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Targeting the mTOR Pathway in Hepatocellular Carcinoma: The Therapeutic Potential of Natural Products

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Abstract: Despite advancements in cancer treatment through surgery and drugs, hepatocellular carcinoma (HCC) remains a significant challenge, as reflected by its low survival rates. The mammalian target of rapamycin (mTOR) signaling pathway plays a crucial role in regulating the cell cycle, proliferation, apoptosis, and metabolism. Notably, dysregulation leading to the activation of the mTOR signaling pathway is common in HCC, making it a key focus for in-depth research and a target for current therapeutic strategies. This review focuses on the role of the mTOR signaling pathway and its downstream effectors in regulating HCC cell proliferation, apoptosis, autophagy, cell cycle, and metabolic reprogramming. Moreover, it emphasizes the potential of natural products as modulators of the mTOR signaling pathway. When incorporated into combination therapies, these natural products have been demonstrated to augment therapeutic efficacy and surmount drug resistance. These products target key signaling pathways such as mTOR signaling pathways. Examples include 11-epi-sinulariolide acetate, matrine, and asparagus polysaccharide. Their inhibitory effects on these processes suggest valuable directions for the development of more effective HCC therapeutic strategies. Various natural products have demonstrated the ability to inhibit mTOR signaling pathway and suppress HCC progression. These phytochemicals, functioning as mTOR signaling pathway inhibitors, hold great promise as potential anti-HCC agents, especially in the context of overcoming chemoresistance and enhancing the outcomes of combination therapies.

Keywords: hepatocellular carcinoma, natural products, mTOR signaling pathway

Introduction

Hepatocellular carcinoma (HCC) is one of most common malignancies globally and poses a significant threat to human health.[1] HCC is recognized as one of the top five leading causes of cancer-related mortality globally, with most patients having a 5-year survival rate of less than 20%.[2] Surgical resection, local therapies, and systemic treatments remain the primary therapeutic strategies for HCC at different clinical stages.[3] Despite advancements in systemic treatments for HCC, most patients show low response rates and ultimately succumb to the disease.[4] Therefore, there is an urgent need to explore new antitumor agents.

Mutations in oncogenes and tumor suppressor genes are the primary pathogenic mechanisms in the development of liver cancer as they disrupt critical cellular signaling pathways. In HCC, the key pathways involved in the carcinogenic process include the mammalian target of rapamycin (mTOR), Wnt/β-catenin, and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways.[5] This paper will mainly focus on the mTOR signaling pathway. The mTOR pathway is a central regulator of cell growth, proliferation, and survival.[6] Dysregulation of this pathway is frequently observed in HCC, contributing to tumorigenesis and cancer progression.[7] The mTOR pathway operates through two distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), each playing a crucial role in cellular metabolism and response

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to environmental signals.[8] Aberrant activation of mTOR signaling has been implicated in the development and maintenance of HCC, making it an attractive target for therapeutic intervention.

Natural products, including phytochemicals and bioactive compounds derived from medicinal plants, have gained significant attention as potential anticancer agents. These compounds often exhibit multiple mechanisms of action, including the modulation of key signaling pathways such as mTOR. Recent studies have highlighted the ability of various natural products to inhibit mTOR signaling pathway, thereby suppressing the growth and proliferation of HCC cells. The exploration of natural products as modulators of the mTOR pathway offers a promising approach for the development of novel therapeutic strategies against HCC.

mTOR Signaling Pathway

mTOR is a serine/threonine kinase and a member of the phosphoinositide 3-kinase (PI3K)-related kinase protein family. It plays a crucial role in regulating cell growth and proliferation in response to nutrient signals. mTOR exists in two distinct cellular complexes: mTORC1 and mTORC2.[9] Both mTOR complexes share the mammalian lethal with SEC13 protein 8, the Tti1/Tel2 complex and the inhibitory protein DEP domain-containing mTOR-interacting protein (DEPTOR). mTORC1 additionally includes the regulatory-associated protein of mTOR (Raptor) and the inhibitory subunit proline-rich Akt substrate of 40kDa (PRAS40), while mTORC2 contains the rapamycin-insensitive companion of mTOR (Rictor) and the regulatory proteins Protor1/2 and mSin1.[10] mTORC1 can be activated by cytokines, oxygen, stress signals, and nutrients. Its activation promotes lipid and protein biosynthesis, cell growth, and proliferation while inhibiting autophagy.[11] In contrast, mTORC2 is not sensitive to nutrients but plays a crucial role in regulating cell metabolism, survival, and growth, as well as controlling cytoskeletal organization.[12,13]

mTOR Signaling Pathway and HCC

The mTOR pathway is a central intracellular signaling pathway that regulates cell cycle, proliferation, apoptosis, metabolism, and angiogenesis through interactions with various upstream and downstream molecules.[11] mTOR is overexpressed in HCC, promoting tumor cell proliferation and growth.[14] Studies have shown that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is significantly upregulated in HCC and accelerates tumor cell transformation and growth by activating the Wnt/β-catenin pathway and inducing the expression of serine/arginine-rich splicing factor 1 (SRSF1).[15] The coordination between mTOR complexes and epithelial-mesenchymal transition (EMT) is closely associated with HCC metastasis.[16] Autophagy is an evolutionarily conserved process that plays a crucial role in maintaining homeostasis under physiological conditions. Targeting autophagy can disrupt the growth and metastasis of HCC and enhance the responsiveness of tumor cells to therapy.[17] Apoptosis plays a key role in development, physiology and homeostasis.[18] Additionally, mTOR inhibits apoptosis and autophagy. Research indicates that downregulation of nitrogen permease regulator like 2 (NPRL2) promotes HCC growth by inhibiting autophagy through the mTOR pathway.[19] Ras-related protein Rap-2a (RAP2A) is aberrantly overexpressed in HCC tissues, enhancing tumor cell proliferation and resistance to apoptosis via activation of the mTOR signaling pathway.[11] mTOR also plays a critical role in metabolic reprogramming in HCC, with increased aerobic glycolysis being a hallmark of cancer metabolism.[20] Inhibiting the protein kinase B (AKT)/mTOR signaling pathway reduces aerobic glycolysis in HCC cells, ultimately leading to suppressed cellular growth.[21] Lipid metabolism is a crucial energy source that supports cell growth and provides intermediates for biosynthesis in cancer cells.[22] In the hypoxic tumor microenvironment, activation of the AKT/mTOR pathway drives lipogenesis and lipid accumulation during HCC progression, resulting in enhanced proliferation, viability, and angiogenesis.[23] mTOR also induces cell cycle arrest, and its inhibition enhances the thermosensitivity of SMMC-7721 cells by increasing apoptosis and inducing S-phase arrest.[24] Inhibiting mTOR signaling pathway can reduce tumor growth by inducing apoptosis, autophagy, and cell cycle arrest.

Natural Products as Inhibitors in HCC

Regulation of Apoptosis-Related Proteins and Pathways

In HCC treatment, regulating apoptosis-related proteins and pathways is vital. Many natural products/extracts target the mTOR signaling pathway, inducing apoptosis and impeding tumor growth (Figure 1 and Table 1). For instance, among

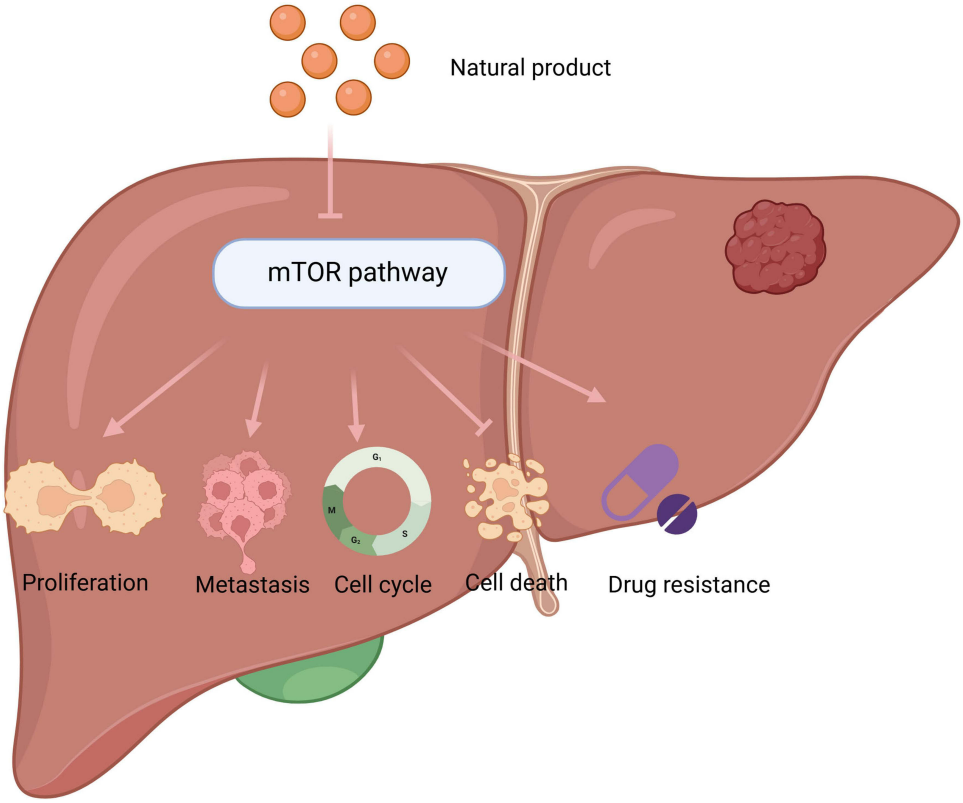

Figure 1 Natural products targeting mTOR pathways improve HCC.
Notes: Created in BioRender. Chen, G. (2024) https://BioRnder.com/x50q835.
Abbreviation: mTOR, mammalian target of rapamycin.

these compounds, 4-Hydroxyderricin from *Angelica sinensis* inhibits HepG2 and Huh7 cell proliferation dose-dependently via mitochondrial apoptosis and cell cycle arrest by suppressing the PI3K/AKT/mTOR pathway.[25,26] Similarly, Artemisia capillaris (ACE-63) has hepatoprotective and anti-inflammatory properties[27] and its ethyl acetate

Table 1 Natural Products Targeting Apoptosis-Related Proteins and Pathways Improve HCC

Name	Effect	References
4-Hydroxyderricin	Promotes apoptosis and cell cycle arrest through inhibiting PI3K/AKT/mTOR pathway	[26]
ACE-63	Induces apoptosis but also inhibits cell growth and angiogenesis by blocking the PI3K/AKT/mTOR pathway	[28]
GGC	Induces apoptosis by blocking the PI3K/AKT/mTOR pathway	[30]
Withagenin A diglucoside	Induces apoptosis by blocking the PI3K/AKT/mTOR pathway	[32]
XS-5 and XS-6	Induce apoptosis and suppress cell growth, migration, and invasion by blocking the PI3K/AKT/mTOR pathway	[33]
Celastrol	Triggers caspase-dependent apoptotic signaling by inhibiting the mTOR pathway	[35]
COE	Enhance apoptosis by downregulating mTOR	[36]
Diosmetin	Inhibits cell proliferation and induces apoptosis by suppressing the mTOR pathway	[37]
Anemoside B4	Induces apoptosis and autophagy by blocking the PI3K/AKT/mTOR pathway	[38]
Arenobufagin	Induces apoptosis and autophagy by blocking the PI3K/AKT/mTOR pathway	[40]
C1	Induces apoptosis and autophagy by blocking the AKT/mTOR/S6K pathway	[41]
Salidroside	Induces apoptosis and autophagy by inhibiting the PI3K/AKT/mTOR pathway	[43]
Ginsenoside RK1	Inhibits HCC development by activating toxic autophagy and promoting apoptosis through the AMPK/mTOR pathway	[45]

(*Continued*)

Table 1 (Continued).

Name	Effect	References
Gundelia (G.) tournefortii	Suppresses primary HCC cell proliferation and induces apoptosis by inhibiting AKT, PI3K, and mTOR phosphorylation	[46]
Kahweol	Induces apoptosis in HCC cells by inhibiting the Src/mTOR/STAT3 signaling pathway	[47]
Lanatoside C	Inhibits HCC cell growth and reduces tumor volume by inducing apoptosis via negatively regulating the AKT/mTOR pathway through PKCδ activation	[48]
Licochalcone B	Inhibits AKT/mTOR signaling pathways, and sensitizes cancer cells to TRAIL-induced apoptosis	[49]
Celastrol, pristimerin, and two novel derivatives (cel-D2 and cel-D7)	Induce apoptosis and promote the degradation and inhibition of protein kinases in the Raf/MEK/ERK and PI3K/AKT/mTOR pathways	[50]
Phyllanthin	Induces caspase-dependent apoptosis by inhibiting the mTOR/PI3K signaling pathway	[51]
Pterostilbene	Induces apoptosis by inhibiting mTOR and S6K1 activation	[52]
Puerarin 6″-O-xyloside	Induces apoptosis at least partly through inhibiting PI3K/AKT/mTOR	[53]
Rotundic Acid	Induces apoptosis through modulation of AKT/mTOR and MAPK signaling pathways	[54]
Alnustone	Induces apoptosis and inhibits the ROS-mediated PI3K/AKT/mTOR signaling pathway	[55]

Abbreviations: ACE-63, Artemisia capillaris; GGC, ginkgolide C; XS, Xanthium strumarium; COE, Celastrus orbiculatus Thunb. Extracts; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

fraction induces apoptosis, inhibits cell growth and angiogenesis by blocking the PI3K/AKT/mTOR pathway.[28] Ginkgolide C (CGC) from *Ginkgo biloba* exhibits anti-inflammatory and antioxidant properties and induces apoptosis and reduces tumorigenic protein expression by inhibiting this pathway.[29,30] Furthermore, *Withania somnifera* (Solanaceae) is a medicinal plant used in Ayurvedic practices to promote health and well-being.[31] Withagenin A diglucoside increases the expression of cleaved caspase-8, Bax, cleaved caspase-9, cleaved caspase-3, and PARP, while reducing Bcl-2 expression by targeting VEGFR2 and downstream signaling pathways, including ERK, PI3K, AKT, and mTOR.[32] Similarly, Xanthium strumarium (XS)-5 and XS-6 effectively induce apoptosis and suppress cell growth, migration, and invasion by blocking the PI3K/AKT/mTOR pathway.[33] Moreover, celastrol is a bioactive natural product isolated from the medicinal plant *Tripterygium wilfordii Hook F*,[34] which triggers caspase-dependent apoptotic signaling by inhibiting the mTOR pathway in HCC cells.[35] Additionally, Celastrus orbiculatus Thunb. extracts (COE) enhance apoptosis by downregulating mTOR and altering the expression of Bcl-2, Bcl-xL, Bax, and caspase-3.[36] In addition, diosmetin inhibits HepG2 cell proliferation and induces apoptosis by suppressing the mTOR pathway.[37] Further supporting this trend, anemoside B4 induces apoptosis and autophagy, with the inactivation of the PI3K/AKT/mTOR pathway.[38] A further example includes arenobufagin, derived from bufadienolides in toad skin and parotid venom, which has been shown to inhibit metastasis across various cancers.[39] Arenobufagin induces mitochondria-mediated apoptosis and autophagy in HCC cells through inhibition of PI3K/AKT/mTOR pathway.[40] A cinchona alkaloid derivative (C1) induces apoptosis and blocks autophagy in HCC cells by suppressing the AKT/mTOR/S6K pathway.[41] Salidroside, a phenylpropanoid mainly isolated from *Rhodiola* species, with various pharmacological effects.[42] Notably, salidroside induces apoptosis by modulating mitochondrial function and autophagy by inhibiting the PI3K/AKT/mTOR pathway.[43] Similarly, Ginsenoside RK1 (RK1), obtained from ginseng plants, has antioxidant, antiapoptotic, anti-inflammatory effects.[44] Particularly, RK1 inhibits HCC development by activating toxic autophagy and promoting apoptosis through the AMP-activated protein kinase (AMPK)/mTOR pathway.[45] *Gundelia (G.) tournefortii* suppresses primary HCC cell proliferation and induces apoptosis by inhibiting AKT, PI3K, and mTOR phosphorylation.[46] Kahweol induces apoptosis in HCC cells by inhibiting the Src/mTOR/STAT3 signaling pathway.[47] Lanatoside C inhibits HCC cell growth by inducing apoptosis via negatively regulating the AKT/mTOR pathway through PKCδ activation.[48] Furthermore, licochalcone B inhibits AKT/mTOR signaling pathways, and sensitizes cancer cells to TRAIL-induced apoptosis by upregulating DR5 expression through ERK and JNK activation.[49] Celastrol, pristimerin, and two novel derivatives (cel-D2 and cel-D7) specifically inhibit HCC growth, with cel-D2 and cel-D7 demonstrating lower toxicity. These compounds induce apoptosis and promote the degradation and inhibition of protein kinases in the Raf/MEK/ERK and PI3K/AKT/

mTOR pathways.[50] Phyllanthin enhances anti-oxidant capacity and induces caspase-dependent apoptosis by inhibiting the mTOR/PI3K signaling pathway.[51] Additionally, pterostilbene induces apoptosis by inhibiting mTOR and S6K1 activation.[52] Puerarin 6″-O-xyloside reduces cell viability, proliferation, and stemness, while promoting autophagy and mitochondria-dependent apoptosis, at least partially through inhibition of the PI3K/AKT/mTOR pathway.[53] Rotundic Acid's anti-HCC proliferative effects are linked to its ability to inhibit angiogenesis and induce apoptosis through modulation of AKT/mTOR and MAPK signaling pathways.[54] Alnustone significantly induces apoptosis and inhibits the ROS-mediated PI3K/AKT/mTOR signaling pathway in HCC cells, with lower toxicity.[55] In conclusion, a diverse range of natural products have demonstrated potential in HCC treatment by targeting the mTOR signaling pathway to regulate apoptosis. This summary provides a foundation for further research into the development of natural-product-based HCC therapies, highlighting the need for additional in vivo and clinical studies to evaluate their efficacy and safety in real-world settings.

Regulation of Autophagy-Related Proteins and Pathways

Autophagy is crucial in the regulation of HCC, and various phytochemicals and natural products have been identified as key modulators of this process (Table 2). Among these, levo-tetrahydropalmatine (l-THP), derived from the clinical drug *Corydalis yanhusuo*, acts as an AMP-activated protein kinase (AMPK) activator.[56] It activates the AMPK-mTOR-ULK1 and ROS-JNK-ATG cascades while impairing ERK/AKT signaling to enhance autophagy.[56] Xanthoangelo also induces

Table 2 Natural Products Targeting Autophagy-Related Proteins and Pathways Improve HCC

Name	Effect	References
l-THP	Enhances autophagic response by activating the AMPK-mTOR-ULK1	[56]
Xanthoangelo	Induces autophagy by activating the AMPK/mTOR signaling pathway	[57]
Baicalein	Suppresses mTORC1 inhibitor-induced autophagy	[57]
Crocin	Induces autophagy in HCC cells via AKT/mTOR inhibition	[61]
Dihydroartemisinin	Induces autophagy by inhibiting AKT/mTOR signaling pathway	[64]
Galangin	Stimulates autophagy through activating AMPK and inhibiting mTOR signaling pathway	[66]
Kaempferol	Induces autophagy via AMPK-mediated ULK1 phosphorylation and mTORC1 inhibition	[68]
Norcantharidin	Induces autophagic cell death by inhibiting c-Met/mTOR signaling pathway	[70]
Sinensetin	Triggers autophagic cell death via p53-related AMPK/mTOR signaling	[72]
Hugan Buzure	Induces autophagy and apoptosis through inhibiting the PI3K/AKT/mTOR pathway	[73]
Muskone	Inhibits xenograft tumor growth in mice via PERK/ATF4/DDIT3 apoptosis signaling and SESN2/AMPK/mTOR autophagy pathways	[75]
Cryptotanshinone	Induces autophagy and apoptosis by inhibiting the PI3K/AKT/mTOR pathway	[77]
Uvangoletin	Induces autophagy and apoptosis by inhibiting the AKT/mTOR, MAPK, and TGF-β/Smad2 pathways	[78]
Isoliquiritigenin	Induces autophagy in HCC cells by suppressing the PI3K/AKT/mTOR pathway	[80]
Isoquercitrin	Induces autophagy and apoptosis through AMPK activation and mTOR/p70S6K inhibition	[82]
Lycorine	Promotes autophagy and apoptosis by suppressing the TCRP1/AKT/mTOR pathway	[84]
Melittin	Induces autophagy and apoptosis by inhibiting the PI3K/AKT/mTOR pathway	[85]
Polyphyllin I	Induces autophagy by suppressing the PI3K/AKT/mTOR pathway	[87]
Quercetin	Induces autophagy by suppressing the AKT/mTOR pathway	[89]
Sarmentosin	Induces autophagy and apoptosis by activating Nrf2 and inhibiting Mtor	[90]
Shikonin	Induces autophagy and apoptosis by inhibiting the PI3K/AKT/mTOR pathway	[92]
Tenacissoside H	Induces autophagy by suppressing the PI3K/AKT/mTOR pathway	[94]
Berberine	Induces autophagy and apoptosis by activating AMPK and inhibiting mTORC1	[96]
Dioscin	Induces autophagy and apoptosis by suppressing the AKT/mTOR pathway	[98]
Salvianolic acid B	Induces autophagy and apoptosis by suppressing the AKT/mTOR pathway	[100]
Trillin	Induces apoptosis by inhibiting autophagy via the mTOR/STAT3 pathway	[102]
Brusatol	Induces autophagy by inhibiting the PI3K/AKT/mTOR pathway	[103]

Abbreviations: l-THP, levo-tetrahydropalmatine; AMPK, AMP-activated protein kinase; c-Met, c-Mesenchymal-epithelial transition factor; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; ULK1, unc-51-like kinase 1; PERK, PKR-like ER kinase; ATF4, activating transcription factor 4; DDIT3, DNA damage-inducible transcript 3; SESN2, sestrin 2; MAPK, mitogen activated protein kinases; TGF-β, transforming growth factor-β; TCRP1, tongue cancer resistance-associated protein 1; Nrf2, nuclear factor-erythroid factor 2-related factor 2; STAT3, signal transducer and activator of transcription 3.

autophagy by activating the AMPK/mTOR signaling pathway.[57] Blocking the AMPK/mTOR axis with compound C abolishes the autophagy-mediated inhibition of metastasis.[57] Baicalein, a primary flavonoid extracted from the dried roots of *Scutellaria baicalensis*, exhibits anti-cancer properties against various malignancies.[58] It suppresses mTORC1 inhibitor-induced autophagy, enhancing chemosensitivity in $CD133^+$ tumor-initiating cells, Huh7 spheroids, and patient-derived HCC xenografts.[59] Crocin, a unique water-soluble carotenoid extracted from saffron, demonstrates anticancer activity.[60] Crocin induces autophagy in HCC cells via AKT/mTOR inhibition, with autophagy suppression leading to apoptosis resistance.[61] Furthermore, dihydroartemisinin from *Artemisia annua*[62,63] potentially induces autophagy in HepG2215 cells by inhibiting AKT/mTOR.[64] Galangin, an extract from the ginger plant galangal, exhibits the ability to inhibit tumor cell proliferation and migration.[65] Galangin stimulates autophagy in HepG2 cells through activating AMPK and inhibiting mTOR signaling pathway.[66] Kaempferol in various plants induces autophagy in HCC cells via AMPK-mediated ULK1 phosphorylation and mTORC1 inhibition.[67,68] Norcantharidin, a demethylated derivative of *cantharidin*,[69] induces autophagic cell death in HCC by inhibiting c-Met/mTOR, alone or with crizotinib.[70] Sinensetin from citrus fruits triggers autophagic cell death in HepG2 cells via the p53-related AMPK/mTOR pathway.[71,72] Additionally, Hugan Buzure induces autophagy and apoptosis through inhibiting the PI3K/AKT/mTOR pathway, leading to HCC cell death.[73] Muskone is a chemical monomer derived from musk,[74] which inhibits xenograft tumor growth in mice via sestrin 2 (SESN2)/AMPK/mTOR autophagy pathways and PKR-like ER kinase (PERK)/activating transcription factor 4 (ATF4)/DNA damage-inducible transcript 3 (DDIT3) apoptosis signaling.[75] Cryptotanshinone from *Salvia miltiorrhiza* suppresses Huh7 and MHCC97-H cell proliferation and induces autophagy and apoptosis by inhibiting PI3K/AKT/mTOR.[76,77] Uvangoletin from *Sarcandra glabra* induces autophagy and apoptosis by inhibiting AKT/mTOR, MAPK, and TGF-β/Smad2.[78] Isoliquiritigenin from *liquorice* induces autophagy in HCC cells by suppressing PI3K/AKT/mTOR.[79,80] Isoquercitrin is widely present in vegetables, medicinal herbs and fruits,[81] which triggers HCC cell death by inducing autophagy and apoptosis through AMPK activation and mTOR/p70S6K inhibition.[82] Lycorine is an alkaloid isolated from plants of the Amaryllidaceae family, exhibiting potent anti-inflammatory and anti-cancer activities.[83] It promotes apoptosis and autophagy in HCC by suppressing the TCRP1/AKT/mTOR pathway.[84] Melittin induces autophagy and apoptosis by inhibiting the PI3K/AKT/mTOR pathway.[85] Polyphyllin I is an active steroidal saponin isolated from *Paris polyphylla*,[86] which induces autophagy by suppressing the PI3K/AKT/mTOR pathway.[87] Quercetin is widely distributed across a variety of fruits and vegetables.[88] It activates autophagy through AKT/mTOR inhibition and MAPK activation.[89] Sarmentosin stimulates autophagy and caspase-dependent apoptosis in HCC cells by activating Nrf2 and inhibiting mTOR.[90] Shikonin, a natural compound derived from the roots of *Lithospermum erythrorhizon*,[91] induces autophagy and apoptosis in HCC cells via PI3K/AKT/mTOR pathway inhibition.[92] Tenacissoside H is a medicinal monomer extracted from *Marsdenia tenacissima* extract, possessing antitumor properties.[93] Tenacissoside H limits HCC cell proliferation and enhances radiosensitivity by inducing autophagic cell death through PI3K/AKT/mTOR inhibition.[94] Berberine is an isoquinoline alkaloid isolated from *Rhizoma Coptis*.[95] Berberine induces autophagy and apoptosis in HepG2 cells by activating AMPK and inhibiting mTORC1.[96] Diosgenin is a steroidal saponin isolated from various vegetables and medicinal herbs, known for its diverse biological activities.[97] Dioscin induces autophagy, apoptosis and DNA damage by inhibiting TIGAR-mediated p53, AKT/mTOR, and CDK5/ATM pathways.[98] Salvianolic acid B is a natural polyphenolic acid found in *Salvia miltiorrhiza*, known for its remarkable anti-oxidant properties.[99] Salvianolic acid B induces autophagy and apoptosis in HCC cells by inhibiting the AKT/mTOR pathway.[100] Trillin is a bioactive compound extracted from *Dioscorea nipponica Makino*.[101] Trillin induces apoptosis by inhibiting autophagy via the mTOR/signal transducer and activator of transcription 3 (STAT3) pathway.[102] Brusatol induces autophagy in HCC cells by inhibiting the PI3K/AKT/mTOR pathway, effectively inhibiting cell proliferation, tumor invasion and migration.[103] Collectively, these findings highlight the potential of phytochemicals and natural compounds in modulating autophagy for the treatment of HCC, offering promising avenues for therapeutic intervention.

Inhibition of Cell Migration and Invasion and Metastasis

HCC is an aggressive cancer with complex molecular mechanisms for proliferation, invasion, and metastasis. A variety of natural and synthetic compounds have been explored for their potential to inhibit these processes, often targeting critical signaling pathways such as mTOR (Table 3). For instance, 11-epi-sinulariolide acetate suppresses metastatic

Table 3 Natural Products Targeting Cell Migration and Invasion and Metastasis Improve HCC

Name	Effect	References
11-epi-sinulariolide acetate	Suppresses metastatic effects through the inhibition of FAK/PI3K/AKT/mTOR signaling pathways	[104]
Matrine	Inhibits HCC cell proliferation and induces apoptosis by suppressing the AKT/mTOR/p70S6K and AKT/GSK3β/β-catenin signaling pathways	[106]
Asparagus polysaccharide	Inhibits the proliferation, migration, and invasion of SK-Hep1 and Hep-3B cells and suppresses p-AKT, p-mTOR expression	[107]
FR5	Inhibits the proliferation and migration of HCC cells by co-inhibiting the Hippo/YAP pathway and PI3K/PTEN/mTOR pathway	[109]
Compound 1a	Inhibits the invasion and migration of HCC cells by inhibiting the PI3K/AKT/mTOR signaling pathway	[110]
Flaccidoxide-13-acetate	Inhibits HCC cell proliferation and metastasis through the inhibition of the FAK/PI3K/AKT/mTOR pathway	[111]
Haprolid	Inhibits the cell proliferation, migration and invasion of HCC through the inhibition of Akt/mTOR pathway	[112]
Hedyotis diffusa Willd	Inhibits cell proliferation and migration by inhibiting the AKT/mTOR pathway	[114]
Isoviolanthin	Inhibits the TGF-β/Smad and PI3K/AKT/mTOR pathways to inhibit EMT	[115]
Stachydrine	Prevents TGF-β1-induced EMT in HCC cells by inhibiting Smad2/3 and PI3K/AKT/mTOR signaling pathways	[117]
Stellettin B	Suppresses HCC invasion and migration through reducing activation of the FAK/PI3K/AKT/mTOR and MAPK pathways	[119]
THIAA and HHIAA	Reduce tumor burden and inhibit HCC cell proliferation by suppressing the NF-κB/TNFα pathway and mTOR activity	[120]
STE, Sm and Sb	Inhibit oxidative stress, HCC cell proliferation and PI3K/AKT/mTOR pathway	[121]
Berberine	Reduces HCC cell survival by inhibiting β-catenin translation and mTOR activity	[122]
Chelerythrine	Inhibits cell migration through the PI3K/AKT/mTOR and MAPK pathways	[124]
Cinobufagin	Inhibits cell proliferation by blocking the AURKA/mTOR/eIF4E signaling pathway	[126]
Usenamine A	Inhibits cell proliferation by downregulating the AKT/mTOR/STAT-3 pathway	[127]
SSA	Inhibits tumor growth and metastatic effects by inhibiting the PI3K/AKT/mTOR and TGF-β/Smad pathways	[128]
Ruscogenin	Inhibits HCC lung metastasis by blocking the PI3K/AKT/mTOR pathway	[130]
Cordycepin	Inhibits inflammatory responses and oxidative stress by suppressing the PI3K/AKT/mTOR and Nrf2/HO-1/NF-κB pathways	[132]
PL	Inhibits inflammatory responses and oxidative stress by suppressing the PI3K/AKT/mTOR and Nrf2/HO-1/NF-κB pathways	[133]
Mallotucin D	Inhibits HepG2 cell proliferation, DNA synthesis, colony formation, and HUVEC angiogenesis by inhibiting the PI3K/AKT/mTOR pathway	[134]

Abbreviations: FAK, focal adhesion kinase; GSK-3β, glycogen synthase kinase 3β; FR5, C21 steroid-enriched fraction from Marsdenia tenacissimae extraction; YAP, yes-associated protein; TNF-α, tumor necrosis factor-α; THIAA and HHIAA, hops tetra- and hexahydro isoalpha acids; SSA, saringosterol acetate; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; Nrf2, nuclear factor-erythroid factor 2-related factor 2; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; MAPK, mitogen-activated protein kinases; HO-1, heme oxygenase-1.

effects in HA22T cells by downregulating matrix metalloproteinase-2 (MMP-2), MMP-9, and uPA protein expression through the inhibition of focal adhesion kinase (FAK)/PI3K/AKT/mTOR signaling pathways.[104] Similarly, matrine is a quinazoline alkaloid extracted from the plant *Sophora flavescens*.[105] Matrine inhibits HCC cell proliferation and induces apoptosis by suppressing the AKT/mTOR/p70S6K and AKT/Glycogen synthase kinase 3β (GSK3β)/β-catenin signaling pathways.[106] Furthermore, asparagus polysaccharide, the extract of *asparagus*, is a polysaccharide that has been identified as the primary active component of asparagus.[107] Asparagus polysaccharide inhibits the proliferation, migration, and invasion of SK-Hep1 and Hep-3B cells and suppresses p-AKT, p-mTOR expression.[107,108] Additionally, C21 steroid-enriched fraction from *Marsdenia tenacissimae extraction* (FR5) inhibits the proliferation and migration of HCC cells by co-inhibiting the Hippo/yes-associated protein (YAP) pathway and PI3K/PTEN/mTOR pathway.[109] Moreover, compound 1a significantly inhibits the invasion and migration of HCC cells by inhibiting the PI3K/AKT/mTOR signaling pathway.[110] Flaccidoxide-13-acetate inhibits HCC cell proliferation and metastasis through the inhibition of the FAK/PI3K/AKT/mTOR pathway.[111] Likewise, haprolid was derived from the myxobacterium *Byssovorax*

cruenta. Haprolid inhibits the cell proliferation, migration and invasion of HCC through the inhibition of Rb/E2F and Akt/mTOR pathways.[112] Moreover, *Hedyotis diffusa* Willd, a herb from the Rubiaceae family,[113] exhibits anti-HCC activity by inhibiting the AKT/mTOR pathway.[114] Furthermore, isoviolanthin extracted from the leaves of *Dendrobium officinale*, inhibits the transforming growth factor β (TGF-β)/Smad and PI3K/AKT/mTOR pathways to inhibit EMT in HCC cells induced by TGF-β1.[115] In addition, stachydrine, extracted from the plant *Leonurus heterophyllus*, has been shown to inhibit the proliferation of cancer cells.[116] Stachydrine also prevents TGF-β1-induced EMT in HCC cells by inhibiting Smad2/3 and PI3K/AKT/mTOR signaling pathways.[117] Similarly, stellettin B is isolated from the sponge *Jaspis stellifera*.[118] Stellettin B suppresses HCC invasion and migration through inhibiting the FAK/PI3K/AKT/mTOR and MAPK pathways.[119] Additionally, hops tetra- and hexahydro isoalpha acids (THIAA and HHIAA) reduce tumor burden in animal models and inhibit HCC cell proliferation by suppressing the NF-κB/tumor necrosis factor-α (TNF-α) pathway and mTOR activity.[120] Furthermore, Silybum marianum total extract (STE), silymarin (Sm), and silibinin (Sb) significantly inhibit oxidative stress, HCC cell proliferation and PI3K/AKT/mTOR pathway.[121] Additionally, berberine antagonizes the β-catenin pathway and reduces HCC cell survival by inhibiting β-catenin translation and mTOR activity.[122] Furthermore, chelerythrine found in various medicinal herbs, exhibits anti-tumor activity.[123] Chelerythrine inhibits cell migration through the PI3K/AKT/mTOR and MAPK pathways.[124] Moreover, cinobufagin is one of the primary active components found in *toad venom*.[125] Cinobufagin inhibits cell proliferation by blocking the AURKA/mTOR/eIF4E signaling pathway.[126] Similarly, usenamine A was first isolated from the *lichen Usnea longissim*i.[127] Usenamine A inhibits cell proliferation by downregulating the AKT/mTOR/STAT3 pathway.[127] Saringosterol acetate (SSA) inhibits tumor growth and metastatic effects by inhibiting the PI3K/AKT/mTOR and TGFβ/Smad pathways.[128] Furthermore, ruscogenin is derived from Radix *Ophiopogon japonicus*.[129] Ruscogenin inhibits HCC lung metastasis by blocking the PI3K/AKT/mTOR pathway and reducing the expression of MMP-2, MMP-9, VEGF and HIF-1α.[130] Similarly, cordycepin, a nucleoside found in the *Cordyceps mushrooms*, exhibits anti-cancer properties.[131] Cordycepin inhibits inflammatory responses and oxidative stress by suppressing the PI3K/AKT/mTOR and Nrf2/heme oxygenase-1 (HO-1)/NF-κB pathways.[132] Portulaca oleracea L. (Purslane) (PL) exhibits protective effects against NDEA-induced HCC by modulating the same pathways.[133] Additionally, mallotucin D inhibits HepG2 cell proliferation, DNA synthesis, colony formation, and HUVEC angiogenesis by inhibiting the PI3K/AKT/mTOR pathway.[134] In conclusion, the compounds discussed above demonstrate significant potential in suppressing HCC progression by modulating key molecular pathways. These findings suggest that continued research into these and similar compounds may provide valuable insights into developing more effective therapeutic strategies against HCC.

Alteration of Cell Cycle

Several natural products have demonstrated significant anti-proliferative effects on HCC cells by inducing cell cycle arrest through mTOR signaling pathways (Table 4). For instance, celastrol modulates gut microbiota and hepatic bile acid metabolism, inhibits the interaction between farnesoid X receptor (FXR) and retinoid X receptor α (RXRα), and induces mTOR/S6K1-related G0/G1 phase cell cycle arrest.[135] Hemistepsin A, a sesquiterpene lactone isolated from plants of *Hemistepta lyrata* Bunge (Compositae),[136] induces G0/G1 phase arrest and mitochondria-related apoptosis by the activation of the AMPK/mTOR pathway.[137] Linalool induces G0/G1 phase cell cycle arrest and apoptosis by generating oxidative stress and inhibiting the AKT/mTOR pathway.[138] Moreover, marsdenia tenacissima (Roxb.) Wight and Arn (MT) is a well-known traditional Chinese medicine used in cancer treatment.[139] Marsdenia tenacissima inhibits cell proliferation and induces autophagy, apoptosis, and S-phase cell cycle arrest by inhibiting the MIF/mTOR signaling pathway.[140] Furthermore, the extract of *I. baumii* (EIB) induces S-phase cell cycle arrest and apoptosis by inhibiting the AMPK/mTOR/ULK1 pathway.[141] β-Thujaplicin is one of the major components of *Chamaecyparis obtusa*.[142] β-Thujaplicin causes apoptosis and S-phase arrest through ROS-mediated inhibition of the AKT/mTOR pathway and activation of the p38/ERK MAPK pathway.[143] Additionally, baicalein inhibits cell proliferation by inducing S-phase and G2/M-phase cell cycle arrest via the PI3K/AKT and mTOR signaling pathway.[144] Moreover, chaetocochin J inhibits HepG2 and Hep3B cell proliferation and induces G2/M phase arrest under both normoxic and hypoxic conditions by inhibiting the PI3K/AKT/mTOR/p7OS6K/4EBP1 pathway.[145] Emodin is a major active component of *Rheum palmatum* and has demonstrated anticancer properties.[146] Emodin suppresses HCC cell proliferation, induces S-phase and G2/

Table 4 Natural Products Targeting Cell Cycle Improve HCC

Name	Effect	References
Celastrol	Induces mTOR/S6K1-related G0/G1 phase cell cycle arrest	[135]
Hemistepsin A	Induces G0/G1 phase arrest and mitochondria-related apoptosis by the activation of the AMPK/mTOR pathway	[137]
Linalool	Induces G0/G1 phase cell cycle arrest and apoptosis in HepG2 cells by generating oxidative stress and inhibiting the AKT/mTOR pathway	[138]
Marsdenia tenacissima	Induces S-phase cell cycle arrest by inhibiting the MIF/mTOR signaling pathway	[140]
EIB	Induces S-phase cell cycle arrest and apoptosis by inhibiting the AMPK/mTOR/ULK1 pathway	[141]
β-Thujaplicin	Causes apoptosis and S-phase arrest through ROS-mediated inhibition of the AKT/mTOR pathway	[143]
Baicalein	Inhibits cell proliferation by inducing S-phase and G2/M-phase cell cycle arrest through inhibition of the PI3K/AKT pathway and mTOR signaling pathway	[144]
Chaetocochin J	Induces G2/M phase arrest under both normoxic and hypoxic conditions by inhibiting the PI3K/AKT/mTOR/p7OS6K/4EBP1 pathway	[145]
Emodin	Suppresses HCC cell proliferation, induces S-phase and G2/M-phase arrest, and triggers apoptosis through inhibiting the PI3K/AKT signaling pathway	[147]
Gamabufotalin	Induces G2/M phase cell cycle arrest through inhibiting the mTOR-ULK1 signaling pathway	[149]
Prunetrin	Induces G2/M phase arrest by inhibiting the AKT/mTOR pathway	[150,151]
PECFS	Inhibits HCC cell proliferation, migration, and invasion, induces G2/M phase arrest, and apoptosis by suppressing the PI3K/AKT/mTOR pathway	[152]
Pectolinarigenin	Suppresses HCC cell viability and induces G2/M phase arrest via inhibition of the PI3K/AKT/mTOR/ERK signaling pathway	[154]
Oleanolic acid	Induces G2/M phase cell cycle arrest and apoptosis by inhibiting the AKT/mTOR pathway	[156]

Abbreviations: AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; AMPK, AMP-activated protein kinase; EIB, the extract of I. baumii; ULK1, unc-51-like kinase 1; PECFS, petroleum ether extract of Chloranthus fortune; ERK, extracellular signal-regulated kinase.

M-phase arrest through inhibiting the PI3K/AKT signaling pathway.[147] Furthermore, gamabufotalin is derived from ChanSu.[148] Gamabufotalin induces G2/M phase cell cycle arrest and induces autophagy and apoptosis through inhibiting the mTOR-ULK1 signaling pathway.[149] Similarly, prunetrin induces G2/M phase arrest and mitochondrial-mediated apoptosis by inhibiting the AKT/mTOR pathway and activating the MAPK pathway.[150] Prunetrin causes G2/M phase cell cycle arrest by activating the caspase cascade and suppressing the AKT/mTOR pathway.[151] Similarly, the petroleum ether extract of *Chloranthus fortunei* (PECFS) markedly inhibits HCC cell proliferation, migration, and invasion, induces G2/M phase arrest, and apoptosis by suppressing the PI3K/AKT/mTOR pathway.[152] Pectolinarigenin, a natural flavonoid, suppresses HCC cell viability and induces G2/M arrest via PI3K/AKT/mTOR/ERK pathway inhibition.[153,154] Oleanolic acid, a phytochemical in many edible and medicinal plants,[155] induces G2/M phase cell cycle arrest and apoptosis by inhibiting the AKT/mTOR pathway.[156] In summary, various natural compounds exhibit potent anti-proliferative effects on HCC cells by targeting key signaling pathways, particularly those involving mTOR. These compounds, including celastrol, hemistepsin A, and marsdenia tenacissima, among others, induce cell cycle arrest at different phases and trigger apoptosis through mechanisms such as mitochondrial dysfunction, oxidative stress, and autophagic cell death. The inhibition of the mTOR pathway appears to be a common mechanism among these compounds, underscoring the therapeutic potential of natural products in the treatment of HCC.

Metabolic Reprogramming

This part focuses on several natural products that adjust mTOR signaling via metabolism modulation (Table 5). These mechanisms are crucial in the treatment of HCC, as they not only inhibit tumor growth but also enhance the responsiveness to other therapeutic approaches. Compound K is a secondary ginsenoside with higher bioavailability and exhibits significant anti-cancer effects.[157] Compound K inhibits glycolysis and AKT/mTOR/c-Myc signaling by down-regulating the expression of hexokinase 2 (HK2) and pyruvate kinase isozymes M2 (PKM2).[158] Similarly, osthol is a coumarin derivative extracted from *Cnidium monnieri*. Osthol has been found to enhance radiosensitivity in HCC by inhibiting glycolysis, likely through inhibiting the GSK-3β/AMPK/mTOR pathway.[159,160] Moreover, zerumbone is

Table 5 Natural Products Targeting Metabolic Reprogramming Improve HCC

Name	Effect	References
Compound K	Inhibits glycolysis and AKT/mTOR/c-Myc signaling in HCC cells by downregulating the expression of HK2 and PKM2	[158]
Osthol	Enhances radiosensitivity in HCC by inhibiting glycolysis, likely through inhibiting the GSK3β/AMPK/mTOR pathway	[159,160]
Zerumbone	Inhibits glycolysis potentially through the downregulation of PI3K/AKT/mTOR and STAT3 pathways	[162]
Morusin	Inhibits glycolysis	[163]
Betulin	Reduces cellular cholesterol levels through the inhibition of the mTOR/IL-1β pathway	[164]
Rhizoma Paridis saponins	Overcomes sorafenib resistance by inhibiting anaerobic glycolysis, and suppressing lipid synthesis via inhibiting the PI3K/AKT/mTOR pathway	[166]
Phytosomal curcumin	Reduces lipid accumulation and decreases overall tumor volume and inhibits oncogenic mTOR activation	[167]

Abbreviations: HK2, hexokinase 2; PKM2, pyruvate kinase isozymes M2; AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; STAT3, signal transducer and activator of transcription 3; GSK-3β, glycogen synthase kinase 3β; HCC, hepatocellular carcinoma.

isolated from the rhizomes of *Zingiber zerumbet (L.) Smith*.[161] Zerumbone inhibits glycolysis and diverts glucose-6-phosphate from the pentose phosphate pathway potentially through the downregulation of PI3K/AKT/mTOR and STAT3 pathways.[162] Likewise, morusin isolated from the roots of *Morus alba*, exhibit anti-angiogenic, anti-migratory, and pro-apoptotic effects.[163] Morusin significantly induces G1 arrest, while attenuating the expression of p-AKT, p-mTOR, HK2, PKM2, and LDH-A through AMPK-mediated G1 arrest and antiglycolytic activity.[163] Furthermore, inhibiting SREBP2 to reduce cellular cholesterol levels has been shown to improve the efficacy of lenvatinib in HCC cells, with the SREBP2 inhibitor betulin significantly enhancing lenvatinib's anti-tumor effects, possibly through the inhibition of the mTOR/IL-1β pathway.[164] Additionally, Rhizoma Paridis saponins are the primary active components of *Rhizoma Paridis*.[165] Rhizoma Paridis saponins overcomes sorafenib resistance by inhibiting the PI3K/AKT/mTOR pathway.[166] Phytosomal curcumin reduces lipid accumulation and decreases overall tumor volume and inhibits oncogenic mTOR activation.[167] Overall, these natural products have significant anti-tumor potential by regulating mTOR signaling through glycolysis and lipid metabolism modulation, especially in surmounting drug resistance and increasing treatment effectiveness. More research is needed to fully understand their clinical applications in HCC treatment.

Sensitization Therapy

The therapeutic efficacy of combining natural products with conventional anti-cancer agents for HCC has been extensively studied both in vitro and in vivo (Table 6). Fucoidan, in combination with sorafenib or Avastin, markedly inhibits HCC cell viability and promotes apoptosis by downregulating the PI3K/AKT/mTOR pathways.[168] Similarly, compounds such as artesunate,[169] tetrandrine,[170] glycyrrhizic acid,[171] Pogostemon cablin,[172] Huaier,[173] a-Mangostin,[174] ellagic acid,[175] cucurbitacin E[176] and amygdalin[177] have been shown to enhance the anti-tumor effects of sorafenib through dual inhibition of the mTOR and other signaling pathways, effectively overcoming chemotherapy resistance. Berberine and rapamycin synergistically induces apoptosis and autophagy by inhibiting the mTOR signaling pathway.[178] Berberine combined with HMQ1611 inhibits HCC growth and induces G1 phase cell cycle arrest by downregulating AKT, mTOR, and ERK/MAPK signaling pathways.[179] Chlorogenic acid enhances the growth-inhibitory effects of regorafenib by suppressing the MAPK and PI3K/AKT/mTORC pathways and inhibiting the anti-apoptotic proteins.[180] Similarly, catalpol and/or regorafenib significantly inhibit the PI3K/p-AKT/mTOR/NF-κB and VEGF/VEGFR2 pathways.[181] The combination of aloin and metformin enhances growth inhibition and apoptosis in HCC cells by inhibiting the PI3K/AKT/mTOR pathway,[182] while metformin and curcumin not only induce apoptosis but also inhibit HCC cell invasion, migration, and angiogenesis by suppressing the PI3K/AKT/mTOR/NF-κB and EGFR/STAT3 pathways.[183] Doxorubicin combined with manuka honey exhibits higher cytotoxicity and enhances apoptosis through the inhibition of ERK1/2 and mTOR pathways,[184] while Shufeng Jiedu Capsule, along with its active components, potentiates the anti-tumor effects of doxorubicin by suppressing the AKT/mTOR, and NF-κB pathways.[185] Lachnum

Table 6 Natural Products Improve the Treatment of HCC Through Sensitization Therapy

Name	Effect	References
Artesunate	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[169]
Tetrandrine	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[170]
Glycyrrhizic acid	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[171]
Pogostemon cablin	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[172]
Huaier	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[173]
a-Mangostin	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[174]
Ellagic acid	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[175]
Cucurbitacin E	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[176]
Amygdalin	Enhances the anti-tumor effects of sorafenib through inhibition of the mTOR signaling pathway	[177]
Berberine and rapamycin	Induces apoptosis and autophagy by inhibiting the mTOR signaling pathway	[178]
Berberine combined with HMQ1611	Inhibits HCC growth and induces G1 phase cell cycle arrest by downregulating AKT, mTOR, and ERK/MAPK signaling pathways	[179]
Chlorogenic acid	Enhances the growth-inhibitory effects of regorafenib by suppressing the MAPK and PI3K/AKT/mTORC pathways	[180]
Catalpol and/or regorafenib	Inhibit the PI3K/p-AKT/mTOR/NF-κB and VEGF/VEGFR2 pathways	[181]
Aloin and metformin	Enhances growth inhibition and apoptosis in HCC cells by inhibiting the PI3K/AKT/mTOR pathway	[182]
Metformin and curcumin	Induce apoptosis by suppressing the PI3K/AKT/mTOR/NF-κB and EGFR/STAT3 pathways	[183]
Doxorubicin combined with manuka honey	Enhances apoptosis through the inhibition of ERK1/2 and mTOR pathways	[184]
Shufeng Jiedu Capsule and doxorubicin	Suppress the AKT/mTOR, and NF-κB pathways	[185]
Lachnum expolysaccharide	Sensitizes HepG2 cells to 5-fluorouracil by inactivating Ras/Raf/MEK/ERK and PI3K/AKT/mTOR pathways	[186]
Curcumin	Enhances the chemosensitivity of HCC cells to 5-fluorouracil, induces G2/M phase arrest, and inhibits the PI3K/AKT/mTOR pathway	[187]
Magnolin combined with SB590885	Inhibits HCC cell proliferation by blocking the ERK/MAPK and PI3K/AKT pathways	[188]
Biochanin A and SB590885	Inhibit HCC cell proliferation through disrupting of the ERK/MAPK and the PI3K/AKT pathways	[189]
Ovatodiolide and antrocin	Enhance apoptosis and autophagy in tumor cells and effectively counteract sorafenib resistance by inhibiting the ERK1/2 and AKT/mTOR pathways	[190]
Oxysophocarpine	Sensitizes FGFR1-overexpressing HCC to lenvatinib by downregulating AKT/mTOR and ERK signaling pathways	[191]
Parthenolide and arsenic trioxide	Enhance anti-HCC efficacy by inhibiting the PI3K/AKT/mTOR pathway	[192]
CDDP/OA-LCC NP	Promote apoptosis and reduce cisplatin-induced hepatotoxicity through downregulating the PI3K/AKT/mTOR signaling pathway	[193]
Babaodan	Enhances the anti-HCC efficacy of camrelizumab by regulating the M1/M2 macrophage ratio and increasing $CD8^+$ T cell abundance via the PI3K/AKT/mTOR signaling pathway	[194]

Abbreviations: HCC, hepatocellular carcinoma; AKT, protein kinase B; mTOR, mammalian target of rapamycin; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinases; PI3K, phosphatidylinositol 3-kinase; NF-κB, nuclear factor κB; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

expolysaccharide significantly sensitizes HepG2 cells to 5-fluorouracil by inactivating Ras/Raf/MEK/ERK and PI3K/AKT/mTOR pathways,[186] and curcumin further enhances the chemosensitivity of HCC cells to 5-fluorouracil, induces G2/M phase arrest, and inhibits the PI3K/AKT/mTOR pathway.[187] The natural product magnolin combined with BRAF inhibitor SB590885 synergistically inhibits HCC cell proliferation by blocking the ERK/MAPK and PI3K/AKT pathways.[188] Biochanin A and SB590885 inhibit HCC cell proliferation through disrupting of the ERK MAPK and the PI3K/AKT pathways.[189] Ovatodiolide and antrocin enhance apoptosis and autophagy in tumor cells and effectively counteract sorafenib resistance by inhibiting the ERK1/2 and AKT/mTOR pathways.[190] Oxysophocarpine sensitizes FGFR1-overexpressing HCC to lenvatinib by downregulating the AKT/mTOR and ERK signaling pathways.[191] Parthenolide and arsenic trioxide enhance anti-HCC efficacy by inhibiting the PI3K/AKT/mTOR pathway.[192] Lipid

coated cisplatin/oleanolic acid calcium carbonate nanoparticles (CDDP/OA-LCC NPs) promote apoptosis and reduce cisplatin-induced hepatotoxicity through downregulating the PI3K/AKT/mTOR signaling pathway.[193] Finally, Babaodan inhibits tumor growth and enhances the anti-HCC efficacy of camrelizumab by regulating the M1/M2 macrophage ratio and increasing $CD8^+$ T cell abundance via the PI3K/AKT/mTOR signaling pathway.[194] In summary, the combination of natural compounds with conventional anti-cancer agents has shown promising results in enhancing therapeutic efficacy against HCC. These combinations generally function by targeting key signaling pathways such as PI3K/AKT/mTOR and ERK/MAPK, leading to augmented apoptosis, autophagy, and tumor growth inhibition. Moreover, these combinations can overcome chemotherapy resistance, enhance drug sensitivity, and reduce toxicity, rendering them valuable strategies in HCC treatment.

Conclusion and Future Perspectives

In recent years, as the understanding of the molecular mechanisms underlying HCC has deepened, researchers have initiated the exploration of novel therapeutic modalities. Emerging studies have increasingly centered on molecular targeting of cancer cells to attain enhanced efficacy and diminished side effects. Consequently, targeting cellular signaling pathways has emerged as a prominent strategy in drug development. Among various signaling pathways, the mTOR signaling pathway plays a central role in hepatocellular carcinoma. Many natural products have emerged as potent modulators of the mTOR signaling pathway, which is critical in regulating various cellular processes such as proliferation, apoptosis, autophagy, cell cycle progression, and metabolic reprogramming in HCC. Compounds like curcumin, berberine, and celastrol have demonstrated significant anti-tumor activities by targeting mTOR and its associated pathways. These compounds can induce cell cycle arrest, promote apoptosis, and modulate autophagy, inhibiting the growth and proliferation of HCC cells. Additionally, the capacity of these natural products to influence metabolic reprogramming presents a novel approach to counteracting the metabolic adaptations frequently witnessed in cancer cells. Moreover, the combination of natural products with conventional therapies, such as chemotherapy or targeted therapy, has shown synergistic effects. These combinations not only enhance therapeutic efficacy but also reduce the likelihood of drug resistance-a significant challenge in HCC treatment. Natural products can sensitize tumor cells to chemotherapeutic agents by modulating the mTOR pathway, thereby reducing the required dose and minimizing side effects. Natural products have unique innovativeness. They act through novel mechanisms targeting specific pathways that traditional treatments usually miss. And compared with traditional treatments, these natural products have advantages in safety, as they cause fewer side effects due to their natural origin and better compatibility with the human body. Moreover, they have potential in long-term prevention and health maintenance by enhancing the body's resistance system.

Nevertheless, notwithstanding these auspicious preclinical discoveries, the clinical application of natural products in HCC therapy confronts several formidable challenges. Firstly, many natural products exhibit low bioavailability due to their poor solubility, instability, and rapid metabolism. As a result, this limitation often results in insufficient therapeutic concentrations at the tumor site, diminishing their efficacy. Curcumin is a very promising chemopreventive agent. This has driven clinical practice to study the pharmacokinetics and efficacy of curcumin in patients. In Phase I clinical studies, it has been proven to be safe and non - toxic, even at high doses (8 g/d). However, its absorption is limited in individuals.[195,196] Despite the challenges of bioavailability, clinical trials of them (used alone or in combination as anticancer drugs) have demonstrated efficacy in several disease sites.[197–199] Secondly, although natural products are generally regarded as safe, their long-term utilization, especially in conjunction with other treatments, elicits concerns regarding potential toxicity and adverse effects. Therefore, comprehensive toxicological studies are necessary to ensure the safety of these compounds in clinical settings. Moreover, the variability in the composition of natural products, influenced by factors such as source, extraction methods, and storage conditions, poses a challenge for their consistent clinical application. Furthermore, the effects of natural products on the mTOR pathway can be intricate and context-dependent, with disparities observed across different cell types, tumor microenvironments, and cancer progression stages. Although numerous preclinical studies support the anti-cancer potential of natural products, clinical evidence remains limited. Few natural compounds have progressed to clinical trials, and those that have often face challenges related to efficacy, safety, and regulatory approval. Through the use of andrographolide in clinical trials, the recovery rates of

different myeloma patients have achieved significant improvement.[200,201] Although research has been conducted with a large amount of information on pre-clinical efficacy, clinical studies are limited in evaluating the true potential of berberine and andrographolide as cancer - modulating agents.[202]

To surmount these challenges and fully exploit the therapeutic potential of natural products in HCC, several strategies ought to be pursued. First and foremost, advancements in drug delivery systems, such as nanoparticle-based carriers, liposomes, and micelles, present promising remedies to enhance the bioavailability and targeted delivery of natural products. These innovations can protect the compounds from degradation, enhance their solubility, and facilitate their accumulation in tumor tissues. In addition, continued exploration of combination therapies involving natural products and conventional treatments is crucial. By identifying the optimal combinations, dosing schedules, and biomarkers for response will maximize therapeutic outcomes while minimizing side effects. Moreover, clinical trials are needed to validate the efficacy and safety of natural products in HCC patients. Additionally, the establishment of standardized protocols for the preparation, characterization, and quality control of compounds will ensure consistency in clinical applications.

In conclusion, while natural products offer a promising avenue for the treatment of HCC through the modulation of the mTOR pathway, significant challenges remain. Overcoming these challenges via innovative research and clinical development will be pivotal in unlocking the complete potential of these compounds in the battle against HCC.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors declare that they have no competing interests.

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