.DC.	$C_{63}H_{102}O_{33}$		Triterpenoid saponin	In vivo	The HCCLM3 cells were injected into the right liALB/c nude mimb of Bce.	NIX	[86]
Deapioplatycodin D	*Platycodon grandiflorus* (Jacq). A.DC.	$C_{52}H_{84}O_{24}$		Triterpenoid saponin	In vitro/ In vivo	Huh-7 cells, HepG2 cells, MHCC97H cells, HCCLM3 cells, SK-Hep1 cells, Huh-6 cells. The HCCLM3 cells were subcutaneously injected into the chest of BALB/c nude mice.	BNIP3L	[87]
Polygalacin D	*Platycodon grandiflorus* (Jacq). A.DC.	$C_{57}H_{92}O_{27}$		Triterpenoid saponin	In vitro/ In vivo	HepG-2 cells, HCCLM3 cells. The HCCLM3 cells were subcutaneously injected into the right thigh of BALB/c nude mice.	BNIP3L	[88]
Artesunate	*Artemisia annua* L.	$C_{19}H_{28}O_8$		Sesquiterpene lactones	In vitro/ In vivo	HepG2 cells, Hep3B cells, MHCC-97H cells, HUH7 cells. The HepG2 cells were implanted into the livers of BALB/c nude mice.	FUNDC1	[89]
Icariin	*Epimedium* L.	$C_{33}H_{40}O_{15}$		Flavonoid	In vitro/ In vivo	SK-Hep1 cells, Huh-7 cells. The SK-Hep1 cells were subcutaneously injected into the flanks of BALB/c nude mice.	PINK1/Parkin	[90]
Morusin	*Morus* L.	$C_{25}H_{24}O_6$		Isoprenoid Flavonoids	In vitro/ In vivo	HepG2 cells, Hep3B cells, SK-HEP-1 cells. The Hep3B cells were injected into the left axilla of BALB/c nude mice.	PINK1/Parkin	[91]
Resveratrol	*Polygonum cuspidatum* Siebold & Zucc.	$C_{14}H_{12}O_3$		Polyphenolic compound	In vitro/ In vivo	HepG2 cells. The HepG2 cells were subcutaneously injected into the right dorsal flank of BALB/c nude mice.	MALAT1/ miR-143-3p/ RRM2	[92]

(*Continued*)

Table 1 (Continued).

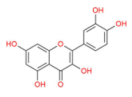
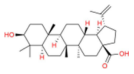
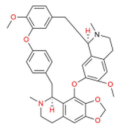
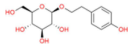
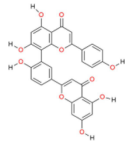
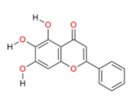
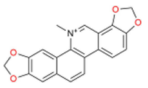
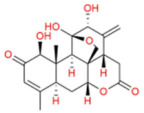
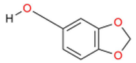
Monomers/ Decoctions	Source	Structure	Molecular Formula	Description	In vivo/ In vitro	Model	Autophagy-Related Targets	References
Quercetin	Fruits and vegetables	$C_{15}H_{10}O_7$		Flavonoid	In vitro/ In vivo	Huh7 cells, Hep3B cells. The Hep3B cells were subcutaneously injected into the bilateral regions of BALB/c nude mice.	Pink1/Parkin	[93]
Betulinic acid	*Betula* L.	$C_{30}H_{48}O_3$		Pentacyclic triterpenoid	In vitro/ In vivo	HepG2/ADM cells, MCF-7/ADR cells. HepG2/ADM cells were subcutaneously injected into BALB/c nude mice.	Parkin/PINK1	[94]
Cepharanthine	*Stephania cephalantha* Hayata	$C_{37}H_{38}N_2O_6$		Alkaloid	In vitro/ In vivo	Huh7 cells, HepG2 cells, SMMC - 7721 cells. Huh7 cells were subcutaneously injected into the flanks of BALB/c nude mice.	GPR30	[95]
Salidroside	*Rhodiola rosea* L.	$C_{14}H_{20}O_7$		Phenylethanoid glycosides	In vitro/ In vivo	Hepa1-6 cells, Huh7 cells, HepG2 cells. H22 cells were injected into the tail veins of BALB/c nude mice under high pressure.	Parkin/ PINK1	[96]
Amentoflavone	*Selaginella tamariscina* (P. Beauv). Spring	$C_{30}H_{18}O_{10}$		Biflavonoids	In vitro	Huh - 7 cells, Li - 7 cells, HCCLM3 cells, MHCC97H cells, HepG2 cells.	miR-124-3p/ CAPN2 axis	[97]
Baicalein	*Scutellaria baicalensis* Georgi	$C_{15}H_{10}O_5$		Flavonoid	In vitro	Huh7 cells, Huh7.5 cells, HepG2 cells.	Parkin, TBK1	[98]

Table 2 Monomers Inhibiting Mitophagy for HCC

Monomers/ Decoctions	Source	Structure	Molecular Formula	Description	In vivo/ In vitro	Model	Autophagy-Related Targets	References
Sanguinarine	*Sanguinaria canadensis* L.	$C_{20}H_{14}NO_4$		Benzophenanthridine alkaloid	In vitro	MHCC - 97H cells	Parkin/PINK1	[99]
Ailanthone	*Ailanthus altissima* (Mill). Swingle	$C_{20}H_{24}O_7$		Primary quassinoid	In vitro/ In vivo	MHCC-97H cells, HepG2 cells, Huh7 cells, HCC-LM3 cells. Huh7 cells were subcutaneously injected into the left axilla of BALB/c nude mice.	PINK1-PRKN	[100]
Sesamol	*Sesamella* Rchb.	$C_7H_6O_3$		Lipophilic lignan compound	In vitro/ In vivo	HepG2 cells. HepG2 cells were injected subcutaneously between the scapulae of BALB/c nude mice.	PI3K Class III/Belin-1, AMPK	[101]

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signaling axis, which in turn blocks the recruitment of FUNDC1 to LC3B and affects the activation process of mitophagy. Zhaochen Ma et al found that ART inhibits the expression of AFAP1L2 protein, thereby blocking the phosphorylation of SRC and FUNDC1. This process promotes the recruitment of FUNDC1 to LC3B, activating AFAP1L2-SRC-FUNDC1 axis-dependent mitophagy. This mechanism significantly enhances apoptosis in sorafenib-resistant HCC cells, thereby restoring the sensitivity of HCC to sorafenib.[89]

Icariin (ICA) is a natural compound extracted from Epimedium L. It has been proven to be safe and effective in the treatment of a variety of solid tumors, especially advanced HCC.[110,111] In China, clinical trials of ICA for the treatment of advanced HCC are underway and have been approved for the treatment of advanced HCC.[112] As an inducer of PINK1/Parkin-dependent mitophagy, ICA can inhibit the growth, proliferation, and migration of HCC cells by inducing mitophagy and apoptosis and exerting its anticancer activity. In addition, ICA also counteracts its own cytotoxicity through mitophagy and enhances the therapeutic effect on HCC.[90] Studies have found that ICA can induce immunogenic cell death (ICD) in mouse and human HCC cells by inducing mitophagy and apoptosis. When combining icaritin and doxorubicin, both at a low dose, can reshape the immunosuppressive tumor microenvironment and stimulate a strong immune memory response. The two show synergistic effects in the induction of ICD. This low-dose strategy of combined therapy is expected to provide significant clinical benefits for HCC patients due to its high efficiency and low toxicity.[113] Siyu Chen et al developed mitochondria-targeted OPDEA-PCL/ICT nanoparticles. These nanoparticles can promote the accumulation of ICT in the mitochondria of HCC cells, thereby enhancing the ICD effect through the activation of mitophagy. In the H22 subcutaneous tumor model, compared with the control group, the tumor inhibition rate of the OPDEA-PCL/ICT nanoparticle group reached 60%, and the median survival time was nearly doubled, demonstrating good clinical therapeutic potential.[114] Axi Shil et al have discovered that icariin can enhance the cytotoxicity of sorafenib through a mitochondria-dependent pathway and significantly augment sorafenib-induced apoptosis in HCC cells. When used in combination with sorafenib, icariin can synergistically inhibit the viability of HCC cells, offering a novel therapeutic strategy for the treatment of HCC.[115]

Morusin (Mor), an isopentenylated flavonoid isolated from the root bark of Morus L., has been shown to have potent antitumor effects.[116–119] Mor can significantly reduce the expression of ATP-citrate lyase (ACLY) in HCC cells, inhibit the activity of ACLY, lead to the accumulation of ROS in HCC cells, trigger mitochondrial damage, lead to mitophagy and apoptosis in HepG2 and Hep3B cells, thereby inhibiting the proliferation of HCC cells. This study also revealed that the expression level of ACLY in HCC tissues was significantly higher than that in the corresponding adjacent normal tissues and was positively correlated with liver cancer grade. Mor is a potent ACLY inhibitor with potential for anti-HCC therapy.[91]

Resveratrol (RSV), a polyphenolic compound extracted from natural plants, has been widely studied for its potential role in anti-HCC.[120–123] Studies have shown that RSV has a significant cell cycle effect on HepG2 cells in vitro experiments and can regulate the expression of genes and proteins related to apoptosis, thereby inhibiting the proliferation and promoting the apoptosis of HCC cells. In vivo experiments, RSV significantly inhibits tumor growth in a dose-dependent manner and exerts its anti-tumor activity by acting on the MALAT1/miR-143-3p/RRM2 signaling axis to induce mitophagy and mitochondrial dysfunction. These findings reveal that RSV, as a potential anti-HCC drug, affects the growth and survival of HCC cells by regulating mitophagy and apoptosis mechanisms.[92]

Quercetin, a flavonoid widely found in nature, has been widely studied for its anticancer effect in HCC and other cancers.[124–126] Studies have found that quercetin can upregulate the expression of Pink1 and Parkin in liver cancer cells, activating mitophagy, exerting its antioxidant effect, and protecting cells from damage. In addition, Sirt1 acts as a key regulator in the process of quercetin triggering mitophagy, and its activation is crucial for enhancing the efficacy of quercetin in liver cancer. Therefore, targeting Sirt1, an upstream regulator, may be an effective way to improve the anticancer effect of quercetin.[93]

Betulinic acid (BA), a pentacyclic triterpenoid found in the bark of Betula L., BA and its derivatives exhibit broad-spectrum anti-cancer activity.[127–129] The research results of Nan Yao and his team revealed that a novel BA derivative, B5 G1, exhibited significant anti-tumor effects against multidrug-resistant tumor cell lines HepG2/ADM and MCF-7/ADR. B5G1 activates mitophagy through a pathway dependent on PINK1/Parkin by promoting ROS production and triggering mitochondrial dysfunction. In addition, the study also found that inhibiting mitophagy sensitized multidrug-

resistant cancer cells to B5 G1 and enhanced the anti-cancer effect of B5 G1. This finding provides new ideas and potential drug candidates for the treatment of multidrug-resistant tumors.[94]

Cepharanthine, an alkaloid extracted from the plant Stephania cephalantha Hayata,[130] has been confirmed to have anti-tumor activity by many studies and is usually used as an adjuvant therapeutic drug for tumors.[131–133] Recent studies have found that Cepharanthine hydrochloride (CH), a semi-synthetic derivative of Cepharanthine, is a novel mitophagy inducer. It acts by targeting the GPR30 receptor. This induced mitophagy plays a protective role in liver cancer models in vitro and in vivo. The study also found that the combination of CH and autophagy inhibitors may be used as a new strategy to enhance the anti-tumor effect of chrysogenin in the treatment of HCC. This combined treatment method is expected to enhance the anti-tumor potential of cryogenic by regulating the mitophagy process, providing a new direction for the treatment of HCC.[95]

Salidroside (Sal) is a naturally active compound extracted from plants of the genus Rhodiola rosea L., belonging to the class of phenylethanoid glycosides. It has been demonstrated to enhance PINK1/Parkin-mediated mitophagy and is important in many diseases.[134,135] A study found that the combination of Sal and 5-fluorouracil (5-FU) exhibits significant synergistic antitumor effects against HCC. Unlike the direct cytotoxic mechanism of 5-FU, Sal specifically activates the YIPF5-induced mitophagy pathway in HCC cells, inducing excessive mitophagy. This leads to mitochondrial dysfunction (such as loss of membrane potential and reduced ATP production), subsequently triggering cellular senescence and mitotic arrest. This unique mechanism enhances the antitumor efficacy of 5-FU and provides a novel potential target for HCC treatment.[96]

Amentoflavone (AF) is an active phenolic compound isolated from Selaginella tamariscina (P. Beauv). Spring, exhibits potential anti-HCC activity. Fengting Zhu et al found that in HCC tissues and cells, the expression of miR-124-3p is downregulated, while the expression of CAPN2 is upregulated. AF can upregulate the expression of miR-124-3p, thereby inhibiting the Wnt/β-catenin pathway through the regulation of the miR-124-3p/CAPN2 axis. This mechanism promotes mitochondrial autophagy in HCC cells and inhibits cell viability.[97]

Baicalein is a flavonoid compound extracted from Scutellaria baicalensis Georgi, and it possesses a variety of pharmacological activities. Studies have shown that baicalein can induce the translocation of Parkin and TBK1 to the mitochondria, thereby promoting the phosphorylation of TBK1 at the Ser172 site and PINK1 at the Ser65 site, thus stabilizing the PINK1 protein. Moreover, baicalein can specifically recruit NDP52 and OPTN, induce the formation of autophagosomes, and promote their fusion with lysosomes, thereby enhancing autophagic flux and inducing mitochondrial autophagy in HCC cells. It is expected to become a novel inducer for regulating mitochondrial autophagy in the liver.[98]

Monomers Inhibiting Mitophagy for HCC

Sanguinarine (Sang) is a benzophenanthridine alkaloid isolated from plants such as Sanguinaria canadensis L. Studies have found that Sang can inhibit the growth of HCC cells through the ROS-mitophagy-apoptosis pathway and has anti-cancer potential. Sang disrupts the acidic environment of lysosomes by inhibiting the maturation of cathepsin D, thereby interfering with the formation of autophagosomes-lysosomes. This effect blocks the degradation of autophagosomes during mitophagy, eventually induces apoptosis, and inhibits the growth of liver cancer cells. In addition, Sang-induced ROS-dependent mitophagy and apoptosis were significantly attenuated after treatment with ROS scavengers, indicating that ROS plays an important role in its mechanism of action.[136] Qi Su et al found that when Parkin/PINK1-mediated mitophagy is blocked, damaged mitochondria cannot be effectively removed. This blocking effect makes HCC cells more sensitive to mitochondrial apoptosis caused by sanguinarine, thus revealing that mitophagy actually plays a role in protecting cells from apoptosis in sanguinarine-treated cells.[99]

Ailanthone is a natural compound extracted from the traditional Chinese medicinal herb Ailanthus altissima (Mill). Swingle and belongs to the primary quassinoid. It has demonstrated potent antitumor activity in both in vitro and in vivo experiments.[137] Ailanthone inhibits PINK1-PRKN-mediated mitophagy, leading to the leakage of mtDNA into the cytoplasm, thereby triggering the production of inflammatory factors. The suppression of mitophagy and the activation of inflammatory responses collectively inhibit the proliferation of HCC cells. Compared to 5-FU, ailanthone

demonstrates stronger anti-HCC activity and shows no significant adverse effects on body weight or the physiological functions of vital organs in animal experiments.[100]

Sesamol is a lipophilic lignan compound extracted from Sesamella Rchb. and possesses potential anticancer activity. Research has shown that sesamol can induce mitochondrial dysfunction, leading to the loss of mitochondrial membrane potential and increased production of H_2O_2, thereby disrupting redox-sensitive signaling pathways. Moreover, sesamol can inhibit mitochondrial autophagy and cellular autophagy by suppressing the PI3K Class III/Belin-1 pathway and the AMPK signaling pathway. These findings have been validated through in vitro and in vivo experiments, which demonstrate that sesamol can effectively inhibit tumor growth, induce S-phase cell cycle arrest, and induce apoptosis.[101]

Conclusion and Future Directions

Mitophagy is a newly discovered type of programmed cell death that is closely related to the occurrence and development of HCC. It plays a double-edged role in the development of HCC and is complex in tumor biology. Some studies have found that mitophagy in the early stage of tumor development can inhibit tumor growth by clearing damaged mitochondria and maintaining cell homeostasis. However, in the late stage of the tumor, mitophagy may promote cell growth by enhancing the adaptability of tumor cells to harsh environments such as hypoxia and nutritional deficiency. Therefore, it is particularly important to regulate the process of mitophagy according to the stage of disease development.[138]

HCC remains a significant public health challenge in China, with an incidence rate reaching as high as 370,000 cases per year. Early liver cancer is mainly surgery, while advanced liver cancer is mostly chemotherapy, immunotherapy, and targeted therapy. Postoperative complications and drug resistance not only reduce the therapeutic effect but also increase the cost. Chinese herbal medicine has shown unique advantages in the treatment of HCC. Chinese herbal medicine has multi-target characteristics, which can promote the occurrence of mitophagy through a variety of pathways, exert its anticancer effect, and improve drug sensitivity. At the same time, Chinese herbal medicine has been proven to be safe and has fewer toxic and side effects. However, while this study primarily focuses on the potential role of TCM in the treatment of liver cancer, it also recognizes the significant importance of non-Chinese herbal medicines in this field. Cynaropicrin is a sesquiterpene lactone extracted from artichoke (Cynara scolymus L). It activates p38 MAPK-mediated mtROS production, inducing PINK1/Parkin-mediated mitophagy in human hepatocellular carcinoma cells, thereby inhibiting cell proliferation.[139] Furthermore, an ethyl acetate extract of Crithmum maritimum L., an edible plant harvested in Apulia, significantly inhibits the growth of hepatocellular carcinoma cells and reshapes their metabolic profiles through multiple target effects, such as suppressing the Warburg effect, downregulating amino acid and phospholipid metabolism, regulating lipid homeostasis, and modulating insulin signaling pathways.[140,141] Plant extracts, being a complex mixture of various metabolites, can target multiple pathways simultaneously, thereby exerting synergistic effects.[142] Due to their multi-component, multi-target characteristics, plant extracts have shown significant advantages in anti-tumor research. However, there is relatively less research on Chinese herbal extracts in this field. Future research should focus more on in-depth studies of Chinese herbal extracts to more fully reveal the essence of their actions and provide a scientific basis for developing new HCC treatment strategies based on the characteristics of Chinese medicine.

This paper primarily reviews the progress in research conducted both in vitro and in vivo on how monomers and derivatives of TCM effectively inhibit the proliferation and migration of HCC cells by targeting the regulation of mitophagy. This provides a solid scientific basis for the application of TCM in cancer treatment. However, compared with well-characterized TCM monomers, research on TCM formulas—which feature multi-component, multi-target synergistic effects—remains insufficient. Their complex pharmacological mechanisms have not yet been fully elucidated, posing significant challenges for researchers. Therefore, we call upon scholars across disciplines to intensify research efforts on TCM formulas, systematically elucidate their regulatory networks and molecular mechanisms in HCC development and progression, and accelerate translational research while actively conducting clinical trials to validate their efficacy. The widespread application of multi-omics technologies (such as genomics, transcriptomics, proteomics, and metabolomics) and network pharmacology enables a multidimensional analysis of the mechanisms of TCM formulas, revealing synergistic interactions among their complex components and providing robust evidence for

precision medicine in TCM. This multidisciplinary research strategy will not only advance the scientific understanding of TCM formulas in HCC treatment but also promote the modernization and internationalization of TCM, ultimately offering more optimized, personalized therapeutic options for HCC patients.

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Data Sharing Statement

All relevant data supporting the findings of this study are included in the main text. Additional data will be provided by the corresponding author upon request.

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Disclosure

The authors report no conflicts of interest in this work.

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