

Therapeutic Implications of Traditional Chinese Medicine in Clinically Relevant Diseases: Perspectives From microRNA-Modulated Apoptotic Signaling

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Abstract: Traditional Chinese medicines (TCMs) have been employed as a potent therapeutic modality within Chinese cultural contexts to address a spectrum of diseases. MicroRNAs (miRNAs) are endogenous, non-coding RNA (ncRNA) molecules that regulate genetic expression via post-transcriptional mechanisms. By modulating miRNA expression, TCMs have been proven to confer protective benefits, notably by facilitating apoptosis induction. Thus, exploring the molecular mechanisms implicating miRNAs within TCMs could offer potential avenues for developing novel strategies to mitigate various lethal illnesses. In this study, we aim to provide a concise overview delineating the contemporary understanding of the functions of TCMs in miRNA-mediated apoptosis across malignant and non-malignant pathologies, including cancer, neurological disorders, and cardiovascular diseases. This review will furnish valuable insights concerning the clinical utilization of TCMs in treatment and prevention across a spectrum of clinically relevant diseases and serve as a catalyst for the innovation of novel therapeutic agents to address these pathologies.

Keywords: traditional Chinese medicine, miRNAs, apoptosis, malignant and non-malignant pathologies, molecular basis of TCMs in disease

Introduction

Examining the evolution of pharmaceutical development over the preceding fifty years reveals that natural resources constitute a noteworthy sector within the pharmaceutical industry when synthesized without specific design.^{1,2} Natural extracts and medicinal plants constitute a significant reservoir for advancing pharmaceutical research and developing therapeutic agents. TCM is a prominent exemplar among natural remedies, enjoying extensive global utilization as an adjunctive therapeutic approach across diverse maladies. TCMs have been extensively employed for millennia in China and neighboring Asian regions as integral modalities for preventive measures and therapeutic interventions across various diseases.^{3–9} Naturally occurring substances and medicinal plants represent a significant reservoir of biologically active compounds with therapeutic potential. Sourcing pharmaceutical agents from natural origins has enjoyed a longstanding tradition within medicine. Despite being employed for millennia in China and having significantly advanced human health, TCM continues to harbor substantial ambiguity regarding its molecular-level therapeutic mechanisms. Therefore, it is imperative to ascertain the primary components and comprehend the molecular mechanisms underlying the observed effectiveness. In the preceding twenty years, an escalating trend has emerged in which an increasing array of bioactive compounds originated from TCM herbs.

A predominant proportion of the identified bioactive compounds fall within the classification of plant secondary metabolites. These agents exhibit diverse effects on cell death pathways. In tumors, specific agents induce apoptosis in cancer cells. Conversely, some agents may inhibit apoptosis in non-malignant conditions like cardiovascular and neurological diseases, thereby protecting cells from further deterioration.^{10–14}

MiRNAs, a subset of small ncRNAs that regulate target gene expression via post-transcriptional mechanisms, have emerged as pivotal regulatory molecules in TCM-induced therapeutic responses. In this context, recent *in silico* and *in vitro* analysis demonstrated that Danggui Buxue Decoction (DGBXD) ameliorates idiopathic pulmonary fibrosis (IPF) through several miRNA-mRNA regulatory networks, including the miR-493-Olr1 and miR-338-Hif1a axes.¹⁵ TCM has demonstrated efficacy in regulating apoptosis via the modulation of particular miRNAs, thereby substantiating its therapeutic efficacy across a spectrum of health disorders.¹⁶ Herein, we comprehensively examine contemporary research investigating the correlation between miRNAs and anti-tumor TCMs alongside their bioactive constituents. This endeavor aims to offer fresh insights into the mechanisms underlying TCMs' anti-tumor properties. In addition, we examine a novel proposition regarding the regulation of genes facilitated by exogenous miRNAs, potentially presenting a novel avenue in cancer therapy through the utilization of Chinese medicinal herbs.

Major Apoptosis Signaling Pathway

Apoptosis is a fundamental biological phenomenon observed in multicellular organisms. It entails the regulated removal of cells. It is pivotal in embryonic morphogenesis and maintaining tissue homeostasis in adult organisms. Apoptosis is primarily mediated by two distinct signaling pathways: the extrinsic pathway, initiated by death receptor engagement, and the intrinsic pathway, triggered by mitochondrial stress.^{17,18} The engagement of death receptors through either their endogenous ligands (eg, TNF α , CD95L, and TRAIL) or agonistic antibodies (eg, anti-APO-1) initiates a stepwise activation cascade involving caspase-8 and -3. This cascade results in the proteolytic cleavage of specific substrates and ultimately triggers apoptosis. Intrinsic triggers of cellular demise, such as reactive oxygen species (ROS), agents inducing DNA damage, and stimuli facilitating calcium ion mobilization, initiate the mitochondrial pathway. This leads to the liberation of cytochrome c and the assembly of the apoptosome complex, comprising cytochrome c, Apaf-1, and caspase-9, either through direct activation or indirect mechanisms.¹⁹ In the interplay of receptor-mediated and mitochondrial signaling pathways, the pro-apoptotic protein Bid assumes a pivotal role as an intermediary agent after its cleavage by activated caspase-8. This cleavage event facilitates the translocation of the pro-apoptotic proteins Bax and/or Bak to the mitochondrial membrane. Cellular fate, including survival and demise, is critically mediated by the interplay between intrinsic pro-apoptotic and anti-apoptotic protein families. In the context of the receptor-mediated pathway, c-FLIP and XIAP function as negative regulators, exerting control over the enzymatic actions of caspase-8 and caspase-3. In the mitochondria-mediated pathway of apoptosis, regulation predominantly ensues through a network of pro-apoptotic proteins such as Bax, Bid, Bak, and Smac, alongside anti-apoptotic counterparts including Mcl-1, Bcl-xL, B-cell lymphoma 2 (Bcl-2), and XIAP.^{20,21}

NF- κ B: In 1986, the identification of the transcription factor nuclear factor of kappa light polypeptide gene enhancer in B cells (NF- κ B) marked a pivotal discovery in molecular biology. It elucidated its role as a nuclear entity that selectively interacts with the enhancer region of the immunoglobulin kappa light chain within activated B cells.²² This seminal observation consequently led to the establishment of the abbreviated designation NF- κ B. Five constituents of this transcription factor cohort have been delineated, denoted as p65 (RelA), RelB, c-Rel, NF- κ B1, and NF- κ B2.²³ In cellular signaling, NF κ B activation is facilitated through two distinct pathways: the canonical pathway, the classical route, and the non-canonical pathway, commonly referred to as the alternative pathway. In the canonical activation cascade, stimulatory signaling pathways may be facilitated via Interleukin-1 receptor (IL-1R), Toll-like receptors (TLRs), tumor necrosis factor receptor (TNFR), and antigen receptors. Commonly encountered signaling molecules that provoke stimulation include tumor necrosis factor α (TNF α), lipopolysaccharides (LPS)—constituents of bacterial cell walls—and interleukin-1 β (IL-1 β). Upon stimulation via these receptors, activation of the I κ B kinase (IKK) complex ensues, resulting in the phosphorylation of I κ B α primarily by IKK2. This pathway is pivotal in initiating innate immune responses and inflammatory processes while suppressing apoptosis.^{24,25} The Non-canonical pathway plays a pivotal role in p100/Rel-B complexes activation, predominantly manifesting during the ontogenesis of lymphoid organs pivotal

for B and T lymphocyte production, with its activation modulated solely by B cell activating factor (BAFF). This signaling route employs an IKK complex composed of two IKK α subunits, excluding NEMO from its composition. In the non-canonical signaling pathway, ligands stimulate NF κ B activation, inducing kinase (NIK), initiating a cascade whereby the IKK α complex becomes phosphorylated and activated. This activated complex subsequently phosphorylates the p100 protein, resulting in its processing and subsequent release of the p52/Rel-B active heterodimers. Contrary to p100, which undergoes cleavage to generate p50, the inducible processing potential of p105 remains a subject of contention. The initiation of p100 processing via BAFFR plays a pivotal role in bolstering the viability of transitional and mature B cells, ostensibly by prompting the activation of anti-apoptotic genes such as bcl-x and bcl-2.²⁶ Notably, the observation that NF- κ B becomes activated concurrently with or near cellular apoptosis in response to stimulatory stimuli has prompted the proposition that NF- κ B activation is closely associated with suppressing apoptosis. In the majority of cellular contexts, the activation of NF- κ B serves to safeguard the cell against apoptosis, primarily achieved by upregulating the expression of various survival genes, including but not limited to TRAF1, Bcl-xL, TRAF2, Bfl-1, c-IAP1, c-IAP2, and IEX-IL. NF- κ B binding motifs have been discerned within the regulatory regions of the interleukin-1b converting enzyme protease, c-myc, and TNF α genes, all of which play integral roles in the induction of apoptotic cell death.²⁷ NF- κ B also mediates the transcription of genes encoding various anti-apoptotic proteins belonging to the bcl-2 family, including Nrl3, bfl-1/A1, and bcl-xl. These proteins collectively inhibit the release of cytochrome-c and the consequent activation of caspase-9, thereby impeding the apoptotic process.^{28,29}

PTEN/PI3K/AKT/mTOR Signaling Pathway

PI3K, also known as phosphatidylinositol-3-kinase, is a protein kinase located on the plasma membrane, which functions as a pivotal mediator linking extracellular growth factor and cytokine signals with intracellular signal transduction pathways downstream.³⁰ Typically, the PI3K activation occurs via receptor tyrosine kinases (RTKs); however, alternative mechanisms exist involving G-protein-coupled receptors and oncogenes, including small GTPase RAS. The activation of PI3K is contingent upon the specific interaction context and the affinity towards particular PI3K subunits. Upon activation, PI3K catalyzes the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PI (4,5)P2) to produce phosphatidylinositol-3,4,5-trisphosphate (PIP3).³¹ IP3 initiates intracellular signaling pathways by enlisting and interacting with various proteins, notably phosphoinositide-dependent kinase 1 (PDK1) and AKT, which possess pleckstrin homology (PH) domains. This recruitment event triggers AKT phosphorylation by PDK1, subsequently inducing activation of AKT.³² The activation of AKT exerts regulatory control over numerous cellular processes through the phosphorylation of a multitude of substrates, including but not limited to IKK α , FOXO, PRAS40, GSK3, MDM2, eNOS, TSC2, WNK1, ASK1, AMPK, RAF1, CHK1, p27, p21, and BAD. The downstream effectors establish a connection between AKT activity and regulating processes such as protein synthesis, transcription, cell survival, apoptosis, and proliferation.^{33,34} Furthermore, the mammalian target of Rapamycin (mTOR) denotes a serine/threonine protein kinase that functions as a prominent downstream mediator within the AKT signaling pathway. The PI3K-AKT-mTOR pathway assumes a pivotal function in regulating pro-survival cellular signaling mechanisms.³⁵ Phosphatase and tensin homologue (PTEN) functions as a regulator within the PI3K-AKT-mTOR signaling cascade by catalyzing the dephosphorylation of PIP3 to PI(4,5)P2. This enzymatic activity ultimately impedes cellular proliferation. So, PTEN inactivation stimulates the PI3K-AKT-mTOR pathway, consequently promoting cellular survival.³⁶ AKT is evidently the principal determinant governing the pro-survival/anti-apoptotic function of the PI3K-AKT-mTOR pathway. It employs various mechanisms to regulate cell survival and apoptosis, either through direct interaction with proteins involved in the apoptotic pathway or by modulating transcription factors responsible for transcribing genes involved in apoptosis. One of the immediate targets of AKT is BAD, an apoptosis-promoting factor and constituent of the BCL-2 protein family. BAD interacts with and suppresses the activity of anti-apoptotic factors such as BCL-XL or BCL-2. BAD inactivation occurs via the phosphorylation of Ser136 by the enzymatically active AKT, activating BCL-2 or BCL-XL and promoting cellular survival.^{35,37}

MAPK Signaling Pathway

Mitogen-activated protein kinases (MAPKs) are serine-threonine protein kinases that exert regulatory control over diverse cellular processes, encompassing proliferation, differentiation, apoptosis, survival, inflammation, and innate immunity.^{38,39}

In mammalian organisms, MAPKs encompass c-Jun NH₂-terminal kinase (JNK), p38 MAPK, and extracellular signal-regulated kinase (ERK), comprising multiple isoforms.⁴⁰ JNK1 and JNK2 exhibit widespread tissue expression, whereas JNK3 is primarily expressed in neuronal cells.⁴¹ The most comprehensive investigations among the four p38 MAPK isoforms (namely p38- α , p38- β , p38- γ , and p38- δ) have predominantly focused on p38- α and p38- β . MAPKs that have been activated catalyze the phosphorylation of a range of target proteins, encompassing transcription factors such as c-Jun, c-Myc, and ATF2, as well as antiapoptotic protein Bcl-2 and the proapoptotic protein Bad.⁴² Furthermore, various substrates for the JNK and p38 MAPK signaling pathways, known to facilitate apoptosis, have been discovered and confirmed through validation processes. Many transcription factors have been documented as subject to regulation by the signaling molecules JNK and p38, leading to upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins.⁴³ A prominent target of the JNK pathway is the transcription factor AP-1, known as activator protein 1. AP-1 is a dimeric complex composed of various combinations of proteins from the Fos (including Fra2, Fra1, c-Fos, and FosB), Jun (such as c-Jun, JunB, and JunD), ATF (activating transcription factor), and MAF (V-maf musculoaponeurotic fibrosarcoma) families.⁴⁴ In addition, one of the most prominent transcription factors modulated by the JNK and p38 MAPK signaling cascades in the context of apoptosis is the p53 tumor suppressor protein. Within cells experiencing stress, the process of phosphorylation mediated by JNK can lead to the stabilization and activation of the p53 protein, thereby facilitating the initiation of programmed cell death. Similar to the c-Jun subunit of the AP-1 complex, the transcription factor p53 collaborates with various other proteins. According to the available literature, the dimerization of p53 and p73 has been identified as a pivotal factor in initiating apoptotic cell death, particularly in cellular stress response mediated by the JNK pathway. JNK activation leads to the phosphorylation of p53 at Thr81 within its proline-rich domain (PRD), facilitating the subsequent dimerization of p73 and p53. The formation of the p53-p73 dimer promotes the transcriptional activation of numerous pro-apoptotic genes, including but not limited to puma and bax^{45,46}(Figure 1).

Apoptosis Dysregulation in Human Diseases

Malfunctioning apoptosis is linked to various illnesses such as autoimmune disorders, neurodegenerative conditions, bacterial and viral infections, cancer, and cardiovascular diseases. In this regard, Kun et al investigated the involvement of apoptosis in the pathogenesis of varicosities. In their study, the apoptotic ratio observed within the walls (intima and media) of the afflicted splenic vein and varicose great saphenous vein groups exhibited a notable reduction compared to the equivalent anatomical sites within the non-afflicted splenic vein and great saphenous vein groups, respectively. Notably, histopathological examination of diseased splenic and varicose great saphenous veins revealed apoptotic features within endothelial and smooth muscle cells of their respective walls. These characteristic morphological changes included fuzzy mitochondrial cristae, alterations in the medullary area, and peripheralization of nuclear chromatin. The results indicate that reduced apoptosis in the vascular wall is implicated in the pathogenesis of splenic vein disorders and varicose great saphenous veins.⁴⁷ As well, apoptosis appears to be a pivotal factor in the advancement of numerous neurological conditions, including Alzheimer's disease (AD). In this regard, platelet levels of caspase-3, caspase-9, Bax, and Bad markedly increased among individuals diagnosed with AD and mild cognitive impairment (MCI). Apoptosis proteins were also upregulated in individuals with amnesic MCI in comparison to both AD patients and cognitively normal controls. In individuals with amnesic MCI, the levels of the anti-apoptotic protein Bcl2 were elevated, whereas in AD, a reduction in Bcl2 expression was noted. In this manner, elevated levels of apoptosis are observed in platelets, potentially reflecting similar apoptotic processes occurring in the brain, with aberrant apoptosis occurring early in Alzheimer's disease, and the balance between pro- and anti-apoptotic protein levels contributing to the platelet's susceptibility to apoptotic signals.⁴⁸ Thus, modulating apoptosis towards a homeostatic equilibrium presents a potential therapeutic strategy for various diseases.

MiRNAs: Biosynthesis in Functioning in Apoptosis

miRNAs are a class of small, highly conserved, ncRNAs, approximately 22 nucleotides in length, that play crucial roles in modulating gene expression. RNA polymerase II (Pol II) facilitates the production of a hairpin intermediate termed "pri-miRNA" during the transcription of a nuclear miRNA gene. The recognition of pri-miRNA involves a microprocessor complex comprising double-stranded RNA-specific endoribonuclease (DROSHA) and DiGeorge

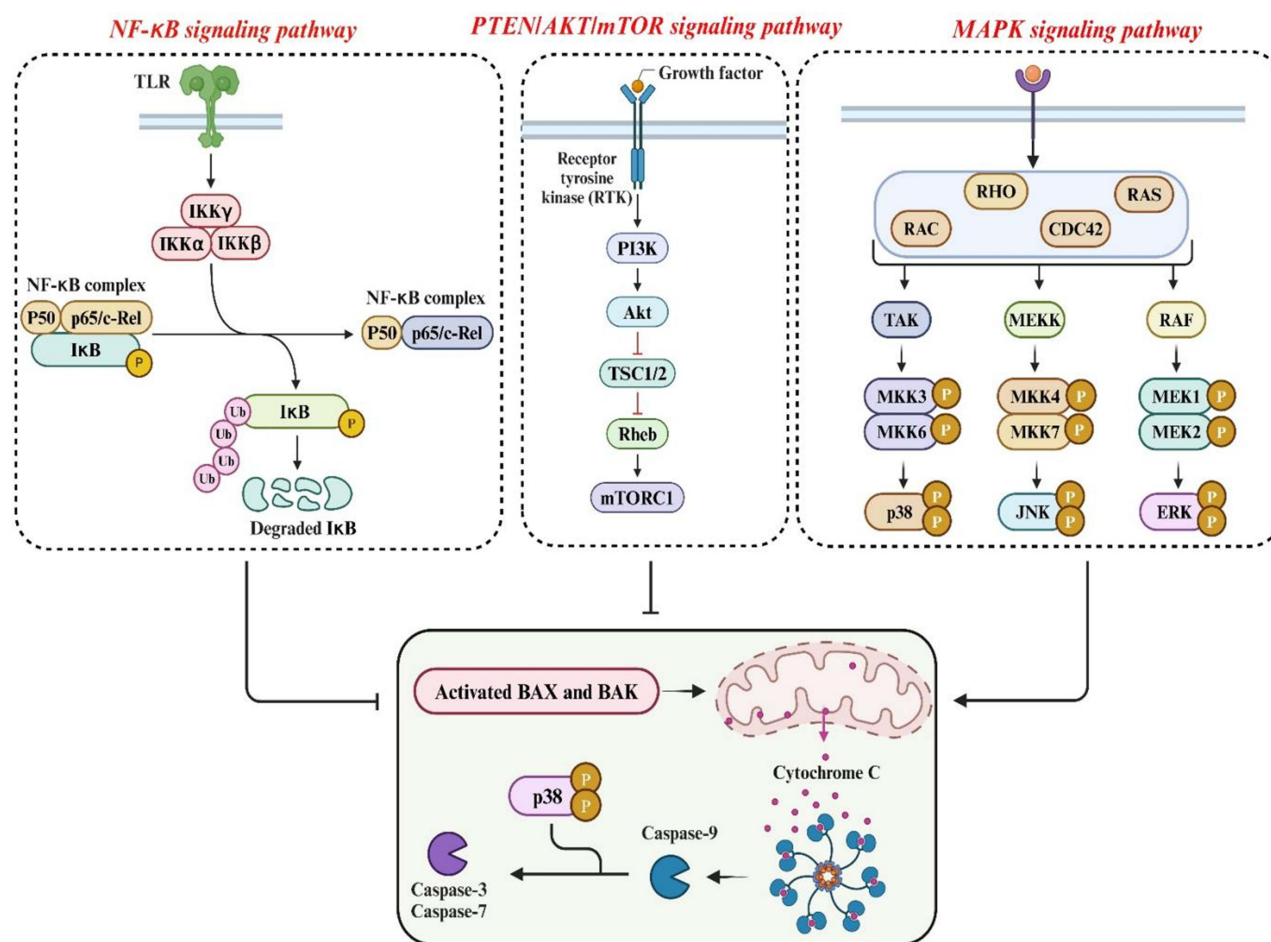


Figure 1 Major signaling pathways involved in apoptosis.

syndrome critical region gene 8 (DGCR8) enzymes, which cleave the molecule to generate precursor miRNA (pre-miRNA).⁴⁹ Pre-miRNAs are subsequently translocated to the cytoplasm for additional processing facilitated by the enzyme DICER, in conjunction with cofactors, including protein activator of protein kinase R (PACT) and Trans-activation response RNA-binding protein (TRBP). The mature miRNA duplex is ultimately incorporated into the RISC, where one of the miRNA strands (–5p or –3p) associates with the Argonaute (AGO) protein, directing the complex to interact with its target mRNA. A single mRNA molecule can possess numerous binding sites accommodating various miRNAs, thereby establishing a complex network of interactions between miRNAs and mRNA.^{50,51} MiRNAs exhibit tissue-specific distributions and can modulate the expression of roughly 30% of the human genome.⁵² MiRNAs, as integral cellular components, are increasingly recognized for their pivotal involvement in a diverse array of fundamental biological processes. Despite lacking complete understanding, multiple strands of evidence suggest that miRNAs modulate apoptosis. It is believed that they regulate the expression of genes involved in both promoting and inhibiting apoptosis. In this context, employing a combination of bioinformatics techniques and experimental methodologies, Druz et al predicted and identified the anti-apoptotic targets of mmu-miR-466h. Their experimental investigation revealed that inhibiting mmu-miR-466h led to heightened expression levels of genes associated with apoptosis, thereby leading to enhanced cellular viability and reduced activation of Caspase-3/7. They additionally revealed that the increase in expression of mmu-miR-466h following nutrient depletion suppresses multiple anti-apoptotic genes. Their results indicate that mmu-miR-466h exhibits a pro-apoptotic function and can regulate the apoptotic pathway within mammalian cells.⁵³ Similarly, through the application of bioinformatics analysis and luciferase reporter assays, Ouyang et al confirmed that miR-181, a miRNA predominantly expressed in the brain, can selectively target the 3'-untranslated

regions (3'-UTRs) of Bcl-2 family members, namely Bcl-2-L11/Bim, Mcl-1, and Bcl-2. Their subsequent investigation revealed that reduced expression levels of miR-181a mitigated apoptosis triggered by glucose deprivation, alleviated mitochondrial dysfunction, and preserved mitochondrial membrane potential in astrocytes.⁵⁴ Thus, the involvement of miRNAs in regulating apoptosis indicates that therapeutic interventions directed towards these molecules hold promise for addressing both malignant and non-malignant conditions.

Targeting miRNAs-Apoptosis Regulatory Network via TCM, and TCM Extracts in Malignant Disorders

Cancer is characterized by the uncontrolled proliferation of abnormal cells in the body. It is currently regarded as a major global health challenge and one of the most prevalent diseases worldwide, with cancer-related mortality is being increased. Regulating the survival and death of cancer cells is a critical strategy in the effective management and treatment of cancer.⁵⁵ Traditional Chinese Medicine can either promote or inhibit the expression of cancer-associated miRNAs, and thus modulating tumorigenicity and cancer progression.

Targeting miRNAs-Apoptosis Regulatory Network via Baicalin

Scutellaria baicalensis Georgi (Lamiaceae or Labiatae) is a widely recognized TCM herb, commonly referred to as Huang-Qin or Chinese skullcap (Radix Scutellariae).⁵⁶ Baicalin, a phytochemical derived from the roots of *Scutellaria baicalensis* Georgi, exhibits various pharmacological properties in neurodegenerative diseases and multiple malignancies through several biological processes, such as anti-inflammatory, antioxidant, and anti-apoptotic effects.^{57,58} Tao et al investigated the molecular pathways implicated in the therapeutic effects of baicalin on colorectal cancer (CRC). They validated that baicalin can efficiently stimulate and increase apoptosis in HT-29 cells in a manner dependent on dosage while also inhibiting tumor proliferation in xenografted nude mice. They conducted a miRNA microarray analysis on HT-29 cells treated with baicalin, revealing significant suppression of numerous oncomiRs, such as miR-205, miR-151a, miR-31, miR-30c, miR-10a, and miR-23a compared to untreated cells. Furthermore, their in vitro and in vivo investigations demonstrated that baicalin inhibited oncomiRs by decreasing c-Myc expression levels. Their research demonstrates a novel pathway through which baicalin exerts its anti-cancer effects by promoting apoptosis in colon cancer cells and inhibiting tumor growth via downregulation of c-Myc and oncomiRs expression.⁵⁹ In addition, Duan et al conducted a study to examine the precise function and potential underlying mechanism of baicalin in breast cancer (BC). Baicalin administration was observed to suppress cellular viability while stimulating apoptosis in BC cells. In their study, reduced miR-338-3p expression was observed in both BC tissues and cells, with overexpression of miR-338-3p leading to reduced cell viability and increased apoptosis. Baicalin exposure resulted in the reversal of miR-338-3p expression, and the inhibition of miR-338-3p mitigated the effects of baicalin on cell viability and apoptosis. Subsequent functional investigations revealed that the mRNA expression of MORC4, a target of miR-338-3p, was elevated in both BC tissues and cells but reduced upon exposure to baicalin. They finally revealed that the upregulation of MORC4 mitigated the impact of miR-338-3p on cellular viability and apoptosis. Their findings suggest that baicalin inhibits cell viability while inducing apoptosis in BC cells by modulating miR-338-3p and MORC4, underscoring its potential as a pharmacological agent for BC therapy.⁶⁰

Targeting miRNAs-Apoptosis Regulatory Network via Baicalein

Baicalein, a flavone compound, serves as a bioactive constituent within the traditional medicinal plant known as *Scutellaria baicalensis* Georgi. A growing body of evidence indicates that baicalein possesses therapeutic potential for treating and preventing diverse forms of cancer.⁶¹ Ma et al explored the mechanisms through which baicalein inhibits pancreatic cancer progression. Initially, they confirmed the significant involvement of baicalein in the suppression of pancreatic tumorigenesis through experimentation both in vitro and in vivo. Through high-throughput sequencing analysis, they observed differential expression of 20 up-regulated and 39 down-regulated miRNAs in Panc-1 cells treated with 100 μ M baicalein compared to the control group. The qPCR analysis substantiated that miR-139-3p exhibited the highest upregulation following treatment with baicalein, whereas miR-196b-5p demonstrated the most pronounced downregulation. Their subsequent investigations into functionality demonstrated that miR-139-3p promoted apoptosis in Panc-1 cells by targeting NOB1, while miR-196b-5p

suppressed apoptosis by targeting ING5. They determined that baicalein's ability to regulate the expression of miR-139-3p or miR-196b-5p induces apoptosis and inhibits tumor growth in pancreatic cancer, indicating its potential as a potent inhibitor in this context.⁶²

Targeting miRNAs-Apoptosis Regulatory Network via Matrine

Matrine, an alkaloid, is extracted from the traditional Chinese medicinal plant *Sophora flavescens* Aiton. Numerous studies have demonstrated the anticancer properties of matrine, showcasing its ability to impede cancer cell proliferation and trigger apoptosis.⁶³ An investigation conducted by An et al explored the therapeutic impacts and molecular mechanisms of matrine on the A549 non-small cell lung cancer (NSCLC) cell line. In their study, a substantial matrine concentration of 1.0 mg/mL resulted in a noteworthy $52.68 \pm 3.32\%$ inhibition of cellular proliferation, accompanied by observable phenomena such as cell shrinkage and disruption. Flow cytometric analysis demonstrated a notable rise in the proportion of G1/G0 cells and a decrease in the proportions of S and G2/M cells after 48-hour matrine treatment. These findings suggest that matrine administration led to the initiation of cellular arrest. Also, via both DNA fragmentation assay and TUNEL assay, they examine the impact of matrine on apoptosis induction in A549 cells, revealing that treatment with matrine resulted in apoptosis of approximately 30% of the A549 cell population. Importantly, treatment with a low concentration of matrine (0.2 mg/mL) resulted in an observed increase in miR-126 expression levels, subsequently leading to a decrease in the expression of its target gene, vascular endothelial growth factor. In conclusion, TCM matrine, possessing antitumor properties, prompted cell cycle arrest and apoptosis while restoring miR-126 expression in the A549 NSCLC cell line.⁶⁴ Furthermore, Fu et al sought to examine the anticancer properties of matrine against papillary thyroid cancer (PTC) in human subjects and elucidate the associated molecular mechanisms. Initially, they provided evidence indicating a notable increase in the expression levels of miR-182-5p in both PTC tissues and cell lines. Matrine suppressed miR-182-5p expression and triggered apoptosis in TCP-1 and BCPAP cells, varying the extent of this effect according to the dosage administered. Matrine elevated the caspase-3 expression and decreased the expression levels of Bcl-2 in both BCPAP and TCP-1 cells. Subsequent functional investigations revealed that upregulation of miR-182-5p attenuated matrine-induced apoptosis and caspase-3 activation while preventing the decrease in Bcl-2 expression induced by matrine. Their study ultimately demonstrated that miR-182-5p upregulation antagonized the suppressive impact of matrine on PTC tumor proliferation. In this manner, Matrine potentially elicits anti-tumor properties through mechanisms such as the promotion of apoptosis in TCP-1 and BCPAP cells, reduction of Bcl-2 levels, activation of caspase 3, and inhibition of PTC tumor progression via the downregulation of miR-182-5p expression. These results elucidate the anti-cancer properties of matrine in PTC and highlight miR-182-5p as a promising therapeutic target for matrine in PTC management.⁶⁵

Targeting miRNAs-Apoptosis Regulatory Network via Berberine

Berberine (BBR) is a benzyloquinoline alkaloid isolated from the Chinese herb *Coptis chinensis* Franch. It is extensively utilized in TCM and exhibits pharmacological effects such as anti-inflammatory and antioxidant properties.^{66,67} Chen et al sought to elucidate the mechanisms underlying the anti-tumor effects of BBR in NSCLC. In their study, BBR inhibited the proliferation of NSCLC and facilitated apoptosis in NSCLC cells by regulating the expression of TF and miR-19a. Their luciferase assays demonstrated that TF was directly targeted and inhibited by miR-19a in NSCLC cells. Their subsequent experiments revealed that BBR triggered apoptosis via modulation of the miR-19a/TF/MAPK axis. Their findings indicate that BBR prompts apoptosis in NSCLC cells by activating the miR-19a/TF/MAPK signaling cascade.⁶⁸

Targeting miRNAs-Apoptosis Regulatory Network via Hd-Sb

The combination of *Hedyotis diffusa* (HD) and *Scutellaria barbata* (SB) is extensively utilized in clinical antitumor prescriptions as a commonly employed herb pair in China. Pan et al sought to examine the antitumor efficacy of the herb-pair (*Hedyotis diffusa* plus *Scutellaria barbata* (Hd-Sb)) in bladder cancer cells. Their findings demonstrate that Hd-Sb suppressed the growth and colony formation of bladder cancer cells in a manner dependent on both dose and time. They also observed that the herb-pair induced cell apoptosis by inhibiting Akt activation and decreasing antiapoptotic protein expression Mcl-1 and Bcl-2. Their subsequent experiments revealed that the herb-pair decreased miR-155 levels, leading

to induction of cell apoptosis and inhibition of Akt activation by miR-155 inhibitor. Notably, exogenous miR-155 abrogated the pro-apoptotic effects of the herbal combination by stimulating the Akt signaling pathway in bladder cancer cell lines. Taken together, Hd-Sb suppressed miR-155 expression and Akt pathways, induced apoptosis, and exhibited anticancer properties in bladder cancer cells.⁶⁹

Targeting miRNAs-Apoptosis Regulatory Network via Artesunate

Artesunate (ART) is a semi-synthetic compound derived from artemisinin, a natural substance obtained from the leaves of Chinese herb *Artemisia annua* L. Artemisinin and its derivatives exhibit activity against cancer cells.⁷⁰ ART effectively suppressed orthotopic tumor growth in rats with bladder cancer, concomitant with upregulation of miR-16 expression and downregulation of cyclooxygenase-2 (COX-2) expression. In vitro studies revealed that ART exhibited selective cytotoxicity towards bladder cancer cells, inducing apoptosis. However, normal human urothelial cells demonstrated significantly lower susceptibility to ART-mediated toxicity. ART notably elevated miR-16 expression and reduced the expression of COX-2 and the production of prostaglandin E2 (PGE2). More importantly, the downregulation of miR-16 expression could counteract the apoptotic effect of ART and the downregulation of COX-2 expression in bladder cells. Moreover, exogenously administered PGE2 demonstrated the ability to abrogate apoptosis in bladder cancer cells previously exposed to ART-based therapy. In conclusion, ART induces an anti-tumor effect against bladder cancer by increasing miR-16 expression, promoting apoptosis, and decreasing COX-2 expression and PGE2 production. Hence, ART shows promise as a potent therapeutic agent for the management of bladder cancer.⁷¹

Targeting miRNAs-Apoptosis Regulatory Network via Shikonin

Shikonin, the principal bioactive compound derived from the roots of *Lithospermum erythrorhizon* Siebold & Zucc, also referred to as “Zicao” in TCM. Recent research indicates that shikonin exhibits diverse bioactive properties relevant to cancer therapy.⁷² Shikonin suppresses proliferation in human endometrioid endometrial cancer (EEC) cell lines in a manner dependent on dosage. Moreover, shikonin induces apoptosis by increasing the expression of pro-apoptotic proteins cleaved-Caspase-3 and Bax while decreasing the expression of the anti-apoptotic protein Bcl-2. Shikonin induces dysregulation of numerous miRNAs, with miR-106b being notably downregulated. Furthermore, the reintroduction of miR-106b expression nullifies the anti-proliferative and pro-apoptotic effects induced by shikonin. Mechanistically, miR-106b targets PTEN, thereby regulating the AKT/mTOR signaling pathway. Therefore, shikonin suppresses proliferation and triggers apoptosis in human EEC cells by modulating the miR-106b/PTEN/AKT/mTOR signaling pathway, underscoring its promise as a therapeutic intervention for EEC.⁷³

Targeting miRNAs-Apoptosis Regulatory Network via Curcumin

Curcumin, sourced from the rhizome of *Curcuma longa* L., has been utilized for centuries in TCM and Ayurvedic medicine throughout Asia for cancer therapy.⁷⁴ Curcumin suppressed cell proliferation, triggered apoptosis, and enhanced caspase-3 activity in A549 cells. The relative expression of miR-192-5p in NCL-H460 cells decreased compared to that in A549 cells, which exhibited higher expression, while BEAS-2E cells demonstrated the highest expression. Furthermore, miR-192-5p mimics attenuated cell proliferation and augmented cell apoptosis in A549 cells, whereas anti-miR-192-5p mimics promoted cell proliferation and hindered cell apoptosis in A549 cells. Curcumin efficiently upregulated the relative expression of miR-192-5p and attenuated the PI3K/Akt signaling pathway. Notably, miR-192-5p mimics potentiated the impact of curcumin on apoptosis and cell viability while inhibiting the PI3K/Akt signaling pathway in A549 cells. Also, anti-miR-192-5p mimics reversed the impact of curcumin on A549 cells and the expression of PI3K/Akt. Therefore, curcumin triggers apoptosis and suppresses cell proliferation in human non-small cell lung cancer cells by increasing miR-192-5p and inhibiting the PI3K/Akt signaling pathway.⁷⁵

Targeting miRNAs-Apoptosis Regulatory Network via Triptolide

Triptolide (TP), identified by Kupchan et al in 1972 from the root of *Tripterygium wilfordii* Hook F. (TWHF), is regarded as the most potent epoxide diterpene lactone compound among various CHM. TP has garnered significant research attention due to its potent anti-cancer properties.⁷⁶ In PC-9 cells, triptolide treatment decreased cell proliferation, enhanced apoptosis, and increased caspase-9 and 3 activity. Triptolide decreased miR-21 expression and increased

PTEN protein levels in PC-9 cells. Significantly, increased expression of miR-21 mitigated the impact of Triptolide on cell viability and PTEN protein levels in PC-9 cells. In this manner, Triptolide attenuated the proliferation and promoted the apoptosis of human NSCLC cells via modulation of PTEN through targeting miR-21.⁷⁷

Targeting miRNAs-Apoptosis Regulatory Network via Isoliquiritigenin

Isoliquiritigenin, a flavonoid derived from the root of *Glycyrrhiza uralensis* Fisch, represents a constituent of TCM with historical significance as one of the earliest recognized herbal remedies. The primary bioactive compound found in licorice root, isoliquiritigenin, exhibits a spectrum of biological functions encompassing antiviral properties, antioxidative effects against free radicals, and mitigation of lipid peroxidation. Isoliquiritigenin suppresses cellular proliferation within nasopharyngeal carcinoma cell lines, encompassing C666-1 and CNE2. Isoliquiritigenin facilitated apoptosis in nasopharyngeal carcinoma cells by enhancing the expression of Caspase-9, Caspase-3, and Bax while inhibiting the expression of Bcl-2. Furthermore, miR-32 markedly increases in nasopharyngeal carcinoma tissues, with isoliquiritigenin demonstrating a significant capacity to decrease miR-32 expression. Elevated levels of miR-32 facilitated the proliferation and migration of nasopharyngeal carcinoma cells while concurrently inhibiting apoptosis. Notably, the administration of isoliquiritigenin significantly impedes the impact mediated by miR-32. Mechanistically, miR-32 targets large tumor suppressor 2 (LATS2) and impedes the growth of nasopharyngeal carcinoma cells by modulating the Wnt signaling pathway. Moreover, isoliquiritigenin displays similar findings in vivo experimentation and suppresses xenograft development in nude mice, concurrent with reductions in tumor volume and modulation of LATS2 and miR-32 expression. So, isoliquiritigenin possesses significant potential as an efficacious anti-nasopharyngeal carcinoma agent, demonstrating effectiveness both in vivo and in vitro through modulation of the miR-32/LATS2/Wnt pathway.⁷⁸ Additionally, Peng et al conducted a study examining the efficacy of 3', 4', 5', 4"-tetramethoxychalcone (TMC), a derivative of ISL, in targeting tumor growth specifically within triple-negative breast cancer (TNBC) cells. Initially, their investigation revealed that TMC prompted apoptosis in TNBC cells in a dosage-correlated fashion. The miR-374a overexpression was observed across multiple TNBC cellular models, encompassing BT549, 4T1, and MDA-MB-231 cell lines. They additionally documented that miR-374a exhibited a direct binding affinity towards the 3'-UTR region of BAX gene, resulting in the downregulation of both Bax mRNA and protein levels. Their findings demonstrated that miR-374a exerted an oncogenic influence on apoptosis within TNBC cells, thereby facilitating tumor initiation. Following a 24-hour treatment with TMC, TNBC cells exhibited a notable reduction in miR-374a expression. Additionally, TMC upregulated Bax mRNA expression, indicating its potential to influence BAX levels through regulatory mechanisms, whether at the transcriptional or post-transcriptional level. Thereby, TMC elicits apoptosis and impedes tumor initiation in TNBC by regulating the miR-374a/BAX axis.⁷⁹

Targeting miRNAs-Apoptosis Regulatory Network via Celastrol

Celastrol (Cel), alternatively referred to as tripterine, is a biologically active compound present in the root of TCM *Tripterygium wilfordii* Hook F. An increasing body of evidence suggests that Celastrol possesses therapeutic potential and displays a range of biological activities, notably demonstrating efficacy in cancer treatment.⁸⁰ Celastrol demonstrated a dose-dependent inhibition of colon cancer cell viability, accompanied by the downregulation of PCNA. Additionally, Celastrol administration significantly reduced the expression of BCL-2 and miR-21, while increasing BAX expression and inducing Caspase-3 activity. Notably, overexpression of a miR-21 mimic enhanced cell viability, suppressed apoptosis, decreased BAX levels, and reduced Caspase-3 activity to some extent. These effects were subsequently reversed by Celastrol treatment. Moreover, the miR-21 mimic activated the PI3K/AKT/GSK-3 β pathway, while the addition of Celastrol partially inhibited this activation. Therefore, Celastrol shows potential in inhibiting colon cancer cell proliferation and promoting apoptosis through its negative regulation of miR-21 and the PI3K/AKT/GSK-3 β pathway.⁸¹ Celastrol has also demonstrated a therapeutic response in gastric cancer. It was found that Celastrol triggered apoptosis in gastric cancer cells by impeding the activation of the PI3K/Akt and NF- κ B signaling pathways. IGF-1, which robustly activates Akt, restored NF- κ B functionality in Celastrol-treated cells. Additionally, Celastrol significantly reduced the expression of miR-21. Moreover, the inhibition of miR-21 led to a reduction in phospho-Akt expression and NF- κ B activity. Notably, miR-21 overexpression enhanced the activity of the PI3K/Akt and NF- κ B pathways while reducing

apoptosis in Celastrol-treated gastric cancer cells—a phenomenon that was potentially reversible with the administration of a PI3K inhibitor. Thus, the impact of Celastrol on apoptosis was attributed to the suppression of the PI3K/Akt-dependent NF- κ B pathway via miR-21 inhibition.⁸²

Targeting miRNAs-Apoptosis Regulatory Network via Aloperine

Aloperine (ALO), found in the seeds and leaves of the *Sophora alopecuroides* L. in TCM, exhibits a diverse array of pharmacological effects, notably including anticancer properties.⁸³ Han et al investigated the upstream pathway through which Aloperine mitigates CRC injury, focusing on elucidating its impact on the regulatory network involving circular RNA (circRNA), miRNAs, and mRNAs. Their findings demonstrated a notable reduction in the viability and proliferation of CRC cells following ALO treatment, alongside a marked elevation in the incidence of apoptotic cancer cell population, indicative of an inhibitory effect on tumor progression. In their study, among the subset of circRNAs exhibiting differential expression in CRC, solely circNSUN2 demonstrates dual functionality by serving as a target for miR-296-5p and being subject to regulation by Aloperine. The findings of their experimental investigation revealed that circNSUN2 silencing resulted in a reduction of proliferation and apoptosis promotion in CRC cells. Additionally, circNSUN2 overexpression counteracted the suppressive impact of Aloperine on cancerous cells. More importantly, they disclosed that ALO could inhibit circNSUN2 activation and counteract the stimulatory impact of circNSUN2 upregulation on the advancement of esophageal cancer. Through the utilization of dual luciferase report assay and subsequent rescue experiments, they confirmed the cellular regulatory impacts of circNSUN2 alongside miR-296-5p/Signal Transducer and Activator of Transcription 3 (STAT3). They ultimately validated their hypothesis that modulation of the circNSUN2/miR-296-5p/STAT3 axis results in decreased proliferation and heightened apoptosis in CRC cells. Thereby, Aloperine, through modulation of the circNSUN2/miR-296-5p/STAT3 pathway and facilitation of apoptotic processes, exhibits a preventative effect against the malignancy progression of CRC cells.⁸⁴

Targeting miRNAs-Apoptosis Regulatory Network via Pien Tze Huang

Pien Tze Huang (PZH) represents a widely recognized TCM formulation whose ingredients are mainly composed of *Panax notoginseng* (Burk). F. H. Chen. It is distinguished by a variety of pharmacological impacts, including the suppression of inflammatory processes and the regulation of cell proliferation.^{85,86} PZH exhibited a notable decrease in both the viability and cell density of HCT-8/5-FU cells in a manner dependent on dose and time. PZH demonstrated inhibitory effects on cellular viability, diminished the percentage of cells in the S-phase, and attenuated the expression of pro-proliferative proteins such as cyclin-dependent kinase and cyclin D1. Furthermore, administration of PZH prompted the condensation and fragmentation of nuclei, triggered the activation of caspase-9 and -3, and elevated the ratio of pro-apoptotic Bcl-2-associated X protein to B-cell lymphoma 2 protein. Notably, treatment with PZH resulted in the upregulation of miR-22 expression and the downregulation of c-Myc expression, which is a target gene of miR-22. So, PZH suppresses the growth of HCT-8/5-FU cells and induces apoptosis, predominantly by regulating the miR-22/c-Myc signaling pathway.⁸⁷ Furthermore, the impact of PZH on both the apoptosis and proliferation of the BEL-7402 HCC cell line, along with the underlying mechanisms, has been investigated recently. PZH markedly reduced the viability, confluence, and clonogenic potential of BEL-7402 cells. It also elicited cell cycle arrest and facilitated the process of apoptosis. PZH significantly reduced the transcriptional activity of the pro-proliferative genes cyclin-dependent kinase 4 and cyclin D1, alongside a reduction in the expression levels of the anti-apoptotic gene Bcl-2. Additionally, PZH also led to an increase in the expression of a pivotal microRNA, specifically miR-16. So, PZH could efficiently impede the proliferation of cancer cells and trigger apoptosis in BEL-7402 HCC cells by upregulating the tumor suppressor miR-16. Therefore, regulating the miR-16 expression along with its target genes potentially constitutes a mechanism by which PZH exerts its anti-tumor effects.⁸⁸

Targeting miRNAs-Apoptosis Regulatory Network via Spica Prunellae

Prunellae Spica (PS) is the dried flower spike of the herb *Prunella vulgaris* L., frequently used as an herbal remedy in China, and is known for its anticancer properties.⁸⁹ Fang et al examine the potential anti-tumor properties of ethanol extract derived from Spica Prunellae (referred to as EESP) in CRC. Initially, EESP exerted a dose-dependent effect on HCT-8 colon carcinoma cells, inducing apoptosis and suppressing cell growth. EESP notably increased the expression of

miR-34a. At the same time, the mRNA and protein levels of its target genes, including *Notch2*, *Notch1*, and *Bcl-2*, significantly decreased. Since these target genes are associated with oncogenic properties and have therapeutic implications in apoptosis-related interventions for malignancies, the findings suggest that EESP may inhibit the proliferation of human colon carcinoma cells by inducing apoptosis, possibly through the modulation of *Bcl-2*, *Notch1*, and *Notch2* expression levels via the activation of miR-34a.⁹⁰

Targeting miRNAs-apoptosis regulatory network via *Scutellaria barbata* D. Don

Scutellaria barbata D. Don (*S. barbata*) is a widely recognized perennial herb employed within the contexts of traditional Chinese and Korean medicinal practices. Modern pharmacological investigations have demonstrated that *S. barbata* exhibits diverse biological properties, notably its efficacy in combating cancer.⁹¹ Zhang et al investigated the potential of the chloroform fraction derived from *Scutellaria barbata* D. Don (SB) to inhibit the proliferation of human colon cancer HCT-8 cells. Their findings revealed that ECSB treatment significantly suppressed HCT-8 cell proliferation and induced apoptosis in a dose-dependent manner. Additionally, they demonstrated that ECSB treatment led to a notable increase in miR-34a expression, while simultaneously reducing the expression levels of *Jagged1*, *Bcl-2*, and *Notch1/2*. Their subsequent experiments indicated that ECSB treatment significantly counteracted miR-34a silencing by introducing anti-miR oligonucleotide. Additionally, miR-34a silencing led to a notable increase in the expression of *Bcl-2*, *Notch1/2*, and *Jagged1*, all subsequently reversed upon ECSB administration. Therefore, ECSB suppresses the proliferation of cancer cells by inducing apoptosis and cell division. The modulation of miR-34a expression mediated this effect. Their findings bolster the utilization of ECSB as a viable therapeutic intervention for colon cancer.⁹²

Targeting miRNAs-Apoptosis Regulatory Network via Luteolin

Luteolin, a flavonoid found in *Chrysanthemum morifolium* Ramat, and commonly used in TCM, has been employed for a long time due to its well-known anti-inflammatory properties. These properties hold promise for clinical applications, particularly in managing cancer patients.^{93,94} Luteolin suppresses cellular proliferation and prompts apoptosis in gastric cancer cell populations. The expression of miR-34a is decreased in a significant proportion of human primary gastric cancer specimens when juxtaposed with their corresponding non-neoplastic counterparts. Furthermore, miR-34a exerts direct regulatory control over *Bcl-2*, reducing *Bcl-2* protein levels in gastric cancer cells upon miR-34a overexpression. Additionally, Luteolin enhances the expression of miR-34a while suppressing the expression of *Bcl-2*. Moreover, anti-miR-34a oligonucleotides (AMO) partially attenuate the Luteolin-induced decrease in *Bcl-2* expression observed in gastric cancer cells. Thereby, Luteolin reduces *Bcl-2* expression by elevating the expression of miR-34a to some extent. In this manner, the miR-34a pathway assumes significance in mediating Luteolin-triggered apoptosis in gastric cancer cell.⁹⁵

Targeting miRNAs-Apoptosis Regulatory Network via Bufalin

Bufalin serves as a bioactive constituent found within the TCM known as “Chan Su”, derived from the desiccated venomous secretions of the skin glands of either *Bufo gargarizans* or *Bufo melanostictus*. Bufalin has been employed as a therapeutic agent for cancer treatment.⁹⁶ Bufalin could stimulate apoptosis in gastric cancer cells by upregulating BAX expression. Also, miR-298 directly targets BAX and functions as a regulator of BAX expression. Additionally, miR-298 increased the proliferation of gastric cancer cells while impeding apoptosis, whereas bufalin hindered cell proliferation and facilitated apoptosis through the reduction of miR-298. So, bufalin-associated miR-298 could indirectly impact cell proliferation and apoptosis by targeting BAX, thereby suggesting its viability as a prospective therapeutic intervention in the treatment of gastric cancer.⁹⁷ In addition, the therapeutic response of bufalin has also been demonstrated in prostate cancer. Bufalin administration led to elevated miR-181a expression, with miR-181a induction triggering bufalin-induced apoptosis by downregulating *Bcl-2* protein expression in PC-3 cells. Conversely, suppressing miR-181a activity can potentially diminish bufalin-triggered apoptosis in PC-3 cells. In this manner, the miR-181a pathway assumes a significant role in mediating bufalin-triggered apoptosis in gastric cancer cells, thereby indicating the potential of bufalin as a viable therapeutic intervention for gastric cancer.⁹⁸ Furthermore, bufalin exerted inhibitory effects on cell proliferation and elicited apoptosis via a mitochondria-dependent pathway in Saos-2 and U-2OS osteosarcoma (OS) cell lines, accompanied by the generation of intracellular ROS. Further, bufalin significantly decreases the expression levels of miR-221. Notably, in silico and in vitro analysis identified *Bcl2* binding component 3 (BBC3) as the direct molecular

target of miR-221. Notably, the reversal of bufalin-induced effects on osteosarcoma cells was achieved by upregulating miR-221 using its mimetic agent (MIMIC) and suppressing BBC3 via siRNA. Thereby, Bufalin triggers mitochondria-dependent apoptosis in OS cells by reducing the expression of miR-221 and inducing the expression of BBC.⁹⁹

Targeting miRNAs-Apoptosis Regulatory Network via Honokiol

Honokiol (HNK) is a small biphenolic compound obtained from the bark of *Magnolia officinalis* Rehder & E.H. Wilson, known for its antineoplastic properties across a spectrum of cancer types. HNK suppresses proliferation and prompts apoptosis in human osteosarcoma cells in a dose-dependent fashion. HNK-mediated apoptosis is marked by an increase in the levels of proapoptotic proteins, such as Bcl-2-associated X protein, cleaved-poly (ADP-ribose) polymerase, and cleaved-caspase-3, alongside a reduction in the expression of the anti-apoptotic protein Bcl-2. HNK induced dysregulated expression of miRNAs in human OS, with miR-21 being among the most notably reduced miRNAs. HNK decreases miR-21 in a dosage-dependent fashion, and miR-21 restoration counteracted the inhibitory effects of HNK on OS cells. Also, miR-21 suppresses the expression of PTEN by directly interacting with its 3'-UTR. In conclusion, HNK effectively attenuated the PI3K/AKT signaling pathway. Nonetheless, the upregulation of miR-21 led to its reactivation. Taken together, HNK exerts its anticancer effects by modulating the miR-21/PTEN/PI3K/AKT signaling pathway, inhibiting cell proliferation and induction of apoptosis in OS cells.¹⁰⁰

Targeting miRNAs-Apoptosis Regulatory Network via Solamargine

Solamargine (SM) is a naturally occurring sugar alkaloid derived from *Solanum nigrum* L. It exhibits notable efficacy in impeding the onset and progression of diverse cancers through various pathways, including those related to apoptosis.^{101,102} Yin et al examined the potential significance of SM in hepatocellular carcinoma (HCC) treatment and elucidated its mechanisms of exerting an antitumor effect. They showed that SM suppressed the proliferation of HCC and efficiently triggered autophagy and apoptosis in HCC cells both in vivo and in vitro. In terms of mechanism, the oncogenic factor LIF exhibited abnormal elevation in HCC tissues but was diminished by SM in HCC cells. Additionally, LIF upregulation could reinstate the anti-HCC effects of SM through the miR-192-5p/CYR61/Akt signaling pathways. Additionally, SM can reprogram tumor-associated macrophages through the LIF/p-Stat3 pathway, leading to the inhibition of HCC growth and epithelial-mesenchymal transition while also modulating other immune cell populations, including T cells, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment.¹⁰³

Targeting miRNAs-Apoptosis Regulatory Network via Zhoushi Qiling Decoction

The Zhoushi Qi Ling decoction (ZQD) represents a TCM formulation capable of eliciting apoptotic pathways within malignant cells.¹⁰⁴ Cao et al sought to assess the effectiveness of ZQD when administered alongside androgen deprivation therapy (ADT) in prostate cancer and to investigate its underlying mechanism of action. Their study enrolled a cohort comprising 151 individuals to undergo either ADT alone or a combination of ADT and ZQD treatment. Evidence showed that the survival rates of patients undergoing combined ADT with ZQD were notably superior to those undergoing ADT monotherapy. Cellular investigations also revealed a notable increase in miR-143 expression within DU145 cells after their ZQD treatment exposure. In serum samples, increased levels of miR-143 expression were identified after treatment with ADT+ZQE. Conversely, such elevated expression was not observed among patients subjected solely to ADT. In DU145 cells, administering ZQD resulted in a dose-dependent elevation of apoptosis, a process mitigated by applying anti-miR-143 treatment. Subsequent investigation into their functional characteristics revealed a specific binding region between miR-143 and Bcl-2. Additionally, it was observed that administration of ZQD resulted in decreased expression levels of Bcl-2. Moreover, they noticed that the administration of ZQD resulted in elevated caspase-3 and Bax expression levels. In this manner, administration of ZQD therapy has the potential to induce apoptosis in prostate cancer cells by increasing miR-143 expression, thus suggesting a plausible mechanism for the observed inhibitory impact of ZQD in prostate cancer patient.¹⁰⁵

Targeting miRNAs-Apoptosis Regulatory Network via Icariin

Icariin, a prenylated flavonol glycoside derived from *Epimedium brevicornum* Maxim., has exhibited various pharmacological properties, notably as an anti-cancer agent.^{106,107} Icariin exerted concurrent inhibitory effects on cell

proliferation, facilitated apoptosis, and elevated caspase-3 activity within the A2780 cell line. In ovarian cancer A2780 cells, icariin led to notable reductions in miR-21 expression levels, concurrently augmenting protein expression levels of PTEN and RECK and diminishing Bcl-2 protein expression levels. Notably, miR-21 modulated the putative anticancer properties of icariin on cellular proliferation and apoptosis in A2780 ovarian cancer cells by targeting Bcl-2, RECK, and PTEN. In this manner, the involvement of miR-21 and its associated target genes could significantly influence the underlying molecular processes contributing to the anticancer properties of icariin.¹⁰⁸

Targeting miRNAs-Apoptosis Regulatory Network via Geniposide

Geniposide, derived from the traditional Chinese herbal remedy “Zhizi”, found in the fruit of *Gardenia jasminoides* J. Ellis.¹⁰⁹ Prior investigations have elucidated its significant involvement in mitigating inflammation, countering oxidative stress, and exhibiting potential antineoplastic properties. Geniposide induces a dose-dependent suppression of OCI-LY7 and OCI-LY3 cell proliferation while concurrently augmenting the proportion of apoptotic cells and elevating cleaved caspase-3 and cleaved PARP levels within DLBCL cellular populations. In DLBCL tissues and cell lines, the expression of long noncoding RNA HLA complex P5 (lncRNA HCP5) increased, whereas administration of geniposide notably attenuated its expression levels. As well, HCP5 silencing led to the suppression of cell proliferation and induction of apoptosis in both OCI-LY3 and OCI-LY7 cell lines. In Vitro, and silico analysis demonstrated miR-27b-3p as a direct target of HCP5, and HCP5 gene suppression and geniposide administration significantly led to an upregulation in the expression of miR-27b-3p within DLBCL cells. Notably, the downregulation of HCP5 led to a decrease in MET protein expression within DLBCL cells, a reduction that was later reversed upon silencing miR-27b-3p. Moreover, exogenous MET administration partially mitigated the proliferative suppression and apoptotic effects of geniposide in DLBCL cells. Thereby, geniposide hinders the proliferation and prompts the apoptosis of DLBCL cells, possibly through modulation of the HCP5/miR-27b-3p/MET axis, suggesting a promising therapeutic approach for managing DLBCL.¹¹⁰

Targeting miRNAs-Apoptosis Regulatory Network via Amentoflavone

Amentoflavone (AMF), an inherent biflavonoid compound, finds extensive application within TCM. AMF was first extracted from the foliage of *Selaginella tamariscina*, *Selaginella rupestris*, and *Ginkgo biloba*. It has been extensively documented as a compound exhibiting diverse biological properties, including anticancer effects.¹¹¹ Zhaohui et al sought to examine the impact of AMF, a bioactive flavonoid constituent found in *Selaginella tamariscina* Spring, on glioma cells, elucidating the mechanistic pathways through which it operates. Their findings indicated a notable decrease in the expression of miR-124-3p within glioma tissues compared to those of normal brain tissues. It was additionally revealed that AF reduced cell viability and induced apoptosis in both glioma cell lines in a dose-dependent fashion. Their further experimentation revealed that AF prompted apoptosis and hindered glycolytic activity within glioma cells by upregulating miR-124-3p. Notably, in their study, upregulation of miR-124-3p induced by AF occurred through the repression of DNMT1 via Sp1, subsequently triggered by AF's activation of the ROS/AMPK signaling pathway. Thereby, AF possesses potent anti-glioma properties by inducing apoptosis and suppressing glycolysis in glioma cells through upregulating miR-124-3p.¹¹²

Targeting miRNAs-Apoptosis Regulatory Network via Oroxin B

Oroxin B (OB), chemically identified as Baicalein-7-O- β -gentiobioside with the molecular formula C₂₇H₃₀O₁₅ and a molecular weight of 594.52 Da, represents a flavonoid monomer constituent sourced from the traditional Chinese medicinal plant *Oroxylum indicum* (L.) Vent. Emerging studies demonstrate the anti-lymphoma activity of OB, with preliminary evidence suggesting a lack of overt toxicity. Li et al endeavor to explore the anticancer properties of OB both in vitro and in vivo, elucidating its role in inducing apoptosis in HCC. They noted that OB demonstrates significant anti-hepatocellular carcinoma efficacy both in vitro and in vivo, accompanied by a notable reduction in miR-221 expression compared to the control group. They also observed a reduction in both PI3K mRNA and protein levels in groups treated with OB, compared to the control group, suggesting an upregulation of PTEN expression. Therefore, OB's anticancer properties manifest through the facilitation of PTEN gene activity, which subsequently leads to the suppression of the PI3K/Akt signaling cascade via the reduction of miR-221 expression, ultimately promoting apoptosis in hepatic cancer cells.¹¹³

Targeting miRNAs-Apoptosis Regulatory Network via Physcion

Physcion, a prominent bioactive constituent found in the TCM Radix et Rhizoma Rhei, possesses an anthraquinone chemical framework and manifests diverse pharmacological attributes encompassing hepatoprotective, laxative, anti-inflammatory, anti-proliferative, and antimicrobial properties. Recently, there has been an investigation into the therapeutic potential of physcion in managing HCC. Physcion administration induced apoptotic cell demise in HCC cells by increasing miR-370 expression, as evidenced by both *in vitro* and *in vivo* findings. Furthermore, physcion regulated the miR-370 expression via the AMPK/Sp1/DNMT1 signaling pathway. Taken together, Physcion exerts anti-tumor effects against HCC through the modulation of the AMPK/Sp1/DNMT1 signaling pathway, leading to the induction of apoptosis in HCC cell lines, facilitated by miR-370.¹¹⁴

Targeting miRNAs-Apoptosis Regulatory Network via Tanshinone

Salvia miltiorrhiza Bunge, an esteemed botanical belonging to the Lamiaceae family, holds significant importance within the realm of TCM. The principal bioactive constituents within *Salvia miltiorrhiza* are tanshinones, demonstrating notable pharmacological effects, notably in the realm of antitumor properties.¹¹⁵ Aurora A, a serine-threonine kinase arising from the AURKA gene, plays a pivotal role in multiple mammalian cellular functions, such as cell proliferation and apoptosis, with its upregulation potentially leading to the inhibition of apoptosis. A recent study revealed that tanshinones by upregulating the expression of miR-32, leading to the suppression of the AURKA. Also, tanshinones demonstrate antineoplastic properties in NSCLC by suppressing cellular proliferation, inducing apoptosis, and hindering cell-cycle progression. Partially through the down-regulation of AURKA, tanshinones achieved these effects. Notably, in NSCLC, comparable outcomes were achieved by utilizing siRNA to inhibit the expression of the AURKA gene. It was additionally confirmed that miR-32 directly targeted AURKA. Collectively, tanshinones demonstrate the potential to impede NSCLC progression by downregulating AURKA through miR-32 upregulation and other associated miRNA expressions.¹¹⁶

Targeting miRNAs-Apoptosis Regulatory Network via 1, 6, 7-Trihydroxyxanthone (THA)

Garcinia oblongifolia, a TCM with a longstanding history of employment spanning numerous centuries, has been investigated for its pharmacological properties. One of its constituents, 1, 6, 7-trihydroxyxanthone (THA), extracted from *Goodyera oblongifolia*, exhibited notable efficacy in inhibiting cellular proliferation and promoting apoptosis in cancerous cell lines. A recent inquiry revealed that the administration of THA resulted in heightened expression of miR-218 while concurrently causing diminished expression levels of Bmi-1. Further, the induction of miR-218 by THA may result in the heightened expression of tumor suppressor genes P16Ink4a and P14ARF, which serve as principal downstream targets of Bmi-1. In conclusion, THA elicits apoptotic processes in hepatocellular carcinoma cells, potentially mediated by the upregulation of miR-218 and concurrent downregulation of Bmi-1 expression.¹¹⁷

Targeting miRNAs-Apoptosis Regulatory Network via Catalpol

Catalpol, an iridoid glucoside derived from *Rehmannia glutinosa* (Gaertn). DC., a TCM herb, has been documented for its diverse pharmacological properties, including its potential anti-cancer effects.^{118,119} Catalpol prompted apoptosis within HCT116 cells, which depended on heightened activities of caspase-9 and caspase-3. In addition, Catalpol administration is associated with the reduction of Akt, p-Akt, and PI3K within HCT116 cells. Also, diminished activity of PI3K/Akt pathways resulted in reduced cellular viability in HCT116 cells after exposure to catalpol, concomitant increased levels of miR-200. In this manner, catalpol induced apoptosis in human HCT116 colorectal cancer cells by increasing miR-200 expression, depending on suppressing the phosphatase and tensin homolog/PI3K-Akt signaling pathway.¹²⁰

Targeting miRNAs-Apoptosis Regulatory Network via Ailanthone

Ailanthone (AIL), categorized as a water-soluble quassinoid, is extracted from the renowned TCM plant *Ailanthus altissima*. The application of AIL resulted in a noteworthy decrease in the viability of Vestibular schwannomas (VS) cells, along with a reduction in cyclin D1 expression and a concomitant elevation in apoptotic cell rate, as evidenced by increased cleaved caspase 9/3. Further, AIL decreased the miR-21 expression, and the apoptotic and autophagic responses induced by AIL were diminished upon upregulation of miR-21. In addition, AIL suppressed the expression of Ras and Raf and inhibited the activity

of MEK, ERK, mTOR, and p70S6K. However, the inhibitory effects of AIL were counteracted by the miR-21 upregulation. In this manner, AIL suppressed the proliferation of VS cells while eliciting autophagic and apoptotic responses. So, the potential antineoplastic effects of AIL within VS cells are purportedly mediated through miR-21 inhibition, alongside inhibition of the Ras/Raf/MEK/ERK and mTOR signaling cascades.¹²¹

Thereby, TCMs, by selectively suppressing oncogenic miRNAs, activate apoptotic signaling pathways, offering a promising therapeutic strategy in cancer (Figures 2 and 3).

Targeting miRNAs-Apoptosis Regulatory Network via TCM, and TCM Extracts in Non-Malignant Disorders

TCM Therapeutic Activity in Cardiovascular Diseases

Cardiovascular diseases (CVDs) represent a major global health burden, characterized by a steady increase in prevalence.¹²² Recent studies have disclosed that patient morbidity and CVDs-related mortality are closely associated with cardiomyocyte loss. Therefore, inhibiting cardiac apoptosis holds promise as an effective therapeutic strategy for CVDs.¹²³

Targeting miRNAs-Apoptosis Regulatory Network via Shen-Yuan-Dan

The Shen-Yuan-Dan (SYD), a frequently utilized traditional Chinese medicinal formula, exhibits protective properties against myocardial ischemia-reperfusion (I/R) injury in both *vitro* and *vivo* systems. These protective effects have been

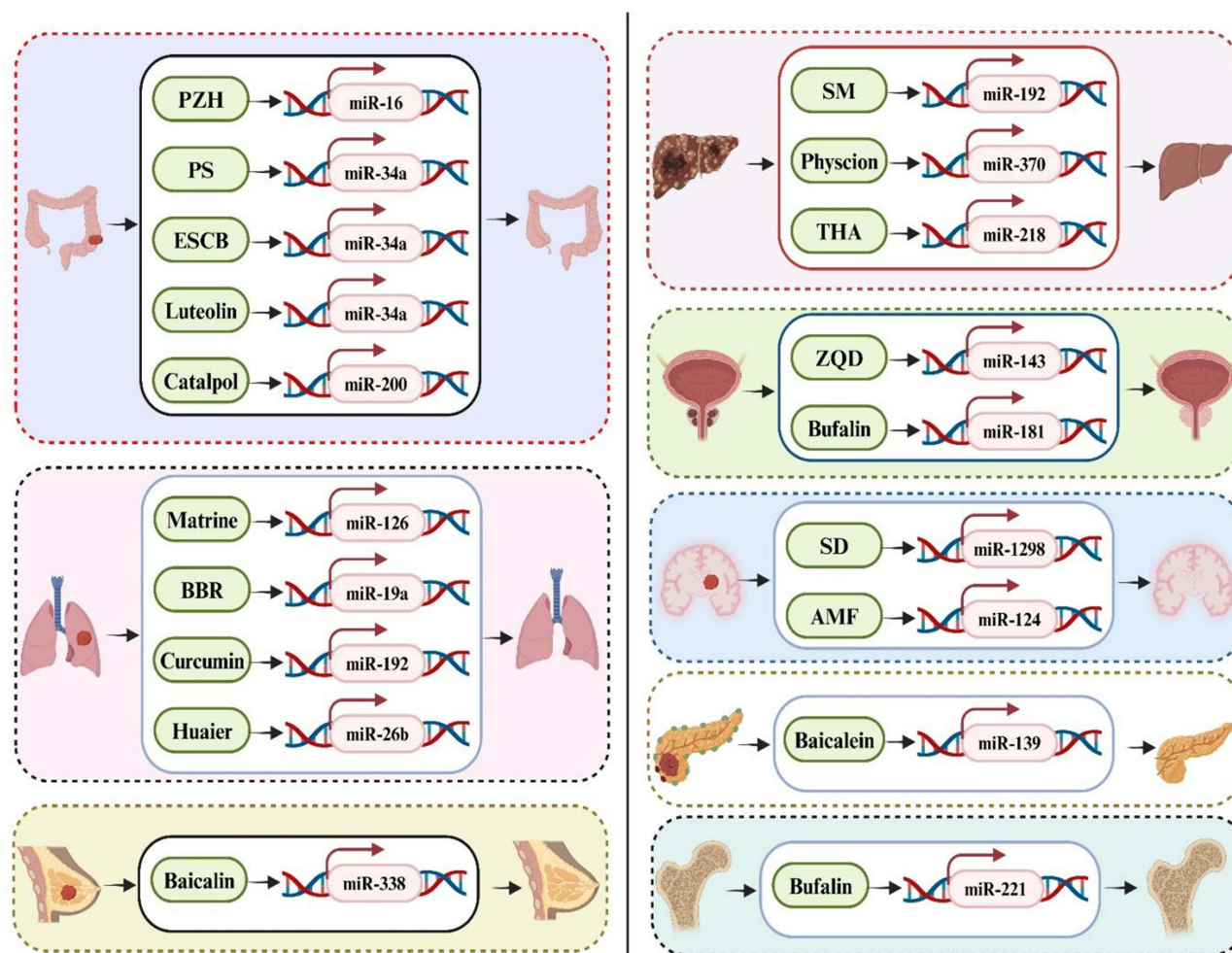


Figure 2 Modulation of miRNAs by TCMs in diverse cancer types. miRNAs are key regulators of gene expression, and by targeting 3'-UTR of apoptosis-related mRNAs, they can suppress apoptosis. The current figure demonstrate that TCM can increase apoptosis-related miRNAs expression, thereby promoting apoptosis and exerting therapeutic effects in different cancers.

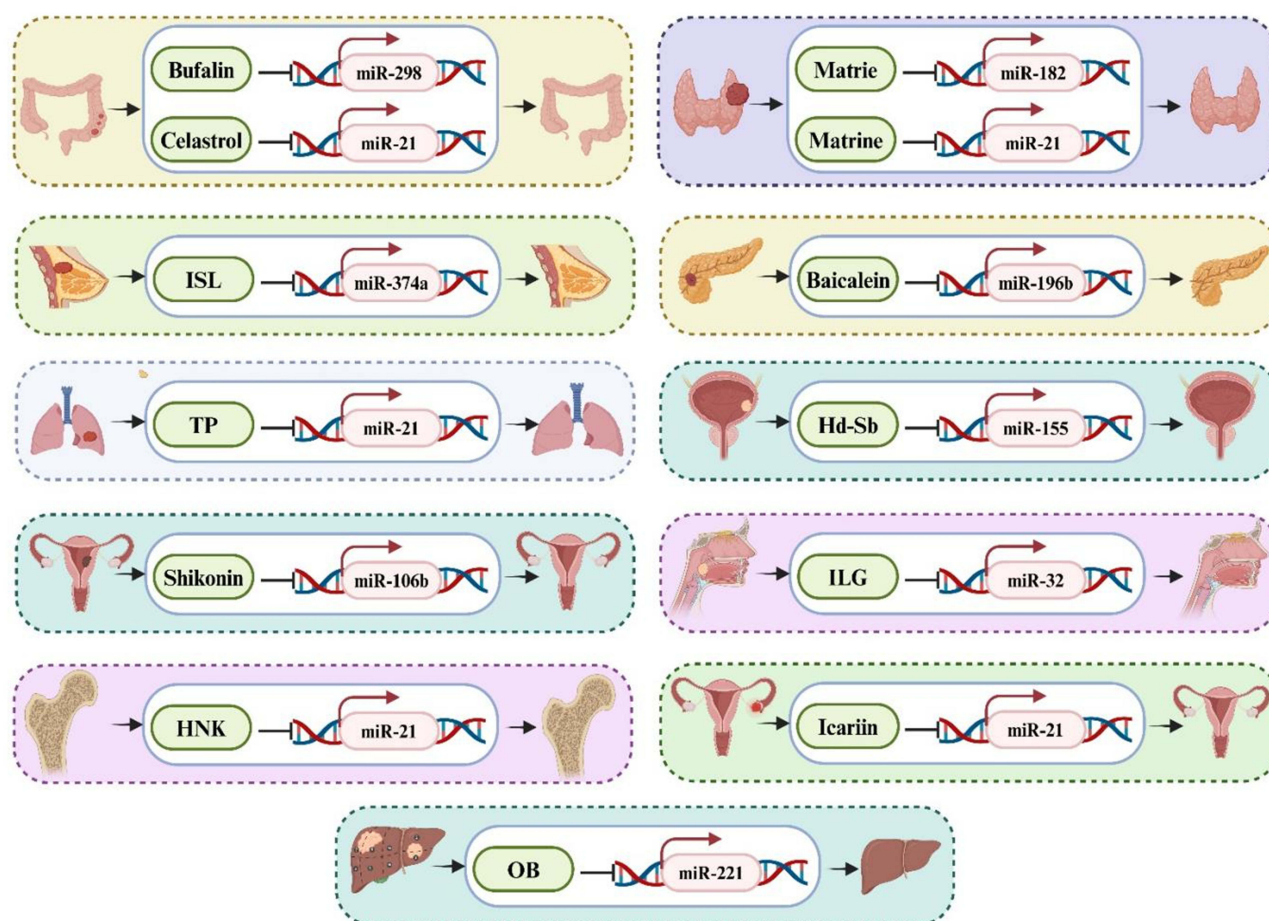


Figure 3 Modulation of miRNAs by TCMs in diverse cancer types. Evasion of apoptosis, and reduced rate of apoptosis are key features of cancer development. This figure illustrates that TCMs, by inhibiting anti-apoptotic miRNAs, can induce apoptosis, thereby holding therapeutic potential in the treatment of various cancers.

attributed to the activation of the PI3K/Akt pathway.¹²⁴ SYD decreased cardiomyocyte injury induced by hypoxia in neonatal rat cardiomyocytes. This mitigation was evidenced by a decrease in CPK and LDH activities, an increase in cell viability, and a reduction in apoptosis. Also, miR-24 directly targets Bim, and SYD suppresses Bim expression by increasing miR-24 levels. Further, miR-24 overexpression substantially augmented the efficacy of SYD, consequently ameliorating myocardial cell apoptosis. Using various experimental assays, they substantiated that Bim was directly targeted by miR-24. In this manner, treatment with SYD decreases hypoxia-induced myocardial apoptosis by increasing the expression of miR-24. This offers novel perspectives on the molecular mechanisms involved in SYD's therapeutic efficacy, potentially facilitating myocardial function recovery and delaying the onset of heart failure.¹²⁵

Targeting miRNAs-Apoptosis Regulatory Network via Dendrobine

Dendrobine exhibits a broad distribution across tropical and subtropical regions spanning Europe, Asia, and Oceania. Dendrobine primarily originates from *Dendrobium nobile* Lindl., exhibiting bioactivity akin to that of picrotoxin. In China, the genus *Dendrobium* comprises approximately 74 species, with over 50 of these species historically utilized in TCM for addressing diseases such as fever, skin aging, cancer, cardiovascular conditions, and chronic atrophic gastritis.¹²⁶ Meng et al aimed to observe the effect of dendrobine in a model of endoplasmic reticulum stress (ERS) using vascular endothelial cells. Initially, they employed tunicamycin (TM) to induce ERS in HUVECs, inhibiting cellular proliferation and initiating apoptosis, which is concomitant with the upregulation of proteins associated with ERS. They observed that TM administration decreased expression levels of miR-381-3p, while Dendrobine treatment facilitated the proliferation and suppressed TM-mediated apoptosis in HUVECs. In their study, following dendrobine

treatment, diminished expression levels of 78-kDa glucose-regulated protein, C/EBP homologous protein, inositol-requiring enzyme 1, caspase-3, and caspase-4 were detected. They additionally revealed that Dendrobine attenuated endothelial cell apoptosis in the ERS model by upregulating miR-381-3p expression, partially reinstating cell proliferation levels. Overall, dendrobine increased miR-381-3p expression, suppressing apoptosis triggered by ERS in HUVECs with caspase-4-mediated pathways. Their discoveries offer novel perspectives on the etiology of endothelial cell apoptosis in atherosclerosis (AS) and unveil the considerable therapeutic potential of dendrobine in mitigating AS.¹²⁷

Targeting miRNAs-Apoptosis Regulatory Network via Tanshinol

Tanshinol (3,4-dihydroxyphenyl lactic acid) is extracted from *Salvia miltiorrhiza* Bunge.¹²⁸ It is extensively employed in TCM and has been documented for its vasodilatory attributes and ability to mitigate methionine-induced hyperhomocysteinemia in rat models. Chen et al explored the molecular mechanisms underlying the protective effect of tanshinol in atherosclerosis. They revealed that tanshinol exhibited a concentration-dependent reduction in the area of aortic atherosclerotic lesions throughout the entire aorta and aortic sinus. It mitigated apoptosis in endothelial cells within ApoE^{-/-} mice. Furthermore, they observed a decrease in the mRNA expression of TUG1 and an upregulation in the expression of miR-26a in endothelial cells following treatment with tanshinol. In their study, TUG1 reduced miR-26a expression within ECV304 cells. Ultimately, they revealed that TUG1 upregulation counteracted the adverse impact of tanshinol on endothelial cell apoptosis induced by oxidized low-density lipoprotein (ox-LDL). Taken together, tanshinol mitigates the apoptosis of endothelial cells in atherosclerotic ApoE^{-/-} mice, with the protective effect attributed to decreased TUG1 expression and elevated miR-26a levels.¹²⁹

Targeting miRNAs-Apoptosis Regulatory Network via Tanshinone IIA

Tanshinone IIA, derived from *Salvia miltiorrhiza* (Danshen in Chinese), a botanical traditionally utilized in TCM, constitutes the principal bioactive compound. The roots of Danshen are esteemed for their therapeutic efficacy in addressing cardiovascular and cerebrovascular ailments, encompassing conditions such as myocardial infarction, hypertension, hyperlipidemia, angina pectoris, and acute ischemic events.¹³⁰ Tanshinone IIA exhibited notable efficacy in mitigating myocardial apoptosis triggered by either DOX or H₂O₂. MiR-133 directly targets Caspase-9 and Tanshinone IIA by inducing miR-133, reducing Caspase-9, thereby eliciting a protective effect. Also, administration of Tanshinone IIA effectively reversed the decreased expression of miR-133 induced by adverse conditions. This change helped to prevent the activation of Caspase-9 and other factors involved in apoptosis, which in turn reduced myocardial injury. Essentially, Tanshinone IIA eased myocardial apoptosis by boosting miR-133 levels and blocking the Caspase-9 signaling pathway.¹³¹

Targeting miRNAs-Apoptosis Regulatory Network via Emodin

Emodin, also known as 1, 3, 8-trihydroxy-6-methylantraquinone, represents a naturally transpiring anthraquinone derivative prominently featured in traditional Chinese botanical remedies, such as *Rheum palmatum* L. Emodin has been observed to exhibit a diverse array of pharmacological properties, including anti-osteoporotic, anti-allergic, and anti-cardiovascular effects. It principally interacts with various molecular targets associated with cardiovascular diseases, encompassing anti-apoptotic inflammation mechanisms and the excessive proliferation of smooth muscle cells. Numerous pieces of evidence extensively elucidate the impact of Emodin on various signaling pathways and cellular functions within cardiovascular disease.¹³² In this context, Emodin attenuates hypoxia-induced damage in H9c2 cells through mechanisms involving the enhancement of cellular viability and mitigating apoptotic processes. Hypoxic conditions elicited a downregulation of miR-138, whereas emodin treatment led to its upregulation. As well, miR-138 overexpression mitigated cellular apoptosis and injury induced by hypoxia. Importantly, the reduction in miR-138 expression mitigated the growth-stimulating impact of Emodin on hypoxia-induced injury. However, the increase in miR-138 expression amplified the growth-stimulating effects of Emodin. Further, Emodin may trigger the activation of Sirt1/AKT and Wnt/ β -catenin signaling pathways, potentially through miR-138 overexpression. Further, miR-138 acts as a direct regulator of MLK3. Notably, increased expression of MLK3 resulted in the deactivation of the Sirt1/AKT and Wnt/ β -catenin signaling pathways. Conversely, Emodin activates these pathways by suppressing MLK3 expression, thus

facilitating the activation of Sirt1/AKT and Wnt/ β -catenin signaling cascades. Thereby, Emodin mitigated hypoxia-induced apoptosis and cellular injury in H9c2 cells by enhancing the expression of miR-138, regulated by MLK3, and activating the Sirt1/AKT and Wnt/ β -catenin signaling pathways.¹³³

Targeting miRNAs-Apoptosis Regulatory Network via Shenfu Formula

The Shenfu Formula, primarily composed of aqueous extract derived from the desiccated root or rhizome of *Panax ginseng* C. A. Mey (Asian ginseng) and the lateral root of *Aconitum carmichaeli* Debx (known as Fuzi or Heishunpian in Chinese), represents a traditional formulation within Traditional Chinese Medicine renowned for its capacity to replenish Qi energy and invigorate the Yang aspect. It represents a potent therapeutic modality in the management of cardiac disorders. In recent experimental investigations, it was observed that the Shenfu Formula reduced the positivity rate of myocardial cells, as assessed through the TUNEL assay, alongside a notable inhibition of caspase 3 expression. Further, the Shenfu Formula could modulate the primary factors Fas/Fas-L within the intrinsic apoptosis pathway and Bcl-2/Bax within the extrinsic apoptosis pathway, thereby attenuating apoptotic processes in rats afflicted with heart failure. Notably, Shenfu Formula has the potential to modulate the equilibrium of miRNAs implicated in both promoting and impeding apoptosis, consequently mitigating apoptotic processes. This modulation induces alterations in miRNA target genes. Thereby, Shenfu Formula exerts an inhibitory effect on myocardial cell apoptosis by modulating apoptosis-associated miRNAs, suggesting a prospective therapeutic utility of Shenfu Formula in managing heart failure.¹³⁴

In summary, TCMs, by upregulating specific miRNAs such as miR-24, miR-381-3p, miR-26a, miR-133, and miR-138, can suppress apoptotic pathways, thereby reducing apoptosis and demonstrating promising therapeutic potential for cardiovascular diseases (Figure 4).

TCM Therapeutic Activity in Neurological Diseases

According to recent studies, disorders affecting the nervous system represent the leading contributor of overall disease burden in the world. Importantly, with increasing global disability adjusted life-years (DALYs) counts, there is an urgent need for effective strategies in prevention, and treatment.¹³⁵ As apoptosis is a critical player in the development of neurological disorders, therapeutic approaches such as TCM aimed at modulating apoptosis could offer promising avenue for their treatment.

Targeting miRNAs-Apoptosis Regulatory Network via Ginsenoside Rg1

Recent exploration revealed that administration of Ginsenoside Rg1 (GRg1) in combination with *Acori graminei* Rhizoma (AGR) notably mitigated the symptoms associated with AD. Notably, in SAMP8 mice, miR-873-5p expression was reduced, while HMOX1 expression exhibited an increase. Administration of GRg1 combined with AGR substantially upregulated the miR-873-5p expression while concurrently downregulating HMOX1 levels. Mechanistically, miR-873-5p directly targets HMOX1 and exerts a negative regulatory effect on its expression levels. Importantly, A β 1–42 markedly reduces miR-873-5p expression while simultaneously elevating HMOX1 levels in PC12 cells. Furthermore, the combination of GRg1 and AGR effectively counteracted the impact induced by A β 1–42, whereas the inhibition of miR-873-5p reversed the beneficial effect mediated by GRg1 and AGR combination. Moreover, in vivo experimentation proved in vitro findings, demonstrating the protective role of AGR+GRg1 in AD. Therefore, treatment of GRg1 and AGR mitigated neuronal cell apoptosis in Alzheimer's disease by modulating the expression of miR-873-5p.¹³⁶

Targeting miRNAs-Apoptosis Regulatory Network via Tetramethylpyrazine

Tetramethylpyrazine (ligustrazine, TMP) constitutes the principal bioactive compound and distinctive alkaloid found within *Ligusticum wallichii* (Chuan Xiong), a traditional Chinese herbal remedy. TMP demonstrates efficacy in enhancing motor function recovery and exerting neuroprotective effects post-spinal cord injury through its capacity to suppress inflammatory processes and ameliorate glial scar hyperplasia.¹³⁷ Fan et al examined the regulatory impact of TMP on miR-214-3p within a rat model of spinal cord injury (SCI), aiming to identify the neuroprotective mechanisms and effects of TMP following SCI. In their study, following SCI, there was an observed upregulation of miR-214-3p concurrent with downregulation of the anti-apoptotic protein Bcl2l2. In their study, it was observed that TMP exerted an inhibitory effect

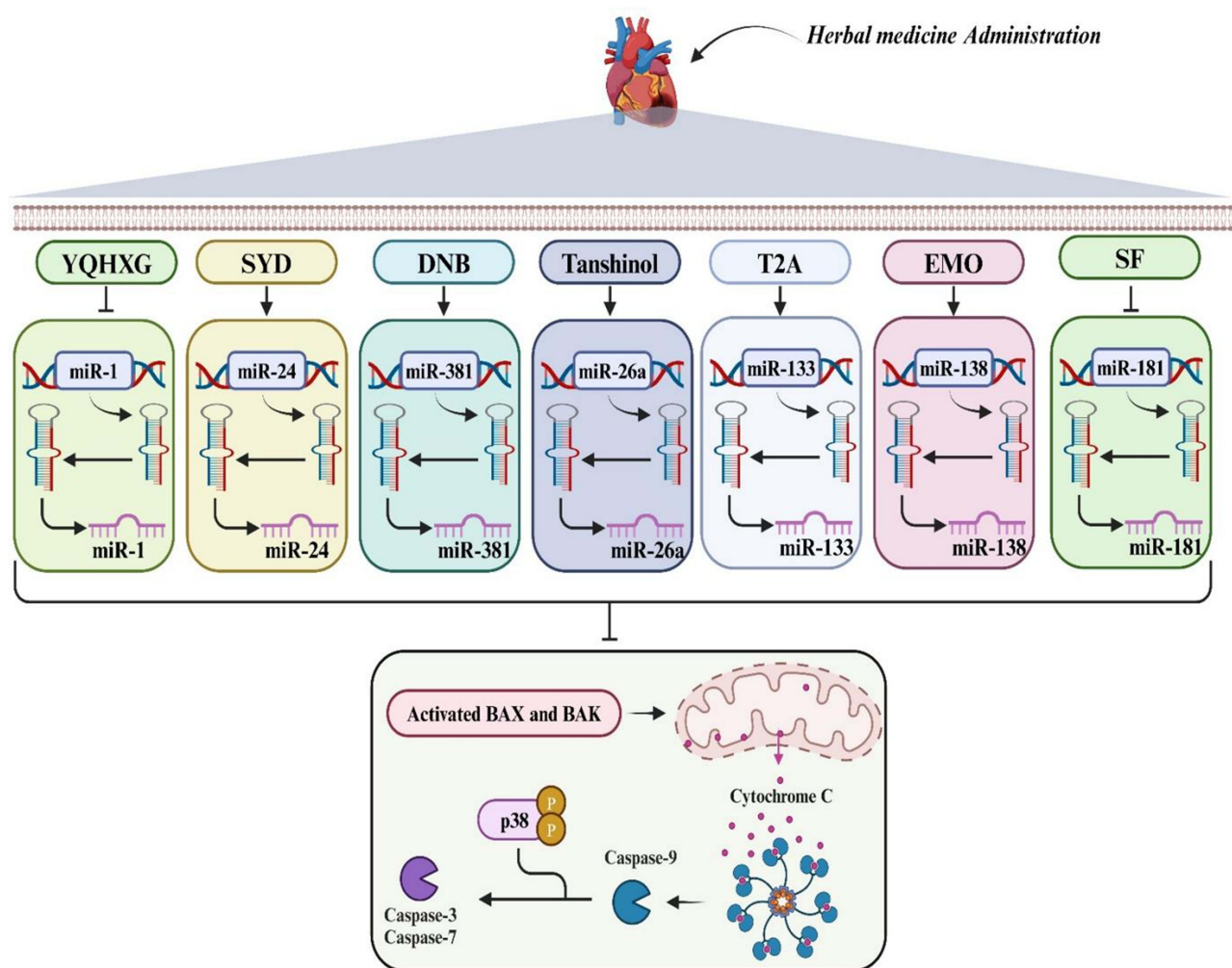


Figure 4 Modulation of miRNAs by TCMs in cardiovascular disease.

on apoptosis *in vivo* by downregulating miR-214-3p expression while simultaneously upregulating Bcl2l2 expression. Through luciferase reporter assay analysis, they additionally confirmed a putative binding site of miR-214-3p within the 3'-UTR of Bcl2l2 mRNA. They finally revealed that, *in vitro* settings, TMP demonstrated efficacy in suppressing apoptosis of neuronal cells. Therefore, TMP mitigated neural apoptosis in the injured spinal cord by reducing the expression of miR-214-3p.¹³⁸

Targeting miRNAs-Apoptosis Regulatory Network via Ligustrazine

Ligustrazine, an essential constituent of *Ligusticum chuanxiong*, a traditional Chinese herbal remedy, represents a bioactive alkaloid derived from *Ligusticum Chuanxiong* Hort, renowned for its pharmacological properties.¹³⁹ Ligustrazine has garnered recent attention for its utilization in managing ischemic cerebrovascular disorders. Li et al explore the neuroprotective effects of ligustrazine in cerebral I/R. In their study, in the Middle cerebral artery occlusion (MCAO) group, circ_0008146 expression exhibited a significant elevation compared to the Sham group, while administration of ligustrazine notably attenuated circ_0008146 expression within the MCAO context. Besides, their RT-qPCR analysis revealed a significant downregulation of miR-709 expression and upregulation of Cx3cr1 expression in the MCAO group compared to the Sham group, while treatment with ligustrazine notably upregulated miR-709 expression and decreased Cx3cr1 expression in MCAO. In their investigation, it was additionally observed that circ_0008146 suppression resulted in decreased levels of TNF- α and Interleukin 6 (IL-6), attenuated neuronal cell apoptosis, and

concurrently increased miR-709 and decreased Cx3cr1 expression in Lipopolysaccharide (LPS)-induced BV-2 cells. They also identified a direct relationship between circ_0008146 and miR-709 through a Dual-Luciferase reporter gene assay. In this manner, Ligustrazine modulates the circ_0008146/miR-709/Cx3cr1 axis, inhibiting cellular apoptosis and inflammation after cerebral ischemia/reperfusion injury.¹⁴⁰

Targeting miRNAs-Apoptosis Regulatory Network via Xiaoyaosan

Pharmacological investigations have demonstrated that Xiaoyao San (XYS), a TCM formulation comprising six herbal components, effectively mitigates inflammation, decreases neuronal apoptosis, and confers notable neuroprotective effects against hippocampal neuron injury induced by lipopolysaccharide.¹⁴¹ Yuan et al examined the potential involvement of the miR-200a/b-3p/NR3C1 pathway inhibition within the prefrontal cortex in mediating the neuroprotective and anti-stress properties of YYS, elucidating the associated mechanism. YYS mitigated anxiety and depression-like behaviors induced by chronic stress, concurrently downregulating the miR-200a/b-3p expression and apoptosis of neuronal cells in the prefrontal cortex (PFC). Importantly, elevated levels of miR-200a/b-3p in primary cortical neurons decreased NR3C1 gene expression, elevated Bax and cleaved caspase-3 protein levels, and reduced expression of the anti-apoptotic protein Bcl-2. Subsequent functional investigations revealed that paeoniflorin, a constituent of YYS, can impede the miR-200a/b-3p-induced apoptosis of primary neurons and aberrant modulation of apoptosis-associated proteins. After increasing miR-200a/b-3p in the ventromedial prefrontal cortex (vmPFC) in vivo, it was revealed that rats exhibited pronounced anxiety-like behaviors akin to those induced by prolonged stress. Thereby, YYS attenuates the upregulation of miR-200a/b-3p induced by chronic unpredictable mild stress (CUMS), modulates the miR-200a/b-3p/NR3C1 signaling pathway within the PFC in response to chronic stress, and mitigate neuronal apoptosis as well as stress-associated behaviors. In this manner, YYS suppressed neuronal apoptosis mediated by miR-200a/b-3p/NR3C1.¹⁴²

In summary, TCMs, including GRg1 in combination with AGR, TMP, Ligustrazine, and YYS, by modulating apoptosis-related miRNAs—such as miR-873-5p, miR-214-3p, miR-709, and miR-200a/b-3p, respectively—effectively suppress apoptotic pathways in neurological disorders, highlighting their therapeutic potential across these conditions (Figure 5).

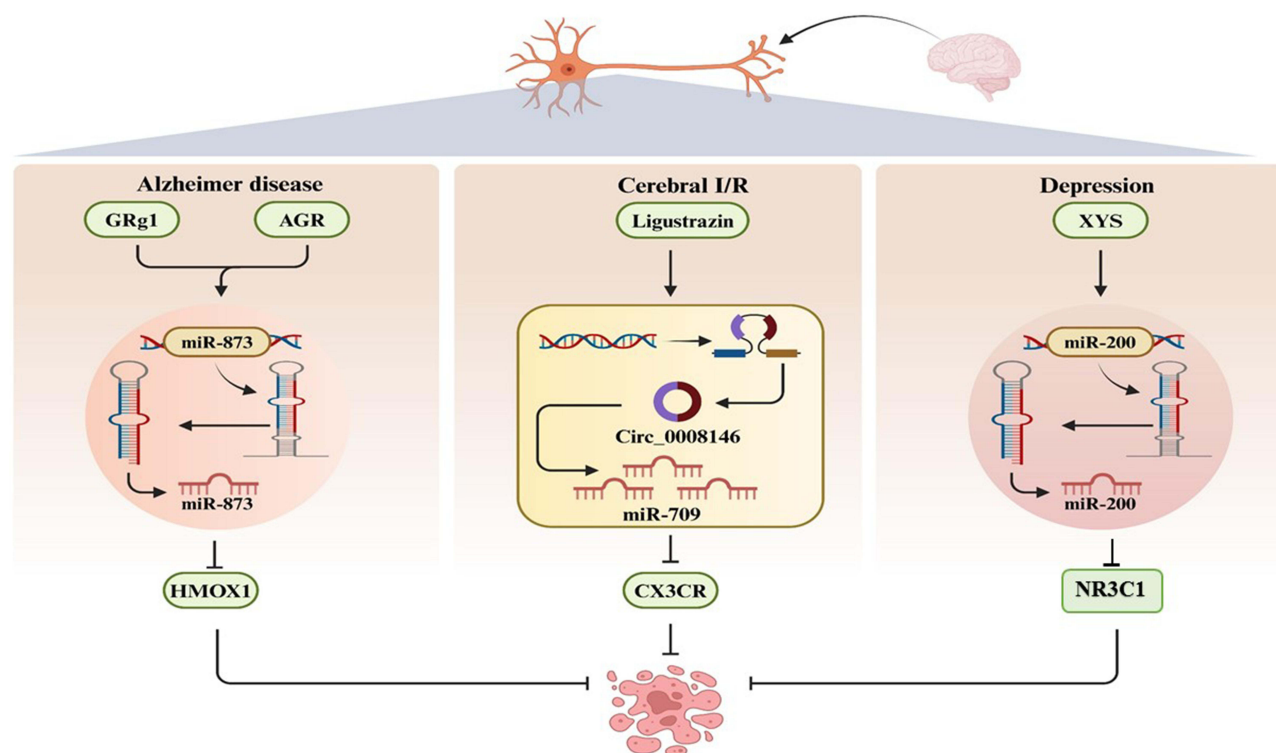


Figure 5 Modulation of miRNAs by TCMs in neurological disorders.

All in all, by modulating apoptosis-related miRNAs, TCM effectively regulates apoptotic pathways, finely balancing cellular survival and apoptosis. This modulation forms the foundation of TCM-induced therapeutic effects across various health conditions, encompassing both malignant and non-malignant disorders (Table 1).

Table 1 An Overview of Major TCMs Involved in miRNA-Apoptosis Modulation

TCM	Disease	miRNAs	Effect on miRNAs expression	Effect of miRNA on apoptosis	Ref.
<i>Baicalin</i>	Colorectal cancer	miR-205, miR-151a, miR-31, miR-30c, miR-10a, and miR-23a	Decrease	Anti-apoptosis	[59]
	Breast cancer	miR-338-3p	Increase	Pro-apoptosis	[38]
<i>Baicalein</i>	Pancreatic Cancer	miR-139-3p	Increase	Pro-apoptosis	[62]
		miR-196b-5p	Decrease	Anti-apoptosis	
<i>Matrine</i>	Non-small cell lung cancer	miR-126	Decrease	Anti-apoptosis	[64]
	Papillary thyroid cancer	miR-182-5p	Decrease	Anti-apoptosis	[65]
		miR-21	Decrease	Anti-apoptosis	[143]
<i>Berberine</i>	Non-small cell lung cancer	miR-19a	Decrease	Anti-apoptosis	[45]
<i>Hd-Sb</i>	Bladder Cancer	miR-155	Decrease	Anti-apoptosis	[46]
<i>Artesunate</i>	Bladder Cancer	miR-16	Increase	Pro-apoptosis	[71]
<i>Shikonin</i>	Endometrioid endometrial cancer	miR-106b	Decrease	Anti-apoptosis	[50]
<i>Curcumin</i>	Non-small cell lung cancer	miR-192-5p	Increase	Pro-apoptosis	[75]
<i>Triptolide</i>	Non-small cell lung cancer	miR-21	Decrease	Anti-apoptosis	[77]
<i>Isoliquiritigenin</i>	Nasopharyngeal carcinoma	miR-32	Decrease	Anti-apoptosis	[78]
	Triple-negative breast cancer	miR-374a	Decrease	Anti-apoptosis	[79]
<i>Celastrol</i>	Colon cancer	miR-21	Decrease	Anti-apoptosis	[81]
	Gastric cancer	miR-21	Decrease	Anti-apoptosis	[82]
<i>Aloperine</i>	Colorectal cancer	miR-296-5p	Increase	Pro-apoptosis	[84]
<i>Pien Tze Huang</i>	Colorectal Cancer	miR-22	Increase	Pro-apoptosis	[87]
	Hepatocellular carcinoma	miR-16	Increase	Pro-apoptosis	[88]
<i>Spica Prunellae</i>	Colorectal Cancer	miR-34a	Increase	Pro-apoptosis	[90]
<i>Scutellaria barbata</i> <i>D. Don</i>	Colorectal Cancer	miR-34a	Increase	Pro-apoptosis	[92]

(Continued)

Table 1 (Continued).

TCM	Disease	miRNAs	Effect on miRNAs expression	Effect of miRNA on apoptosis	Ref.
Luteolin	Gastric cancer	miR-34a	Increase	Pro-apoptosis	[95]
Bufalin	Gastric cancer	miR-298	Decrease	Anti-apoptosis	[97]
	Prostate cancer	miR-181a	Increase	Pro-apoptosis	[98]
	Osteosarcoma	miR-221	Decrease	Anti-apoptosis	[99]
Honokiol	Osteosarcoma	miR-21	Decrease	Anti-apoptosis	[100]
Solamargine	Hepatocellular carcinoma	miR-192-5p	Decrease	Anti-apoptosis	[80]
Zhoushi Qiling Decoction	Prostate cancer	miR-143	Increase	Pro-apoptosis	[105]
Icariin	Ovarian cancer	miR-21	Decrease	Anti-apoptosis	[108]
Geniposide	Diffuse large B-cell lymphoma	miR-27b-3p	Increase	Pro-apoptosis	[110]
Amentoflavone	Glioma	miR-124-3p	Increase	Pro-apoptosis	[112]
Oroxin B	Hepatocellular carcinoma	miR-221	Decrease	Anti-apoptosis	[113]
Physcion	Hepatocellular carcinoma	miR-370	Increase	Pro-apoptosis	[114]
Tanshinone	Non-small cell lung cancer	miR-32	Increase	Pro-apoptosis	[116]
1, 6, 7-trihydroxyxanthone	Hepatocellular carcinoma	miR-218	Increase	Pro-apoptosis	[117]
Catalpol	Colorectal Cancer	miR-200	Increase	Pro-apoptosis	[120]
Ailanthone	Vestibular schwannomas	miR-21	Decrease	Anti-apoptosis	[98]
Shezhi Huangling decoction	Glioma	miR-1298-5p	Increase	Pro-apoptosis	[144]
Shen-Yuan-Dan	Acute myocardial infarction	miR-24	Increase	Anti-apoptosis	[100]
Dendrobine	Atherosclerosis	miR-381-3p	Increase	Anti-apoptosis	[127]
Tanshinol	Atherosclerosis	miR-26a	Increase	Anti-apoptosis	[129]
Tanshinone IIA	Cardiovascular disease	miR-133	Increase	Anti-apoptosis	[131]
Emodin	Myocardial infarction	miR-138	Increase	Anti-apoptosis	[108]
Shenfu Formula	Heart failure	miR-23a and miR-29a	Increase	Anti-apoptosis	[134]
		miR-30b-3p	Decrease	Pro-apoptosis	
Ginsenoside Rg1	Alzheimer's disease	miR-873-5p	Increase	Anti-apoptosis	[136]
Tetramethylpyrazine	Spinal cord injury	miR-214-3p	Decrease	Pro-apoptosis	[138]

(Continued)

Table 1 (Continued).

TCM	Disease	miRNAs	Effect on miRNAs expression	Effect of miRNA on apoptosis	Ref.
Ligustrazine	Cerebral ischemia/ reperfusion damage	miR-709	Increase	Anti-apoptosis	[145]
Xiaoyao San	Depression	miR-200a/b-3p	Decrease	Pro-apoptosis	[142]
Kudiezi (KDZ)	Cerebral ischemia	miR-21	Increase	Anti-apoptosis	[146]
Astragalus polysaccharides	Diabetic retinopathy	miR-204	Decrease	Pro-apoptosis	[147]
Catalpol	Diabetic cardiomyopathy	miR-140-5p	Increase	Anti-apoptosis	[148]
Astragaloside IV	Lung injury	miR-21-5p	Increase	Anti-apoptosis	[149]
Panax notoginseng saponin	Intervertebral disc degeneration	miR-222-3p	Decrease	Pro-apoptosis	[150]
Arctigenin	Intervertebral disc degeneration	miR-483-3p	Increase	Anti-apoptosis	[151]
Yiqi Huoxue granule	Acute myocardial infarction	miR-1	Decrease	Pro-apoptosis	[152]
Dioscin	Intestinal ischemia/ reperfusion injury	miR-351-5p	Decrease	Pro-apoptosis	[153]

Conclusion

In recent years, TCM has gained global acceptance as a complementary and alternative therapeutic approach for managing various illnesses, encompassing both malignant and non-malignant conditions.^{154–164} Increasing evidence indicates that dysregulated apoptosis contributes to the pathological depletion or accumulation of cells observed in numerous human disorders. Recent *in vitro* and *in vivo* investigations disclosed that TCM primarily functions through regulating apoptotic pathways. The modulation of apoptosis pathways constitutes a foundational element of TCM's therapeutic effectiveness, exerting influence on many physiological functions and substantially contributing to its comprehensive approach to addressing various health conditions. Recent research findings suggest that TCM exhibits varying modes of action across different disease conditions. In this regard, in malignancies, TCM demonstrates notable efficacy in selectively triggering apoptosis within malignant cells, thereby facilitating the specific eradication of abnormal proliferative masses. For instance, Baicalin, Baicalein, matrine, berberine, Artesunate, and shikonin demonstrate therapeutic efficacy in CRC, pancreatic cancer, PTC, NSCLC, bladder cancer, and endometrial cancer, respectively, through their ability to induce apoptosis. In contrast, TCM frequently exhibits therapeutic efficacy in non-malignant conditions by inhibiting apoptosis, thus preserving essential cells and tissue. For instance, Shen-yuan-dan, Dendrobine tanshinol, and Yiqi Huoxue granule exert cardioprotective effects by inhibiting apoptosis in cardiomyocytes, thereby mitigating the progression of cardiovascular diseases. Therefore, the sophisticated capacity to regulate apoptosis, enhancing it in cancerous states while suppressing it in non-cancerous contexts highlights the precise and complex strategy employed by TCM in managing diverse health challenges. Based on preceding research, miRNAs are known to selectively regulate a considerable portion of the human genome, potentially targeting more than 5000 genes, constituting approximately 30% of the entire human genomic content. These short, ncRNAs, consisting of single strands, are pivotal in modulating genetic expression and significantly influence the development and advancement of numerous human diseases. While the comprehensive understanding of miRNAs' involvement in apoptosis regulation remains incomplete, recent investigations indicate a pronounced influence exerted by miRNAs through regulating pro-apoptotic and anti-apoptotic genes, thereby

contributing significantly to the modulation of apoptosis processes. In this study, we have illustrated how TCM manifests its complex therapeutic efficacy through the regulation of particular microRNAs, notably highlighting the influence on miR-21, miR-26b, miR-32, miR-374a, and miR-155. By modulating these microRNAs, TCM effectively exerts control over apoptotic cascades, thereby intricately adjusting the equilibrium between cellular viability and apoptosis. The meticulous regulation of apoptotic pathways highlights the therapeutic effectiveness of TCM, indicating its versatile methodology in managing diverse health ailments and laying groundwork for prospective innovative therapeutic strategies. In conclusion, TCMs, subject to rigorous examination through both *in vitro* and *in vivo* investigations, have demonstrated promising safety profiles and substantial therapeutic efficacy across various human diseases by modulating the miRNAs-apoptosis regulatory network.

The Potential of TCM-microRNAs in the Future Therapeutic Directions: Limitations and Solutions

Advancements in molecular biology techniques, including next-generation sequencing, have significantly transformed translational research and the development of novel therapeutic strategies for a wide range of diseases. These advancements have significantly improved the ability to identify predictive molecular alterations, shifting organ-centric approach toward in-depth molecular analysis and personalized therapeutic strategies.¹⁶⁵ However, the use of TCM encounters several challenges, notably the lack of systematic standardization of its efficacy, largely due to the limited availability of robust clinical practice.¹⁶⁶ Another major challenge in TCM is the heterogeneous response observed among patients diagnosed with the same condition when treated with a specific TCM formulation. Consequently, recent studies indicate that circulating microRNA expression profiles may serve as predictive biomarkers to predict individual patient responses to particular TCM. These findings highlight the potential for personalized therapeutic approaches within TCM, which could be incorporated into future clinical practice.¹⁶⁷ Low blood–brain barrier (BBB) permeability is another key limitation in TCM, often leading to subtherapeutic concentrations in brain tissue and restricting its therapeutic potential for CNS diseases.^{168,169} Nanotechnology, recognized for its vast potential, presents promising approaches in modern therapeutics. Recent research has highlighted that nanotechnology-based drug delivery systems can improve bioavailability, facilitate targeted delivery, and provide controlled release profiles.^{170,171} In the case of TCM, development of nano-TCM, can deliver active components of TCM across the BBB to the targeted brain region, demonstrating the great potential of nano-TCM in the treatment of CNS diseases. Extracellular vesicles (EVs) are membrane-bound particles secreted by cells that play an integral role in intercellular communication through the transfer of cellular constituents such as DNA and RNA to recipient cells.¹⁷¹ Extracellular vesicles (EVs), including exosomes and microvesicles, could cross BBB, facilitating the transfer of substances from peripheral circulation into the CNS. Consequently, EVs serve as effective carriers for delivering TCM, ensuring therapeutic concentrations and exerting beneficial effects in disease treatment.^{172–174}

Highlights

TCMs have been employed as a potent therapeutic modality to address a spectrum of diseases. miRNAs implicate in both pathological and physiological phenomena, notably in processes such as apoptosis. CMs have been proven to confer protective benefits, notably by modulating miRNA-modulated apoptotic signaling.

Abbreviation

3'-UTRs, 3'-untranslated regions; TP, Triptolide; AD, Alzheimer's disease; ADT, Androgen deprivation therapy; AGO, Argonaute; AGR, Acori graminei Rhizoma; AIL, Ailanthone; Akt, Serine/threonine-protein kinase; ALO, Aloperine; AMF, Amentoflavone; AMO, Anti-miR-34a oligonucleotides; ART, Artesunate; AS, Atherosclerosis; ATF, Activating transcription factor; BAFF, B cell activating factor; BBC3, Bcl2 binding component 3; BBR, Berberine; BC, Bcl-2, B-cell lymphoma 2; Breast cancer; Cel, Celastrol; circRNA, Circular RNA; COX-2, Cyclooxygenase-2; CRC, Colorectal cancer; CUMS, Chronic unpredictable mild stress; DCs, Dendritic cells; DGBXD, Danggui Buxue Decoction; DGCR8, DiGeorge syndrome critical region gene 8; DROSHA, Double-stranded RNA-specific endoribonuclease; EEC, Endometrioid endometrial cancer; EESP, Ethanol extract derived from Spica Prunellae; ERK, Extracellular signal-regulated kinase; ERS, Endoplasmic reticulum stress;

GRg1, Ginsenoside Rg1; HCC, Hepatocellular carcinoma; HD, Hedyotis diffusa; HNK, Honokiol; H/R, Hypoxia-reoxygenation; IKK, I κ B kinase; IL-1 β , interleukin-1 β ; IL-1R, Interleukin-1 receptor; IL-6, Interleukin 6; IPF, Idiopathic pulmonary fibrosis; I/R, Ischemia-reperfusion; JNK, c-Jun NH2-terminal kinase; LATS2, large tumor suppressor 2; LPS, Lipopolysaccharide; LncRNA HCP5, Long noncoding RNA HLA complex P5; OB, Oroxin B; MAPK, Mitogen-activated protein kinase; MCAO, Middle cerebral artery occlusion; MCI, mild cognitive impairment; MDSCs, Myeloid-derived suppressor cells; MIMIC, mimetic agent; MIRI, myocardial ischemia-reperfusion injury; miRNAs, MicroRNAs; mTOR, mammalian target of rapamycin; ncRNAs, non-coding RNAs; NF- κ B, Nuclear factor of kappa light polypeptide gene enhancer in B cells; NIK, NF κ B inducing kinase; NSCLC, Non-small cell lung cancer; OS, osteosarcoma; ox-LDL, oxidized low-density lipoprotein; PACT, Protein activator of protein kinase R; PDK1, Phosphoinositide-dependent kinase 1; PFC, prefrontal cortex; PGE2, Prostaglandin E2; PH, pleckstrin homology; PIP3, Phosphatidylinositol-3,4,5-triphosphate; Pol II, RNA polymerase II; Pre-miRNA, Precursor miRNA; PRD, Proline-rich domain; PS, *Prunellae Spica*; PTEN, Phosphatase and tensin homologue; PTC, Papillary thyroid cancer; PZH, Pien Tze Huang; ROS, Reactive oxygen species; RTKs, Receptor tyrosine kinases; SB, *Scutellaria barbata*; SCI, spinal cord injury; SD, Shezhi Huangling decoction; SM, Solamargine; STAT3, Signal Transducer and Activator of Transcription 3; SYD, Shen-Yuan-Dan; TCMS, Traditional Chinese Medicines; THA, 1, 6, 7-trihydroxyxanthone; TLRs, Toll-like receptors; TM, Tunicamycin; TMC, 3', 4', 5', 4''-tetramethoxychalcone; TMP, Tetramethylpyrazine; TNBC, Triple-negative breast cancer; TNF α , Tumor necrosis factor α ; TNFR, Tumor necrosis factor receptor; TRBP, Trans-activation response RNA-binding protein; TWHF, *Tripterygium wilfordii* Hook F.; VmPFC, Ventromedial prefrontal cortex; VS, Vestibular schwannomas; YYS, Xiaoyao San; YQHXG, Yiqi Huoxue granule; ZQD, Zhoushi Qi Ling decoction.

Data Sharing Statement

No data was used for the research described in the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing or financial interests in this work.

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