Research progress on the molecular mechanisms of tanshinone IIA in the treatment of cardiovascular and cerebrovascular diseases (Review)

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Abstract. Cardiovascular and cerebrovascular diseases (CCVDs) have become prominent global health threats, presenting substantial challenges due to their intricate pathological mechanisms and diverse clinical manifestations. Tanshinone IIA (TSA), an active compound derived from the traditional Chinese medicinal herb Salvia miltiorrhiza, exhibits notable therapeutic potential in these diseases due to its multi-faceted mechanism of action. TSA protects the cardiovascular and cerebrovascular systems by inhibiting inflammation, reducing oxidative stress, preventing apoptosis and fibrosis, and modulating key signaling pathways, including toll-like receptor 4/NF-κB, PI3K/AKT and nuclear factor erythroid 2-related factor 2/heme oxygenase-1. Notably, considerable progress has been made in applying TSA to conditions such as atherosclerosis, myocardial infarction, heart failure and hypertension. The present review synthesizes current research on the molecular mechanisms of TSA in treating CCVDs and highlights innovations in nanodelivery systems (for example, rHDL, TPP-TPGS/LPNs and CBSA-PEG-TSA-NPs) that enhance its therapeutic efficacy by improving solubility, prolonging its half-life and enhancing targeting capabilities. These advancements not only establish a foundation for the broader clinical application of TSA in CCVDs but also offer valuable insights for the development of new therapeutic agents.

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Contents

1. Introduction

As public awareness of health issues grows, traditional Chinese medicine (TCM) has gained increasing recognition for its unique role in preventive healthcare and disease treatment. In particular, Chinese herbal formulas have garnered broad market acceptance due to their proven efficacy and relatively low side effects (1,2). Concurrently, active herbal monomers have emerged as a key research focus within TCM, attracting considerable attention from the scientific community (1). Methodological advances have enabled researchers to isolate high-purity herbal monomers from medicinal herbs with greater precision, utilizing advanced separation and purification techniques, thus providing a strong foundation for further exploration (3,4). In the realm of disease treatment, herbal monomers have demonstrated notable therapeutic efficacy (5,6).

Cardiovascular and cerebrovascular diseases (CCVDs) refer to disorders affecting the heart and brain vasculature, including ischemic and hemorrhagic conditions in these areas, as well as in systemic tissues. These conditions are

primarily caused by factors such as hyperlipidemia, blood hyperviscosity, atherosclerosis (AS) and hypertension (7,8), posing a major threat to human health (9,10). Although medications and surgical interventions can alleviate symptoms, they do not support tissue regeneration or functional recovery (9,10). Consequently, the development of novel drugs and therapeutic targets for CCVDs is of key importance (11). The TCM Salvia miltiorrhiza (Danshen), known for its ability to promote blood circulation, resolve stasis, dredge collaterals and relieve pain, is widely used in the treatment of CCVDs (12-15). Modern research has identified >40 lipophilic compounds and 50 hydrophilic active components in Danshen (15-18). The lipophilic components, primarily tanshinones, include tanshinone I, tanshinone IIA (TSA), tanshinone IIB, cryptotanshinone and dihydrotanshinone. The hydrophilic components, such as phenolic acids, include alvianolic acids A, B and C (16-18) (Fig. 1). Among these, TSA is the most abundant and pharmacologically active lipophilic compound in Danshen and has been approved for treating cardiovascular diseases (19). Extensive studies confirm that TSA exhibits anti-inflammatory, antioxidant, antitumor, vasodilatory and neuroprotective effects (20-22). It has demonstrated therapeutic potential in a range of conditions, including myocardial injury, pulmonary injury, non-alcoholic fatty liver disease, hepatic fibrosis, gastritis, glomerulonephritis, diabetes, depression, Alzheimer's disease and cancer (for example, breast, liver and lung cancer) (23-29).

Understanding the molecular targets and mechanisms of action of TCM not only offers scientific explanations for its role in disease prevention and treatment but also aids in the identification of novel therapeutic targets and lead compounds. The present discusses the structure and pharmacological effects of TSA, with a particular emphasis on recent research advancements regarding its molecular mechanisms in the treatment of CCVDs. Additionally, the present review highlights challenges in TSA research and proposes strategies to overcome them. TSA shows considerable therapeutic potential, and the present review aims to provide a comprehensive overview of the current research landscape, offering valuable insights for future studies. Furthermore, it is hoped that the present review will contribute to a deeper understanding of the pathological mechanisms underlying CCVDs and promote the development of precision medicine.

2. Chemical structure of TSA

Tanshinone compounds, a class of diterpenoids (30), include tanshinone I, TSA, tanshinone IIB, cryptotanshinone, dihydrotanshinone and tanshinlactone. TSA features a polycyclic aromatic hydrocarbon skeleton with a phenanthrenequinone group and multiple ring structures, forming the basis of its biological activity (17,30). Its molecular formula is C19H18O3, with a molecular weight of 294.33. TSA appears as orange-red needle-like crystals, soluble in ethanol but poorly soluble in water, exhibiting strong lipophilicity (30). It melts at 209-210˚C and is sensitive to light, darkening upon exposure to heat or light (17,31), requiring storage in airtight, light-protected conditions. Its low water solubility limits its bioavailability (30,31).

3. Pharmacological activities and functions of TSA

TSA demonstrates a wide range of pharmacological effects, including anti-inflammatory, antioxidant, anti-mitochondrial apoptosis, anti-allergic, anti-thrombotic, anti-fibrotic, anti-tumor, immunomodulatory, vasodilatory (modulating the renin-angiotensin system) and neuroprotective activities (28,32-39) (Fig. 2). These mechanisms have been substantiated through various studies.

Anti-inflammatory. Inflammatory responses induced by cytokines and chemokines are implicated in several inflammatory diseases, highlighting the importance of anti-inflammatory therapies (40). In lipopolysaccharide (LPS)-induced RAW264.7 macrophages, TSA markedly inhibited LPS-induced mRNA expression of pro-inflammatory factors such as TNF-α, IL-1β and cyclo-oxygenase (COX)-2 (32). Mechanistically, TSA suppressed inflammatory signaling by downregulating the activation of key proteins [toll-like receptor (TLR) 4, myeloid differentiation primary response 88 (MyD88) and NF-κB] in the TLR4-MyD88-NF-κB pathway (32). A separate study showed that TSA reduced Propionibacterium acnes-induced expression of pro-inflammatory factors (IL-1β, IL-8, and TNF-α) and activation of key proteins [TLR2, NF-κB and intercellular adhesion molecule 1 (ICAM-1)] in the TLR2/NF-κB signaling pathway in THP-1 cells, suggesting that TSA alleviates inflammation by blocking this pathway (41). Additionally, TSA was found to downregulate microRNA-33 expression in THP-1 macrophages, thereby reducing oxidized low-density lipoprotein (ox-LDL)-induced expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α (42).

Anti-oxidative stress. Oxidative stress is a key factor in the development of various pathological conditions, disrupting the redox balance and causing excessive free radical accumulation, which damages cellular structures and macromolecules (43). TSA upregulates both mRNA expression and enzymatic activity of glutathione (GSH) peroxidase (GPx), reducing hydrogen peroxide (H_2O_2)-induced apoptosis in J774 macrophages (33). Furthermore, TSA decreases intracellular reactive oxygen species (ROS) production, inhibiting macrophage uptake of ox-LDL and foam cell formation (44). In transverse aortic constriction (TAC) model rats, TSA markedly reduced malondialdehyde (MDA) levels in myocardial tissue and decreased pro-inflammatory cytokine levels (TNF-α and IL-6), while increasing superoxide dismutase (SOD) activity, ultimately attenuating pressure overload-induced cardiac remodeling (45). In LPS-induced brain injury mouse models, TSA alleviated oxidative stress and inflammatory responses by reducing serum levels of TNF-α and IL-1β, while enhancing SOD activity and decreasing MDA content, thus improving pathological brain damage (46).

Anti-apoptotic effects. Mitochondrial apoptosis, a form of programmed cell death, is a normal process during development and aging, serving to maintain homeostasis within tissue cell populations (47). However, dysregulated mitochondrial apoptosis can accelerate disease progression (47). TSA exerts anti-cardiac remodeling effects by activating the sirtuin

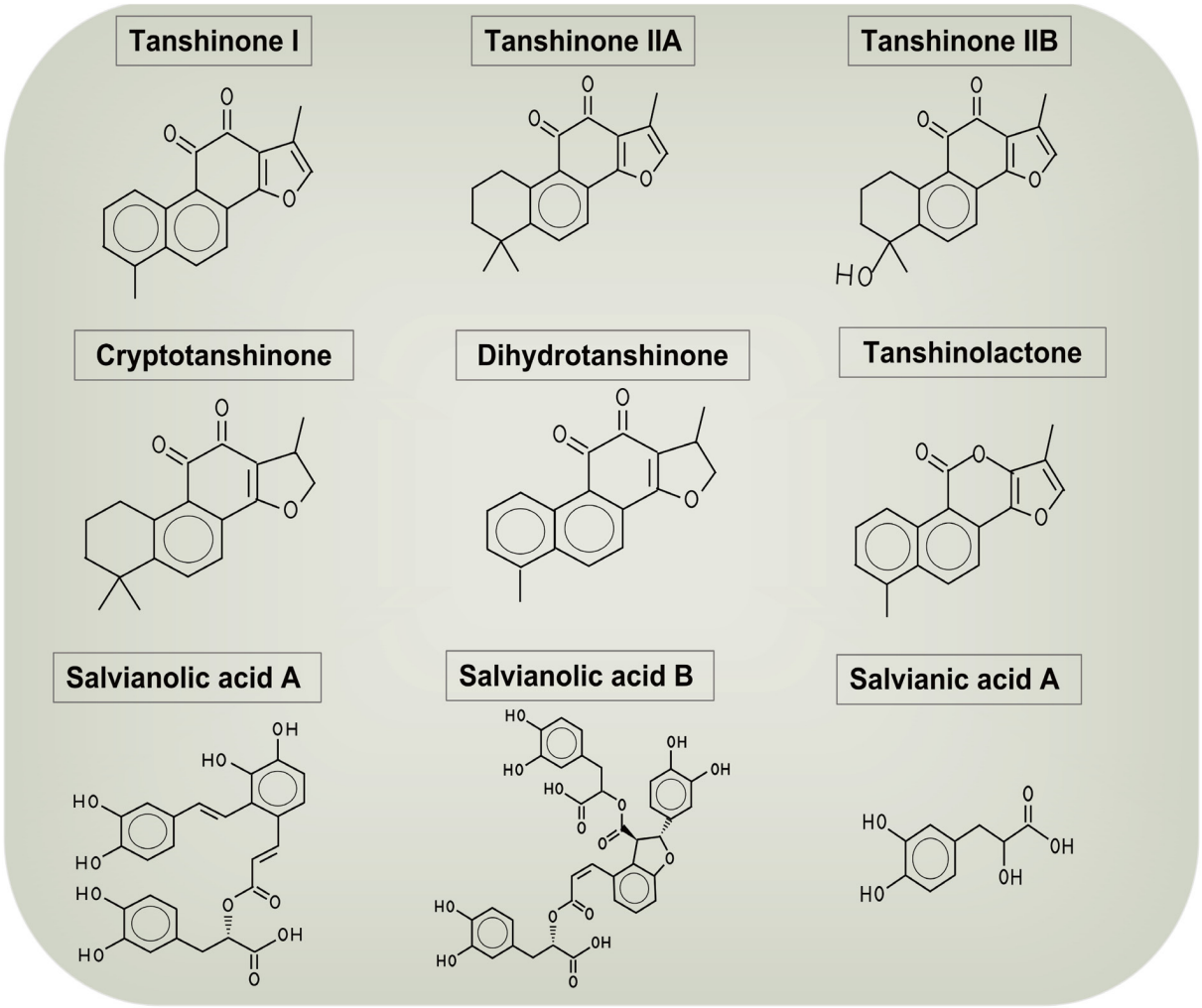

Figure 1. Major active components of Salvia miltiorrhiza. The active components of Salvia miltiorrhiza can be categorized into lipophilic and hydrophilic constituents. The lipophilic components (tanshinones) include Tanshinone I, Tanshinone IIA, Tanshinone IIB, Cryptotanshinone, Dihydrotanshinone and Tanshinolactone. The hydrophilic components (phenolic acids) comprise Salvianolic acid A, Salvianolic acid B and Salvianic acid A.

(SIRT) 1 signaling pathway, which upregulates the anti-apoptotic protein Bcl-2 while downregulating pro-apoptotic proteins Bax and Caspase-3 (45). TSA markedly reduces angiotensin II (AngII)-induced apoptosis in H9C2 rat cardiomyocytes by inducing microRNA-152-3p expression, which in turn downregulates PTEN and suppresses cardiomyocyte apoptosis (48). Another study demonstrated that TSA mitigates H_2O_2 and doxorubicin (DOX)-induced apoptosis in H9C2 cardiomyocytes by upregulating microRNA (miR)-133, leading to the inhibition of Caspase-9 (49). TSA has also been shown to activate the MAPK ERK1/2 pathway, which upregulates miR-133 expression, thereby protecting neonatal rat cardiomyocytes from apoptosis under hypoxic conditions (50). Moreover, TSA inhibits oxidative stress-induced cardiomyocyte apoptosis by binding to Kelch-like ECH-associated protein 1 (Keap1) and promoting its degradation, which enhances nuclear factor erythroid 2-related factor 2 (Nrf2) gene transcription and stimulates Nrf2-driven antioxidant gene expression. Additionally, TSA ameliorates H_2O_2-induced Caspase-3/9 activation and mitochondrial dysfunction by inhibiting the p38 and mTOR signaling pathways, ultimately reducing oxidative stress-induced cardiomyocyte apoptosis (51).

Anti-allergy effects. In allergic and inflammatory diseases, mast cells play a pivotal role by releasing histamine, leukotrienes, prostaglandins and various cytokines, which interact synergistically to exacerbate allergic and inflammatory symptoms (52). TSA can suppress FcεRI-mediated mast cell signaling and allergic responses through activation of Sirt1/LKB1/AMPK pathway (34). The anti-allergic properties of TSA hold considerable clinical potential, particularly in allergic rhinitis and allergic asthma, where mast cell activation in the nasal mucosa and airway inflammation leading to bronchospasm are key pathological factors (53-57). TSA may alleviate symptoms such as sneezing, rhinorrhea, nasal congestion and itching by inhibiting mast cell degranulation and reducing the release of mediators such as histamine and leukotrienes, thus serving as a potential novel intranasal spray or oral therapeutic agent (53,57). Alternatively, through its anti-allergic and anti-inflammatory properties, it may help control chronic airway inflammation in asthma and reduce acute exacerbations, acting as a complementary or alternative therapy to existing inhaled corticosteroids or leukotriene receptor antagonists (55). However, further research is still required to explore this potential.

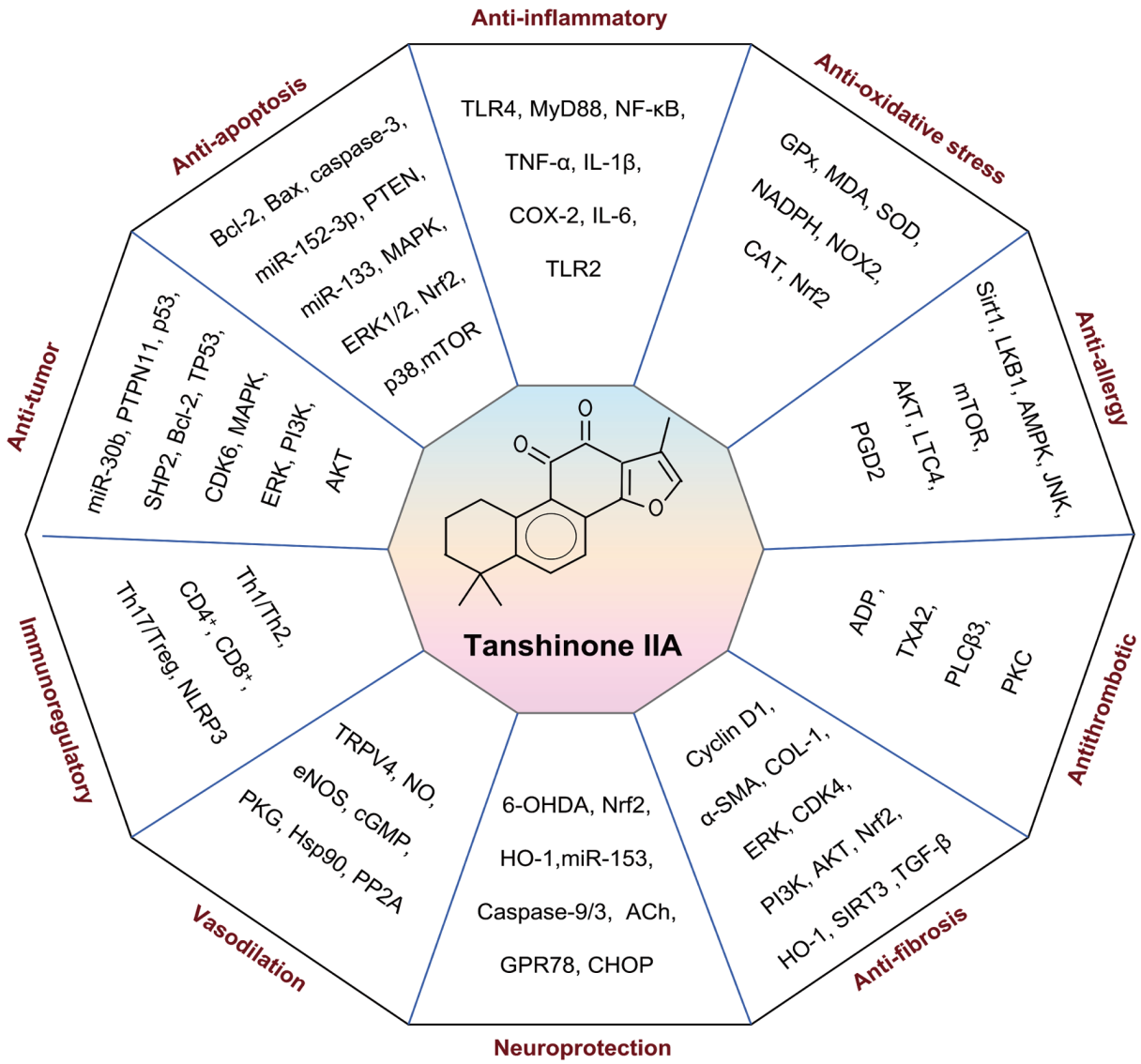

Figure 2. Pharmacological activities and functions of Tanshinone IIA. Tanshinone IIA exerts multiple pharmacological effects through modulation of various molecular pathways, including anti-inflammatory, antioxidant, anti-mitochondrial apoptosis, antiallergic, antithrombotic, antifibrotic, antitumor, immunomodulatory, vasodilatory (via regulation of the RAS system) and neuroprotective activities. ACh, acetylcholine; ADP, adenosine diphosphate; AKT, protein kinase B; α-SMA, alpha-smooth muscle actin; AMPK, AMP activated protein kinase; CAT, catalase; CHOP, CCAAT-enhancer-binding protein homologous protein (C/EBP homologous protein); CDK4, cyclin, dependent kinase 4; cGMP, cyclic guanosine monophosphate; COX2, cyclooxygenase2; COL-1, collagen type 1; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; Gpx, glutathione peroxidase; JNK, c-Jun N-terminal kinase; GPR78, glucose-regulated protein 78; HO-1, heme oxygenase 1; Hsp90, heat shock protein 90; IL-6, interleukin-6; LKB1, liver kinase B1; LTC4, leukotriene C4; MDA, malondialdehyde; MyD88, myeloid differentiation primary response gene 88; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain-containing 3; NOX2, NADPH oxidase 2; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol 3 kinase; PGD2, prostaglandin D2; PKC, protein kinase C; PKG, protein kinase G; PLCβ3, phosphorylation of phospholipase cβ3; PP2A, protein phosphatase 2A; PTEN, phosphatase and tensin homolog; PTPN, protein tyrosine phosphatase non-receptor type; SHP, Src homology 2 domain-containing protein tyrosine phosphatase; SIRT1, sirtuin 1; SOD, superoxide dismutase; TP53, tumor protein 53; TGF-β, transforming growth factor-β; TLR4, toll like receptor 4; TNF-α, tumor necrosis factor-alpha; TRPV4, transient receptor potential vanilloid 4; TXA2, thromboxane A2; 6-OHDA,6-hydroxydopamine.

Anti-thrombotic effects. Thrombi present considerable risks to cardiovascular and cerebrovascular health by causing vascular occlusion, thereby disrupting blood flow to important organs such as the heart and brain, which can lead to conditions such as myocardial infarction and cerebral infarction (58). TSA has been shown to inhibit ADP (3 μM)-induced reversible platelet aggregation in rats. Mechanistic studies indicate that TSA suppresses platelet activation by modulating tubulin acetylation and inhibiting ERK-2 phosphorylation (35). However, *in vivo* experiments reveal that TSA (10 mg/kg) notably prolongs murine bleeding time by 58% compared with controls (35). In a permanent middle cerebral artery occlusion rat model, TSA exhibited antiplatelet effects by inhibiting platelet aggregation, reducing thromboxane A2 release and down-regulating phosphorylation of phospholipase Cβ3 and protein kinase C (PKC), thereby blocking the PLC/PKC signaling pathway (59). These results suggest that TSA holds potential as a therapeutic agent for improving blood viscosity, microcirculation and preventing CCVDs (59).

Anti-fibrosis effects. TSA also demonstrates antifibrotic properties by reducing collagen deposition (60). Studies have shown that TSA downregulates extracellular matrix (ECM) gene transcription and collagen expression in dermal fibroblasts by inhibiting the TGF-β/Smad and MAPK/ERK signaling pathways, contributing to its antifibrotic effects (60,61). One study indicated that TSA markedly reduced serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and γ-GT in carbon tetrachloride (CCl_4)-induced hepatic fibrosis mice, diminished collagen deposition and downregulated the expression of fibrosis markers such as α-smooth muscle acting (α-SMA) and type I collagen, alleviating hepatic fibrosis (62). Mechanistic analysis revealed that TSA inhibited ERK phosphorylation, reduced cyclin D1 and CDK4 expression, and blocked the formation of cyclin D1-CDK4 complexes, thereby decreasing Smad3 linker region phosphorylation and inhibiting hepatic stellate cell (HSC) proliferation, resulting in cell cycle arrest at the G_1 phase (62). Another study demonstrated that TSA hindered HSC activation by inhibiting KRAS protein and modulating the PI3K/AKT and Nrf2/heme oxygenase-1 (HO-1) pathways, reducing collagen deposition and reversing the progression of CCl_4-induced hepatic fibrosis in mice (63). Additionally, TSA upregulated SIRT3 expression to inhibit TGF-β1 activation and its downstream target TSP-1, thereby decreasing collagen deposition, downregulating the fibrosis marker fibronectin and improving DOX-induced renal fibrosis in mice (36).

Anti-tumor effects. TSA exerts antitumor effects by inhibiting cancer cell proliferation, inducing apoptosis, arresting cell cycle progression and suppressing invasion and migration (64-66). Specifically, TSA suppresses HepG2 cell proliferation by modulating the miR-30b-p53-PTPN11/SHP2 pathway (64). TSA also induces apoptosis in triple-negative breast cancer by downregulating Bcl-2 and upregulating TP53 expression (65). Furthermore, TSA inhibits tumor cell proliferation, migration and invasion through regulation of the MAPK/ERK/TRIB3 and PI3K/AKT signaling pathways (28,66). These findings highlight the antitumor potential of TSA.

Immunomodulation. A study using cecal ligation and puncture (CLP)-induced septic mice models explored the immunomodulatory effects of TSA on sepsis-induced immunosuppression (67). TSA at different doses (5, 15 and 45 mg/kg, i.p.) were used at different time-points (0, 3, 6 and 12 h) after treatment with CLP to evaluate its effect on the survival of septic mice. Results demonstrated that TSA markedly improved survival rates in a dose- and time-dependent manner (67). Immunologically, TSA reversed CLP-induced reductions in splenic $CD4^+$ and $CD8^+$ T lymphocyte counts, mitigated their apoptosis and suppressed regulatory T cell (Treg) expansion. It also restored T-helper (Th) 1/Th2 cytokine secretion by increasing IFN-γ and IL-2 levels, while decreasing IL-4 and IL-10 levels (67). Additionally, TSA improved T cell function by reducing serum levels of high-mobility group box 1 (HMGB1), enhancing macrophage phagocytic activity and promoting bacterial clearance (67). Furthermore, TSA alleviated coxsackievirus B3-induced myocardial inflammation by inhibiting pro-inflammatory Th1 cytokines (IFN-γ and IL-2) and promoting anti-inflammatory Th2 cytokines (IL-4 and IL-10), thereby modulating the Th1/Th2 immune balance (37). Another *in vitro* study showed that TSA enhanced IL-15-driven NK cell differentiation through activation of the p38 MAPK phosphorylation pathway (68). Another study demonstrated that TSA exerted anti-inflammatory and cardioprotective effects by inhibiting NLRP3 inflammasome activation and its downstream effectors (Caspase-1, IL-1β and IL-18), while modulating Th17/Treg cell balance (69). Collectively, these findings indicate that TSA improves immune status by regulating immune cell activity and function, thereby enhancing both anti-infective and antitumor responses.

Promotion of vasodilation. Endothelial function is vital for maintaining cardiovascular and cerebrovascular health, with nitric oxide (NO) released by vascular endothelium playing a key role in promoting vasodilation (70). TSA markedly enhances NO production in vascular endothelial cells (ECs) (71). Research by Wang *et al* (38) revealed that TSA enhances transient receptor potential vanilloid 4 (TRPV4) channel currents by reducing TRPV4 protein degradation and increasing its expression, thereby promoting endothelial NO synthase (eNOS) expression and NO production. NO activates soluble guanylate cyclase, elevating cGMP and protein kinase G (PKG) levels, which ultimately leads to vascular smooth muscle relaxation (38). These findings highlight the key role of the TRPV4-NO-PKG signaling pathway in TSA-induced vasodilation. A study examining the protective effects of TSA on diabetes-induced endothelial dysfunction revealed that high glucose environments reduce eNOS expression and NO production, impairing vasodilation (72). TSA ameliorates these abnormalities through multiple post-transcriptional mechanisms: i) Prolonging eNOS mRNA half-life; ii) inhibiting eNOS protein degradation and enhancing its stability; iii) reducing eNOS uncoupling by increasing tetrahydrobiopterin concentration and Hsp90/eNOS interaction; and iv) inhibiting the translocation of protein phosphatase 2A (PP2A) subunit PP2A-A, blocking PP2A-A/eNOS interaction and preventing eNOS dephosphorylation at serine 1177 (72). This research demonstrates that TSA enhances the eNOS/NO pathway through multiple mechanisms, providing novel strategies for treating diabetic cardiovascular complications.

Neuroprotection. A previous study investigated the protective effects of TSA on dopaminergic neurons in a 6-hydroxydopamine (6-OHDA)-induced Parkinson's disease model (73). *In vitro* experiments demonstrated that TSA considerably reduced 6-OHDA-induced LDH release and ROS generation in SH-SY5Y cells, promoted nuclear translocation of Nrf2 and enhanced the expression of antioxidant response element (ARE)-regulated genes (for example, HO-1 and glutamate-cysteine ligase catalytic subunit/glutamate-cysteine ligase modifier subunit), while inhibiting mitochondrial membrane potential damage, cytochrome *c* (cyt *c*) release and activation of Caspase-9/3 (73). *In vivo* experiments showed that TSA improved rotational behavior in 6-OHDA-treated rats, reduced dopaminergic neuron loss in the substantia nigrostriatal pathway and increased striatal dopamine and its metabolites. The specific molecular mechanism involved TSA maintaining Nrf2/ARE pathway activity by inhibiting

Table I. Comparison of pharmacological properties of tanshinone I, salvianolic acid A, tanshinone IIB and tanshinone IIA.

Component	Chemical type	Relative content	Isolation and purification	Common properties	Core advantages	Applicable scenarios	(Refs.)
Tanshinone I	Liposoluble diterpenoid quinone	Medium	Moderate	Anti-inflammatory and anti-oxidant, improves microcirculation, inhibits thrombosis, synergistically protects cardiovascular and cerebrovascular systems	Anti-bacterial-and anti inflammatory, immunomodulatory, anti-tumor (gastric cancer, liver cancer)	Cardiovascular diseases with infection risk, adjuvant tumor therapy	(76,77, 79-83)
Salvianolic acid A	Water-soluble phenolic acid	Very low	Difficult		Anti-oxidant, inhibits thrombosis, protects organs (heart, brain, liver, kidney)	Hyperlipidemia, fibrosis, tumor prevention	(78-90)
Tanshinone IIB	Liposoluble diterpenoid quinone	Very low	Difficult		Regulates blood lipids, neuroprotective, cardioprotective	Hyperlipidemia, stroke	(13,91-93)
Tanshinone IIA	Liposoluble diterpenoid quinone	Very high	Easy		Dilates coronary arteries, anti-myocardial ischemia, inhibits thrombosis	Coronary heart disease angina pectoris, recovery phase of cerebral infarction, heart failure	(21,24,75, 78,94-96)

6-OHDA-induced upregulation of miR-153, which targets the 3'-untranslated region of Nrf2, thereby exerting neuroprotective effects (73). Another study demonstrated that TSA protected against hippocampal-dependent cognitive impairment in diabetic rats by attenuating endoplasmic reticulum stress-induced apoptosis (74). TSA alleviated oxidative stress by enhancing SOD activity and reducing ROS and MDA levels, while inhibiting endoplasmic reticulum stress markers GRP78 and CHOP and reducing hippocampal neuronal apoptosis (Caspase-3) (74). Additionally, TSA-pretreated mesenchymal stem cells (TSA-MSCs) notably improved spatial learning and memory deficits in Alzheimer's disease rats modeled by unilateral intrahippocampal injection of β-amyloid (25-35) peptide, showing superior efficacy when compared with untreated MSCs (39). This effect was achieved by downregulating pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) and upregulating neurotransmitter the acetylcholine (ACh) levels, thereby reducing hippocampal neuronal damage (39). These findings collectively indicate the potent neuroprotective effects of TSA, highlighting its ability to protect neuronal cells from injury.

Comparative pharmacological characteristics of major tanshinones. Tanshinone I, salvianolic acid A, TSA and tanshinone IIB are the core components of Salvia miltiorrhiza, collectively contributing to its cardiocerebrovascular protective effects through synergistic actions (Table I) (13,21,24,75-96). All four components possess anti-inflammatory and antioxidant properties, improve microcirculation and inhibit thrombosis, thereby synergistically protecting the cardiovascular and cerebrovascular systems (13,75-78). However, they differ in their specific pharmacological profiles and clinical applications.

Tanshinone I has a moderate content and is relatively easy to isolate and purify. It has been shown to inhibit pathogens such as Staphylococcus aureus and Streptococcus hemolyticus (79,80) and enhance immune function, aiding in anti-infection (81). It also demonstrates inhibitory effects on tumor cells, including those of gastric and liver types of cancer (82,83). Thus, it is more suitable for cardiovascular diseases with infection risks and as an adjunct in tumor therapy. Salvianolic acid A, although hydrophilic, has low content and is prone to oxidative degradation, limiting its application (78,84). It scavenges free radicals, inhibits inflammatory mediators such as TNF-α and IL-6, and suppresses platelet aggregation, reducing blood viscosity (85-87). It also protects myocardial cells and liver and kidney functions (88-90). Therefore, it is suitable for hyperlipidemia, fibrosis and tumor prevention. Tanshinone IIB is present in very low quantities in Salvia miltiorrhiza, and its isolation and purification are difficult and expensive, limiting large-scale research (13). Existing studies indicate

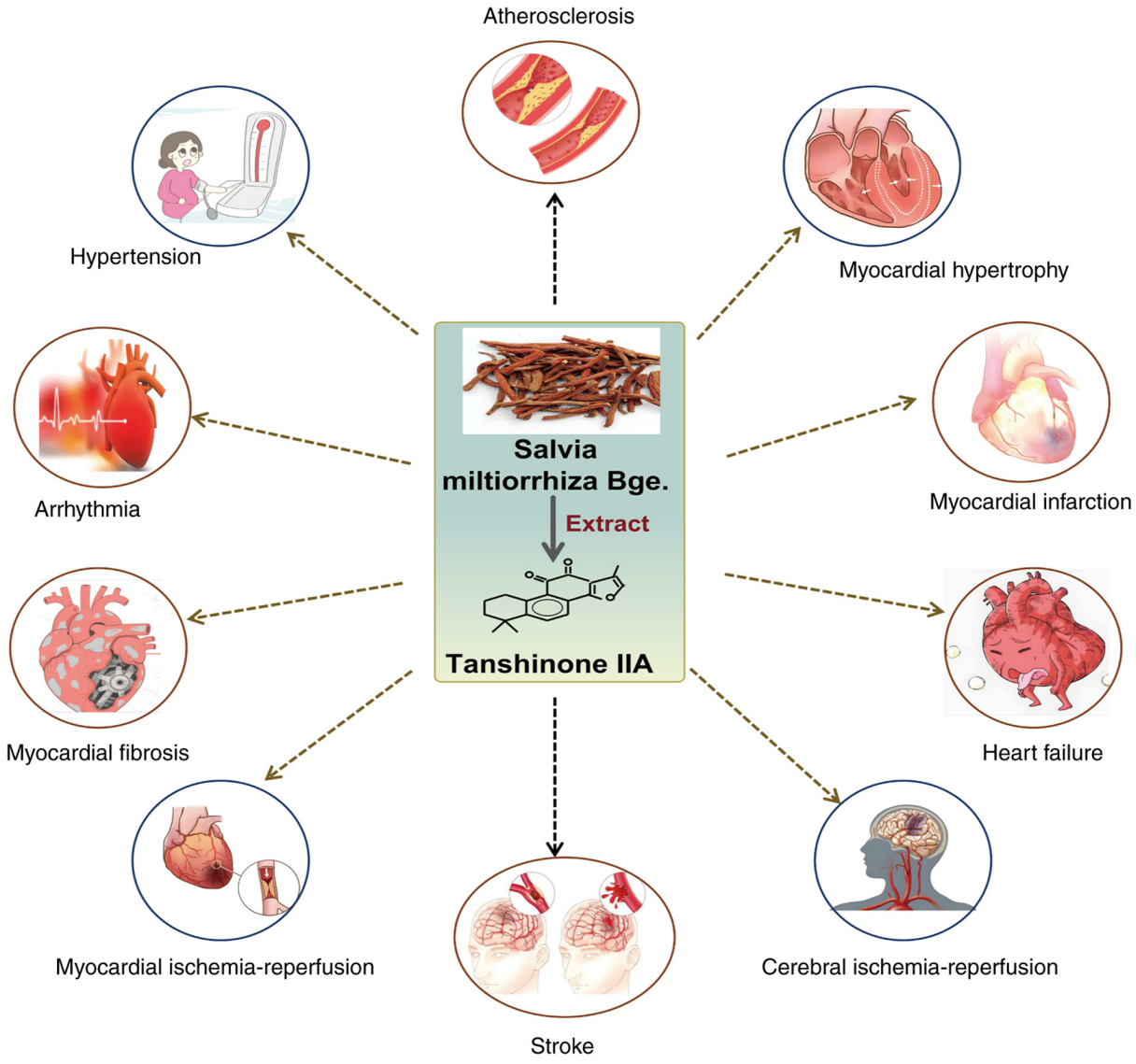

Figure 3. Role of Tanshinone IIA in the development of cardiovascular and cerebrovascular diseases. Tanshinone IIA demonstrates therapeutic efficacy against a wide range of cardiovascular and cerebrovascular diseases, including atherosclerosis, cardiac hypertrophy, myocardial infarction, myocardial ischemia-reperfusion injury, cerebral ischemia-reperfusion injury, heart failure, hypertension, cardiac fibrosis, arrhythmia and stroke.

that tanshinone IIB has antioxidant, lipid-regulating, neuroprotective and cardioprotective effects (91-93). Therefore, it is suitable for the treatment of hyperlipidemia and stroke. TSA, with a high content, is the most abundant lipophilic component in Salvia miltiorrhiza, making it easy to extract (78). It dilates coronary arteries, increases myocardial blood flow and reduces blood viscosity (21,24,94). It also scavenges oxygen free radicals, alleviates ischemia-reperfusion injury and reduces myocardial infarction area (95,96). Therefore, it is more suitable for the treatment of coronary heart disease, angina, the recovery period of cerebral infarction and HF. In summary, TSA offers unique advantages in the treatment of CCVDs and is the preferred component for further development.

4. The molecular mechanisms of TSA in the progression of CCVDs

TSA exhibits various pharmacological effects, including anti-inflammatory, antioxidant, antitumor, vasodilatory and neuroprotective properties. It carries out a therapeutic role in multiple CCVDs, such as AS, cardiac hypertrophy, myocardial infarction, myocardial ischemia-reperfusion, cerebral ischemia-reperfusion, HF, hypertension, myocardial fibrosis, arrhythmia and stroke (Fig. 3 and Table II) (42,46,48,49,69, 97-144).

AS. AS is a disease characterized by lipid accumulation and inflammation, serving as a notable risk factor for CCVDs (145). AS is a chronic immune-inflammatory condition driven by pro-inflammatory molecules that act on various cell types, including ECs, vascular smooth muscle cells (VSMCs) and monocytes/macrophages (145). TSA, a bioactive compound with multifaceted properties, effectively inhibits the progression of AS through mechanisms such as suppressing adipogenesis, exerting anti-inflammatory and antioxidant effects (97,98,146), and inhibiting autophagy, demonstrating notable therapeutic potential in cardiovascular disease management (Fig. 4).

Table II. TSA is involved in alleviating the development of CCVDs.

Disease	Mechanism	(Refs.)
Atherosclerosis	TSA decreases miR-33 expression, resulting in reduced ox-LDL levels. This leads to decreased expression of IL-1β, IL-6 and TNF-α, thereby reducing inflammatory responses.	(42)
	TSA downregulates ApoB, which leads to upregulation of SREBP-1. This, in turn, results in downregulation of MTP, ultimately causing a decrease in TG levels.	(97)
	TSA inhibits phosphorylation of ERK1/2, JNK, p38 and NF-κB signaling pathways. This suppression reduces expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, ultimately attenuating inflammatory responses.	(98)
	TSA activates PI3K signaling, leading to increased eNOS expression and enhanced NO production. Elevated NO levels induce ATF3 expression, which subsequently downregulates ET-1 expression.	(99)
	TSA downregulates METTL3 expression, leading to decreased SIRT5 levels. This subsequently reduces PERK, CHOP and ATF5 expression, ultimately attenuating ERS responses.	(100)
	TSA suppresses NF-κB activation, resulting in upregulation of LOX-1 receptor expression. Increased LOX-1 facilitates reduced ox-LDL uptake, thereby decreasing foam cell formation.	(101)
	TSA reduces miR-375 expression, leading to upregulation of KLF4 transcription factor. Increased KLF4 promotes STAT6 activation and M2 polarization of macrophages, while simultaneously suppressing NF-κB signaling. This results in decreased expression of IL-6, TNF-α and reduced inflammatory responses.	(102)
	TSA increases miR-13b expression, which downregulates WNT5A signaling. Reduced WNT5A activity leads to decreased ox-LDL levels and subsequent downregulation of IL-1β, IL-6 and TNF-α expression, ultimately attenuating inflammatory responses.	(103)
	TSA reduces NADPH, NOX2, MDA, IL-6, TNF-α and MCP-1 expression while increasing SOD activity, resulting in decreased ROS production.	(104)
	TSA decreases TG, TC and LDL levels while increasing HDL expression, leading to overall lipid homeostasis improvement.	(105)
	TSA reduces ox-LDL and MDA levels while increasing Cu/Zn SOD expression, resulting in decreased reactive oxygen species production.	(106)
Hypertension	TSA decreases Caspase-3 expression while increasing Bcl-2/Bax ratio, resulting in reduced apoptosis.	(108)
	TSA reduces MMP2 and TIMP2 expression, leading to decreased fibrosis progression.	(108,109)
	TSA reduces NADPH levels, which subsequently downregulates NOX2, NOX4 and p47phox expression. This leads to decreased MDA levels and increased SOD activity, ultimately reducing ROS production.	(110)
	TSA downregulates PDK1 expression, resulting in decreased AKT signaling. This subsequently inhibits smooth muscle cell proliferation.	(111)
Myocardial hypertrophy	TSA reduces Cys-C levels, leading to decreased Wnt signaling activation. This suppression reduces β-catenin and WISP-1 expression levels.	(107)
	TSA activates PI3K signaling, leading to increased AKT phosphorylation. Enhanced AKT activity inhibits calcineurin activity, which subsequently reduces NFATc3 nuclear translocation. This results in decreased expression of ANP, BNP and β-MHC.	(112)
	TSA downregulates ALKBH5 expression, resulting in decreased galectin expression. This subsequently reduces ANP, BNP and β-MHC levels.	(113)
Myocardial infarction	TSA inhibits p38MAPK signaling, leading to decreased SRF and MEF2 expression. This results in reduced miR-1 levels and increased Cx43 expression, ultimately protecting against myocardial injury.	(114)
	TSA reduces TNF-α levels, which suppresses NF-κB activation and subsequently decreases MCP-1 expression, leading to reduced inflammatory responses.	(115)
	TSA increases PGK1 expression, resulting in decreased PDHK1 levels. This promotes M1 to M2 macrophage conversion and subsequently reduces IL-1β, IL-6 and TNF-α expression, attenuating inflammation.	(116)
	TSA downregulates TGF-β signaling, leading to decreased Smad3 activation. This results in increased miR-29b expression and subsequent downregulation of TGF-β1, Col1α1 and α-SMA, ultimately reducing fibrosis.	(117)

Table II. Continued.

Disease	Mechanism	(Refs.)
	TSA inhibits TLR4 expression, which suppresses NF-κB activation and subsequently reduces NLRP3 inflammasome formation. This leads to decreased IL-1β and IL-18 expression, attenuating inflammatory responses.	(118)
	TSA reduces NOX4, NADPH and MDA levels while increasing SOD activity, resulting in decreased ROS production.	(119)
Myocardial ischemia-reperfusion	TSA reduces NLRP3 inflammasome formation, leading to decreased Caspase-1, IL-1β and IL-18 expression. This results in increased Th17/Treg ratio and reduced inflammatory responses.	(69)
	TSA activates PI3K signaling, leading to increased AKT phosphorylation. Enhanced AKT activity suppresses NF-κB activation and subsequently reduces IL-6 and TNF-α expression, attenuating inflammatory responses.	(120)
	TSA activates PI3K signaling, resulting in increased AKT phosphorylation and mTOR activation. This leads to decreased MDA, SDH and COX expression while increasing Bax and Bcl-2 levels, ultimately reducing oxidation and apoptosis.	(121)
	TSA decreases LDH levels while increasing 14-3-3η expression. This promotes Bcl-2 upregulation and mPTP inhibition, subsequently reducing ROS and cytochrome c levels and decreasing Caspase-3 expression, thereby suppressing apoptosis.	(122)
	TSA downregulates HSA2 expression, resulting in decreased FGF9 levels. This leads to reduced Bax and Caspase-3 expression, ultimately suppressing apoptosis.	(123)
	TSA increases HDAC1 expression, leading to Nrf2 activation and HO-1 upregulation. This results in decreased Bax/Bcl-2 ratio and reduced TNF-α and IL-1β expression, while decreasing MDA, Fe^{2+} and increasing GSH and Gpx4 levels, ultimately attenuating apoptosis, inflammation and ferroptosis.	(124)
	TSA increases ATM expression, leading to GADD45 upregulation and ORC activation. This enhances DNA damage repair and DNA biosynthesis processes.	(125)
	TSA-MSCexo increases miR-223-5p expression, which downregulates CCR2 and subsequently reduces inflammatory responses.	(126)
	TSA combined with Astragaloside IV suppresses STING pathway activation, leading to decreased Bax, Caspase-3 and increased Bcl-2 expression, ultimately reducing apoptosis.	(127)
	TSA combined with Astragaloside IV inhibits STING pathway signaling, resulting in decreased IL-1β, IL-6, TNF-α and iNOS expression, thereby attenuating inflammatory responses.	(127)
	TSA combined with Astragaloside IV suppresses STING pathway activation, leading to decreased MDA levels and increased GSH and SOD expression, ultimately reducing reactive oxygen species production.	(127)
Heart failure	TSA increases miR-152-3p expression, resulting in decreased PTEN levels and reduced apoptosis.	(48)
	TSA increases miR-133 expression, leading to decreased Caspase-3 and Caspase-9 expression, ultimately reducing apoptosis.	(49)
	TSA activates PI3K signaling, leading to increased AKT phosphorylation. Enhanced AKT activity results in decreased Caspase-3 expression and increased Bcl-2 levels, ultimately reducing apoptosis.	(128)
	TSA increases DAXX, MEK and ERK1/2 expression while upregulating p38, Caspase-3 and Caspase-8 expression. This leads to decreased apoptosis through multiple pathways.	(129)
	TSA activates AMPK signaling, resulting in decreased mTOR activity. This leads to increased LC3, Beclin1 and Bcl-2/Bax ratio while decreasing p62, Caspase-3 and Caspase-9 expression, ultimately reducing both autophagy and apoptosis.	(130)
Myocardial fibrosis	TSA upregulates GPER expression, leading to decreased COL-1 and increased MMP-1 expression. This results in reduced fibrosis progression.	(131)
	TSA increases GPER expression, which activates PKA signaling and subsequently upregulates CREB expression. Enhanced CREB activity promotes elastin expression while reducing MMP2/9 levels, ultimately attenuating fibrosis.	(131)
	TSA increases miR-618 expression, resulting in decreased α-SMA, Col-1 and TIMP1/4 levels. This leads to reduced fibrosis progression.	(132)
	TSA reduces NADPH levels, which subsequently downregulates Colα1, MMP2/9, TIMP1/2, NOX2 and p67phox expression. This results in decreased fibrosis and ROS production.	(133)

Table II. Continued.

Disease	Mechanism	(Refs.)
Arrhythmia	TSA reduces SRF expression, leading to decreased miR-1 levels. This subsequently downregulates Kir2.1 expression and reduces IK1 current, ultimately affecting cardiac repolarization.	(134)
Cerebral ischemia-reperfusion	TSA upregulates Nrf2 expression, leading to increased HO-1 levels. This results in upregulation of Claudin-5 and ZO-1 expression, ultimately reducing inflammation and ROS production.	(46)
	TSA reduces HMGB1 expression, which suppresses NF-κB activation and subsequently decreases inflammatory and apoptotic responses.	(135)
	TSA increases miR-124-5p expression, resulting in decreased FoxO1 levels. This leads to reduced IL-1β, IL-6 and TNF-α expression, along with decreased Bax and Caspase-3 while increasing Bcl-2 expression, ultimately attenuating inflammation and apoptosis.	(136)
	TSA downregulates TLR4 expression, resulting in decreased MyD88 levels and subsequent NF-κB suppression, ultimately reducing inflammatory responses.	(137)
	TSA reduces TGM2 expression, leading to decreased PANX1 levels and subsequently attenuating inflammatory responses.	(138)
	TSA increases miR-449a expression, leading to decreased ACSL4 levels and reduced ferroptosis.	(139)
Stroke	TSA increases Bcl-2/Bax ratio, leading to reduced apoptosis.	(140)
	TSA upregulates Nrf2 expression, resulting in increased SOD and CAT levels while decreasing MDA and 8-OHdG expression, ultimately reducing ROS production.	(141)
	TSA activates TORC1 signaling, leading to increased pCREB expression and subsequently upregulating BDNF levels, which enhances neuroprotection.	(142)
	TSA combined with Puerarin increases Nrf2 expression, activating ARE signaling and upregulating HO-1 and NQO1 while decreasing Keap1 levels. This results in increased T-AOC, CAT, SOD and GSH levels while reducing GSSG and MDA, ultimately decreasing ROS.	(143)
	TSA combined with Puerarin upregulates Nrf2 expression, activating ARE signaling and increasing HO-1 and NQO1 while decreasing Keap1 levels. This leads to reduced IL-6, TNF-α, ICAM-1 and COX-2 expression, attenuating inflammatory responses.	(143)
	TSA inhibits NF-κB activation, resulting in decreased NLRP3 inflammasome formation and subsequently reducing IL-1β and IL-18 expression, ultimately attenuating inflammatory responses.	(144)

ACSL4, acyl-CoA synthetase long-chain family member 4; AKT, protein kinase B; AMPK, AMP activated protein kinase; Ang-II, angiotensin II; ANP, atrial natriuretic peptide; APOB, apolipoprotein B; ATF3, activating transcription factor 3; ATF5, activating transcription factor 5; ATM, ataxia telangiectasia mutated; BDNF, brain derived neurotrophic factor; BNP, brain natriuretic peptide; βMHC, β myosin heavy chain; CAT, catalase; CCR2, C-C chemokine receptor type 2; CCVDs, cardiovascular and cerebrovascular diseases; CDK4, cyclin dependent kinase 4; CDK6, cyclin dependent kinase 6; CHOP, CCAAT/enhancer-binding protein homologous protein; COX2, cyclooxygenase2; CREB, CAMP response element binding protein; Cx43, connexin 43; Cys-C, cystatin c; eNOS, endothelial nitric oxide synthase; ET-1, endothelin 1; FGF9, fibroblast growth factor 9; GADD45, growth arrest and DNA damage-inducible 45; GPER, G-protein coupled estrogen receptor; Gpx4, glutathione peroxidase 4; HAS2, hyaluronan synthase 2; HDAC1, histone deacetylase 1; HO-1, heme oxygenase 1; ICAM1, intercellular adhesion molecule 1; Keap1, Kelch-like ECH-associated protein 1; LDH, lactate dehydrogenase; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; METTL3, methyltransferase like 3; MMP2, matrix metalloproteinase 2; mPTP, mitochondrial permeability transition pore; MyD88, myeloid differentiation primary response 88; NO, nitric oxide; Nox4, NADPH oxidase 4; NPC, nutritional preconditioning; NQO1, NADPH oxidoreductase 1; ox-LDL, oxidized low-density lipoprotein; ORC, origin recognition complex; PANX1, pannexin 1; PDHK1, pyruvate dehydrogenase kinase 1; PERK, PKR-like endoplasmic reticulum kinase; PI3K, phosphatidylinositol 3 kinase; PKC, protein kinase C; PKG, protein kinase G; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SIRT1, sirtuin 1; SIRT5, sirtuin 5; SOD, superoxide dismutase; TAC, transverse aortic constriction; TAOC, total antioxidant capacity; TGF-β1, transforming growth factor-β1; TGM3, transglutaminase 3; TIMP2, tissue inhibitor of metalloproteinases 2; TLR2, toll like receptor 2; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; TSA, tanshinone IIA; VDAC-1, voltage-dependent anion channel 1; Wnt2, Wnt family member 2.

TSA dose-dependently inhibits the secretion of ApoB and triglycerides (TGs) in HepG2 cells by downregulating the transcriptional levels of microsomal triglyceride transfer protein (MTP), thereby suppressing lipoprotein assembly and reducing ApoB secretion (97). Additionally, TSA enhances ApoB degradation via the ubiquitin-proteasome pathway and promotes nuclear translocation of the transcription factor sterol regulatory element-binding protein 1, further inhibiting MTP expression (97). In a study utilizing a low density lipoprotein receptor knockout mouse model induced by a high-fat diet and LPS-stimulated RAW264.7 macrophages, TSA alleviated AS by markedly reducing atherosclerotic plaque area, lowering serum and hepatic lipid levels (TCs and TGs), improving liver function (AST and ALT) and decreasing serum and tissue levels of inflammatory cytokines (IL-1β, IL-6 and TNF-α) (98). Furthermore, TSA inhibited the phosphorylation

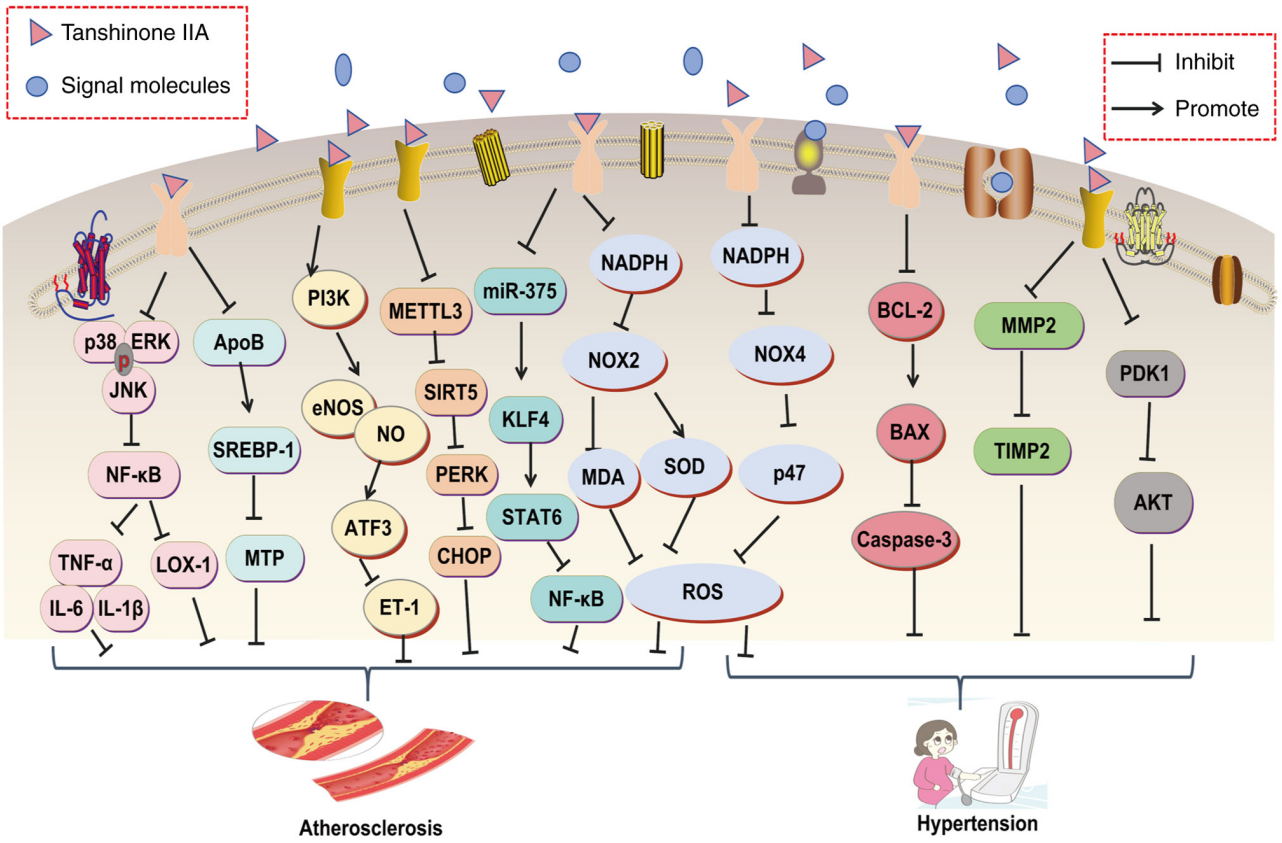

Figure 4. Molecular mechanisms of Tanshinone IIA in the treatment of atherosclerosis and hypertension. AKT, protein kinase B; APOB, apolipoprotein B; ATF3, activating transcription factor 3; eNOS, endothelial nitric oxide synthase; ET-1, endothelin 1; KLF4, Krüppel-like Factor 4; LOX-1, lectin-like oxidized LDL receptor 1; MDA, malondialdehyde; MMP2, matrix metalloproteinase 2; MTP, microsomal triglyceride transfer protein; NO, nitric oxide; PDK1, pyruvate dehydrogenase Kinase 1; PI3K, phosphatidylinositol 3 kinase; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT6, signal transducer and activator of transcription 6; TIMP2, tissue inhibitor of metalloproteinases 2; TNF-α, tumor necrosis factor-α; TSA, tanshinone IIA; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; IL-6, interleukin-6.

of ERK1/2, JNK, p38, NF-κB and p65, thereby modulating the MAPKs/NF-κB signaling pathway and attenuating inflammatory responses during AS progression (98). These findings suggest that TSA holds therapeutic potential in alleviating AS and treating cardiovascular diseases by inhibiting lipid secretion and inflammation.

ECs form the interface between vascular walls and blood, allowing permeability for the exchange of oxygen and nutrients between blood and tissues (70). ECs carry out a key role in inflammatory responses, anti-(pro-)thrombotic regulation and vascular tone modulation, all of which are associated with the onset and progression of cardiovascular diseases (147). NO, produced by eNOS, is essential for maintaining cardiovascular homeostasis, and its dysregulation often leads to endothelial dysfunction and cardiovascular disorders. TSA markedly enhances NO production in human vascular ECs, potentially through the activation of eNOS (71). Research by Hong *et al* (99) revealed that TSA markedly inhibits endothelin-1 (ET-1) mRNA expression and protein secretion in HUVECs, while increasing NO production and eNOS phosphorylation. ET-1, a potent vasoconstrictive peptide, carries out a key role in cardiovascular diseases such as AS, ischemic heart disease and stroke (148,149). Mechanistic studies suggest that TSA promotes NO generation by activating the PI3K/eNOS pathway, upregulating the expression of activating transcription factor (ATF) 3 and ultimately suppressing ET-1 expression (99). A recent study demonstrated that TSA protects myocardial ECs by stabilizing mitochondrial membrane potential, regulating calcium homeostasis and inhibiting endoplasmic reticulum stress markers (CHOP, PERK and ATF5) through enhancing the interaction between SIRT5 and methyl transferase-like 3 (100).

Macrophages play a pivotal role in the initiation and progression of AS (150). Upon engulfing ox-LDL, macrophages transform into foam cells, a key event in atherosclerotic plaque formation. The ox-LDL not only exerts pro-inflammatory effects but also induces macrophages to release a variety of inflammatory cytokines, thereby exacerbating vascular inflammation (151). Lectin-like, oxidized low-density lipoprotein receptor (LOX)-1, a scavenger receptor expressed in vascular ECs, smooth muscle cells and macrophages, is responsible for recognizing and internalizing ox-LDL. It carries out a key role in endothelial dysfunction, inflammatory responses and foam cell formation during AS (101). Studies by Xu *et al* (44) demonstrated that TSA downregulates LOX-1 expression in macrophages (both the RAW 264.7 cell line and primary mouse peritoneal macrophages) by inhibiting the NF-κB signaling pathway, thus reducing ox-LDL uptake and foam cell formation, and ultimately exerting anti-atherosclerotic effects. *In vivo* experiments further confirmed that TSA decreases ROS generation, blocks the nuclear translocation and DNA binding activity of NF-κB p65 subunit and lowers LOX-1 expression

and lesion area in atherosclerotic plaques of apolipoprotein E knockout ($ApoE^{-/-}$) mice (44). This study identified a novel mechanism through which TSA exerts anti-atherosclerotic effects via the LOX-1/NF-κB axis.

Macrophage autophagy and polarization also carry out key roles in AS development (151). Research by Chen *et al* (102) showed that TSA markedly reduces plasma levels of TG, TC and LDL in high-fat diet-fed $ApoE^{-/-}$ mice, while decreasing aortic plaque area and lipid deposition. Moreover, TSA promotes M2 macrophage polarization by increasing CD206 and anti-inflammatory cytokine IL-10/Arg-1 expression and inhibits M1 polarization by reducing CD197 and pro-inflammatory cytokines (TNF-α/IL-6). TSA also enhances the expression of autophagy markers, including LC3-II and Beclin1 (102). Mechanistically, TSA upregulates transcription factor, Krüppel-like factor (KLF4) by inhibiting miR-375, activating the STAT6/monocyte chemotactic protein-induced protein pathway to promote M2 polarization, and simultaneously suppressing the NF-κB pathway to reduce inflammation. *In vitro* experiments with ox-LDL-induced RAW264.7 cells revealed that miR-375 directly targets KLF4. These findings suggest that TSA regulates macrophage autophagy and polarization balance through the miR-375/KLF4 axis, offering a novel therapeutic target for AS (102).

miRNAs have been implicated in the development of AS. One study demonstrated that TSA inhibits adipogenesis and inflammatory responses in ox-LDL-induced human monocyte-derived macrophages (THP-1 cells) (103). The primary mechanism involves TSA upregulating miR-130b, which suppresses WNT5A protein expression, thereby reducing ox-LDL-induced lipid accumulation and decreasing the mRNA levels of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α (103). Another study revealed that TSA attenuates ox-LDL-induced inflammatory responses in THP-1 macrophages by downregulating miR-33, inhibiting the secretion of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and alleviating atherosclerotic inflammation (42). These findings provide novel mechanistic insights into the potential of TSA as a therapeutic agent for AS.

Oxidative stress can lead to vascular EC damage, promoting monocyte adhesion and migration into the subendothelial space, where they differentiate into macrophages (152). A study by Xu *et al* (104) showed that TSA mitigates high-cholesterol diet-induced atherosclerotic plaque formation and enhances plaque stability in $ApoE^{-/-}$ mice by suppressing the NF-κB signaling pathway, thereby reducing oxidative stress and inflammatory responses. *In vitro* experiments confirmed that TSA inhibits ox-LDL-induced ROS generation in macrophages by downregulating the gp91phox subunit of NADPH oxidase, as well as reducing pro-inflammatory cytokine expression (IL-6, TNF-α and MCP-1) and matrix metalloproteinase (MMP) -9 activity, independent of lipid regulation (104). These findings suggest that TSA exerts anti-atherosclerotic effects through dual antioxidant and anti-inflammatory mechanisms. Another study investigated the anti-inflammatory and antioxidant effects of TSA in an ovariectomized $ApoE^{-/-}$ mouse model of AS (105). The results showed that TSA markedly reduced aortic lipid deposition, lowered serum levels of total cholesterol, TG and LDL, while increasing high-density lipoprotein levels (105). Additionally, TSA enhanced SOD activity, reduced MDA content and suppressed the expression of inflammatory factors such as NF-κB, AP-1, sICAM-1 and E-selectin in serum. These effects resembled those of estrogen (17β-estradiol) and were partially inhibited by an estrogen receptor (ER) antagonist (ICI182780) (105). The study further revealed that TSA exerts its protective effects by inhibiting p-ERK1/2 protein expression in the ERK signaling pathway without directly affecting serum estrogen levels (105). These results suggest that TSA, as a phytoestrogen, may have therapeutic potential for cardiovascular diseases in postmenopausal women by activating ERs and the ERK signaling pathway.

Atherosclerotic calcification (AC), a severe pathological manifestation of AS, is characterized by abnormal deposition of calcium salts in the arterial wall, leading to reduced vascular elasticity, lumen stenosis and increased risk of cardiovascular and cerebrovascular events (153). A study investigated the inhibitory effect of TSA on vitamin D2- and high-cholesterol diet-induced AC in rats, exploring its underlying mechanisms (106). The research showed that TSA mitigates AC by reducing serum levels of ox-LDL, decreasing superoxide anion production and MDA content in blood vessels, while simultaneously enhancing Cu/Zn SOD activity and its mRNA and protein expression, thereby suppressing ox-LDL generation. The study concluded that TSA alleviates AC through antioxidant stress and upregulation of Cu/Zn SOD expression, providing experimental support for the application of natural antioxidants in cardiovascular disease treatment (106).

Hypertension. Hypertension is a prevalent cardiovascular condition characterized by persistently elevated arterial blood pressure, which can lead to long-term damage to vital organs such as the heart, blood vessels and kidneys (154). Vasodilation effectively reduces blood pressure and protects target organs through several mechanisms, including ATP-sensitive potassium (KATP) channel activation, improved endothelial function and modulation of calcium signaling (154,155). TSA selectively activates KATP channels, causing membrane hyperpolarization in VSMCs. This process reduces intracellular calcium ion concentration (Ca^{2+}), inducing vasodilation and lowering systolic blood pressure (SBP) in spontaneously hypertensive rats (SHRs). This research identifies KATP channel activation and calcium signaling regulation as the primary mechanisms underlying the antihypertensive and vasodilatory effects of TSA (156). Another study revealed that TSA inhibits the Cys-C/Wnt signaling pathway, reducing SBP in SHR while also protecting against myocardial hypertrophy (107). Myocardial hypertrophy, a frequent complication of hypertension, increases cardiac oxygen demand, disrupts diastolic-systolic coordination and worsens cardiac dysfunction (157). Pang *et al* (108) demonstrated that TSA mitigates hypertension-induced left ventricular hypertrophy through multiple mechanisms, including antioxidant, anti-apoptotic and anti-fibrotic effects. Specifically, TSA reduces cardiomyocyte apoptosis by decreasing TUNEL-positive cell proportion, downregulating Caspase-3 activity and lowering the Bax/Bcl-2 ratio (108). It alleviates oxidative stress by reducing MDA levels and enhancing SOD activity in cardiomyocytes (108). Additionally, TSA suppresses cardiac fibrosis by modulating paracrine factors (for example, decreasing TGF-β1 and increasing bFGF), regulating the TGF-β/Smads

signaling pathway and altering matrix MMP-2 and tissue inhibitor of metalloproteinase-2 (TIMP2) expression, which reduces the MMP2/TIMP2 ratio (108). TSA also regulates the apelin-apelin receptor (APJ) system by increasing plasma apelin levels while downregulating APJ expression (108).

TSA improves myocardial contractility and reduces ECM deposition, without notably affecting blood pressure (108). Myocardial fibrosis, a common complication of hypertension, can also be alleviated by TSA (158). Fang *et al* (109) demonstrated that TSA, while not notably lowering blood pressure, effectively alleviated cardiac interstitial fibrosis and improved cardiac function in renovascular hypertensive rats (2K2C model). Its mechanism likely involves modulating the transcriptional balance of MMPs/TIMPs by inhibiting MMP-2/9 and TIMP-2 (109). Supporting this, Wang *et al* (110) found that TSA notably improved cardiac function in two-kidney, two-clip (2K2C) hypertensive rats [reducing left ventricular end-diastolic pressure and increasing ejection fraction and left ventricular fractional shortening (LVFS)], while attenuating myocardial hypertrophy and fibrosis, independent of its antihypertensive effect (no notable impact on blood pressure) (110). TSA achieved these effects by inhibiting NADPH oxidase (Nox) activity and downregulating the expression of its subunits (Nox2, Nox4 and p47phox), reducing superoxide anion (O_2^-) generation in the heart and aorta. This ultimately ameliorated cardiac remodeling through its antioxidant properties (110). These findings suggest a novel therapeutic strategy for managing hypertension-related myocardial pathology.

Excessive proliferation of VSMCs leads to arterial wall thickening and lumen narrowing, increasing peripheral vascular resistance and cardiac afterload. Long-term consequences may include cardiac hypertrophy and HF (159,160). This process also disrupts vascular tone regulation, destabilizes hemodynamics, exacerbates blood pressure fluctuations and creates a vicious cycle that elevates the risk of cardiovascular events (159,160). A study demonstrated that TSA at doses of 0.5/5 mg/kg administered for 2 weeks markedly reduced blood pressure in hypertensive rats (2K1C model) and inhibited ET-1-induced proliferation of basilar artery smooth muscle cells, though without affecting PI3K phosphorylation (111). The primary mechanism involves TSA targeting phosphoinositide-dependent kinase-1 (PDK1) to suppress the PI3K/PDK1/AKT pathway, inhibiting arterial smooth muscle cell proliferation and alleviating hypertension-associated cerebrovascular remodeling (111). As a multi-targeted agent, TSA demonstrates promising potential in mitigating cardiac fibrosis, suppressing arterial smooth muscle cell proliferation and improving cardiac function. These findings offer valuable insights into the treatment of hypertension-related myocardial pathology (Fig. 4).

Myocardial hypertrophy. Myocardial hypertrophy is a complex adaptive response characterized by increased cardiomyocyte volume and ventricular wall thickening, with both physiological and pathological manifestations (161). Pathological myocardial hypertrophy not only impairs diastolic and systolic cardiac function but also predisposes individuals to severe complications such as arrhythmias and HF, presenting notable health risks (161). In an earlier study, a rat model of myocardial hypertrophy was established by constricting the thoracic aorta. Compared with the model group, treatment groups showed marked reductions in heart mass index, left ventricular mass index, left ventricular posterior wall thickness, interventricular septal thickness and myocardial fiber diameter as observed in H&E staining. The primary molecular mechanism underlying these effects involved TSA inhibiting the AKT signaling pathway, thus preventing myocardial hypertrophy (162). Another study explored the protective effects of TSA against isoproterenol (ISO)-induced myocardial hypertrophy and its underlying mechanisms (163). TSA markedly inhibited ISO-induced increases in cardiomyocyte surface area and downregulated mRNA and protein expression of hypertrophy markers such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and β-myosin heavy chain (β-MHC). Additionally, TSA exerted anti-hypertrophic effects by suppressing intracellular calcium transients and the calcineurin/nuclear factor of activated T cells (Calcineurin/NFATc3) signaling pathway (163). This research provided new pharmacological evidence supporting TSA as a treatment for pathological myocardial hypertrophy. Further supporting evidence came from Weng *et al* (112), who found that TSA enhanced the activation of the PI3K/AKT signaling pathway by binding to ER, inhibiting Leu27IGF-II-induced calcineurin activation and preventing NFATc3 nuclear translocation, ultimately alleviating cardiomyocyte hypertrophy (112). Moreover, TSA reduced cardiac hypertrophy in SHRs by inhibiting the Cys-C/Wnt signaling pathway, decreasing protein expression of Cys-C, Wnt2, β-catenin and WISP-1 (107). Zhang *et al* (113) discovered that TSA alleviated myocardial hypertrophy through m6A modification of galectin-3. Using both an Ang II-induced *in vitro* cardiomyocyte hypertrophy model and a TAC-induced *in vivo* cardiac hypertrophy model, they observed that TSA markedly inhibited cardiomyocyte hypertrophy and downregulated hypertrophy markers such as ANP, BNP and β-MHC. TSA reduced galectin-3 mRNA stability and protein expression by inhibiting the RNA demethylase ALKBH5, thereby enhancing m6A modification of galectin-3 mRNA (113). This study revealed a novel mechanism through which TSA regulates galectin-3 expression via ALKBH5-mediated m6A modification, providing a potential therapeutic target for cardiac hypertrophy (Fig. 5).

Myocardial infarction. Myocardial infarction is a severe cardiovascular condition that causes extensive cardiomyocyte necrosis, impairs cardiac function and can lead to HF (164). Ischemia and hypoxia are central to the pathophysiology of myocardial infarction. Acute coronary artery occlusion induces regional myocardial ischemia and hypoxia, triggering complex intracellular biochemical reactions in cardiomyocytes, leading to energy metabolic dysfunction, calcium ion overload, and ultimately cardiomyocyte injury and death (164). In a study by Zhang *et al* (114), a rat myocardial infarction model (ligation of the left anterior descending coronary artery; LAD) and an *in vitro* hypoxic cardiomyocyte culture system were used to demonstrate that TSA protects cardiomyocytes from ischemic and hypoxic injury. TSA achieves this by inhibiting p38 MAPK phosphorylation, downregulating the expression of cardiac-specific transcription factors serum response factor (SRF) and myocyte enhancer factor 2, reducing excessive

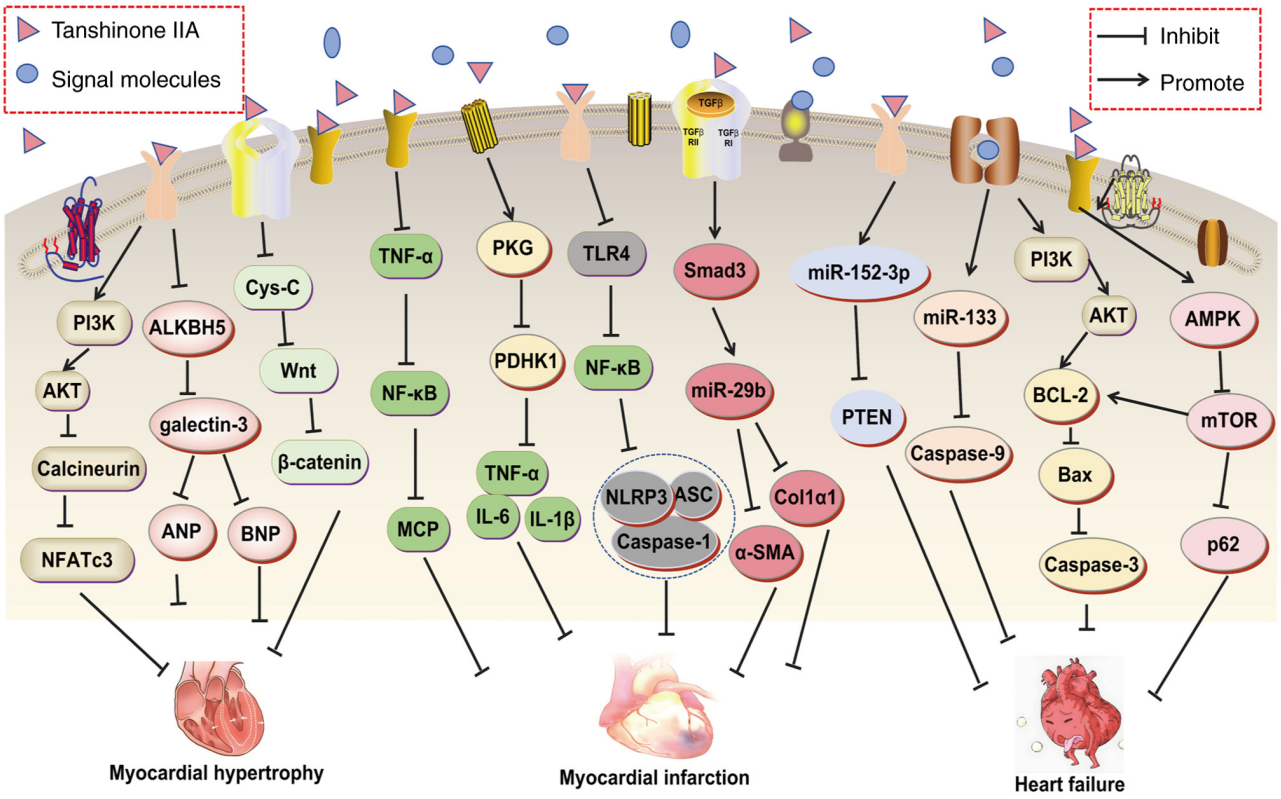

Figure 5. Molecular mechanisms of Tanshinone IIA in the treatment of myocardial hypertrophy, myocardial infarction, and heart failure. α-SMA, α-smooth muscle actin; AKT, protein kinase B; ALKBH5, AlkB Homolog 5; ASC, Apoptosis-associated speck-like protein containing a CARD; AMPK, AMP activated protein kinase; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; COL-1, collagen type 1; Cys-C, cystatin c; IL-6, interleukin-6; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain-containing 3; PDHK1, pyruvate dehydrogenase kinase 1; PI3K, phosphatidylinositol 3 kinase; PKG, protein kinase G; PTEN, phosphatase and tensin homolog; TLR4, toll like receptor 4; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells.

miR-1 expression and restoring its target protein, connexin-43 levels (114).

Ischemia and hypoxia activate inflammatory signaling pathways in the body, promoting the infiltration of inflammatory cells into the infarcted area and releasing large amounts of inflammatory cytokines, which exacerbate myocardial injury and contribute to the development of HF (165). A study by Ren *et al* (115) investigated the inhibitory effect of TSA on post-myocardial infarction inflammatory responses and its underlying mechanisms. Using an *in vivo* rat myocardial infarction model (LAD ligation), they found that TSA notably improved cardiac function, reduced infarct size and collagen deposition, and downregulated the expression of MCP-1 and TGF-β1, while also reducing macrophage infiltration (115). *In vitro* experiments demonstrated that TSA inhibited MCP-1 and TGF-β1 secretion in TNF-α-stimulated rat primary cardiac fibroblasts (CFs) but had no notable effect on rat primary cardiomyocytes. The study suggested that the cardioprotective effects of TSA might be achieved by suppressing TNF-α/NF-κB signaling-mediated inflammatory responses, with CFs as the primary target (115). Another study using a mouse myocardial infarction model revealed that TSA improved cardiac function, reduced inflammatory cell infiltration and fibrosis, and decreased pro-inflammatory cytokine expression (for example IL-1β, TNF-α or IL-6) and increased anti-inflammatory IL-10 secretion. Additionally, TSA promoted M2 macrophage polarization and inhibited M1 polarization (116). Mechanistically, TSA targeted PGK1 (a key glycolytic enzyme) to inhibit its binding to mitochondria, reducing PDHK1 (pyruvate dehydrogenase kinase 1) activity, restoring mitochondrial function and reprogramming macrophage metabolism. This reprogramming shifted macrophage metabolism from glycolysis to oxidative phosphorylation, driving a shift from M1 pro-inflammatory to M2 anti-inflammatory phenotypes (116). This study identified the PGK1-PDHK1 axis as a novel target of TSA in regulating the immune microenvironment through metabolic reprogramming, offering a new innovative energy metabolism-based strategy for anti-inflammatory therapy in myocardial infarction.

After myocardial infarction, cardiomyocyte necrosis triggers a repair process in which fibroblasts proliferate and produce ECM, leading to scar formation (166). This excessive fibrosis alters cardiac structure, including ventricular wall thickening and chamber dilation, impairing both systolic and diastolic function (166). Therefore, myocardial infarction is associated with fibrosis, a key factor in cardiac dysfunction. Studying this relationship is essential for developing therapeutic strategies. A study by Yang *et al* (117), using a rat acute myocardial infarction model and *in vitro* CF experiments, demonstrated that medium-to-high doses of TSA notably improved left ventricular function, reduced collagen deposition and downregulated TGF-β1, Col1a1, Col3a1 and α-SMA expression while upregulating miR-29b (117). Further experiments showed that miR-29b inhibition prevented the

antifibrotic effects of TSA, whereas Smad3 small interfering (si)RNA treatment suppressed miR-29b expression, confirming that TSA exerts its antifibrotic effects by upregulating miR-29b via the TGF-β-Smad3 signaling pathway (117). To the best of our knowledge, this study is the first to identify miR-29b as a direct effector molecule mediating the antifibrotic effects of TSA, unveiling a novel pathway through which TCM active components target miRNAs to modulate cardiac remodeling. It also offers a potential therapeutic strategy for post-myocardial infarction fibrosis based on the TGF-β/miR-29b axis (117).

Ischemia-hypoxia injury triggers a complex pathophysiological cascade, with pyroptosis emerging as a form of programmed cell death (167). Pyroptosis involves cellular swelling followed by rupture, resulting in the release of cellular contents that initiate inflammatory responses (168). In myocardial infarction, pyroptosis contributes to cardiomyocyte loss, activates immune cells and exacerbates inflammation and fibrosis (168). In a study using a rat HF model and an H9C2 cardiomyocyte hypoxia-reoxygenation model, TSA notably improved cardiac function [increasing left ventricular ejection fraction (LVEF) and LVFS], reduced serum NT-pro-BNP, IL-1β and IL-18 levels, and suppressed NLRP3 inflammasome activation by inhibiting the TLR4/NF-κB p65 pathway (118). This led to decreased Caspase-1-dependent GSDMD-N cleavage and IL-1β/IL-18 maturation, alleviating myocardial inflammation and pyroptosis (118). This study is the first to demonstrate that TSA inhibits cardiomyocyte pyroptosis by targeting the TLR4/NF-κB p65 axis, offering a novel therapeutic target for TSA-mediated regulation of programmed cell death in post-myocardial infarction HF.

Myocardial infarction is a leading cause of HF, with post-myocardial infarction inflammatory responses, oxidative stress, fibrotic processes and neuroendocrine activation playing key roles in the progression of HF (169). Chen *et al* (119) established an myocardial infarction rat model by ligating the LAD and found that TSA treatment prevented myocardial infarction-induced declines in cardiac function, including LVEF and LVFS, while alleviating structural abnormalities such as left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV). TSA also suppressed the upregulation of collagen I, collagen III, TGF-β, α-SMA, MMP2 and MMP9 in myocardial infarction rat hearts and mitigated Ang II-induced CF fibrosis. Additionally, TSA reduced oxidative stress by enhancing SOD activity and decreasing MDA, superoxide anion levels and Nox4 activity (119). Further experiments revealed that Nox4 overexpression attenuated TSA-mediated improvements in cardiac function and fibrosis in HF rats, suggesting that Nox4 critically regulates the inhibitory effects of TSA on HF and cardiac fibrosis (119). This study is the first to demonstrate that TSA ameliorates post-myocardial infarction HF-related cardiac remodeling by targeting Nox4-dependent oxidative stress pathways (119).

A study by Zhu *et al* (170) found that TSA exerts cardioprotective effects by modulating the gut-brain axis following myocardial infarction. Their research demonstrated that TSA markedly improved cardiac function in mice after MI (increasing LVEF and LVFS, decreasing LVEDV and LVESV), alleviated myocardial hypertrophy, fibrosis and cardiomyocyte apoptosis, and suppressed inflammatory responses in cardiac tissue (reducing TNF-α, IL-1β and p-NF-κB p65 expression) (170). Additionally, TSA improved myocardial infarction-induced intestinal pathological damage, including increasing villus length, reducing intestinal edema and fibrosis, and enhancing intestinal barrier integrity (upregulating ZO-1, Occludin and Cingulin expression). 16S rDNA sequencing revealed that TSA reshapes the gut microbiota, increasing α-diversity (Chao1 and Shannon indices) and altering β-diversity. Furthermore, TSA reduced serum levels of LPS, inhibited microglial activation and neuroinflammation in the paraventricular nucleus (PVN; reducing IL-6 and TNF-α expression) and decreased sympathetic nervous system activity (reducing tyrosine hydroxylase [TH] and norepinephrine [NE] levels) (170). Consequently, it was concluded that TSA alleviates myocardial injury by improving gut microbiota and barrier function, reducing LPS release into the bloodstream, thereby inhibiting PVN neuroinflammation and sympathetic nervous system overactivation (170). However, the study did not definitively conclude whether the cardioprotective effects of TSA are independent of the gut microbiota, as it did not use antibiotics to deplete the microbiota or fecal microbiota transplantation to validate causality, which remains to be explored in future research (Fig. 5).

Myocardial ischemia-reperfusion. Myocardial ischemia-reperfusion is a common clinical condition characterized by the restoration of blood flow to the myocardium after a period of ischemia (171). During this process, myocardial cells undergo pathophysiological changes that cause notable damage. Upon reperfusion, excessive oxygen-free radicals trigger oxidative stress, damaging myocardial cell membranes, proteins and nucleic acids, which disrupts cellular structure and function (171). Simultaneously, ischemia-reperfusion activates inflammatory responses, leading to infiltration of inflammatory cells into myocardial tissue and the release of inflammatory cytokines, further exacerbating myocardial injury and increasing cell necrosis and apoptosis (171). TSA mitigates myocardial ischemia-reperfusion injury (MIRI) through multiple mechanisms, including antioxidant effects (elevating SOD and reducing MDA), anti-inflammatory actions (inhibiting TNF-α and IL-6), anti-apoptotic effects (regulating Bcl-2/Bax and Caspase-3) and improving energy metabolism (enhancing ATP production) (172,173).

One study found that TSA notably reduced the myocardial infarction area, improved left ventricular ejection fraction and decreased cardiomyocyte apoptosis in streptozotocin-induced diabetic rats. Additionally, TSA enhanced AKT phosphorylation, inhibited NF-κB phosphorylation and downregulated inflammatory cytokine expression (TNF-α and IL-6), thereby alleviating MIRI in rats (120). These results suggested that TSA exerts anti-apoptotic, anti-inflammatory and cardioprotective effects by activating the PI3K/AKT-dependent pathway (120).

Another study demonstrated that TSA notably reduced the myocardial infarction area, serum CK-MB and LDH levels in a rat model of myocardial ischemia-reperfusion induced by left anterior descending coronary artery ligation. TSA also decreased mitochondrial oxidative stress markers (MDA and H_2O_2) while increasing SOD activity and SDH/COX levels, and inhibiting cardiomyocyte apoptosis (increased Bcl-2 expression and decreased Bax expression) (121). Mechanistic

studies revealed that TSA exerts its protective effects by upregulating PI3K, p-AKT/AKT, p-mTOR/mTOR and p-eNOS/eNOS expression, suggesting that TSA activates the PI3K/AKT/mTOR pathway to mitigate oxidative stress and apoptosis, thus protecting against MIRI (121). Furthermore, Li *et al* (69) demonstrated through *in vivo* experiments that TSA reduced myocardial infarction area, improved cardiac contractile function and decreased serum levels of myocardial injury markers such as LDH and creatine kinase in a rat model of MIRI. Additionally, TSA exerted anti-inflammatory and cardioprotective effects by inhibiting the NLRP3 inflammasome and its downstream targets (Caspase-1, IL-1β and IL-18), while modulating Th17/Treg cell balance (69).

Myocardial ischemia leads to hypoxia in cardiac tissue, and after reperfusion, the myocardium regains oxygen, entering the reoxygenation phase. However, reperfusion and reoxygenation induce notable changes in cellular redox status and trigger inflammatory responses (174). A study demonstrated that TSA pretreatment (8 μM for 48 h) notably enhanced the survival rate of H9c2 cells subjected to hypoxia/reoxygenation (A/R) injury, reduced LDH activity and upregulated 14-3-3η protein expression (122). This promoted the translocation of Bcl-2 to the outer mitochondrial membrane, where it interacted with voltage-dependent anion channel 1, inhibiting mitochondrial permeability transition pore (mPTP) opening. As a result, TSA reduced ROS generation and cyt *c* release, ultimately suppressing Caspase-3 activation and apoptosis (122). The protective effect of TSA was comparable to ischemic preconditioning, suggesting that TSA may serve as a nutritional preconditioning strategy to mitigate MIRI (122). TSA can also inhibit the expression of the HAS2/FGF9 axis, alleviating hypoxia-induced apoptosis in AC16 cardiomyocytes (reducing Cleaved Caspase-3 and Bax expression), inflammation (reducing IL-6, IL-1β and TNF-α) and oxidative damage (reducing MDA levels) (123). Yan *et al* (124) established an *in vitro* oxygen-glucose deprivation/reoxygenation (OGD/R) cardiomyocyte model and an *in vivo* rat myocardial ischemia-reperfusion model. Their results showed that TSA pretreatment downregulated histone deacetylase 1 (HDAC1) expression, thereby promoting nuclear translocation of Nrf2 and upregulating antioxidant proteins, including HO-1, cystine transporter xCT and GSH peroxidase 4 (Gpx4). This led to reduced cardiomyocyte apoptosis (decreased Bax/Bcl-2 ratio), lower inflammatory cytokine release (TNF-α and IL-1β) and inhibition of ferroptosis, as evidenced by reduced MDA and Fe^{2+} levels, along with increased GSH levels (124). These findings suggest that TSA exerts anti-inflammatory, anti-apoptotic and anti-ferroptotic effects by activating the Nrf2-xCT/Gpx4/HO-1 axis, which is otherwise suppressed by HDAC1, thereby ameliorating MIRI (124). Additionally, TSA pretreatment markedly improved the survival rate of H9c2 cardiomyocytes in an A/R model, reduced LDH activity, MDA levels, total iron content and ROS levels, while upregulating GSH and Gpx4 expression. TSA also inhibited VDAC1-mediated mPTP opening and apoptosis (96). This study revealed that TSA exerts dual cardioprotective mechanisms by targeting VDAC1 to simultaneously inhibit ferroptosis and apoptosis, providing novel molecular targets and a theoretical basis for using TSA, an active component of Salvia miltiorrhiza, in treating ischemic heart disease (96). The study also found that TSA activates the ATM/GADD45/ORC pathway to promote DNA damage repair and DNA biosynthesis, thereby alleviating injury in H9C2 cardiomyocytes induced by OGD/R (125). However, the majority of these studies are based solely on *in vitro* cell models, lacking validation from animal models or clinical data, and further exploration is still required.

A study by Li *et al* (126) demonstrated that TSA enhances the therapeutic efficacy of MSC-derived exosomes (MSCexo) in MIRI by upregulating miR-223-5p within these exosomes. TSA-preconditioned MSCexo (TSA-MSCexo) notably improved cardiac function and reduced infarct size in rats compared with untreated MSCexo. TSA-MSCexo also suppressed CCR2 activation, thereby reducing monocyte infiltration and promoting angiogenesis (126). Mechanistically, TSA-MSCexo delivered miR-223-5p to target CCR2 expression, modulating inflammatory responses and enhancing vascular repair (126). These findings provide experimental evidence for the development of a cell-free exosome-based therapy combining TSA and MSCs, offering a novel approach for the clinical treatment of ischemic cardiomyopathy.

In the exploration of therapeutic strategies for MIRI, combination drug therapy has shown distinct advantages (175,176). In addition to the aforementioned combination of TSA and MSCexo, the synergistic use of multiple drugs or bioactive substances has gained increasing attention (175,176). For example, a study investigated the protective effects and molecular mechanisms of combining TSA and astragaloside IV (As-IV) in the treatment of MIRI (127). The results revealed that this combination therapy (Co) exhibited notably enhanced efficacy when compared with either TSA or As-IV alone, both *in vivo* and *in vitro*. In a MIRI mouse model, Co more effectively reduced myocardial infarct size, decreased myocardial enzyme levels (CK, CK-MB and LDH), improved cardiac function (LVEF and LVFS) and alleviated myocardial pathological damage (127). *In vitro* experiments showed that Co provided stronger protection against HR and H_2O_2-induced HL-1 cell injury. It considerably inhibited apoptosis (reducing Bax and cleaved Caspase-3 while increasing Bcl-2), mitigated oxidative stress (reducing ROS and MDA levels while enhancing GSH and SOD activity) and suppressed inflammatory responses (downregulating IL-6, IL-1β, TNF-α and iNOS mRNA expression) (127). A mechanistic study indicated that the combined administration of TSA and As-IV exerted anti-apoptotic, antioxidant and anti-inflammatory effects in MIRI by synergistically inhibiting the STING pathway, with superior efficacy compared with monotherapy (127). These findings provide theoretical understanding for the use of TSA in treating MIRI, confirming its multi-target mechanisms in mitigating reperfusion injury and laying the foundation for clinical translation. However, further high-quality research is needed to validate its standardized application.

HF. HF often results from extensive cardiomyocyte apoptosis, as these cells are essential functional units of the heart and their loss directly impairs both contractile and diastolic function (177). Ischemic or hypoxic conditions can induce cardiomyocyte apoptosis, leading to notable negative impacts on cardiac structure and function (178,179). Therefore, identifying effective strategies to inhibit cardiomyocyte apoptosis is important for preventing and treating HF. Previous research

has shown that TSA can prevent DOX-induced cardiomyocyte apoptosis in rats by suppressing ROS generation, reducing Caspase-3 activation and cyt *c* release, increasing Bcl-2 expression and enhancing AKT phosphorylation via the PI3K/AKT signaling pathway, thereby protecting cardiomyocytes from DOX-induced toxicity (128). A previous study further revealed that TSA inhibits DOX-induced cardiomyocyte apoptosis in HF mice by activating the DAXX/MEK/ERK1/2 pathway (increasing phosphorylation of p-ERK1/2 and p-MEK) and downregulating Caspase-8, p-P38 and Caspase-3 expression (129).

Additionally, two studies have shown that miRNAs play a role in TSA-mediated inhibition of cardiomyocyte apoptosis (48,49). TSA upregulates miR-152-3p, reducing PTEN expression and notably suppressing Ang II-induced apoptosis in rat cardiomyocyte H9C2 cells (48). TSA also upregulates miR-133, inhibiting the activation of Caspase-9 and its downstream apoptotic effectors (including Caspase-3 and PARP), thereby ameliorating H_2O_2- and DOX-induced apoptosis in H9C2 cells (49). Oxidative stress is another key factor in cardiomyocyte apoptosis. A study using H_2O_2 to induce oxidative stress demonstrated that the miR-133-Caspase-9 pathway serves as a core mechanism by which TSA counters oxidative stress-induced myocardial injury (49).

Autophagy, an intracellular degradation and recycling process, plays a key role in HF development (180). During HF, cardiomyocytes encounter various stressors, triggering autophagy to remove damaged organelles and proteins, thus maintaining cellular homeostasis. However, dysregulated autophagy, whether excessive or insufficient, can impair cardiomyocytes and exacerbate HF (181). Modulating autophagy levels may therefore provide a novel therapeutic approach for HF. A study by Zhang *et al* (130) demonstrated that TSA notably improved cardiac function in HF rats (induced by LAD ligation), reduced cardiomyocyte apoptosis and promoted autophagy by activating AMPK (increasing p-AMPK phosphorylation) while inhibiting mTOR signaling (reducing mTOR phosphorylation). This regulation led to altered expression of key autophagy-related proteins (upregulated LC3/Beclin-1, downregulated p62) and apoptosis-related proteins (increased Bcl-2/Bax ratio, reduced Caspase-3/7 levels) (130). This study first elucidated that TSA improves cardiac function through dual mechanisms, autophagy activation and apoptosis inhibition, providing a novel therapeutic target for HF (Fig. 5).

Myocardial fibrosis. Myocardial fibrosis plays a pivotal role in cardiac remodeling, marked by the abnormal accumulation of collagen and ECM components (182). This fibrotic transition, often associated to aging (183), obesity (184) and diabetes (185), markedly impairs cardiac function through multiple mechanisms (182). TSA reduces collagen deposition and promotes elastic fiber formation in human CFs (131). Specifically, TSA selectively activates the G protein-coupled ER (GPER) in human CFs, notably suppressing COL-1 gene expression, protein synthesis and deposition, while upregulating matrix MMP-1 expression (131). Additionally, TSA triggers the PKA/CREB phosphorylation pathway via GPER, enhancing elastin transcription, secretion and cross-linking (by upregulating elastin-binding protein EBP and lysyl oxidase LOX), while inhibiting the elastase activity of MMP-2/9 (131). This study is the first to demonstrate that TSA coordinates collagen reduction with elastic fiber generation through the GPER-PKA-CREB axis, offering a novel approach for treating cardiac fibrosis. Another study found that TSA considerably inhibits Ang II-induced activation of CFs and α-SMA production *in vitro*, while reducing collagen I/II and TIMP1/4 expression (132). In a TAC rat model, TSA (10 mg/kg) improved cardiac function, alleviated cardiac hypertrophy and decreased collagen deposition, effects dependent on miR-618 induction (inhibition of miR-618 abolished the protective effects of TSA) (132). This study is the first to reveal that TSA suppresses myocardial fibrosis via the miR-618/TIMPs axis, providing new molecular evidence for TSA-based cardiovascular therapy (132). Furthermore, Huang *et al* (133) investigated the protective effects of TSA on subclinical LPS-induced cardiac fibrosis in mice and its underlying mechanisms. The results showed that TSA effectively alleviated LPS-induced myocardial fibrosis by inhibiting NADPH oxidase activity, suppressing the expression of fibrosis-related genes (Col1α1, Col3α1, MMP2, MMP9, TIMP1 and TIMP2), reducing protein levels of NOX2 and p67phox, and decreasing ROS generation (133). These findings suggest potential drug targets and strategies for preventing and treating subclinical LPS-associated cardiac fibrosis.

Arrhythmia. Arrhythmia is a prevalent cardiovascular disorder associated with cardiocerebrovascular function (186). It can lead to abnormal cardiac pumping, disrupt blood circulation and potentially trigger or worsen various cardiocerebrovascular diseases, such as coronary artery disease, cardiomyopathy and hypertensive heart disease, thereby increasing the risk of severe events such as stroke and HF (186). A study explored the activating effects of TSA on human KCNQ1/KCNE1 (IKs) potassium channels expressed in HEK 293 cells (134). The results demonstrated that TSA concentration-dependently enhanced IKs current amplitude (EC50=64.5 μM), accelerated channel activation kinetics, slowed inactivation and shifted the voltage dependence of IKs activation toward hyperpolarization (134). Notably, the effects of TSA were independent of β-adrenergic stimulation (for example, isoproterenol), NO donor (for example, sodium nitroprusside), protein kinase A inhibitor (for example, H-89 dihydrochloride) or soluble guanylate cyclase inhibitor (1H-[1,2,4]Oxadiazolo[4,3-a] quinoxalin-1-one), indicating its direct and specific action on channel dynamics (134). Furthermore, TSA showed no notable effects on hERG, Kv1.5 or IK1 channels expressed in HEK 293 cells (134). These findings suggest that TSA may specifically enhance IKs to treat arrhythmias associated with IK dysfunction, particularly during cardiac electrical remodeling. Another study revealed that chronic TSA administration (10 mg/kg/d for 3 months) markedly reduced the incidence and mortality of acute myocardial ischemia-induced arrhythmias in rats (left anterior descending coronary artery ligation model) (187). Electrophysiological analysis showed that TSA restored the reduced inward rectifier potassium current (IK1) density and Kir2.1 channel protein expression post-myocardial infarction, thereby reversing resting membrane potential depolarization (187). Mechanistically, myocardial infarction upregulated miR-1 expression by 2.9-fold, which targeted the

3'-untranslated region of KCNJ2 (encoding Kir2.1) to reduce Kir2.1 protein levels without affecting mRNA (187). TSA normalized miR-1 levels by suppressing SRF, a transcriptional activator of miR-1, thereby alleviating translational inhibition of Kir2.1 (187). To the best of our knowledge, this study is the first to identify the SRF/miR-1/Kir2.1/IK1 signaling axis as a novel therapeutic target for ischemic arrhythmias.

He *et al* (188) investigated the preventive effects of TSA on atrial fibrillation (AF) and its electrophysiological mechanisms using a rabbit model of chronic HF (CHF) induced by rapid ventricular pacing. The results showed that combined perfusion with ACh (1 μM) and ISO (1 μM) induced AF in all failing hearts and 11 out of 12 control hearts. However, co-perfusion with TSA (10 μM) notably reduced AF inducibility by 50% in both control and CHF groups (188). Electrophysiological analysis revealed that TSA did not alter atrial action potential duration but notably prolonged the effective refractory period, increased atrial post-repolarization refractoriness and moderately prolonged interatrial conduction time (188). Mechanistically, TSA exerted antiarrhythmic effects by inhibiting Na+ channel recovery and modulating calcium handling (for example suppressing RyR2-mediated calcium leak) (188). This study first demonstrated that TSA suppresses AF through dual modulation of prolonged post-repolarization refractoriness and conduction slowing, offering a novel therapeutic strategy for AF in patients with CHF.

Cerebral ischemia-reperfusion. Cerebral ischemia-reperfusion refers to the restoration of blood flow to brain tissue after ischemia (189,190). This process induces changes in blood-brain barrier (BBB) permeability, leading to barrier dysfunction and enabling substances that typically cannot cross the BBB to infiltrate, triggering complex pathological responses. These alterations disrupt normal brain metabolism and hinder functional recovery, potentially worsening cerebral injury (189,190). TSA can inhibit the increase in BBB permeability, reduce oxidative stress and inflammation, enhance the expression of tight junction proteins such as Claudin-5 and ZO-1, and activate the Nrf2/HO-1 signaling pathway, thereby protecting brain microvascular EC function (46). Chen *et al* (191) showed that both *in vitro* using a rat brain microvascular EC model and *in vivo* with a rat brain perfusion model, PgP or Mrp1/2 inhibitors (such as verapamil or quinidine) markedly enhanced TSA brain penetration, indicating that PgP and Mrp1/2 carry out a key role in restricting the passage of TSA across the BBB (191).

Cerebral ischemia-reperfusion therapy aims to mitigate or reverse brain injury but may paradoxically induce oxidative stress, inflammation and apoptosis, thereby exacerbating cerebral damage (189). Wang *et al* (135) demonstrated that TSA markedly reduced cerebral infarct volume, decreased HMGB1 protein levels, inhibited NF-κB nuclear translocation, downregulated glial fibrillary acidic protein (GFAP) expression and suppressed apoptosis, thereby alleviating ischemia-reperfusion injury in a rat MCAO model. Their findings indicated that TSA exerts anti-inflammatory and anti-apoptotic effects by inhibiting the activation of the HMGB1/NF-κB signaling pathway (135). Further studies confirmed that TSA markedly reduced infarct volume, decreased brain water content, improved neurological function scores and suppressed inflammatory responses and neuronal apoptosis (136-138). Using both an MCAO/R rat models and an *in vitro* OGD/R cell models (136,137), researchers found that TSA inhibited the expression of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), reduced levels of pro-apoptotic proteins (Bax and Cleaved-Caspase-3) and enhanced the expression of the anti-apoptotic protein Bcl-2. Notably, TSA downregulated the mRNA and protein expression of TLR4, MyD88 and NF-κB (p105) in brain tissue, inhibited the phosphorylation of IκB-α and NF-κB p65, thereby stabilizing IκB-α and p65 proteins (137). These findings demonstrate that TSA exerts neuroprotective effects by targeting the inhibition of the TLR4/NF-κB signaling cascade, alleviating neuroinflammation following cerebral ischemia-reperfusion injury (137). Additionally, research by Yu *et al* (138) suggests that TSA alleviates cerebral ischemia-reperfusion injury by downregulating TGM2, inhibiting PANX1 expression and suppressing microglial activation and neuroinflammation (TNF-α, IL-1β and IL-6), highlighting the multi-target regulation of TSA in the same disease.

Moreover, studies indicate that TSA can improve cerebral ischemia-reperfusion injury by regulating miRNA expression (136,139). TSA exerts neuroprotective effects by upregulating miR-124-5p and inhibiting the expression of FoxO1 (136). Research by Yu *et al* (139) found similar therapeutic effects (137,138), where TSA alleviates cerebral ischemia-reperfusion injury in a rat MCAO/R model and in SH-SY5Y cells subjected to OGD/R by promoting the expression of miR-449a. This upregulation of miR-449a inhibits the expression of its target gene ACSL4, thereby suppressing neuronal ferroptosis (139). These findings provide theoretical support for the potential application of TSA in treating cerebral ischemia-reperfusion injury (Fig. 6).

Stroke. Stroke is an acute cerebrovascular disease caused by vascular rupture or occlusion, which disrupts blood flow to the brain and leads to subsequent tissue damage. It encompasses both ischemic and hemorrhagic strokes, with ischemic stroke being the more prevalent form (192). The pathological mechanisms of stroke are multifaceted: Ischemic stroke results from vascular occlusion, leading to cerebral hypoperfusion (ischemia-hypoxia), which triggers energy metabolic dysfunction, calcium overload, oxidative stress and inflammatory responses, further exacerbating neuronal injury and mortality (193). By contrast, hemorrhagic stroke involves vascular rupture, resulting in hematoma formation that causes direct toxic effects and mass effects on brain tissue, leading to severe damage (194). Additionally, stroke induces secondary complications such as cerebral edema and BBB disruption, impairing neurological function and resulting in cognitive and motor deficits (193).

Emerging evidence suggests that TSA may alleviate oxidative stress-related neuronal injury. One study shows that TSA notably reduces H_2O_2-induced cytotoxicity in primary rat cortical neurons by inhibiting intracellular calcium elevation and modulating the Bcl-2/Bax protein ratio to suppress apoptosis (140). Furthermore, TSA reverses H_2O_2-induced long-term potentiation (LTP) impairment in hippocampal neurons without affecting basal synaptic transmission or LTP induction (140). These findings suggest that TSA may exert

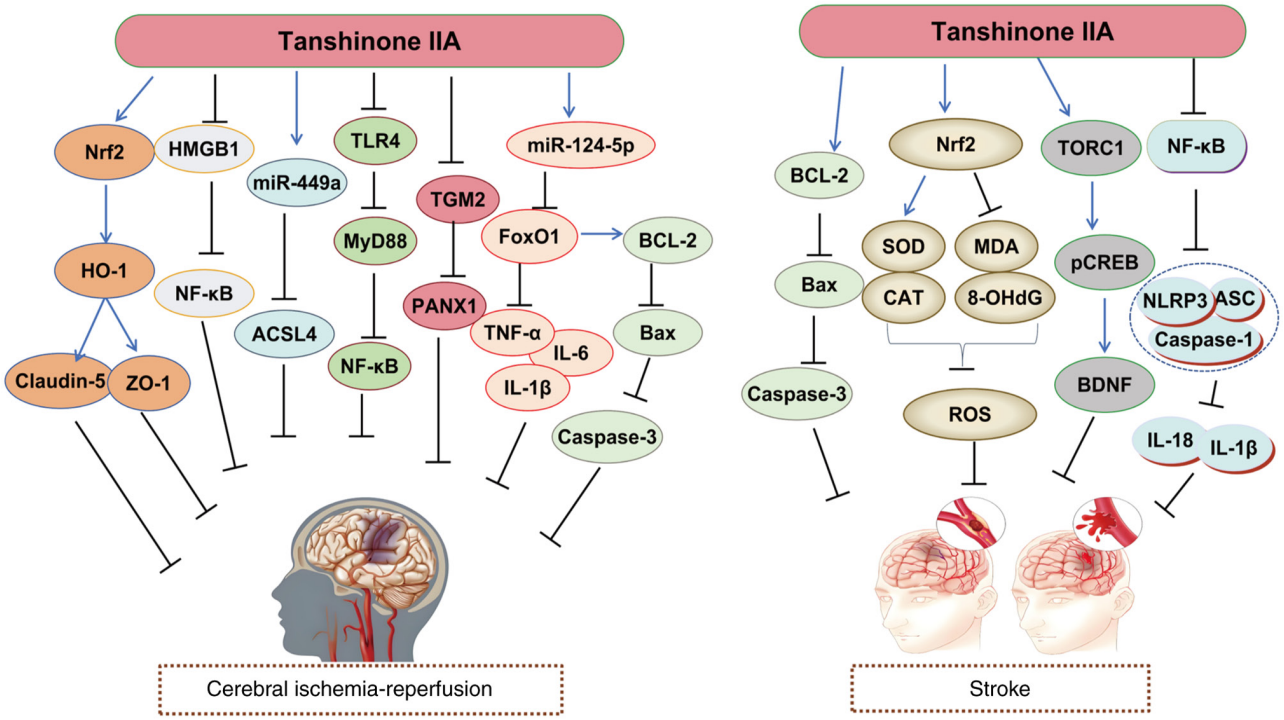

Figure 6. Molecular mechanisms of Tanshinone IIA in the treatment of cerebral ischemia-reperfusion injury and stroke. BDNF, brain-derived neurotrophic factor; CAT, catalase; CREB, CAMP response element binding protein; FoxO3, forkhead box O3; HO-1, heme oxygenase 1; IL-6, interleukin-6; HMGB1, high mobility group box 1; MDA, malondialdehyde; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol 3 kinase; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TORC1, target of rapamycin complex 1; 8-OHdG, 8-Hydroxy-2'-deoxyguanosine.

antioxidant and anti-apoptotic effects, making it a potential therapeutic agent for neurodegenerative diseases such as stroke and AD (140). Another study suggested neuroprotective effects of TSA via antioxidant pathways (141). Using a MCAO mouse model, TSA treatment notably improved neurological function scores, reduced infarct volume and inhibited apoptosis (141). Mechanistically, TSA upregulates Nrf2 mRNA expression, promotes Nrf2 nuclear translocation and enhances antioxidant enzyme activity (for example, SOD and catalase), while reducing oxidative byproducts such as MDA and 8-hydroxy-2'-deoxyguanosine (8-OHdG) (141). Notably, Nrf2 knockout and small interfering RNA-mediated knockdown experiments revealed that Nrf2 deficiency abrogates the neuroprotective and antioxidant effects of TSA, confirming that Nrf2 activation is the key mechanism underlying the efficacy of TSA (141).

Additionally, an earlier study demonstrated that TSA exerts neuroprotective effects in ischemic stroke rats (MCAO model) by considerably reducing neurological deficit scores, brain water content and infarct volume, while markedly enhancing the nuclear accumulation of TORC1 and upregulating the expression of TORC1, pCREB and BDNF (142). Another study explored the neuroprotective effects and synergistic mechanisms of puerarin (Pue) combined with TSA in rats with ischemic stroke (143). The results showed that the Pue-TSA combination therapy considerably reduced neurological scores, infarct volume and levels of S-100b and NSE in MCAO rats, indicating effective mitigation of ischemic brain injury. Furthermore, the combined treatment markedly enhanced total antioxidant capacity and the activities of CAT, SOD and reduced GSH, while decreasing oxidized GSH activity and MDA levels. It also reduced the levels of inflammatory mediators such as TNF-α, IL-6, ICAM-1 and COX-2 (143). A mechanistic study revealed that Pue-TSA combination therapy markedly activated the Nrf2/ARE signaling pathway, increased the nuclear expression of Nrf2, decreased its cytoplasmic expression and markedly upregulated HO-1 and NAD(P)H oxidoreductase 1, while downregulating Keap1 (143). These findings suggest that the combined use of Pue and TSA exerts synergistic neuroprotective effects by activating the Nrf2/ARE pathway, inhibiting oxidative stress and inflammatory responses, providing experimental evidence for clinical application (143).

Subarachnoid hemorrhage (SAH), a type of hemorrhagic stroke, has also been shown to benefit from TSA treatment. Yang *et al* (144) demonstrated that TSA markedly improved neurological deficits, reduced cerebral edema and inhibited neuronal apoptosis in SAH rats (established by the endovascular perforation method). It also downregulated the expression of inflammatory factors such as IL-6, MCP-1, TNF-α, IL-1β and IL-18. Mechanistically, TSA inhibited the phosphorylation of NF-κB and the activation of NLRP3 inflammasome-related proteins (NLRP3, Caspase-1, IL-1β and IL-18) (144). *In vitro* experiments using oxygenated hemoglobin-induced primary neuronal models further confirmed that TSA protected neurons from SAH injury by blocking the NF-κB/NLRP3 pathway (144). This study provides a potential therapeutic strategy for the treatment of SAH (Fig. 6).

Multi-targeting of TSA and pathway crosstalk. TSA exhibits multifaceted pharmacological functions, suggesting its

multi-target characteristics. For example, in MIRI, TSA suppresses disease progression by activating the PI3K/AKT and Nrf2/HO-1 pathways. However, due to limitations in existing research, the interplay between these pathways within the same study remains insufficiently understood. Based on previous reports, it is hypothesized that AKT may phosphorylate Keap1, reducing its binding to Nrf2 and thereby enhancing Nrf2 nuclear translocation and the expression of downstream antioxidant genes. Such cross-talk is particularly important in cancer contexts, where, for example, PI3K/AKT-driven tumor cells activate Nrf2/HO-1 to evade oxidative stress-induced apoptosis, fostering drug resistance (28,195,196). Conversely, Nrf2 activation can inhibit excessive PI3K/AKT pathway activity by modulating ROS levels, indirectly affecting AKT phosphorylation status and preventing excessive cellular proliferation. This negative feedback mechanism may protect neurons from metabolic disturbances in neurodegenerative diseases (197,198). However, the specific interaction mechanisms between PI3K/AKT and Nrf2/HO-1 in cardiovascular diseases warrant further investigation in future studies.

Notably, in hypertension, cancer and hepatic fibrosis, TSA alleviates disease progression by inhibiting the PI3K/AKT pathway (28,63,111). Conversely, in diseases such as AS, cardiac hypertrophy, HF and MIRI, TSA mitigates disease progression by activating the PI3K/AKT pathway (99,112,121,128). This differential regulation of the PI3K/AKT pathway by TSA across various diseases is primarily the result of the combined effects of disease-specific pathological mechanisms and the multi-target nature of the drug. First, disease-specific pathological mechanisms determine the functional role of the PI3K/AKT pathway. The biological functions of the PI3K/AKT pathway are highly context-dependent, with its effects varying dynamically according to disease type, cell type and pathological stage. In hypertension, sustained activation of PI3K/AKT promotes vascular smooth muscle cell proliferation and migration, leading to vascular wall thickening and, ultimately, vascular remodeling (111). In cancer, PI3K/AKT drives tumor angiogenesis by upregulating factors such as vascular endothelial growth factor and hypoxia inducible factor-1α, supporting tumor growth and metastasis (28). In fibrosis (for example, hepatic and pulmonary fibrosis), PI3K/AKT activation promotes myofibroblast transdifferentiation and collagen deposition (63). In these contexts, inhibiting this pathway can block the pathological process. However, in AS, cardiac hypertrophy, HF and ischemia-reperfusion injury (99,112,121,128), the protective function of the PI3K/AKT pathway is impaired or insufficiently upregulated, making it an ally that requires activation. Under physiological conditions, PI3K/AKT inhibits cardiomyocyte apoptosis, reduces oxidative stress and improves energy metabolism, thereby exerting cardioprotective effects (199,200). Furthermore, activating PI3K/AKT can promote the differentiation of endothelial progenitor cells and repair vascular endothelial damage (for example in AS) (99). In these scenarios, activating this pathway enhances cellular protective mechanisms.

Second, the multi-target nature of TSA enables its bidirectional regulatory effects of inhibition or activation. TSA does not simply activate or inhibit a single pathway; instead, it dynamically modulates PI3K/AKT activity by influencing upstream and downstream signaling molecules and their interactive networks. In hypertension, TSA inhibits PDK1 or the PI3K p110 subunit, blocking AKT phosphorylation (111). In AS, TSA inhibits NF-κB or the NLRP3 inflammasome, reducing the release of inflammatory cytokines (TNF-α and IL-1β), thereby alleviating their inhibitory effect on the PI3K/AKT pathway (99). In HF, TSA inhibits pro-apoptotic factors downstream of AKT or upregulates Bcl-2 (an anti-apoptotic protein), synergistically enhancing the anti-apoptotic effect of AKT (128). In MIRI, TSA scavenges ROS, preventing ROS-mediated PTEN activation and subsequent inhibition of the PI3K/AKT pathway (121). Depending on the dysregulation of the PI3K/AKT pathway (overactivation or inhibition) in a specific disease state, TSA can recalibrate pathway activity to a physiological equilibrium point by modulating its upstream and downstream molecular network, thereby alleviating the pathological process in a targeted manner (99,111,121).

In summary, the pathological mechanisms of CCVDs primarily involve endothelial dysfunction, inflammatory responses, oxidative stress and cell necrosis or apoptosis (201-203). TSA can inhibit the progression of these diseases by modulating various signaling pathways. The underlying mechanisms of these core targets stem from its pharmacological functions. For instance, the NF-κB pathway, which contributes to the development of AS (98), myocardial infarction (115), MIRI (120), cerebral ischemia-reperfusion injury (135) and stroke (144), serve as a key regulator of inflammation in cardiovascular diseases. Its activation triggers the release of pro-inflammatory cytokines, such as TNF-α and IL-6, promoting inflammation. Given the anti-inflammatory properties of TSA, it can suppress inflammation in these diseases by inhibiting the NF-κB pathway. Notably, intervention of TSA is not simply inhibition; rather, it involves context-dependent modulation, either directly blocking activation or indirectly regulating activity through upstream pathways, demonstrating the multi-target therapeutic characteristics of TCM.

5. Research on nanodelivery systems for TSA

TSA suffers from poor water solubility and a short half-life (30,31). The development of nanodelivery systems with specific structural features can considerably enhance the water solubility of TSA and prolong its *in vivo* circulation half-life (204,205). Additionally, surface modification of these nanocarriers enables targeted drug delivery, improving both bioavailability and therapeutic specificity (204,205).

A TSA-loaded reconstituted high-density lipoprotein (TA-rHDL) system was developed, with spherical and discoidal TA-rHDL structures prepared and characterized to investigate their targeting mechanisms in foam cell models and pharmacokinetics in rabbits (206,207). Results indicated that spherical TA-rHDL targeted foam cells via scavenger receptor class B type I and cholesteryl ester-triglyceride exchange pathways, while discoidal TA-rHDL could reconvert into spherical structures, enhancing targeting efficiency through similar mechanisms (206). TA-rHDL markedly prolonged circulation time, with a 4- to 13-fold increase in area under the curve (AUC) and apolipoprotein modification further optimized pharmacokinetic parameters. TA-rHDL serves both as a drug delivery vehicle and an anti-atherogenic carrier, offering a

long-acting, targeted delivery strategy for hydrophobic cardiovascular drugs (206). Moreover, by leveraging the inherent anti-atherosclerotic properties of rHDL, this system facilitates drug-carrier synergy therapy, presenting a novel strategy for treating cardiovascular disease.

Zhang *et al* (208) developed a lipid-polymer hybrid nanoparticle (LPN) system for mitochondrial-targeted TSA delivery. The study involved synthesizing a targeting ligand, triphenylphosphonium (TPP)-Lys-D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), by conjugating TPGS with TPP cations. TPP-TPGS/TSA/LPNs were then prepared using nanoprecipitation. *In vitro* experiments showed sustained release, with >80% of TSA released within 60 h, considerably enhancing uptake efficiency in cardiomyocytes (208). *In vivo* pharmacokinetic studies revealed that TPP-TPGS/TSA/LPNs achieved an AUC of 129.27 mg/l h, notably higher when compared with unmodified TSA/LPNs (42.27 mg/l h) and TSA/NPs (20.46 mg/l h) (208). In a rat myocardial infarction model, the TPP-TPGS/TSA/LPNs treatment group reduced infarct size to 28%, outperforming unmodified groups (37%) and free TSA groups (51%) (208). These findings suggest that TPP-TPGS/TSA/LPNs are an advanced nanocarrier system capable of improving the aqueous solubility, bioavailability and mitochondrial targeting in myocardial tissue of TSA, offering a promising drug delivery strategy for cardiovascular diseases (208). Furthermore, Fan *et al* (209) developed a composite material, sodium alginate (SA)/liquid metal (LM)/TSA, by ultrasonically dispersing LM nanoparticles and the drug TSA into a SA solution for intrapericardial injection in the treatment of myocardial infarction. This material exhibits low viscosity, allowing smooth injection *via* syringe, and is X-ray opaque due to the incorporation of LM. *In vitro* experiments showed that SA/LM/TSA possesses excellent biocompatibility and hemocompatibility, enabling the slow and stable release of TA. In a rat myocardial infarction model, intrapericardial injection of SA/LM/TSA proved to be a safe and effective administration method (209). After 7 days of treatment, compared with the control and TSA direct injection groups, the SA/LM/TSA group demonstrated considerable improvements in cardiac function (LVEF and LVFS), recovery of ST-segment elevation on electrocardiogram and substantial reductions in infarct size and fibrotic area (209). Concurrently, myocardial injury markers (cTnT, cTnI, CK, CK-MB and LDH) decreased, pro-inflammatory cytokine levels (TNF-α and TGF-β) declined and anti-inflammatory cytokine levels (IL-4 and IL-10) increased, indicating that SA/LM/TSA exerts synergistic anti-inflammatory and cardioprotective effects (209). However, the study did not explore the specific molecular mechanisms by which SA/LM/TSA improves cardiac function, such as the involvement of specific signaling pathways. Additionally, only a rat model with a short observation period (7 days) was used, lacking long-term efficacy and safety assessments. Further large animal experiments and pharmacokinetic studies are needed for validation (209).

In ischemic stroke research, Ma *et al* (210) developed a TSA microemulsion (TSA ME), a reformulated delivery system utilizing microemulsion technology to enhance bioavailability and targeting. The study demonstrated that TSA ME notably improved neurological deficits, reduced infarct volume in a rat MCAO model and inhibited histone deacetylase activity in an OGD/R hippocampal neuron model (210). Mechanistically, TSA ME upregulated H3K18ac and H4K8ac expression, downregulated excitotoxicity-related NMDAR1 protein and apoptosis-related Caspase-3 and concurrently promoted neuronal cytoskeletal protein MAP-2 expression (210). Compared with the conventional TSA solution, the microemulsion markedly improved drug delivery efficiency, with efficacy comparable to valproic acid (positive control) (210). These findings provide experimental evidence for TSA ME as a therapeutic candidate for ischemic stroke, highlighting its neuroprotective role via epigenetic modulation in cerebral ischemia-reperfusion injury.

In another study, the effects of cationized bovine serum albumin-conjugated PEGylated TSA nanoparticles (CBSA-PEG-TSA-NPs) on neuronal signaling pathways and neuroprotection in cerebral ischemia were investigated (211). CBSA-PEG-TSA-NPs considerably prolonged the circulation time, increased plasma concentration and enhanced brain accumulation of TSA (211). The nanoparticles effectively reduced infarct volume, neurological dysfunction, neutrophil infiltration and neuronal apoptosis, while suppressing pro-inflammatory cytokines (TNF-α and IL-8) and upregulating anti-inflammatory cytokines (IL-10 and TGF-β1) (211). Additionally, CBSA-PEG-TSA-NPs markedly downregulated GFAP, MMP-9 and COX-2 protein levels and reduced phosphorylation of ERK1/2, p38MAPK and JNK (211). The study concluded that CBSA-PEG-TSA-NPs exert neuroprotective effects in ischemic stroke by modulating MAPK signaling pathways (211). Further research explored the neuroprotective effects of TSA-loaded PLGA nanoparticles (TSA-NPs) in a porcine ischemic stroke model (204). The study evaluated the acute-phase therapeutic efficacy of TSA-NPs on cerebral pathological damage and motor dysfunction (204). TSA-NPs markedly reduced hemispheric swelling, midline shift and ischemic lesion volume, while alleviating cytotoxic edema, white matter injury and cerebral hemorrhage. Moreover, TSA-NPs improved post-stroke gait parameters (for example, step frequency and stride length) by inhibiting oxidative stress and inflammation (for example, reducing circulating neutrophil proportion) (204). These studies address clinical translation challenges of TSA, including its short half-life, poor solubility and limited BBB penetration, offering efficient targeted delivery solutions for ischemic stroke (204). Waters *et al* (204) work validated the neuroprotective mechanisms of nanocarrier systems in large animal models, providing preclinical evidence closer to human pathology.

A recent study explored the therapeutic efficacy of ROS-responsive TPP-modified TSA micelles (TK-TPP-TSA@Ms) in mitigating DOX-induced HF (205). The research developed a microenvironment-responsive micellar system targeting myocardial mitochondria by encapsulating TSA within micelles and conjugating TPP-modified DSPE-PEG2000 as a targeting moiety, with ROS-cleavable TK bonds serving as linkers. *In vitro* experiments demonstrated that TK-TPP-TSA@Ms exhibited robust uptake in H9c2 cells, considerably reducing ROS levels induced by DOX, suppressing inflammatory cytokine secretion, inhibiting apoptosis and restoring mitochondrial membrane potential (205). *In vivo* studies further confirmed that TK-TPP-TSA@Ms effectively alleviated DOX-induced myocardial tissue damage, reduced apoptosis

and inflammatory cytokine expression, mitigated oxidative stress and inhibited HF progression in mice. Fluorescence microscopy and flow cytometry analyses validated the targeting capability and ROS responsiveness of micelles. Under HF conditions, ROS cleaved the TK bonds, exposing TPP targeting ligands and enhancing micelle accumulation in damaged cardiomyocytes (205). Additionally, TK-TPP-TSA@Ms demonstrated favorable biocompatibility and stability, with negligible hemolytic effects, making them suitable for clinical applications. The study concluded that TK-TPP-TSA@Ms represent a safe and effective targeted therapeutic strategy for cardiac diseases, with potential as a promising treatment for HF (205).

In summary, nanomedicine delivery systems offer notable advantages in treating CCVDs. They enhance drug solubility and stability, addressing the challenges of poor water solubility and short half-life of TSA, thus improving bioavailability and ensuring greater drug accumulation at target sites. Additionally, these systems enable precise lesion targeting, reducing drug distribution to non-target tissues and minimizing adverse effects while enhancing therapeutic efficacy. Moreover, nanocarriers facilitate sustained or controlled drug release, prolonging the duration of action and maintaining effective concentrations, which further improves treatment outcomes.

6. Conclusion and future prospects

In recent years, active components of TCM have gained recognition for their unique advantages and potential in treating CCVDs. Various TCM monomers, such as Panax notoginseng saponins (212), astragaloside (213) and ginsenosides (214), effectively alleviate symptoms and reduce the risk of complications in CCVDs through multiple mechanisms, including lipid regulation, antioxidant effects, anti-inflammatory actions and the improvement of vascular endothelial function (212-214). TSA, a monomer derived from Salvia miltiorrhiza, is a prime example. It not only exhibits these therapeutic mechanisms but also shows notable protective effects against MIRI and cerebral infarction in numerous preclinical studies and preliminary clinical trials. Its mechanisms include regulating multiple signaling pathways, such as inhibiting inflammation-related pathways and activating antioxidant stress-related pathways, thereby improving cardiovascular and cerebrovascular function through diverse channels (26,143,215).

However, due to insufficient foundational research, the molecular mechanisms underlying the multi-target effects of TSA remain incompletely understood, particularly its interactions with ERs and regulatory networks involving specific miRNAs. Future studies could integrate single-cell sequencing technology to analyze the target sites of TSA in specific cell types, such as cardiomyocytes and neurons. Combining proteomics to explore the interaction networks of TSA with ERs and miRNAs (for example, miR-29b and miR-133) and utilizing gene editing techniques, such as CRISPR-Cas9, to validate key pathways (for example, Nrf2/HO-1 or PI3K/AKT/mTOR) by knocking out the ALKBH5 gene would help clarify the role of m6A modification in the anti-myocardial hypertrophy effects of TSA.

Moreover, the interactions between TSA and other drugs remain largely unexplored. While TSA is often used in combination with other medications, the mechanisms behind these interactions and their impact on efficacy and safety remain unclear, creating challenges for rational clinical drug use. Future research could investigate the synergistic effects of TSA with other Chinese herbal components (for example, salvianolic acid B) to develop compound formulations. Interdisciplinary collaboration will be essential to overcome current limitations and improve formulation development.

Finally, in terms of clinical translation, the lipophilic nature of TSA limits its oral absorption, making it difficult to achieve effective plasma concentrations and hindering its utilization (21). Thus, the majority of clinical studies have been small-scale trials lacking the support of large-scale, multicenter data (216-218). Additionally, the study periods are short, and the limited duration of observations is insufficient to evaluate long-term efficacy and safety. Currently, the most studied clinical formulations are Danshen injection and TSA sulfonate sodium injection (218-220). TSA is converted into TSA sulfonate sodium through a sulfonation reaction (221). This process involves specific chemical conditions that promote the binding of functional groups in the TSA molecule to sulfonate ions, resulting in the formation of TSA sulfonate sodium, which exhibits increased water solubility and enhanced bioactivity (221). This transformation not only improves the pharmacokinetic properties of TSA but also boosts its stability and efficacy *in vivo* (221). TSA sulfonate sodium can improve myocardial ischemia, inhibit platelet aggregation and provide antioxidative, anti-inflammatory and cardioprotective effects (222-225). It has been used clinically to treat CCVDs, such as coronary heart disease (226), angina pectoris (220) and stroke (227). Although clinical research still has limitations, including variable trial quality, limited sample sources and a lack of long-term follow-up data, the positive efficacy and favorable safety profile demonstrated by TSA sulfonate sodium injection have laid a solid foundation for its clinical application.

Through sulfonation structural modification and nanodrug delivery systems (such as rHDL (206), TPP-TPGS/LPNs (208), and CBSA-PEG-TSA-NPs (211), TSA's water solubility has been enhanced, its half-life extended and its targeting ability improved. As a result, TSA has transitioned from traditional applications to precision therapy, making notable strides in areas such as cardiovascular diseases (94,118), diabetic nephropathy (228,229) and tumor-targeted therapy (29,230). However, several challenges remain in achieving broader clinical application and precision therapy for TSA. In the treatment of cardiovascular diseases, while TSA sulfonate sodium injection has shown efficacy, individual patient variability may lead to inconsistent therapeutic outcomes (231-233). Future research should focus on investigating genetic characteristics, metabolic status and other factors to enable personalized, precision medicine. In diabetic nephropathy, research is still in its early stages, and the precise mechanisms through which TSA acts on renal lesions require further exploration (228,229). A deeper understanding of its mechanism will facilitate the optimization of treatment regimens and improve therapeutic efficacy. In tumor-targeted therapy, although nanodrug

delivery systems have improved the targeting ability of TSA (208), tumor cell heterogeneity and the complex tumor microenvironment complicate treatment (234). Continuous optimization of nanodrug delivery systems is necessary to enhance their specificity for tumor cells and efficiency in targeted delivery. Additionally, combining TSA with other tumor therapies should be explored to leverage its synergistic effects in comprehensive cancer treatment. To further promote clinical translation of TSA, interdisciplinary collaboration among experts in medicine, pharmacology, biology and other fields is essential for conducting large-scale, high-quality clinical trials. A robust long-term follow-up system must be established to accumulate more clinical data and evaluate the long-term efficacy and safety of TSA. Moreover, the standardization of drug development should be strengthened to ensure the effectiveness and safety of TSA-related drugs in clinical practice.

With ongoing technological advancements and deeper research, TSA is poised to carry out a pivotal role in treating more diseases. Overcoming existing challenges will expand treatment options and improve therapeutic outcomes for patients. The potential of TSA in precision therapy is expected to be fully realized, paving the way for new breakthroughs and transformative changes in clinical treatments.

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Authors' contributions

WP was responsible for conceptualization, validation and writing the original draft of the manuscript. PL revised and edited the manuscript. CD contributed to literature collection and the design of the manuscript framework. YoLi contributed to investigation, methodology and revision. WP and YiLi were responsible for the acquisition of funding and YiLi was responsible for the project administration and formal analysis. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests

References

1. Miao K, Liu W, Xu J, Qian Z and Zhang Q: Harnessing the power of traditional Chinese medicine monomers and compound prescriptions to boost cancer immunotherapy. Front Immunol 14: 1277243, 2023.
2. Wang K, Chen Q, Shao Y, Yin S, Liu C, Liu Y, Wang R, Wang T, Qiu Y and Yu H: Anticancer activities of TCM and their active components against tumor metastasis. Biomed Pharmacother 133: 111044, 2021.
3. Zhang H and Gu J: Progress of experimental study on treatment of psoriasis by Chinese medicinal monomer and single or compound recipe in Chinese materia medica. Chin J Integr Med 13: 312-316, 2007.
4. Liang J, Zhu Y, Liu S, Kuang B, Tian Z, Zhang L, Yang S, Lin M, Chen N, Liu X, *et al*: Progress of exosomal MicroRNAs and traditional Chinese medicine monomers in neurodegenerative diseases. Phytother Res 38: 5323-5349, 2024.
5. Lv D, Liu Y, Tang R, Fu S, Kong S, Liao Q, Li H and Lin L: Analysis of clinical trials using anti-tumor traditional Chinese medicine monomers. Drug Des Devel Ther 18: 1997-2020, 2024.
6. Wu X, Zhang Y, Yi F, Geng Z, Guo M, Ling X, Li J and Li L: Anti-inflammatory and barrier repair mechanisms of active components in Daemonorops draco Bl. for UVB-induced skin damage. Sci Rep 15: 17124, 2025.
7. Pan Y, Wu W, Jiang X and Liu Y: Mesenchymal stem cell-derived exosomes in cardiovascular and cerebrovascular diseases: From mechanisms to therapy. Biomed Pharmacother 163: 114817, 2023.
8. Chen C, Ai Q, Tian H and Wei Y: CKLF1 in cardiovascular and cerebrovascular diseases. Int Immunopharmacol 139: 112718, 2024.
9. Liu C, Du L, Wang S, Kong L, Zhang S, Li S, Zhang W and Du G: Differences in the prevention and control of cardiovascular and cerebrovascular diseases. Pharmacol Res 170: 105737, 2021.
10. Wang S, Yin X, Jiang T, Xu J and Wang D: Impact of cardiovascular and cerebrovascular diseases mortality on life expectancy in tianjin, 2004 and 2020. Asia Pac J Public Health 36: 455-462, 2024.
11. Luan J and Zhai G: Targeted drug delivery for cardiovascular and cerebrovascular diseases. Curr Drug Targets 17: 467-474, 2016.
12. Lan Q, Chen L, Chen MT, Wan ZX, Peng T, Mazhar M, Liu P, Luo G, Jiang Y and Liu MN: Salvia miltiorrhiza: Insights on the protective effect and mechanism of myocardial ischemia-reperfusion injury. Braz J Med Biol Res 58: e14723, 2025.
13. Li ZM, Xu SW and Liu PQ: Salvia miltiorrhizaBurge (Danshen): A golden herbal medicine in cardiovascular therapeutics. Acta Pharmacol Sin 39: 802-824, 2018.
14. Wei B, Sun C, Wan H, Shou Q, Han B, Sheng M, Li L and Kai G: Bioactive components and molecular mechanisms of Salvia miltiorrhiza Bunge in promoting blood circulation to remove blood stasis. J Ethnopharmacol 317: 116697, 2023.
15. Kim MS, Bang JH, Lee J, Kim HW, Sung SH, Han JS and Jeon WK: Salvia miltiorrhiza extract protects white matter and the hippocampus from damage induced by chronic cerebral hypoperfusion in rats. BMC Complement Altern Med 15: 415, 2015.
16. Jiang Z, Gao W and Huang L: Tanshinones, critical pharmacological components in salvia miltiorrhiza. Front Pharmacol 10: 202, 2019.
17. Pang H, Wu L, Tang Y, Zhou G, Qu C and Duan JA: Chemical analysis of the herbal medicine salviae miltiorrhizae radix et rhizoma (Danshen). Molecules 21: 51, 2016.
18. Ma XH, Ma Y, Tang JF, He YL, Liu YC, Ma XJ, Shen Y, Cui GH, Lin HX, Rong QX, *et al*: The biosynthetic pathways of tanshinones and phenolic acids in Salvia miltiorrhiza. Molecules 20: 16235-16254, 2015.
19. Wang X, Yang Y, Liu X and Gao X: Pharmacological properties of tanshinones, the natural products from Salvia miltiorrhiza. Adv Pharmacol 87: 43-70, 2020.
20. Shi MJ, Dong BS, Yang WN, Su SB and Zhang H: Preventive and therapeutic role of Tanshinone IIA in hepatology. Biomed Pharmacother 112: 108676, 2019.
21. Guo R, Li L, Su J, Li S, Duncan SE, Liu Z and Fan G: Pharmacological activity and mechanism of tanshinone IIA in related diseases. Drug Des Devel Ther 14: 4735-4748, 2020.

22. Zhong C, Lin Z, Ke L, Shi P, Li S, Huang L, Lin X and Yao H: Recent research progress (2015-2021) and perspectives on the pharmacological effects and mechanisms of tanshinone IIA. Front Pharmacol 12: 778847, 2021.
23. Li Z, Zou J, Cao D and Ma X: Pharmacological basis of tanshinone and new insights into tanshinone as a multitarget natural product for multifaceted diseases. Biomed Pharmacother 130: 110599, 2020.
24. Du L, Guan C, Zhang H, Jia H and Wan Q: Harnessing the therapeutic value of Tanshinone IIA: A breakthrough therapy in cardiovascular diseases. Front Pharmacol 16: 1620152, 2025.
25. Fu L, Han B, Zhou Y, Ren J, Cao W, Patel G, Kai G and Zhang J: The anticancer properties of tanshinones and the pharmacological effects of their active ingredients. Front Pharmacol 11: 193, 2020.
26. Lu TC, Wu YH, Chen WY and Hung YC: Targeting oxidative stress and endothelial dysfunction using tanshinone IIA for the treatment of tissue inflammation and fibrosis. Oxid Med Cell Longev 2022: 2811789, 2022.
27. Cao Y, Tang H, Wang G, Li P, Song Z, Li W, Sun X, Zhong X, Yu Q, Zhu S and Zhu L: Targeting survivin with Tanshinone IIA inhibits tumor growth and overcomes chemoresistance in colorectal cancer. Cell Death Discov 9: 351, 2023.
28. Jiang Y, Bi Y, Zhou L, Zheng S, Jian T and Chen J: Tanshinone IIA inhibits proliferation and migration by downregulation of the PI3K/Akt pathway in small cell lung cancer cells. BMC Complement Med Ther 24: 68, 2024.
29. Luo N, Zhang K, Li X, Hu Y and Guo L: Tanshinone IIA destabilizes SLC7A11 by regulating PIAS4-mediated SUMOylation of SLC7A11 through KDM1A, and promotes ferroptosis in breast cancer. J Adv Res 69: 313-327, 2025.
30. Lee AR, Wu WL, Chang WL, Lin HC and King ML: Isolation and bioactivity of new tanshinones. J Nat Prod 50: 157-160, 1987.
31. Wu WY and Wang YP: Pharmacological actions and therapeutic applications of Salvia miltiorrhiza depside salt and its active components. Acta Pharmacol Sin 33: 1119-1130, 2012.
32. Fan G, Jiang X, Wu X, Fordjour PA, Miao L, Zhang H, Zhu Y and Gao X: Anti-inflammatory activity of tanshinone IIA in LPS-Stimulated RAW264.7 Macrophages via miRNAs and TLR4-NF-κB pathway. Inflammation 39: 375-384, 2016.
33. Li YI, Elmer G and Leboeuf RC: Tanshinone IIA reduces macrophage death induced by hydrogen peroxide by upregulating glutathione peroxidase. Life Sci 83: 557-562, 2008.
34. Li X, Park SJ, Jin F, Deng Y, Yang JH, Chang JH, Kim DY, Kim JA, Lee YJ, Murakami M, *et al*: Tanshinone IIA suppresses FcεRI-mediated mast cell signaling and anaphylaxis by activation of the Sirt1/LKB1/AMPK pathway. Biochem Pharmacol 152: 362-372, 2018.
35. Maione F, De Feo V, Caiazzo E, De Martino L, Cicala C and Mascolo N: Tanshinone IIA, a major component of Salvia milthorriza Bunge, inhibits platelet activation via Erk-2 signaling pathway. J Ethnopharmacol 155: 1236-1242, 2014.
36. Fan Y, Kang S, Shao T, Xu L and Chen J: Activation of SIRT3 by Tanshinone IIA ameliorates renal fibrosis by suppressing the TGF-β/TSP-1 pathway and attenuating oxidative stress. Cell Signal 122: 111348, 2024.
37. Guo G, Zhao Q, Wang Q and Li E: Tanshinone IIA ameliorate coxsackie virus B3-induced viral myocarditis through the inhibition of inflammation and modulation T Helper 1/T Helper 2 balance in mice. Pharmacology 103: 136-142, 2019.
38. Wang P, Gu Y, Lu J, Song M, Hou W, Li P, Sun Y, Wang J and Chen X: Endothelial TRPV4 channel mediates the vasodilation induced by Tanshinone IIA. Chem Biol Interact 402: 111181, 2024.
39. Huang N, Li Y, Zhou Y, Zhou Y, Feng F, Shi S, Ba Z and Luo Y: Neuroprotective effect of tanshinone IIA-incubated mesenchymal stem cells on Aβ(25-35)-induced neuroinflammation. Behav Brain Res 365: 48-55, 2019.
40. Dinarello CA: Anti-inflammatory agents: Present and future. Cell 140: 935-950, 2010.
41. Li Y and Zhou Y: The therapeutic effect of tanshinone IIA on propionibacterium acnes-induced inflammation in vitro. Dermatol Ther 31: e12716, 2018.
42. Yang C, Lei X and Li J: Tanshinone IIA reduces oxidized low-density lipoprotein-induced inflammatory responses by downregulating microRNA-33 in THP-1 macrophages. Int J Clin Exp Pathol 12: 3791-3798, 2019.
43. Filomeni G, De Zio D and Cecconi F: Oxidative stress and autophagy: the clash between damage and metabolic needs. Cell Death Differ 22: 377-388, 2015.
44. Xu S, Liu Z, Huang Y, Le K, Tang F, Huang H, Ogura S, Little PJ, Shen X and Liu P: Tanshinone II-A inhibits oxidized LDL-induced LOX-1 expression in macrophages by reducing intracellular superoxide radical generation and NF-κB activation. Transl Res 160: 114-124, 2012.
45. Feng J, Li S and Chen H: Tanshinone IIA inhibits myocardial remodeling induced by pressure overload via suppressing oxidative stress and inflammation: Possible role of silent information regulator 1. Eur J Pharmacol 791: 632-639, 2016.
46. Wang X, Wang WM, Han H, Zhang Y, Liu JL, Yu JY, Liu HM, Liu XT, Shan H and Wu SC: Tanshinone IIA protected against lipopolysaccharide-induced brain injury through the protective effect of the blood-brain barrier and the suppression of oxidant stress and inflammatory response. Food Funct 13: 8304-8312, 2022.
47. Elmore S: Apoptosis: A review of programmed cell death. Toxicol Pathol 35: 495-516, 2007.
48. Zhang Z, Li Y, Sheng C, Yang C, Chen L and Sun J: Tanshinone IIA inhibits apoptosis in the myocardium by inducing microRNA-152-3p expression and thereby downregulating PTEN. Am J Transl Res 8: 3124-3132, 2016.
49. Song T, Yao Y, Wang T, Huang H and Xia H: Tanshinone IIA ameliorates apoptosis of myocardiocytes by up-regulation of miR-133 and suppression of Caspase-9. Eur J Pharmacol 815: 343-350, 2017.
50. Zhang L, Wu Y, Li Y, Xu C, Li X, Zhu D, Zhang Y, Xing S, Wang H, Zhang Z and Shan H: Tanshinone IIA improves miR-133 expression through MAPK ERK1/2 pathway in hypoxic cardiac myocytes. Cell Physiol Biochem 30: 843-852, 2012.
51. Yan SH, Zhao NW, Geng ZR, Shen JY, Liu FM, Yan D, Zhou J, Nie C, Huang CC and Fang ZY: Modulations of Keap1-Nrf2 signaling axis by TIIA ameliorated the oxidative stress-induced myocardial apoptosis. Free Radic Biol Med 115: 191-201, 2018.
52. Bellanti JA and Settipane RA: Allergy and immunology: At the crossroad of inflammation and disease. Allergy Asthma Proc 44: 1-2, 2023.
53. Costanzo G, Marchetti M, Ledda AG, Sambugaro G, Bullita M, Paoletti G, Heffler E, Firinu D and Costanzo GAML: Mast cells in allergic and non-allergic upper airways diseases: Sentinel in the watchtower. Int J Mol Sci 25: 12615, 2024.
54. Kaminuma O, Nishimura T, Saeki M, Mori A and Hiroi T: T cell-mediated nasal hyperresponsiveness in allergic rhinitis. Biol Pharm Bull 43: 36-40, 2020.
55. Méndez-Enríquez E and Hallgren J: Mast cells and their progenitors in allergic asthma. Front Immunol 10: 821, 2019.
56. Thangam EB, Jemima EA, Singh H, Baig MS, Khan M, Mathias CB, Church MK and Saluja R: The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: The hunt for new therapeutic targets. Front Immunol 9: 1873, 2018.
57. Zhang J, Xie X, Ma R and Liu P: The role of mast cells in allergic rhinitis. PeerJ 13: e19734, 2025.
58. Asada Y, Yamashita A, Sato Y and Hatakeyama K: Thrombus formation and propagation in the onset of cardiovascular events. J Atheroscler Thromb 25: 653-664, 2018.
59. Fei YX, Wang SQ, Yang LJ, Qiu YY, Li YZ, Liu WY, Xi T, Fang WR and Li YM: Salvia miltiorrhiza Bunge (Danshen) extract attenuates permanent cerebral ischemia through inhibiting platelet activation in rats. J Ethnopharmacol 207: 57-66, 2017.
60. Jiang Y, Hu F, Li M and Li Q: Tanshinone IIA ameliorates the development of dermal fibrosis in systemic sclerosis. Clin Exp Pharmacol Physiol 51: e13834, 2024.
61. Wang DT, Huang RH, Cheng X, Zhang ZH, Yang YJ and Lin X: Tanshinone IIA attenuates renal fibrosis and inflammation via altering expression of TGF-β/Smad and NF-κB signaling pathway in 5/6 nephrectomized rats. Int Immunopharmacol 26: 4-12, 2015.
62. Liao W, Wu F, Hao Z, Ye R, Liu C, Wu J, Wu M, Zhou X, Sun M, Liu Y and Fang M: Tanshinone IIA alleviates liver fibrosis by suppressing hepatic stellate cell proliferation via ERK/cyclin D1/p-Smad3L signaling axis. Iran J Basic Med Sci 28: 638-646, 2025.
63. Li Q, Huang D, Liao W, Su X, Li J, Zhang J, Fang M and Liu Y: Tanshinone IIA regulates CCl(4) induced liver fibrosis in C57BL/6J mice via the PI3K/Akt and Nrf2/HO-1 signaling pathways. J Biochem Mol Toxicol 38: e23648, 2024.
64. Ren X, Wang C, Xie B, Hu L, Chai H, Ding L, Tang L, Xia Y and Dou X: Tanshinone IIA induced cell death via miR30b-p53-PTPN11/SHP2 signaling pathway in human hepatocellular carcinoma cells. Eur J Pharmacol 796: 233-241, 2017.

65. Liu J, Zhang C, Liu S, Wang X, Wu X and Hao J: Tanshinone IIA promotes apoptosis by downregulating BCL2 and upregulating TP53 in triple-negative breast cancer. Naunyn Schmiedebergs Arch Pharmacol 396: 365-374, 2023.
66. Zhang W, Liu M, Ji Y, Yu D, Ma C, Zhao J and Qu P: Tanshinone IIA inhibits endometrial carcinoma growth through the MAPK/ERK/TRIB3 pathway. Arch Biochem Biophys 743: 109655, 2023.
67. Gao M, Ou H, Jiang Y, Wang K, Peng Y, Zhang H, Yang M and Xiao X: Tanshinone IIA attenuates sepsis-induced immunosuppression and improves survival rate in a mice peritonitis model. Biomed Pharmacother 112: 108609, 2019.
68. Kim WS, Kim DO, Yoon SJ, Kim MJ, Yoon SR, Park YJ, Jung H, Kim TD, Kwon BM and Choi I: Cryptotanshinone and tanshinone IIA enhance IL-15-induced natural killer cell differentiation. Biochem Biophys Res Commun 425: 340-347, 2012.
69. Li D, Yang Z, Gao S, Zhang H and Fan G: Tanshinone IIA ameliorates myocardial ischemia/reperfusion injury in rats by regulation of NLRP3 inflammasome activation and Th17 cells differentiation. Acta Cir Bras 37: e370701, 2022.
70. Godo S and Shimokawa H: Endothelial functions. Arterioscler Thromb Vasc Biol 37: e108-e114, 2017.
71. Huang KJ, Wang H, Xie WZ and Zhang HS: Investigation of the effect of tanshinone IIA on nitric oxide production in human vascular endothelial cells by fluorescence imaging. Spectrochim Acta A Mol Biomol Spectrosc 68: 1180-1186, 2007.
72. Li YH, Xu Q, Xu WH, Guo XH, Zhang S and Chen YD: Mechanisms of protection against diabetes-induced impairment of endothelium-dependent vasorelaxation by Tanshinone IIA. Biochim Biophys Acta 1850: 813-823, 2015.
73. Zhang XS, Ha S, Wang XL, Shi YL, Duan SS and Li ZA: Tanshinone IIA protects dopaminergic neurons against 6-hydroxydopamine-induced neurotoxicity through miR-153/NF-E2-related factor 2/antioxidant response element signaling pathway. Neuroscience 303: 489-502, 2015.
74. Chen J, Bi Y, Chen L, Zhang Q and Xu L: Tanshinone IIA exerts neuroprotective effects on hippocampus-dependent cognitive impairments in diabetic rats by attenuating ER stress-induced apoptosis. Biomed Pharmacother 104: 530-536, 2018.
75. Huang X, Deng H, Shen QK and Quan ZS: Tanshinone IIA: Pharmacology, total synthesis, and progress in structure-modifications. Curr Med Chem 29: 1959-1989, 2022.
76. Huang X, Jin L, Deng H, Wu D, Shen QK, Quan ZS, Zhang CH and Guo HY: Research and development of natural product tanshinone I: Pharmacology, total synthesis, and structure modifications. Front Pharmacol 13: 920411, 2022.
77. Ke L, Zhong C, Chen Z, Zheng Z, Li S, Chen B, Wu Q and Yao H: Tanshinone I: Pharmacological activities, molecular mechanisms against diseases and future perspectives. Phytomedicine 110: 154632, 2023.
78. Luo L, Xue J, Shao Z, Zhou Z, Tang W, Liu J, Hu H and Yang F: Recent developments in Salvia miltiorrhiza polysaccharides: Isolation, purification, structural characteristics and biological activities. Front Pharmacol 14: 1139201, 2023.
79. Wang D, Lu C, Sun F, Cui M, Mu H, Duan J and Geng H: A tanshinone I derivative enhances the activities of antibiotics against Staphylococcus aureus in vitro and in vivo. Res Microbiol 168: 46-54, 2017.
80. Zhao J, Liu H, Hong Z, Luo W, Mu W, Hou X, Xu G, Fang Z, Ren L, Liu T, *et al*: Tanshinone I specifically suppresses NLRP3 inflammasome activation by disrupting the association of NLRP3 and ASC. Mol Med 29: 84, 2023.
81. Hu C, He X, Zhang H, Hu X, Liao L, Cai M, Lin Z, Xiang J, Jia X, Lu G, *et al*: Tanshinone I limits inflammasome activation of macrophage via docking into Syk to alleviate DSS-induced colitis in mice. Mol Immunol 173: 88-98, 2024.
82. Jing X, Xu Y, Cheng W, Guo S, Zou Y and He L: Tanshinone I induces apoptosis and pro-survival autophagy in gastric cancers. Cancer Chemother Pharmacol 77: 1171-1181, 2016.
83. Qian Z, Feng N and Geng A: Tanshinone I suppresses hepatocellular carcinoma cells growth through targeting DNA double-strand break repair. Cancer Biol Ther 24: 2229958, 2023.
84. Ho JH and Hong CY: Salvianolic acids: Small compounds with multiple mechanisms for cardiovascular protection. J Biomed Sci 18: 30, 2011.
85. Feng S, Cong H and Ji L: Salvianolic acid a exhibits anti-inflammatory and antiarthritic effects via inhibiting NF-κB and p38/MAPK pathways. Drug Des Devel Ther 14: 1771-1778, 2020.
86. Wu Y, Wang Z, Lin Z, Fu X, Zhan J and Yu K: Salvianolic acid a has anti-osteoarthritis effect in vitro and in vivo. Front Pharmacol 11: 682, 2020.
87. Zhou AM, Xiang YJ, Liu EQ, Cai CH, Wu YH, Yang LB and Zeng CL: Salvianolic acid a inhibits platelet activation and aggregation in patients with type 2 diabetes mellitus. BMC Cardiovasc Disord 20: 15, 2020.
88. Wang R, Song F, Li S, Wu B, Gu Y and Yuan Y: Salvianolic acid A attenuates CCl(4)-induced liver fibrosis by regulating the PI3K/AKT/mTOR, Bcl-2/Bax and caspase-3/cleaved caspase-3 signaling pathways. Drug Des Devel Ther 13: 1889-1900, 2019.
89. Yang D, Xia X and Xi S: Salvianolic acid A attenuates arsenic-induced ferroptosis and kidney injury via HIF-2α/DUOX1/GPX4 and iron homeostasis. Sci Total Environ 907: 168073, 2024.
90. Zhu J, Guo J, Liu Z, Liu J, Yuan A, Chen H, Qiu J, Dou X, Lu D and Le Y: Salvianolic acid A attenuates non-alcoholic fatty liver disease by regulating the AMPK-IGFBP1 pathway. Chem Biol Interact 400: 111162, 2024.
91. Han JY, Fan JY, Horie Y, Miura S, Cui DH, Ishii H, Hibi T, Tsuneki H and Kimura I: Ameliorating effects of compounds derived from Salvia miltiorrhiza root extract on microcirculatory disturbance and target organ injury by ischemia and reperfusion. Pharmacol Ther 117: 280-295, 2008.
92. Yu XQ, Xue CC, Zhou ZW, Li CG and Zhou SF: Tanshinone IIB, a primary active constituent from Salvia miltiorrhiza, exerts neuroprotective effect via inhibition of neuronal apoptosis in vitro. Phytother Res 22: 846-850, 2008.
93. Yu XY, Lin SG, Zhou ZW, Chen X, Liang J, Duan W, Yu XQ, Wen JY, Chowbay B, Li CG, *et al*: Tanshinone IIB, a primary active constituent from Salvia miltiorrhza, exhibits neuro-protective activity in experimentally stroked rats. Neurosci Lett 417: 261-265, 2007.
94. Ma X, Zhang L, Gao F, Jia W and Li C: Salvia miltiorrhiza and Tanshinone IIA reduce endothelial inflammation and atherosclerotic plaque formation through inhibiting COX-2. Biomed Pharmacother 167: 115501, 2023.
95. Fang Y, Duan C, Chen S, Liu Z, Jiang B, Ai W, Wang L, Xie P and Fang H: Tanshinone-IIA inhibits myocardial infarct via decreasing of the mitochondrial apoptotic signaling pathway in myocardiocytes. Int J Mol Med 48: 158, 2021.
96. Hu T, Zou HX, Le SY, Wang YR, Qiao YM, Yuan Y, Liu JC, Lai SQ and Huang H: Tanshinone IIA confers protection against myocardial ischemia/reperfusion injury by inhibiting ferroptosis and apoptosis via VDAC1. Int J Mol Med 52: 109, 2023.
97. Kang YJ, Jin UH, Chang HW, Son JK, Lee SH, Son KH, Chang YC, Lee YC and Kim CH: Inhibition of microsomal triglyceride transfer protein expression and atherogenic risk factor apolipoprotein B100 secretion by tanshinone IIA in HepG2 cells. Phytother Res 22: 1640-1645, 2008.
98. Zhang Y, Wang J, Yang S, Kou H and Liu P: Tanshinone IIA alleviate atherosclerosis and hepatic steatosis via down-regulation of MAPKs/NF-κB signaling pathway. Int Immunopharmacol 152: 114465, 2025.
99. Hong HJ, Hsu FL, Tsai SC, Lin CH, Liu JC, Chen JJ, Cheng TH and Chan P: Tanshinone IIA attenuates cyclic strain-induced endothelin-1 expression in human umbilical vein endothelial cells. Clin Exp Pharmacol Physiol 39: 63-68, 2012.
100. Pu X, Wu Q, Yan Z, Zhou S, Zhang Q, Zhang X, Cai Y, Liu Z, Liu R and Chang X: Tanshinone IIA modulates Sirt5 and Metll3 interaction to govern mitochondria-endoplasmic reticulum unfolded protein response in coronary microvascular injury. Phytomedicine 145: 156982, 2025.
101. Jin P and Cong S: LOX-1 and atherosclerotic-related diseases. Clin Chim Acta 491: 24-29, 2019.
102. Chen W, Li X, Guo S, Song N, Wang J, Jia L and Zhu A: Tanshinone IIA harmonizes the crosstalk of autophagy and polarization in macrophages via miR-375/KLF4 pathway to attenuate atherosclerosis. Int Immunopharmacol 70: 486-497, 2019.
103. Yuan L, Li Q, Zhang Z, Liu Q, Wang X and Fan L: Tanshinone IIA inhibits the adipogenesis and inflammatory response in ox-LDL-challenged human monocyte-derived macrophages via regulating miR-130b/WNT5A. J Cell Biochem 121: 1400-1408, 2020.
104. Xu S, Little PJ, Lan T, Huang Y, Le K, Wu X, Shen X, Huang H, Cai Y, Tang F, *et al*: Tanshinone II-A attenuates and stabilizes atherosclerotic plaques in apolipoprotein-E knockout mice fed a high cholesterol diet. Arch Biochem Biophys 515: 72-79, 2011.

105. Liu X, Guo CY, Ma XJ, Wu CF, Zhang Y, Sun MY, Pan YT and Yin HJ: Anti-inflammatory effects of tanshinone IIA on atherosclerostic vessels of ovariectomized ApoE mice are mediated by estrogen receptor activation and through the ERK signaling pathway. Cell Physiol Biochem 35: 1744-1755, 2015.
106. Tang F, Wu X, Wang T, Wang P, Li R, Zhang H, Gao J, Chen S, Bao L, Huang H and Liu P: Tanshinone II A attenuates atherosclerotic calcification in rat model by inhibition of oxidative stress. Vascul Pharmacol 46: 427-438, 2007.
107. Feng J, Chen HW, Pi LJ, Wang J and Zhan DQ: Protective effect of tanshinone IIA against cardiac hypertrophy in spontaneously hypertensive rats through inhibiting the Cys-C/Wnt signaling pathway. Oncotarget 8: 10161-10170, 2017.
108. Pang H, Han B, Yu T and Peng Z: The complex regulation of tanshinone IIA in rats with hypertension-induced left ventricular hypertrophy. PLoS One 9: e92216, 2014.
109. Fang J, Xu SW, Wang P, Tang FT, Zhou SG, Gao J, Chen JW, Huang HQ and Liu PQ: Tanshinone II-A attenuates cardiac fibrosis and modulates collagen metabolism in rats with renovascular hypertension. Phytomedicine 18: 58-64, 2010.
110. Wang P, Wu X, Bao Y, Fang J, Zhou S, Gao J, Pi R, Mou YG and Liu P: Tanshinone IIA prevents cardiac remodeling through attenuating NAD (P)H oxidase-derived reactive oxygen species production in hypertensive rats. Pharmazie 66: 517-524, 2011.
111. Yu ZL, Wang JN, Wu XH, Xie HJ, Han Y, Guan YT, Qin Y and Jiang JM: Tanshinone IIA Prevents rat basilar artery smooth muscle cells proliferation by inactivation of PDK1 during the development of hypertension. J Cardiovasc Pharmacol Ther 20: 563-571, 2015.
112. Weng YS, Wang HF, Pai PY, Jong GP, Lai CH, Chung LC, Hsieh DJ, HsuanDay C, Kuo WW and Huang CY: Tanshinone IIA Prevents Leu27IGF-II-induced cardiomyocyte hypertrophy mediated by estrogen receptor and subsequent Akt activation. Am J Chin Med 43: 1567-1591, 2015.
113. Zhang M, Chen Y, Chen H, Shen Y, Pang L, Wu W and Yu Z: Tanshinone IIA alleviates cardiac hypertrophy through m6A modification of galectin-3. Bioengineered 13: 4260-4270, 2022.
114. Zhang Y, Zhang L, Chu W, Wang B, Zhang J, Zhao M, Li X, Li B, Lu Y, Yang B and Shan H: Tanshinone IIA inhibits miR-1 expression through p38 MAPK signal pathway in post-infarction rat cardiomyocytes. Cell Physiol Biochem 26: 991-998, 2010.
115. Ren ZH, Tong YH, Xu W, Ma J and Chen Y: Tanshinone II A attenuates inflammatory responses of rats with myocardial infarction by reducing MCP-1 expression. Phytomedicine 17: 212-218, 2010.
116. Gao S, Yang Z, Li D, Wang B, Zheng X, Li C and Fan G: Intervention of Tanshinone IIA on the PGK1-PDHK1 pathway to reprogram macrophage phenotype after myocardial infarction. Cardiovasc Drugs Ther 38: 1359-1373, 2024.
117. Yang F, Li P, Li H, Shi Q, Li S and Zhao L: microRNA-29b mediates the antifibrotic effect of tanshinone IIA in postinfarct cardiac remodeling. J Cardiovasc Pharmacol 65: 456-464, 2015.
118. Chai R, Ye Z, Xue W, Shi S, Wei Y, Hu Y and Wu H: Tanshinone IIA inhibits cardiomyocyte pyroptosis through TLR4/NF-κB p65 pathway after acute myocardial infarction. Front Cell Dev Biol 11: 1252942, 2023.
119. Chen R, Chen W, Huang X and Rui Q: Tanshinone IIA attenuates heart failure via inhibiting oxidative stress in myocardial infarction rats. Mol Med Rep 23: 404, 2021.
120. Zhang Y, Wei L, Sun D, Cao F, Gao H, Zhao L, Du J, Li Y and Wang H: Tanshinone IIA pretreatment protects myocardium against ischaemia/reperfusion injury through the phosphatidylinositol 3-kinase/Akt-dependent pathway in diabetic rats. Diabetes Obes Metab 12: 316-322, 2010.
121. Li Q, Shen L, Wang Z, Jiang HP and Liu LX: Tanshinone IIA protects against myocardial ischemia reperfusion injury by activating the PI3K/Akt/mTOR signaling pathway. Biomed Pharmacother 84: 106-114, 2016.
122. Zhang Z, He H, Qiao Y, Huang J, Wu Z, Xu P, Yin D and He M: Tanshinone IIA Pretreatment Protects H9c2 cells against anoxia/reoxygenation injury: Involvement of the translocation of Bcl-2 to mitochondria mediated by 14-3-3η. Oxid Med Cell Longev 2018: 3583921, 2018.
123. Wang Y, Sun W, Shen L, Yu P, Shen Q, Zhou Y, Yao L and Chen X: Tanshinone IIA protects ischemia/reperfusion-induced cardiomyocyte injury by inhibiting the HAS2/FGF9 Axis. Cardiol Res Pract 2024: 2581638, 2024.
124. Yan K, Yu S, Gao X, Li L and Ding L: Tanshinone IIA ameliorates myocardial ischemia-reperfusion injury via activating HDAC1-Repressed Nrf2-xCT/Gpx4/HO-1 Axis. Chem Biol Drug Des 105: e70095, 2025.
125. Sang Y, Du J, Zulikala D and Sang Z: Mechanistic analysis of Tanshinone IIA's regulation of the ATM/GADD45/ORC signaling pathway to reduce myocardial ischemia-reperfusion injury. Front Pharmacol 15: 1510380, 2024.
126. Li S, Yang K, Cao W, Guo R, Liu Z, Zhang J, Fan A, Huang Y, Ma C, Li L and Fan G: Tanshinone IIA enhances the therapeutic efficacy of mesenchymal stem cells derived exosomes in myocardial ischemia/reperfusion injury via up-regulating miR-223-5p. J Control Release 358: 13-26, 2023.
127. Zhai P, Chen Q, Wang X, Ouyang X, Yang M, Dong Y, Li J, Li Y, Luo S, Liu Y, *et al*: The combination of Tanshinone IIA and Astragaloside IV attenuates myocardial ischemia-reperfusion injury by inhibiting the STING pathway. Chin Med 19: 34, 2024.
128. Hong HJ, Liu JC, Chen PY, Chen JJ, Chan P and Cheng TH: Tanshinone IIA prevents doxorubicin-induced cardiomyocyte apoptosis through Akt-dependent pathway. Int J Cardiol 157: 174-179, 2012.
129. Xu L, He D, Wu Y, Shen L, Wang Y and Xu Y: Tanshinone IIA inhibits cardiomyocyte apoptosis and rescues cardiac function during doxorubicin-induced cardiotoxicity by activating the DAXX/MEK/ERK1/2 pathway. Phytomedicine 107: 154471, 2022.
130. Zhang X, Wang Q, Wang X, Chen X, Shao M, Zhang Q, Guo D, Wu Y, Li C, Wang W and Wang Y: Tanshinone IIA protects against heart failure post-myocardial infarction via AMPKs/mTOR-dependent autophagy pathway. Biomed Pharmacother 112: 108599, 2019.
131. Mao S, Wang Y, Zhang M and Hinek A: Phytoestrogen, tanshinone IIA diminishes collagen deposition and stimulates new elastogenesis in cultures of human cardiac fibroblasts. Exp Cell Res 323: 189-197, 2014.
132. Yan N, Xiao C, Wang X, Xu Z and Yang J: Tanshinone IIA from Salvia miltiorrhiza exerts anti-fibrotic effects on cardiac fibroblasts and rat heart tissues by suppressing the levels of pro-fibrotic factors: The key role of miR-618. J Food Biochem 46: e14078, 2022.
133. Huang L, Zhu J, Zheng M, Zou R, Zhou Y and Zhu M: Tanshinone IIA protects against subclinical lipopolysaccharide induced cardiac fibrosis in mice through inhibition of NADPH oxidase. Int Immunopharmacol 60: 59-63, 2018.
134. Sun DD, Wang HC, Wang XB, Luo Y, Jin ZX, Li ZC, Li GR and Dong MQ: Tanshinone IIA: A new activator of human cardiac KCNQ1/KCNE1 (I(Ks)) potassium channels. Eur J Pharmacol 590: 317-321, 2008.
135. Wang JG, Bondy SC, Zhou L, Yang FZ, Ding ZG, Hu Y, Tian Y, Wen PY, Luo H, Wang F, *et al*: Protective effect of Tanshinone IIA against infarct size and increased HMGB1, NFκB, GFAP and apoptosis consequent to transient middle cerebral artery occlusion. Neurochem Res 39: 295-304, 2014.
136. Su W, Lv M, Wang D, He Y, Han H, Zhang Y, Zhang X, Lv S and Yao L: Tanshinone IIA alleviates traumatic brain injury by reducing ischemia-reperfusion via the miR-124-5p/FoxO1 Axis. Mediators Inflamm 2024: 7459054, 2024.
137. Zhou C, Yu Z, Chen T, Chen Q, Zhang Y, Cai J, Xu C and Yu L: Tanshinone IIA attenuates cerebral-ischemia-reperfusion-induced neuroinflammation by inhibiting the TLR4/NF-κB signaling cascade: A study integrating network pharmacology, bioinformatics, and experimental validation. Phytomedicine 149: 157548, 2025.
138. Yu H, Zhang R, Wang Q, Zhang H, Lei Z, Li R, Shen W, Zhang Y, Lv S and Qian Y: Tanshinone IIA inhibits microglial activation and inflammation and relieves cerebral ischemia-reperfusion injury through TGM2/PANX1. Biochem Genet: Dec 6, 2025 (Epub ahead of print).
139. Yu H, Li Y, Yang Y, Qian Y, Gao X, Wang X, Zhan P, Tang D, Qin M and Qian Y: Tanshinone IIA inhibits neuronal ferroptosis and relieves cerebral ischemia-reperfusion injury by regulating miR-449a/ACSL4. Metab Brain Dis 40: 231, 2025.
140. Wang W, Zheng LL, Wang F, Hu ZL, Wu WN, Gu J and Chen JG: Tanshinone IIA attenuates neuronal damage and the impairment of long-term potentiation induced by hydrogen peroxide. J Ethnopharmacol 134: 147-155, 2011.
141. Cai M, Guo Y, Wang S, Wei H, Sun S, Zhao G and Dong H: Tanshinone IIA elicits neuroprotective effect through activating the nuclear factor erythroid 2-related factor-dependent antioxidant response. Rejuvenation Res 20: 286-297, 2017.

142. Liu L, Zhang X, Wang L, Yang R, Cui L, Li M, Du W and Wang S: The neuroprotective effects of Tanshinone IIA are associated with induced nuclear translocation of TORC1 and upregulated expression of TORC1, pCREB and BDNF in the acute stage of ischemic stroke. Brain Res Bull 82: 228-233, 2010.
143. Miao Q, Wang R, Sun X, Du S and Liu L: Combination of puerarin and tanshinone IIA alleviates ischaemic stroke injury in rats via activating the Nrf2/ARE signalling pathway. Pharm Biol 60: 1022-1031, 2022.
144. Yang F, Ma N, Li S, Chen F, Huang X, Zhao L and Cao L: Tanshinone IIA alleviates early brain injury after subarachnoid hemorrhage in rats by inhibiting the activation of NF-κB/NLRP3 inflammasome. Biol Pharm Bull 47: 279-291, 2024.
145. Falk E: Pathogenesis of atherosclerosis. J Am Coll Cardiol 47 (Suppl 8): C7-C12, 2006.
146. Xuan Y, Gao Y, Huang H, Wang X, Cai Y and Luan QX: Tanshinone IIA attenuates atherosclerosis in apolipoprotein E knockout mice infected with porphyromonas gingivalis. Inflammation 40: 1631-1642, 2017.
147. Trepels T, Zeiher AM and Fichtlscherer S: The endothelium and inflammation. Endothelium 13: 423-429, 2006.
148. Maguire JJ, Kuc RE and Davenport AP: Vasoconstrictor activity of novel endothelin peptide, ET-1(1-31), in human mammary and coronary arteries in vitro. Br J Pharmacol 134: 1360-1366, 2001.
149. Wang Y, Ruan Y and Wu S: ET-1 regulates the human umbilical vein endothelial cell cycle by adjusting the ERβ/FOXN1 signaling pathway. Ann Transl Med 8: 1499, 2020.
150. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT and Sahebkar A: Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 233: 6425-6440, 2018.
151. Cao H, Jia Q, Yan L, Chen C, Xing S and Shen D: Quercetin suppresses the progression of atherosclerosis by regulating MST1-Mediated Autophagy in ox-LDL-Induced RAW264.7 macrophage foam cells. Int J Mol Sci 20: 6093, 2019.
152. Rendra E, Riabov V, Mossel DM, Sevastyanova T, Harmsen MC and Kzhyshkowska J: Reactive oxygen species (ROS) in macrophage activation and function in diabetes. Immunobiology 224: 242-253, 2019.
153. Durham AL, Speer MY, Scatena M, Giachelli CM and Shanahan CM: Role of smooth muscle cells in vascular calcification: Implications in atherosclerosis and arterial stiffness. Cardiovasc Res 114: 590-600, 2018.
154. Elliott WJ: Systemic hypertension. Curr Probl Cardiol 32: 201-259, 2007.
155. Zicha J and Vaněčková I: Altered balance between vasoconstrictor and vasodilator systems in experimental hypertension. Physiol Res 73: 901-928, 2024.
156. Chan P, Liu IM, Li YX, Yu WJ and Cheng JT: Antihypertension induced by tanshinone IIA isolated from the roots of salvia miltiorrhiza. Evid Based Complement Alternat Med 2011: 392627, 2011.
157. Musumeci MB, Mastromarino V, Casenghi M, Tini G, Francia P, Maruotti A, Romaniello A, Magrì D, Lillo R, Adduci C, *et al*: Pulmonary hypertension and clinical correlates in hypertrophic cardiomyopathy. Int J Cardiol 248: 326-332, 2017.
158. Zhang Z, Tang J, Song J, Xie M, Liu Y, Dong Z, Liu X, Li X, Zhang M, Chen Y, *et al*: Elabela alleviates ferroptosis, myocardial remodeling, fibrosis and heart dysfunction in hypertensive mice by modulating the IL-6/STAT3/GPX4 signaling. Free Radic Biol Med 181: 130-142, 2022.
159. Deng HW, Ye ZM, Hu RT and Qin C: The role of long noncoding RNAs in vascular smooth muscle cell phenotype and the pathogenesis of cardiovascular and cerebrovascular aneurysms. J Cardiovasc Pharmacol 84: 125-135, 2024.
160. Gao M, Ma MM, Lu FT, Huang CC, Sun L, Lv XF, Zhang B, Wang GL and Guan YY: Low chloride-regulated ClC-5 contributes to arterial smooth muscle cell proliferation and cerebrovascular remodeling. Hypertension 79: e73-e85, 2022.
161. Nakamura M and Sadoshima J: Mechanisms of physiological and pathological cardiac hypertrophy. Nat Rev Cardiol 15: 387-407, 2018.
162. Tu EY, Zhou YG, Wang ZH, Liang QS and Yang GT: Effects of tanshinone II A on the myocardial hypertrophy signal transduction system protein kinase B in rats. Chin J Integr Med 15: 365-370, 2009.
163. Tan X, Li J, Wang X, Chen N, Cai B, Wang G, Shan H, Dong D, Liu Y, Li X, *et al*: Tanshinone IIA protects against cardiac hypertrophy via inhibiting calcineurin/NFATc3 pathway. Int J Biol Sci 7: 383-389, 2011.
164. Lu L, Liu M, Sun R, Zheng Y and Zhang P: Myocardial infarction: Symptoms and treatments. Cell Biochem Biophys 72: 865-867, 2015.
165. Liu X, Zhang W, Luo J, Shi W, Zhang X, Li Z, Qin X, Liu B and Wei Y: TRIM21 deficiency protects against atrial inflammation and remodeling post myocardial infarction by attenuating oxidative stress. Redox Biol 62: 102679, 2023.
166. Prabhu SD and Frangogiannis NG: The biological basis for cardiac repair after myocardial infarction: From inflammation to fibrosis. Circ Res 119: 91-112, 2016.
167. Vasudevan SO, Behl B and Rathinam VA: Pyroptosis-induced inflammation and tissue damage. Semin Immunol 69: 101781, 2023.
168. Zhang J, Huang L, Shi X, Yang L, Hua F, Ma J, Zhu W, Liu X, Xuan R, Shen Y, *et al*: Metformin protects against myocardial ischemia-reperfusion injury and cell pyroptosis via AMPK/NLRP3 inflammasome pathway. Aging (Albany NY) 12: 24270-24287, 2020.
169. Bahit MC, Kochar A and Granger CB: Post-Myocardial infarction heart failure. JACC Heart Fail 6: 179-186, 2018.
170. Zhu T, Chen J, Zhang M, Tang Z, Tong J, Hao X, Li H, Xu J and Yang J: Tanshinone IIA exerts cardioprotective effects through improving gut-brain axis post-myocardial infarction. Cardiovasc Toxicol 24: 1317-1334, 2024.
171. Algoet M, Janssens S, Himmelreich U, Gsell W, Pusovnik M, Van den Eynde J and Oosterlinck W: Myocardial ischemia-reperfusion injury and the influence of inflammation. Trends Cardiovasc Med 33: 357-366, 2023.
172. Zhu PC, Shen J, Qian RY, Xu J, Liu C, Hu WM, Zhang Y and Lv LC: Effect of tanshinone IIA for myocardial ischemia/reperfusion injury in animal model: preclinical evidence and possible mechanisms. Front Pharmacol 14: 1165212, 2023.
173. Zhang X, Jiang H, Zhang L, Chen C, Xing M, Du D, Li Y, Ma Y, Ma Y and Li C: Efficacy of tanshinone IIA in rat models with myocardial ischemia-reperfusion injury: A systematic mini-review and meta-analysis. PeerJ 12: e17885, 2024.
174. Wang L, Qiu S, Li X, Zhang Y, Huo M and Shi J: Myocardial-Targeting tannic cerium nanocatalyst attenuates ischemia/reperfusion injury. Angew Chem Int Ed Engl 62: e202305576, 2023.
175. Ma T, Wang J, Sun G, Li K, Qu H, Wang Y, Li S and Wu B: Irisin and liraglutide combination therapy mitigates myocardial reperfusion injury in obese rats: Role of endoplasmic reticulum stress and apoptosis. Arch Biochem Biophys 768: 110370, 2025.
176. Dong Z, Yang L, Jiao J, Jiang Y, Li H, Yin G, Yang P and Sun L: Aspirin in combination with gastrodin protects cardiac function and mitigates gastric mucosal injury in response to myocardial ischemia/reperfusion. Front Pharmacol 13: 995102, 2022.
177. Rogers C and Bush N: Heart failure: Pathophysiology, diagnosis, medical treatment guidelines, and nursing management. Nurs Clin North Am 50: 787-799, 2015.
178. Tanai E and Frantz S: Pathophysiology of heart failure. Compr Physiol 6: 187-214, 2015.
179. Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, Burkhoff D, Zannad F, Udelson JE and Voors AA: Congestion in heart failure: A contemporary look at physiology, diagnosis and treatment. Nat Rev Cardiol 17: 641-655, 2020.
180. Du J, Liu Y and Fu J: Autophagy and heart failure. Adv Exp Med Biol 1207: 223-227, 2020.
181. Shirakabe A, Zhai P, Ikeda Y, Saito T, Maejima Y, Hsu CP, Nomura M, Egashira K, Levine B and Sadoshima J: Drp1-Dependent mitochondrial autophagy plays a protective role against pressure overload-induced mitochondrial dysfunction and heart failure. Circulation 133: 1249-1263, 2016.
182. Espeland T, Lunde IG, Amundsen BA, Gullestad L and Aakhus S: Myocardial fibrosis. Tidsskr Nor Laegeforen: Oct 12, 2018 (Epub ahead of print). doi: 10.4045/tidsskr.17.1027.
183. Tamiato A, Tombor LS, Fischer A, Muhly-Reinholz M, Vanicek LR, Toğru BN, Neitz J, Glaser SF, Merten M, Rodriguez Morales D, *et al*: Age-dependent RGS5 loss in pericytes induces cardiac dysfunction and fibrosis. Circ Res 134: 1240-1255, 2024.
184. Deng Y, Liu X, Xie M, Zhao R, Ji L, Tang K, Yang W, Ou W, Xie M and Li T: Obesity enables NLRP3 activation and induces myocardial fibrosis via hyperacetylation of HADHa. Diabetes 72: 1597-1608, 2023.
185. Li XM, Jiang L, Liu X, Guo YK, Li Y, Gao Y, Han PL, Xia CC, Peng WL, Hu BY, *et al*: Myocardial interstitial fibrosis and subclinical left ventricular systolic dysfunction in type 2 diabetes mellitus patients with obesity: A 3.0 T MRI study. Cardiovasc Diabetol 25: 22, 2025.

186. Fu DG: Cardiac arrhythmias: Diagnosis, symptoms, and treatments. Cell Biochem Biophys 73: 291-296, 2015.
187. Shan H, Li X, Pan Z, Zhang L, Cai B, Zhang Y, Xu C, Chu W, Qiao G, Li B, *et al*: Tanshinone IIA protects against sudden cardiac death induced by lethal arrhythmias via repression of microRNA-1. Br J Pharmacol 158: 1227-1235, 2009.
188. He Z, Sun C, Xu Y and Cheng D: Reduction of atrial fibrillation by Tanshinone IIA in chronic heart failure. Biomed Pharmacother 84: 1760-1767, 2016.
189. Jurcau A and Simion A: Neuroinflammation in cerebral ischemia and ischemia/reperfusion injuries: From pathophysiology to therapeutic strategies. Int J Mol Sci 23: 14, 2021.
190. Jiang F, Xu C, Fan X, Yang S, Fan W, Li M, Song J, Wei W, Chen H, Zhong D and Li G: MyD88 inhibition attenuates cerebral ischemia-reperfusion injury by regulating the inflammatory response and reducing blood-brain barrier damage. Neuroscience 549: 121-137, 2024.
191. Chen X, Zhou ZW, Xue CC, Li XX and Zhou SF: Role of P-glycoprotein in restricting the brain penetration of tanshinone IIA, a major active constituent from the root of Salvia miltiorrhiza Bunge, across the blood-brain barrier. Xenobiotica 37: 635-678, 2007.
192. Guzik A and Bushnell C: Stroke epidemiology and risk factor management. Continuum (Minneap Minn) 23 (1, Cerebrovascular Disease): 15-39, 2017.
193. Zhao Y, Zhang X, Chen X and Wei Y: Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment (Review). Int J Mol Med 49: 15, 2022.
194. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM and Donnan GA: Ischaemic stroke. Nat Rev Dis Primers 5: 70, 2019.
195. Fang M, Huang DR, Zhang JW, Liao WJ, Wu F and Liu YW: Tanshinone II_A exerts anti-hepatocellular carcinoma effects by inhibiting oxidative stress via PI3K/Akt and Nrf2/HO-1 signaling pathway. Zhongguo Zhong Yao Za Zhi 49: 6724-6734, 2024 (In Chinese).
196. Liu H, Wang L, Hu M, Hua J, Lian X, Lian C and Zhang J: Brusatol regulates ferroptosis of ovarian cancer through the Nrf2/HO-1/NQO1 and AKT/mTOR double signaling pathways. Curr Pharm Des: Aug 19, 2025 (Epub ahead of print).
197. Fu C, Wu Y, Liu S, Luo C, Lu Y, Liu M, Wang L, Zhang Y and Liu X: Rehmannioside A improves cognitive impairment and alleviates ferroptosis via activating PI3K/AKT/Nrf2 and SLC7A11/GPX4 signaling pathway after ischemia. J Ethnopharmacol 289: 115021, 2022.
198. Wu X, Wang J, Song L, Guan Y, Cao C, Cui Y, Zhang Y and Liu C: Catalpol weakens depressive-like behavior in mice with streptozotocin-induced hyperglycemia via PI3K/AKT/Nrf2/HO-1 signaling pathway. Neuroscience 473: 102-118, 2021.
199. Chen Q, Wang Q, Zhao Y, Xie X, Feng H, Wei Y, Yu M, Pan X and Hu T: Flavonoids from Polygonum hydropiper L. regulate PCV2-induced oxidative stress of RAW264.7 cells via Pi3k/AKT and Nrf2/HO-1 signaling pathways. Sci Rep 15: 29112, 2025.
200. Huang Q, Zhang C, Dong S, Han J, Qu S, Xie T, Zhao H and Shi Y: Asafoetida exerts neuroprotective effect on oxidative stress induced apoptosis through PI3K/Akt/GSK3β/Nrf2/HO-1 pathway. Chin Med 17: 83, 2022.
201. Hannawi Y: Cerebral small vessel disease: A review of the pathophysiological mechanisms. Transl Stroke Res 15: 1050-1069, 2024.
202. Katusic ZS, d'Uscio LV and He T: Cerebrovascular endothelial dysfunction: Role of BACE1. Arterioscler Thromb Vasc Biol 44: 1737-1747, 2024.
203. You N, Liu G, Yu M, Chen W, Fei X, Sun T, Han M, Qin Z, Wei Z and Wang D: Reconceptualizing Endothelial-to-mesenchymal transition in atherosclerosis: Signaling pathways and prospective targeting strategies. J Adv Res 77: 419-441, 2025.
204. Waters ES, Kaiser EE, Yang X, Fagan MM, Scheulin KM, Jeon JH, Shin SK, Kinder HA, Kumar A, Platt SR, *et al*: Intracisternal administration of tanshinone IIA-loaded nanoparticles leads to reduced tissue injury and functional deficits in a porcine model of ischemic stroke. IBRO Neurosci Rep 10: 18-30, 2021.
205. Zhao Y, Wang J, Zhang Z, Kong L, Liu M, Chen M and Gao L: A ROS-responsive TPP-modified tanshinone IIA micelle improves DOX-induced heart failure. Int J Pharm 672: 125318, 2025.
206. Zhang W, Li J, Liu J, Wu Z, Xu Y and Wang J: Tanshinone IIA-loaded reconstituted high density lipoproteins: Atherosclerotic plaque targeting mechanism in a foam cell model and pharmacokinetics in rabbits. Pharmazie 67: 324-330, 2012.
207. Zhang W, He H, Liu J, Wang J, Zhang S, Zhang S and Wu Z: Pharmacokinetics and atherosclerotic lesions targeting effects of tanshinone IIA discoidal and spherical biomimetic high density lipoproteins. Biomaterials 34: 306-319, 2013.
208. Zhang S, Li J, Hu S, Wu F and Zhang X: Triphenylphosphonium and D-α-tocopheryl polyethylene glycol 1000 succinate-modified, tanshinone IIA-loaded lipid-polymeric nanocarriers for the targeted therapy of myocardial infarction. Int J Nanomedicine 13: 4045-4057, 2018.
209. Fan L, Qu H, Wang B, Li HZ, Yang WW, Guo H, Zhang SS, Long LZ, Liu Y, Zhou G, *et al*: Delivery of liquid metal particles and tanshinone IIA into the pericardial cavity for myocardial infarction treatment. J Mater Chem B 12: 11916-11925, 2024.
210. Ma H, Hu ZC, Long Y, Cheng LC, Zhao CY and Shao MK: Tanshinone IIA microemulsion protects against cerebral ischemia reperfusion injury via regulating H3K18ac and H4K8ac in vivo and in vitro. Am J Chin Med 50: 1845-1868, 2022.
211. Liu X, Ye M, An C, Pan L and Ji L: The effect of cationic albumin-conjugated PEGylated tanshinone IIA nanoparticles on neuronal signal pathways and neuroprotection in cerebral ischemia. Biomaterials 34: 6893-6905, 2013.
212. Wang D, Lv L, Xu Y, Jiang K, Chen F, Qian J, Chen M, Liu G and Xiang Y: Cardioprotection of Panax notoginseng saponins against acute myocardial infarction and heart failure through inducing autophagy. Biomed Pharmacother 136: 111287, 2021.
213. Liang Y, Chen B, Liang D, Quan X, Gu R, Meng Z, Gan H, Wu Z, Sun Y, Liu S and Dou G: Pharmacological effects of astragaloside IV: A review. Molecules 28: 6118, 2023.
214. Zheng Q, Bao XY, Zhu PC, Tong Q, Zheng GQ and Wang Y: Ginsenoside Rb1 for myocardial ischemia/reperfusion injury: Preclinical evidence and possible mechanisms. Oxid Med Cell Longev 2017: 6313625, 2017.
215. Ma J, Hou D, Wei Z, Zhu J, Lu H, Li Z, Wang X, Li Y, Qiao G and Liu N: Tanshinone IIA attenuates cerebral aneurysm formation by inhibiting the NF-κB-mediated inflammatory response. Mol Med Rep 20: 1621-1628, 2019.
216. Lu Y, Yan Y and Liu X: Effects of alprostadil combined with tanshinone IIa injection on microcirculation disorder, outcomes, and cardiac function in AMI patients after PCI. Ann Palliat Med 10: 97-103, 2021.
217. Xu Q, Li H, Zhang X, Ding H and Cao J: Tanshinone IIA elevates serum soluble klotho levels and decreases cardiovascular events in patients on maintenance hemodialysis: a prospective before-after study. Ann Palliat Med 9: 2131-2140, 2020.
218. Zhang M, Liu Y, Sun X, Zhang X and Hua L: Salvia miltiorrhiza adjuvant therapy facilitates cardiac function recovery in patients with myocardial infarction. Pak J Pharm Sci 38: 45-53, 2025.
219. Mao S, Taylor S, Chen Q, Zhang M and Hinek A: Sodium tanshinone IIA sulfonate prevents the adverse left ventricular remodelling: Focus on polymorphonuclear neutrophil-derived granule components. J Cell Mol Med 23: 4592-4600, 2019.
220. Mao S, Wang L, Zhao X, Guo L, Lin Q, Wang X, Dai X, Shang H, Zhang M and Hinek A: Efficacy of sodium tanshinone IIA sulfonate in patients with Non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention: results from a multicentre, controlled, randomized trial. Cardiovasc Drugs Ther 35: 321-329, 2021.
221. Zhou ZY, Zhao WR, Zhang J, Chen XL and Tang JY: Sodium tanshinone IIA sulfonate: A review of pharmacological activity and pharmacokinetics. Biomed Pharmacother 118: 109362, 2019.
222. Guan R, Yao H, Li Z, Qian J, Yuan L, Cai Z, Ding M, Liu W, Xu J, Li Y, *et al*: Sodium tanshinone IIA sulfonate attenuates cigarette smoke extract-induced mitochondrial dysfunction, oxidative stress, and apoptosis in alveolar epithelial cells by enhancing SIRT1 pathway. Toxicol Sci 183: 352-362, 2021.
223. Lan J, Li K, Gresham A and Miao J: Tanshinone IIA sodium sulfonate attenuates inflammation by upregulating circ-Sirt1 and inhibiting the entry of NF-κB into the nucleus. Eur J Pharmacol 914: 174693, 2022.
224. Wu P, Du Y, Xu Z, Zhang S, Liu J, Aa N and Yang Z: Protective effects of sodium tanshinone IIA sulfonate on cardiac function after myocardial infarction in mice. Am J Transl Res 11: 351-360, 2019.
225. Zhong L, Ding W, Zeng Q, He B, Zhang H, Wang L, Fan J, He S, Zhang Y and Wei A: Sodium tanshinone IIA sulfonate attenuates erectile dysfunction in rats with hyperlipidemia. Oxid Med Cell Longev 2020: 7286958, 2020.
226. Li S, Jiao Y, Wang H, Shang Q, Lu F, Huang L, Liu J, Xu H and Chen K: Sodium tanshinone IIA sulfate adjunct therapy reduces high-sensitivity C-reactive protein level in coronary artery disease patients: A randomized controlled trial. Sci Rep 7: 17451, 2017.

227. Ji B, Zhou F, Han L, Yang J, Fan H, Li S, Li J, Zhang X, Wang X, Chen X and Xu Y: Sodium tanshinone IIA sulfonate enhances effectiveness Rt-PA treatment in acute ischemic stroke patients associated with ameliorating blood-brain barrier damage. Transl Stroke Res 8: 334-340, 2017.
228. Wu Q, Guan YB, Zhang KJ, Li L and Zhou Y: Tanshinone IIA mediates protection from diabetes kidney disease by inhibiting oxidative stress induced pyroptosis. J Ethnopharmacol 316: 116667, 2023.
229. Xu Z, Cai K, Su SL, Zhu Y, Liu F and Duan JA: Salvianolic acid B and tanshinone IIA synergistically improve early diabetic nephropathy through regulating PI3K/Akt/NF-κB signaling pathway. J Ethnopharmacol 319: 117356, 2024.
230. Chen S, Li P, Shi K, Tang S, Zhang W, Peng C, Li T, Xie H, Liu C and Zhou J: Tanshinone IIA promotes ferroptosis in cutaneous melanoma via STAT1-mediated upregulation of PTGS2 expression. Phytomedicine 141: 156702, 2025.
231. Zhang H, Long M, Wu Z, Han X and Yu Y: Sodium tanshinone IIA silate as an add-on therapy in patients with unstable angina pectoris. J Thorac Dis 6: 1794-1799, 2014.
232. Wu X, Fan M, Wei S and Guo D: The efficacy and safety of sodium tanshinone IIA sulfonate injection in the treatment of unstable angina pectoris: A systematic review and meta-analysis. PLoS One 18: e0290841, 2023.
233. Liu F, Zhao Q, Sun L, Yan M, Gao M, Wang H, Li Z, Zhou D, Li C, Li T, *et al*: A systematic review and meta-analysis of randomized controlled trials on the efficacy and safety of tanshinone IIA sodium sulfonate injection as adjunctive therapy for stroke. J Ethnopharmacol 353: 120413, 2025.
234. Zhao R, Wang H, Li S, Wang L, Lei X, Peng P, Du L and Dong J: Tanshinone IIA@β-cyclodextrin encapsulated with Eucommia ulmoides rubber/acetylated starch film as novel oral delivery system for therapy of orthotopic colon cancer. Carbohydr Polym 353: 123295, 2025.