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REVIEW

Unveiling the Mechanism of Protective Effects of Tanshinone as a New Fighter Against Cardiovascular Diseases: A Systematic Review

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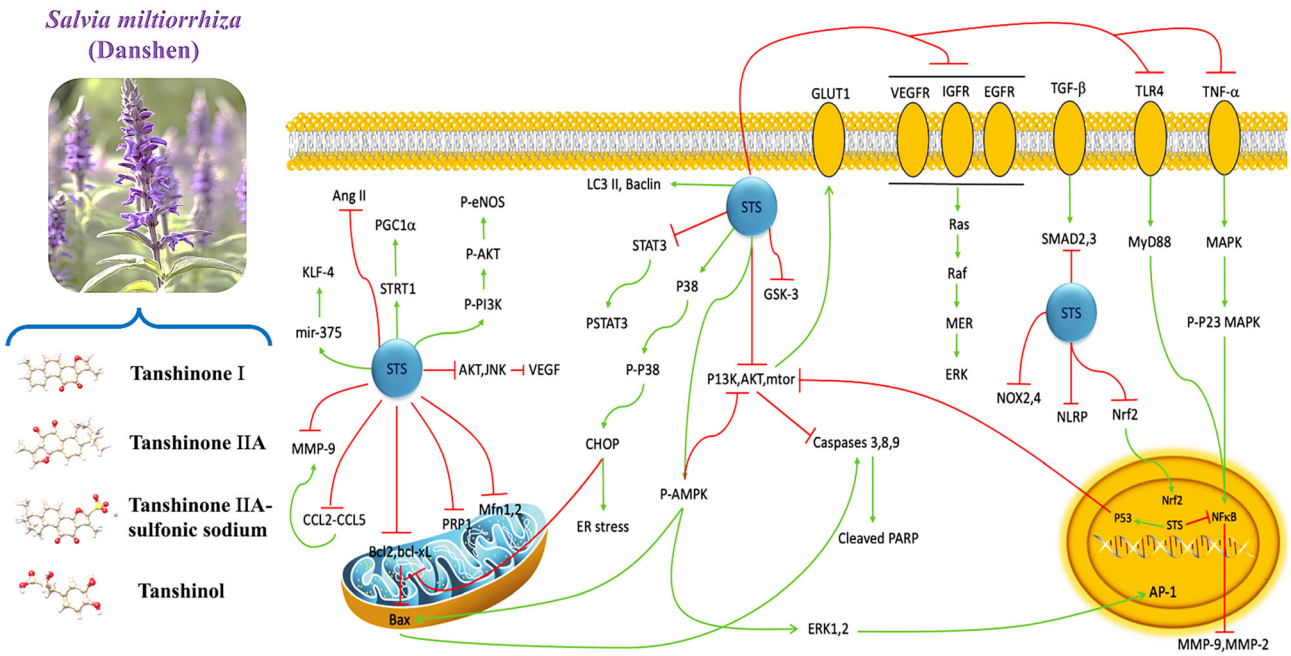
Abstract

Tanshinone, a natural compound found in the roots of *Salvia miltiorrhiza*, has been shown to possess various pharmacological properties, including anti-inflammatory, antioxidant, and cardiovascular protective effects. This article aims to review the literature on the cardiovascular protective effects of tanshinone and its underlying mechanisms. Tanshinone has been demonstrated to improve cardiac function, reduce oxidative stress, and inhibit inflammation in various animal models of cardiovascular diseases. Additionally, it has been shown to regulate multiple signaling pathways involved in the pathogenesis of cardiovascular diseases, such as the PI_3K/AKT, MAPK, and NF-κB pathways. Clinical studies have also suggested that tanshinone may have therapeutic potential for treating cardiovascular diseases. In conclusion, tanshinone has emerged as a promising natural compound with significant cardiovascular protective effects, and further research is warranted to explore its potential clinical applications.

Graphical Abstract



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Keywords *Salvia miltiorrhiza* · Tanshinone · Cardiovascular disease · Inflammation · Myocardial fibrosis · Cardiotoxicity

Abbreviations

ACC	Acetyl CoA carboxylase
Akt	Serine-threonine protein kinase B
AMP	Adenosine monophosphate
AMPK	AMP-activated protein kinase
ANG II	Angiotensin II
ANP	Atrial natriuretic peptide
AP-1	Activated protein-1
ARE	Antioxidant response element
ASC	Apoptosis-associated Speck-like protein containing
AST	Aspartate transaminase
AVM	Arteriovenous malformations
BH4	Tetrahydrobiopterin4
BNP	Brain natriuretic peptide
BW	Body weight
CAD	Coronary artery disease
CAT	Catalse
CF	Cardiac fibroblasts
CHD	Coronary heart disease
CHO	Total cholesterol
CIH	Chronic intermittent hypoxia
CK-MB	Creatine kinase-myocardial band
CME	Coronary microembolization
CNR	Coronary no-reflow
CPH	Chronic pulmonary hypertension
CPT1	Carnitine palmitoyl transferase 1
CVB3	Coxsackie virus B3
CVD	Cardiovascular diseases
DAMP	Danger-associated molecular patterns
DAXX	Death-domain associated protein
DM	Diabetes mellitus
DOX	Doxorubicin
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
ET	Endothelin
FFA	Free fatty acid
FGL2	Fibrinogen-like protein 2
FS	Fractional shortening
GLUT4	Glucose transporter
GPx	Glutathione peroxidase
GSH	Glutathione
GSK3	Glycogen synthase kinase-3
GSSG	Glutathione disulfide
HDL	High-density lipoprotein
HF	Heart failure
HFC	High-fat and cholesterol-rich
H-LVH	Hypertension-induced left ventricular hypertrophy
HO-1	Heme oxygenase-1
HR	Heart rate
HUVEC	Human umbilical vein endothelial cell
HW	Heart weight
IGF-IIR	Insulin-like growth factor II receptor
IL	Interleukin
IL-1R	Interleukin-1 receptor
iNOS	Inducible nitric oxide synthase neuronal nitric oxide synthase (nNOS)
IP	Intraperitoneally
I/R	Ischemia/reperfusion
ISO	Isoproterenol
IV	Intravenously
IVSd	Interventricular septal thickness at end diastole
IκB	Inhibitor of kappa B
JNK	C-Jun N-terminal kinase
LAD	Left anterior descending
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LPS	Lipopolysaccharide
LV	Left ventricular
LVDP	Left ventricular developed pressure
LVEDD	Left Ventricular end-diastolic diameter
LVEDP	Left Ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVEF	Left Ventricular ejection fraction
LVESD	Left Ventricular end-systolic diameter
LVESV	Left Ventricular end-systolic volume
LVFS	Left ventricular fractional shortening
LVIDd	Left ventricular diameter in diastole
LVIDs	Left ventricular diameter in systole
LVPWd	Left ventricular posterior wall thickness at end diastole
LVSP	LV systolic pressure
MABP	Mean arterial blood pressure
MAPK	Mitogen-activated protein kinase
MDA	Malondialdehyde
MEK1/2	Mitogen-activated protein kinase kinase 1/2
MI	Myocardial infarction
MPO	Myeloperoxidase
mTOR	Mammalian target Of rapamycin
NADPH	Nicotinamide adenine dinucleotide phosphate
NCX	Sodium-calcium exchanger
NF-κB	Nuclear factor Kappa B

NLR	Nucleotide-binding DOMAIN and leucine-rich repeat
NLRP3	NLR family pyrin domain containing 3
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
NOX2	Nicotinamide adenine dinucleotide phosphate oxidases 2
Nrf2	Nuclear factor erythroid 2–Related Factor 2
NRP	Neuropilin
OGD/R	Oxygen–glucose deprivation/recovery
OSA	Obstructive sleep apnea
PAD	Peripheral artery disease
PAMP	Pathogen-associated molecular patterns
PAR-1	Protease activated receptor-1
PASMC	Pulmonary artery smooth muscle cell
PCNA	Proliferating cell nuclear antigen
PDCD4	Programmed cell death protein 4
PDE4	Phosphodiesterase 4D
PGC	Peroxisome proliferator-activated receptor gamma coactivator
PGC1α	PGC 1 alpha
PI3K	Phosphatidylinositol 3-kinase
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PPAR-α	Peroxisome proliferator-activated receptor α
RAF	Rapidly accelerated fibrosarcoma
RAS	Reticular activating system
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
SBP	Systolic blood pressure
SERCA	Sarcoplasmic endoplasmic reticulum Ca2 + -ATPase
SMC	Smooth muscle cell
SOD	Superoxide dismutase
STS	Sodium tanshinone IIA sulfonate
SV	Stroke volume
TAN-IIA	Tanshinone IIA
TC	Total cholesterol
TG	Triglycerides
TGF-β1	Transforming growth factor-beta1
Th1	T helper-1
TLR	Toll-like receptor
TNFR	Tumor necrosis factor receptor
TNF-α	Tumor necrosis factor α
VEGF	Vascular endothelial growth factor
VLDL	Very low-density lipoprotein
VMC	Viral myocarditis
VSMC	Vascular SMOOTH MUSCLE CELL
WHO	World health organization

Introduction

The *Lamiaceae* is one of the most important plant families, and it includes a wide range of medicinal plants. This family consists of 236 genera and more than 6000 species [1]. Among the most important plants of this group, we can mention thyme, mint, oregano, basil, sage, savory, rosemary, self-heal, hyssop, lemon balm, and some other plants that have limited uses [2]. This family is widely distributed and is a native plant of various ecosystems. The species of this family are easily identifiable due to their distinctively shaped stems and opposite leaves. The flowers of this family are symmetrical, have five sepals and five petals, and are bisexual [3]. Most species of this family have aromatic compounds and natural essential oils, which are mostly present in their leaves. Of course, these aromatic compounds can also be found in other parts of the plant. Also, members of this family are widely used in traditional medicine to treat several diseases [1]. One of these plants is Danshen, scientifically named *Salvia miltiorrhiza*, which belongs to the *Lamiaceae* family [4]. This plant is used in the treatment of many diseases such as atherosclerosis [5], high blood pressure [6], myocardial infarction [4], coronary artery disease (CAD) [5], and diabetes [4]. Danshen has microcirculatory, vasodilatory, anti-clotting, anti-clogging, anti-inflammatory, anti-thrombosis, and mitochondrial protective effects [7–9]. It has two active ingredients. One of them is tanshinol, which is hydrophilic. Tanshinone IIA (TAN-IIA) is another major lipophilic active compound isolated from the Danshen root [10] (Fig. 1). Many research and clinical studies have shown that TAN-IIA can prevent or slow down the progression of a significant number of diseases, such as cardiovascular diseases (CVD), cancer, ischemia due to lack of oxygen, and neurological diseases [5, 11–13].

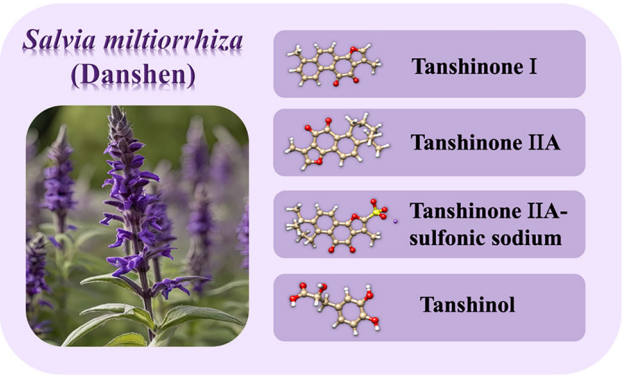

Fig. 1 *Salvia miltiorrhiza* (Danshen) and its active constituents

Cardiovascular diseases are known as the primary cause of mortality and a significant contributor to incapacity and reduced efficiency in adults [14–18]. According to the World Health Organization (WHO), an estimated 17.9 million individuals succumbed to CVDs in the year 2019, accounting for 32% of all global fatalities. Among these fatalities, 85% were attributed to heart attacks and strokes. Of the 17 million premature deaths (occurring before the age of 70) caused by noncommunicable diseases in 2019, 38% were due to CVDs. The majority of CVD-related deaths, over three-quarters, occurred in low- and middle-income countries [19]. The burden of CVDs is further compounded by the fact that it is considered the most expensive disease, surpassing Alzheimer's disease and diabetes, with indirect costs estimated at $237 billion per year, projected to increase to $368 billion by 2035 [20–24].

The cardiovascular system can encounter a diverse range of issues, such as conduction system abnormalities, rheumatic heart disease, and endocarditis [25]. A range of conditions can be included in cardiovascular diseases, including CAD or coronary heart disease (CHD), which affects the reduction of myocardial perfusion and angina due to ischemia. This condition covers one-third to half of all CVD incidents. Additionally, cerebrovascular disease interferes with the blood vessels supplying the brain and is often associated with strokes. Peripheral artery disease (PAD) affects the vessels supplying blood to superior or cranial body parts, while streptococcal bacteria cause rheumatic heart disease through rheumatic fever, which damages the myocardium and heart valves. Congenital heart disease is characterized by congenital anomalies that alter the regular heart development and functioning, caused by genetic deformities of the heart structure. Finally, deep vein thrombosis and pulmonary embolism are conditions that are caused by thrombosis in the leg veins, and blood clots can displace and move to vital organs such as the heart and lungs [19, 26, 27].

Research has indicated that nine modifiable risk factors, including dyslipidemia, smoking, diabetes, hypertension, psychosocial factors, abdominal obesity, regular alcohol intake, eating fruit and vegetables, and physical inactivity, significantly ($p = 0.03$ for alcohol and $p < 0.0001$ for the rest of the risk factors) contribute to 90% percent of the risk of experiencing a first MI in men and 94% in women, [28]. Conversely, unmodifiable issues such as age, family history, and gender play variable effects [29, 30]. Furthermore, the presence of elevated inflammatory markers [31], HIV [32], microalbuminuria [33], and a mediastinal history or chest wall radiation [34] have also been linked to a higher incidence of CVD. The prevention of CVDs, in most cases, can be achieved by managing behavioral risk elements. It is common for the underlying disease of the blood vessels to present no symptoms. In some cases, a heart attack or stroke occurrence might be the initial indication of the underlying condition. Detection of CVD early in the process is crucial to initiate management with counseling and medication [19, 21–24]. A comprehensive clinical history and physical examination, focusing mostly on the cardiovascular system, are essential for diagnosing CVD [26]. Management of CVD is a complex process and varies based on the patient's clinical situation. For instance, angioplasty is recommended for peripheral vascular disease, catheter-directed thrombolysis is for acute ischemic stroke, and coronary stenting for CHD [35–38]. In the current paper, we reviewed various CVDs and the protective effects of tanshinone on them.

Method

A comprehensive search was performed using Scopus, ScienceDirect, and PubMed databases from inception to June 2024 without date limitation. In this review article, all *in vitro* and *in vivo* studies were considered. The following medical keywords were investigated alone or in combinations: "Cardiac Injury, cardiac Function, myocardial calcium regulation, myocardial Rhythm, cardiac oxidative stress, cardiac Inflammation, cardiac mitochondrial function, cardiac apoptosis, or myocardial fibrosis" "cardiovascular disease, major adverse cardiac events, cardiac events, cardiac event, adverse cardiac event, or adverse cardiac events" "cardiotoxicities, cardiac toxicity, cardiac toxicities, or cardioprotective" with "tanshinone."

Findings and Discussion

We have provided explanations about various CVDs, the protective effect of tanshinone against them, and related signaling pathways. The promising effects of tanshinone have been reported in different *in vitro* and *in vivo* studies (Table 1).

Tanshinone in Cardiac Functions and Reduction of CVDs

Reduction in Cardiac Apoptosis

Experimental models and human cardiac disease provide evidence that the loss of cardiomyocytes due to apoptosis is a significant factor in various heart diseases, ultimately resulting in heart failure [39, 40]. Cardiomyocyte apoptosis is a significant pathogenic mechanism contributing to myocardial ischemia/reperfusion (I/R) injury. Blocking the apoptosis process could prevent the loss of contractile cells, minimize cardiac injury, and, therefore, slow down or even

Table 1 Protective effects of tanshinone and its derivatives against cardiovascular diseases

Animal	Model	Dose and duration	Findings	Reference
H9C2 and HL-1 cells	Doxorubicin-induced HF	2.5, 5, and 10 mg/kg/day	↑ Cell viability	[167]
			↓ Myocardial structural alteration	
			↓ Myofibril disruption	
			↑ DAXX	
			↑ p-MEK	
			↑ p-ERK1/2	
			↓ Caspase-8	
Mice	LAD-ligation-induced myocardial ischemia	0.3 mg/20g/day (p.o.) for 28 days	↓ CK activity	[253]
			↓ LDH activity	
			↓ CK-MB	
			↑ end-diastolic thickness of the LAD	
			↓ LVIDs	
			↓ LVIDd	
			↑ LVPWs	
			↓ left ventricular mass of myocardial infarction	
			↑ outflow of blood flow	
			↓ systolic and diastolic intervals	
			↑ ejection time	
			↑ systolic blood pressure	
			↓ iNOS expression	
			↓ IL-6 mRNA expression	
			↓ TNF-α concentration	
			↓ IL-1β mRNA expression	
			↑ IL-10 mRNA expression	
Rat	LAD-ligation injury	10 mg/kg (p.o.) for 20 days	↓ Cell viability	[85]
			↓ LVEDD	
			↓ LVESD	
			↑ LVEF	
			↑ LVFS	
Mice	LAD-ligation injury	30 mg/kg/day (i.p.) for 3 weeks	↑ Survival rate	[254]
			↑ LVEF	
			↑ LVFS	
			↓ TNF-α concentration	
			↓ IL-1β expression	
			↓ TGF-β expression	
			↑ SOD activity	
			↑ GSH concentration	
			↓ MDA concentration	
			↑ Bcl-2 activity	
			↑ Bcl-2/Bax ratio	
Rat	LAD-ligation injury	15 mg/kg (p.o.)	↑ EF%	[69]
			↑ FS%	
			↓ LDH	
			↓ CK	
			↓ CK-MB	
			↓ NLRP3 expression	
			↓ Caspase-1 expression	
			↓ IL-18 mRNA expression	
			↓ IL-1β mRNA expression	

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Mice	LPS-induced cardiac fibrosis	10 mg/kg (i.p.) for 2 weeks	↓ Cardiac fibrosis ↓ Oxidative stress	[255]
Mice	Ethanol-induced cardiac injury	5 and 10 mg/kg (i.p.) for 2 weeks	↓ LVESD ↑ FS ↑ EF ↓ Apoptosis rate ↑ Bcl-2/Bax ratio ↓ P53 expression ↓ Caspase-3 expression PDCD4 expression ↑ pAkt/Akt ratio	[233]
Mice	LAD-ligation injury	20 mg/kg (p.o.) for 4 weeks	↓ H/BW ↓ Infarcted size ↓ LVEDV ↓ LVESV ↑ LVEF ↑ LVFS ↑ p-eNOS/eNOS ↑ p-AMPK/AMPK ↑ p-Akt/Akt	[160]
Beagle dog	LAD-ligation injury	1.3, 2.6, and 5.2 mg/kg (i.v.)	↓ Infarct area ↓ CK-MB activity ↓ ROS level ↓ IL-18 concentration ↓ IL-1β concentration ↓ TXNIP protein level ↓ NLRP3 ↓ ASC ↓ Caspase1 ↑ p-ERK1/2 level ↑ p-Akt level ↑ p-IR protein level ↓ TC ↓ TG	[205]
Rat	Clamping-induced CME	10 and 20 mg/kg (i.p.) for 1 week	↓ LVESD ↓ LVEDD ↑ LVFS ↑ LVEF ↓ CK-MB ↓ LDH ↓ cTnl ↓ Infarction size ↓ IL-18 concentration ↓ IL-1β concentration ↓ Caspase-1 concentration ↓ TLR4 level ↓ NLRP3 level ↓ ASC level ↓ NF-κB level	[247]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Mice	LAD-ligation injury	0.5 ml/kg (i.v.) for 5 days	↓ LVEDD ↓ LVESD ↑ LVEF ↑ LVFS ↓ H/BW ↓ Infarcted size ↓ Caspase-3 activity ↓ Bax activity ↑ Bcl-2 activity ↓ IL-18 concentration ↓ IL-1β concentration ↓ TNFα concentration ↓ IL-6 concentration ↓ MCP-1 concentration ↓ TGF-β1 concentration	[201]
Rat	Clip-induced hypertension	5, 10, and 15 mg/kg for 8 weeks	↓ H/BW ↓ IVSd ↓ LVPWd ↓ MDA concentration ↑ SOD activity ↓ Cardia fibrosis ↓ TGF-β1 concentration ↑ bFGF level ↑ Plasma apelin	[48]
Mice	Injection of CVB3-induced VMC	20 mg/kg/day (i.p.) for 14 days	↓ H/BW ↓ HR ↑ SBP ↑ LVEF ↓ LVEDD ↓ LVESD ↓ CK activity ↓ IFN-γ ↓ IL-2 concentration ↑ IL-4 concentration ↑ IL-10 concentration	[68]
Rat	LAD-ligation injury	4 and 8 mg/kg (i.v.)	↓ AAN/AAR ratio ↓ AAI/AAR ratio ↓ LVIDd ↓ LVIDs ↑ FS ↑ EF ↓ FGL2 ↑ p-Akt/Akt ↓ NF-κB level ↓ fibrin ↓ MPO	[202]
Rat	IR-induced model	20 mg/kg for 15 days	↓ Infarct size ↑ LVDP ↑ Coronary flow ↓ Caspase-3 activity ↑ P-Akt/Akt	[234]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Rat	STZ-induced diabetes	5 mg/kg (i.p.) for 7 days	↓ Infarct size ↓ LVESV ↓ LVEDV ↑ EF ↓ Apoptosis index ↓ Caspase-3 activity ↑ p-Akt ↓ IL-6 ↓ MPO activity ↓ TNF-α ↓ p-p65	[47]
Mice	Doxorubicin-induced cardiotoxicity	15 and 30 mg/kg (i.p.) for 7 days	↓ AST activity ↓ LDH activity ↓ CK activity ↓ CK-MB activity ↑ GSH concentration ↑ SOD activity ↑ CAT activity ↓ MDA concentration ↑ Nrf2 mRNA expression ↑ Cell viability	[216]
Rat	STZ-induced diabetes	5 mg/kg (i.p.) for 7 days	↓ H/BW ↓ LVESV ↓ LVEDV ↑ EF ↓ Apoptosis index ↓ Caspase-3 activity ↑ p-Akt ↓ IL-6 ↓ MPO activity ↓ TNF-α ↓ p-p65 ↑ p-GSK-3β	[67]
Mice	LPS-induced cardiomyopathy	5, 10, and 50 mg/kg (i.p.)	↑ Survival rate ↑ SV ↑ EF ↑ FS ↓ LVESD ↓ LVEDD ↓ BNP ↓ TNF-α ↓ IL-6 ↓ IL-18 ↓ IL-1β ↓ NLRP3 ↓ Caspase-1	[206]
Rat	LAD-ligation injury	30 mg/kg for 7 days	↑ LVP ↓ LVEDP ↓ H/BW ↑ Infarct size ↑ SOD activity ↓ MDA concentration ↑ GSH-Px	[117]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Rat	Infarction model	20 mg/kg (p.o.) for 7 days	↑ LVSP ↓ LVEDP	[256]
Mice	LAD-ligation injury	10 mg/kg (i.p.) for 4 weeks	↑ EF ↑ FS ↓ LVESD ↓ LVEDD ↓ H/BW ↓ Fibrotic area ↓ ANP ↓ Apoptosis index ↓ Caspase-3 positive cells ↓ Bax activity ↑ Bcl-2 activity ↑ p-AMPK	[239]
Rat	Clip-induced hypertension	35 and 70 mg/kg (p.o.) for 6 weeks	↓ H/BW ↓ LVEDP ↓ Superoxide production ↓ IVSd ↑ LVDd ↓ PWd ↓ IVSs ↓ LVDs ↓ PWs ↑ EF ↑ FS	[257]
Rat cardiac fibroblasts	Radiation-induced damage	2.5, 5, 10, and 20 μg/ml for 24 h and 48 h	↓ Ang II release ↓ BNP release ↓ Cell apoptosis ↑ SOD activity ↓ MDA concentration ↓ ROS activity ↓ p-P38/P38 ratio ↑ p-ERK1/2 /ERK1/2 ratio ↑ Bcl-2/Bax ratio ↓ Caspase-3 expression	[168]
Rat	CIH-induced myocardial injury	20 mg/kg (i.p.) for 21 days	↓ Arterial pressure ↑ FS ↑ NO concentration in serum ↓ ET-1 concentration in serum ↑ eNOS expression	[179]
Rat	LAD-ligation injury	60 mg/kg (p.o.) for 7 days	↑ LVSP ↓ LVEDP ↓ Infarct size ↓ MCP-1 positive cells ↓ NF-κB expression ↓ TGF-β_1 expression ↓ TNF-α ↑ Cell viability	[240]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Rat	Isoproterenol-induced myocardial infarction	4, 8, and 16 mg/kg (i.v.) for 7 days	↓ MDA ↑ SOD ↑ GSH ↑ GPx ↑ p-ERK/ERK ratio ↑ Nrf2 ↓ TC ↓ TG ↓ p-AMPK/AMPK ratio ↑ p-ACC/ACC ↑ Heartbeat ↑ MABP ↑ LVSP ↓ LVEDP	[66]
Rat	2K2C model	35 and 70 mg/kg (p.o.) for 6 weeks	↓ LV/BW ratio ↓ CVF ↓ Collagen ↓ IVSd ↑ LVDd ↓ PWd ↑ EF ↑ FS ↓ LVEDP ↓ IVSs ↓ LVDs ↓ TIMP-2 ↓ MMP-9 ↓ TIMP-1	[258]
Rat cardiac cell, rat	H_2O_2, LAD ligation	15, 30, and 60 mg/kg (p.o.) for 14 days	↑ Cell viability ↓ Nuclear fragmentation ↓ MDA ↑ SOD ↑ Bcl-2/Bax ratio	[259]
Rat	Cecal ligation	5 and 15 mg/kg (i.v.) for 3 days	↑ MAP ↑ LVSP ↓ LVEDP ↑ HR ↓ CRP concentration ↓ PCT concentration ↓ cTn-1 concentration ↓ BNP concentration ↓ TNF-α ↓ IL-6 ↓ Inflammatory score ↑ Survival rate	[260]
Rat	LAD-ligation injury	8 mg/kg (i.v.)	↓ Infarct size ↓ CK-MB activity ↓ LDH activity ↓ AST activity ↑ SOD activity ↑ GSH concentration ↓ MDA concentration ↑ GPx activity ↓ TNF-α ↑ HR	[77]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
			↓ LVEDP	
			↑ Work index	
			↓ NF-κB level	
Rats	LAD-induced HF	1.5 mg/kg	↑ EF	[136]
		(p.o.) for 4 weeks	↑ FS	
			↓ LVIDs	
			↓ LVIDd	
			↓ Apoptotic Rate	
			↑ Bcl-2	
			↑ Bax	
			↓ Cleaved Caspase-3	
			↓ Cleaved Caspase-7	
			↑ LC3	
			↑ Beclin1	
			↓ p62	
			↑ p-AMPK^{T172}	
			↓ p-mTOR^{Ser2448}	
			↓ p-ULK1^{Ser757}	
			↑ p-TSC2^{Ser1387}	
			↓ S6K1	
H9C2 cells	H_2O_2-induced cell death	Tanshinone (0.01, 0.1, 0.3, 1, 3, 10 μM) alone or in combination with H_2O_2 (50, 100, 200, 400, or 800 μM)	↑ miR-133	[261]
			↑ PI3K/Akt	
			↑ Bcl-2	
Rats	Renal IR-induced AMI	10 mg/kg.d	↑ EF	[58]
			↑ FS	
			↓ LVIDs	
			↓ LVIDd	
			↓ CK-MB	
			↓ cTn-1	
			↓ TNF-α	
			↓ IL-1β	
			↓ Cleaved Caspase-9/3	
			↓ ROS	
			↓ mPTP	
			↑ MOCR	
			↑ RCR	
			↑ MMP	
			↑ long/short mtDNA fragments	
			↑ mitochondrial respiratory chain complex enzymes	
			↑ ATP	
			↑ PGC-1α	
			↑ Nrf1	
			↑ Tfam	
			↑ Drp1	
			↓ Mfn1	
			↓ Mfn2	
			↓ Bax	
			↓ Cyt-c	
			↓ PARP	
			↑ PI3K	
			↑ Bad	
			↑ Akt	
			↑ Bcl-2	

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Mice	LAD-induced MI	20 mg/kg (p.o.)	↓ LVEDV	[262]
			↓ LVESV	
			↑ LVEF	
			↑ LVFS	
			↓ PI3K	
			↑ Akt	
			↑ AMPK	
			↑ NO production	
			↑ CAT-1	
			↑ CAT-2B	
			↑ NOX generation	
			↑ H–L-arginine uptake	
Rats	STZ-induced diabetes	-	↑ LVEF	[263]
			↑ ± dP/dt	
			↓ Myocardial Apoptotic Death	
			↓ Cardiac Fibrosis	
			↓ Collagen Deposition	
			↑ GSK-3β	
			↑ Akt	
			↓ NF-κB	
			↓ TNF-α	
			↓ IL-6	
			↓ MPO	
Rabbit	I/R	10/μmol/kg (i.v.)	↑ Cell Necrosis Time	[264]
			↓ Organ Necrosis (%)	
Mice	Endotoxin-induced septic shock	10 mg/kg (i.p.) injection	↓ TNF-α	[265]
			↓ IL-1β	
			↓ ROS	
			↓ Nox2	
			↓ ERK1/2	
			↓ p38 MAPK	
			↑ EF	
			↑ FS	
			↑ SV	
			↓ iNOS	
			↑ eNOS	
HUVECs	High glucose culture	1 μM, 3 μM, 10 μM	↓ Superoxide production	[161]
			↓ NADPH oxidase	
			↑ eNOS	
			↓ NOX4	
			↑ BH4/BH2	
			↑ GTPCH1	
			↑ DHFR	
			↑ Hsp90	
			↓ PI3K	
Mice	Intimal hyperplasia	0.3 and 0.6 g/kg BW/d (p.o.)	↓ PCNA-positive indice	[101]
			↓ neointima formation	
			↓ intimal area	
			↓ medial area	
			↓ ratio of intima to media	
			↑ relative lumen area	

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
ApoE$^{-/-}$ C57BL/6J mice & RAW 264.7 cells	HCD-induced atherosclerosis	Rats: 30 or 10 mg/kg (p.o.) Cells: 1 μM, 10 μM	↓ lesion formation ↓ necrotic core area ↓ macrophage accumulation ↑ smooth muscle cell content ↑ collagen content ↑ plaque stability score ↓ superoxide production ↓ p65 ↓ ROS ↓ gp91^{phox} ↓ p65 ↓ MCP-1 ↓ TNF- α ↓ IL-6 ↓ MMP-9	[266]
VSMCs & Mice	Carotid arterial neointimal hyperplasia	Rats: 10 mg· kg − 1· day − 1 by (i.p.) injection VSMCs: 10 ng/ml, 1.0 μg/ml	↓ neointimal formation ↓ ratio of intima to media ↓ intimal area ↓ IL-1β ↓ IL-6 ↓ TNF-α ↑ KLF4 ↓ p-p65 ↓ NF-κB ↓ miR-712-5p	[100]
ApoE$^{-/-}$ mice & Raw264.7 Cells	HCD-induced atherosclerosis	Rats: 10 mg/kg (i.p.) injection Cells: 10 μg/μl	↓ TG ↓ CHO ↓ LDL ↑ HDL ↓ intimal lesion area ↓ lipid accumulation ↓ CD197 ↑ CD206 ↑ KLF4 ↑ MCPIP ↓ miR-375 ↑ MDC-labeled vacuoles ↓ TNF- α ↓ IL-6 ↓ IL-12 ↑ IL-10 ↑ Arg-1 ↓ iNOS ↑ Beclin1 ↑ LC3 II ↓ NF-κB	[91]
Neonatal rat cardiac cells	Angiotensin II-induced hypertrophy	5–80 μM	↓ [^{3}H]phenylalanine ↓ myocyte cell size ↓ c-*jun* ↓ Ca-T	[11]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Rats	LAD-induced MI	5 mg/kg & 20 mg/kg (i.p.) injection	↓ LVEDD ↓ LVESD ↑ LVEF ↑ LVFS ↑ ventricular systolic function ↑ MAP ↑ LVESP ↓ LVEDP ↑ + dP/dt ↑ -dP/dt ↑ BW ↓ HW/BW ↓ HW ↑ cardiac volume ↑ ventricular wall elasticity ↑ ventricular wall toughness ↓ ventricular dilatation ↑ cell size ↓ myocardial fibrosis ↓ inflammatory cell infiltration ↓ degree of fibrosis ↓ myocardial infarct size ↓ LVWT ↓ IVST ↓ TLR4 ↓ NF-κB-P65 ↓ MyD88 ↓ IL-2 ↓ IL-6 ↓ IL-8 ↓ TNF- α ↓ ED-1-positive macrophage infiltration ↓ cell apoptosis	[248]
P. *gingivalis* strain FDC381 & ApoE$^{-/-}$ mice	P. gingivalis infection-induced atherosclerosis	60 mg kg^{-1} day^{-1}	↓ atherosclerotic plaque lesions ↓ bFGF ↓ eotaxin-1 ↓ G-CSF ↓ IFN-γ ↓ IL-1β ↓ IL-6 ↓ MCP-1 ↓ MIP-3α ↓ RANTES ↓ TNF-α ↓ VEGF ↓ TNF-α ↓ IL-12 ↓ CRP ↓ ox-LDL ↓ HDL ↓ CCL-2 ↓ CD40 ↓ MMP-2	[267]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
			↓ miR-146b	
			↓ miR-155	
human endothelial EA.hy926 cells	H_2O_2-induced endothelial cell injury	-	↑ cell viability	[268]
			↓ LDH	
			↑ SOD	
			↓ Apoptotic rate	
			↑ ARE-driven luciferase activity	
			↑ HO-1	
			↑ GCLC	
			↑ GCLM	
Rats	Rats: CHPH and MCT-induced PAH	Rats: 10 mg/kg/d for 21 days (i.p.) injection	↓ RVSP	[269]
& PASMCs	Cells: prolonged hypoxia or isolated from CHPH rats	Cells: 0–25 μM	↓ RV/(LV + S)	
			↓ RV/BW	
			↓ Mn^{2+} quenching	
			↓ basal [Ca^{2+}]	
			↓ TRPC1	
			↓ TRPC6	
			↓ cell proliferation	
			↓ cell migration	
Rats	LAD-ligation induced MI	1, 3, 10, 30 mg/kg (i.p.) for 15 min before LAD ligation	↓ infarct sizes	[190]
			↓ blood LDH	
			↓ number of apoptotic cardiomyocytes in the infarcted hearts	
Rats	LAD ligation	120 mg/kg/ day (p.o.)	↓ infarct size	[270]
			↓ LVIDs	
			↓ LVIDd	
			↑ LVPWd	
			↑ EF	
Primary cultured neonatal rat cardiomyocytes	doxorubicin-induced cardiomyocyte apoptosis	0.1, 0.3, 1, and 3 μM for 30 min	↓ cleaved caspase-3	[271]
			↓ cytosol CYT-c	
			↓ doxorubicin-induced ROS formation	
			↑ BcL-xL expression	
			↓ Akt phosphorylation in cardiomyocytes	
H9c2 rat myocardial cells	cardiomyocyte apoptosis induced by OGD/R	1,3,10 μM	↓ OGD/R-induced apoptosis	[191]
			↓ caspase-3 activity	
			↓ caspase-8 activity	
			↓ Bax expression	
			↓ NF-κB	
			↓ phosphorylation of IκKb	
			↓ phosphorylation and ubiquitination of IκB	
			↓ TNF-α	
			↓ positive feedback signaling of the NF-κB/TNF-α pathways	
			↓ JNK activity	
			↑ MMP	
			↑ Bcl-2 expression	
			↓ activation of the PI3K-Akt pathway	

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Rats	LCA-induced myocardial I/R injury	5,10, 20 mg/kg (i.v.)	↓ infarct size ↓ PI3K ↓ MPT ↑ phospho-endothelial NO synthase ↑ p-Akt/t-Akt ↓ p-eNOS/t-eNOS	[78]
Mice	HFD OVX and normal diet sham OVX mice	30, 60 mg/kg/d (p.o.) for three months	↓ lipid deposition in the aorta ↓ TC ↓ TG ↓ LDL ↓ very low-density lipoprotein (VLDL) ↓ MDA ↓ NF-κB ↓ sICAM-1 ↓ AP-1 ↓ E-selectin ↓ p-ERK1/2 expression ↑ HDL ↑ SOD	[70]
Rats	Isoproterenol-Induced Myocardial Infarction Rats	100 mg/Kg/d (o.p.) for 4 weeks	↓ AF inducibility ↓ AF duration ↓ Type I collagen in left atrium ↓ Type III collagen in left atrium ↓ MMP-9 ↓ TIMP-1 ↑ MMP-9/TIMP-1 ratio	[272]
Rats	ADP-induced platelet aggregation	0.5, 5, 50 μM for 1 min	↓ platelet aggregation of AUC ↓ platelet aggregation of amplitude ↓ Erk-2 phosphorylation ↓ PGE2 ↑ blood viscosity ↑ modulation of tubulin acetylation	[273]
H9c2 and Neonatal rat cardiomyocytes	Leu27IGF-II(IGF-II analog)-Induced Cardiomyocyte Hypertrophy	10 and 100 nM	↓ Leu27IGF-II-induced calcineurin expression ↓ Leu27IGF-II-induced NFATC3 ↓ cell size ↓ ANP ↓ BNP ↓ antihypertrophic effects induced by Leu27IGF-II ↑ Akt phosphorylation ↑ ER activation	[180]
Primary cultures of neonatal rat cardiomyocytes	tunicamycin (Tm)-induced ERS-mediated apoptosis	cultured under a condition TSA (10 106mol/L) for 30 min	↓ GRP78 ↓ CHOP ↓ active-caspase 12 ↓ apoptosis of cardiomyocytes ↓ caspase 3 activity ↑ miR-133	[274]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
Rats	pressure overload-induced myocardial	15 mg/kg/day (i.p.) for 8 weeks	↓ apoptosis and myocardial remodeling ↓ SIRT1 ↓ Bcl-2 expressions ↓ MDA ↓ TNF-α ↓ IL-6 ↓ LVPWT ↓ IVST ↓ HW/BW ↓ LVW/HW ↓ CSAs ↑ Bax expression ↑ caspase-3 expressions ↓ SOD	[275]
Rat myocardium-derived H9C2	AngII-induced Apoptosis	1,2,5,10 μg/ml	↓ PTEN expression ↓ apoptosis ↑ miR-152-3p	[276]
Rat H9c2 cardiomyocytes	hypoxia-induced myocardial injury	10 μM for 16 h	↓ CCL2 expression ↓ CCL5 expression ↓ CXCL2 expression ↓ CCL19 expression ↓ TNF-α ↓ IL-6 ↓ p-ERK1/2 ↓ p-p38 ↓ p-JNK ↓ cell apoptosis ↓ Bax ↓ Bax/Bcl-2 ↑ phosphorylation of Akt ↑ Bcl-2 ↑ hypoxia-induced SG ↑ G3BP expression	[277]
Mice	Apo $E^{-/-}$ mice with HFC diet	10, 20 mg/kg/day (i.p.) for 4 weeks	↓ atherosclerotic lesion area ↓ TC ↓ TG ↓ LDL-C ↓ MDA ↓ GSSG ↓ TNF-α ↓ p-ERK ↓ IL-6 ↓ CLIC1 expression ↓ ICAM-1 expression ↓ VCAM-1 expression ↑ GSH ↑ SOD	[90]
HUVECs	H2O2 induction	0.5, 0.4, and 0.3 mmol/l	↓ ROS ↓ MDA ↓ TNF-α ↓ IL-6 ↓ ICAM-1 ↓ VCAM-1 ↓ CLIC1 expression	[90]

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
			↓ intracellular Cl concentration	
			↑ SOD	
Mice	oxidative stress-induced myocardial apoptosis	10 mg/kg/day (i.v.) for 4 weeks	↓ p38 signaling	[54]
			↓ mTOR signaling	
			↓ Keap1	
			↓ LVIDd	
			↓ LVIDs	
			↓ TdT	
			↓ ROS	
			↓ phosphorylation of Bax	
			↓ DNMT activity	
			↑ caspase-3/9	
			↑ Nrf2 gene transcription	
			↑ CPT-1	
			↑ GLUT-4	
			↑ function of myocardial tissues	
			↑ mitochondrial membrane integrity	
			↑ phosphorylation of Bcl-2	
			↑ Complex I/V activity	
			↑ MMP	
			↑ ATP production	
			↑ ARE-driven luciferase activity	
Mice	HFD and Apo $E^{-/-}$ mice	90, 30, 10 mg/kg/day (o.p.) for 13 weeks	↓ AS lesion	[278]
			↓ extracellular lipid to plaque	
			↓ TC	
			↓ LDL	
			↓ ox-LDL	
			↓ MCP-1	
			↓ TNF-α	
			↓ TLR4 expression	
			↓ MyD88 expression	
			↓ NF-κB p65 expression	
			↑ collagenous fiber	
			↑ HDL	
Human	ST-elevated myocardial infarction (STEMI)	80 mg/day for 7 days	↓ progressive left ventricular remodeling	[279]
			↓ neutrophil elastase	
			↓ myeloperoxidase	
			↓ proteinase 3	
			↓ MMP-8	
			↓ MMP-9	
			↑ NGAL	
Zebrafish, mice and H9C2	Doxorubicin-Induced Cardiotoxicity	20 μM 10 mg/kg 1 μM	↓ proliferative activity ↓ cardiotoxicity of DOX	[153]
			↓ LVEDD	
			↓ LVESD	
			↓ Pyknosis	
			↓ plasma-dissolved cardiomyocytes	
			↓ LDH	
			↓ CK-MB	
			↓ apoptotic rate	
			↓ Bax expression	
			↓ accumulation of autolysosomes	

Table 1 (continued)

Animal	Model	Dose and duration	Findings	Reference
			↓ LC3-II	
			↓ P62	
			↓ p-mTOR	
			↓ p-ULK1	
			↓ p- S6K1	
			↓ Autolysosomes	
			↓ cytoplasmic localization of TFEB	
			↑ heart function	
			↑ Beclin1	
			↑ LAMP1	
			↑ EF	
			↑ FS	
			↑ Myofibrillar	
			↑ BW	
			↑ Bcl-2 exprssion	
			↑ cathepsin B activity	
			↑ nuclear recruitment of TFEB	
			↑ cell viability	
			↑ autophagosomes	
Human	non-ST elevation acute coronary syndrome (NSTE-ACS)	80 mg/day STS dissolved in saline for 5 days	↓ myocardial infarction	[280]
			↑ Post-procedural elevation of troponin-I	
Mice and H9C2	Oxidative Stress-Induced Cardiomyocyte Injury	10 mg/kg BW (o.p.) for 1 week 0.625, 1.25, and 2.5 μM	↓ MAPK signaling activation	[217]
			↓ P38 MAPK	
			↓ SAPK/JNK	
			↓ ERK1/2	
			↓ ROS	
			↓ MDA	
			↓ cell apoptosis	
			↓ BAX expression	
			↓ cleaved caspase3 expression	
			↓ HW/BW	
			↓ LVESD	
			↓ LVEDD	
			↓ collagen formation	
			↑ NFE2	
			↑ Nrf2 expression	
			↑ SOD	
			↑ cell viability	
			↑ Bcl-2 expression	
			↑ LVEF	
			↑ LVFS	
HCM and rat	permanent ligation of the left coronary artery	10, 20 mg/kg (i.v.)	↓ infarct size	[281]
			↑ cell viability	
Cultured rat cardiac fibroblasts	Ang II-Induced	0.1, 0.3, 1, 3, and 10 μM for 30 min	↓ cell proliferation	[282]
			↓ ET-1 expression	
			↓ ROS	
			↓ ERK phosphorylation	
			↑ NO generation	
			↓ eNOS phosphorylation	
HUVEC	cyclic strain treatment	1–10 μmol/L for 6 h	↓ ET-1 expression	[283]
			↑ NO production	
			↑ eNOS phosphorylation	

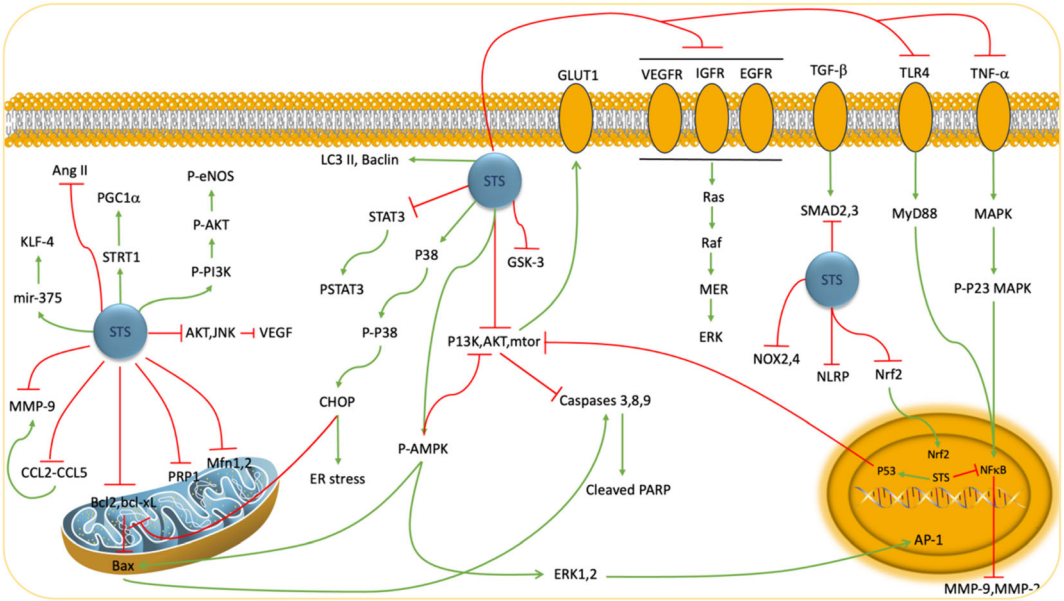

Fig. 2 Moderating effects of Sodium Tanshinone IIA Sulfonate on intracellular signaling pathways

prevent the occurrence of heart failure [41, 42]. Numerous signaling pathways were implicated in mediating the process of apoptosis, such as Bcl-2 family proteins [43]. The Bcl-2 family of proteins comprises both pro- and anti-apoptotic members, with the equilibrium between Bax, a pro-apoptotic protein, and Bcl-2, an anti-apoptotic protein, being a crucial factor in myocardial apoptosis [44] (Fig. 2). Recent studies have also shown that activation of the phosphatidylinositol 3-kinase (PI_3K)/serine-threonine protein kinase B (AKT) signaling pathway and caspases protects the myocardium from myocardial I/R injury and prevents cardiac myocyte apoptosis [41, 45]. The altered redox in oxidative stress induces impaired contractility and structural impairment in the myocardium, ultimately resulting in subcellular apoptosis [46]. The interaction between oxidative stress and apoptosis plays a pivotal role in the pathophysiology of myocardial injury. TAN-IIA manages to limit myocardial apoptosis and improve cardiac function through regulation of these pathways.

In a study performed by Zhang et al., the cardioprotective effect of pretreatment of TAN-IIA on streptozotocin-induced diabetic rats was investigated. The I/R model was induced by left anterior descending (LAD)-ligation. The pretreatment with TAN-IIA decreased infarct size. Also, it reduced left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and inflammation of cardiomyocytes. Moreover, TAN-IIA caused the left ventricular ejection fraction (LVEF) parameter elevation. Additionally, the apoptosis index was reduced by 10 percent because of pretreatment with TAN-IIA. The authors concluded pretreatment with TAN-IIA improves cardiac function and I/R injury in diabetic rats [47].

Pang et al. studied the improvement effect of TAN-IIA on cardiac dysfunction in hypertension-induced left ventricular hypertrophy (H-LVH) rats. The two-kidney, one-clip-induced hypertensive rats received three doses of TAN-IIA for eight weeks. After eight weeks, the heart was removed and plasma extracted. The cardiac parameters had significant changes. For example, left ventricular (LV) mass/body weight (BW), left ventricular posterior wall thickness at end-diastole (LVPWd), and interventricular septal thickness at end-diastole (IVSd) were decreased after treatment. Also, the percentage of apoptotic cells and expression of apoptotic proteins were reduced in the treatment group. For example, the expression of caspase-3, Bax, and the Bax/Bcl-2 ratio was reduced. Also, treatment with TAN-IIA improved oxidative function. It decreased the malondialdehyde (MDA) activity and elevated superoxide dismutase (SOD) content. It was concluded that TAN-IIA reduced apoptosis of cardiomyocytes, oxidative damage, and improved cardiac function [48].

Cardiac Mitochondrial Function

Mitochondria, the primary source of cellular energy, assumes a crucial function in the mechanism of cell apoptosis. It is an abundant organelle in cardiomyocytes that governs cellular metabolism, the cell cycle, and signal transduction. Numerous studies have demonstrated that mitochondrial alterations are linked to the development of heart failure. Consequently, dysfunction of mitochondria gives rise to pathological modifications, impedes the

production of ATP at regular levels, augments oxidative stress, and ultimately impacts the operation of the myocardium. In fact, this persists to the extent of causing cardiomyocyte demise, which signifies the commencement of cardiac insufficiency [49–52]. Research demonstrated that a lack of free fatty acid (FFA) oxidation and mitochondrial biogenesis may account for the decline in mitochondrial function [53]. The transfer of FFA and glucose into mitochondria, which serve as indicators of mitochondrial metabolic activity, is regulated by CPT-1 and GLUT-4 and restored by TAN-IIA administration [54]. Importantly, deficiencies in mitochondrial respiration have the potential to result in reactive oxygen species (ROS). This, in turn, can facilitate the exacerbation of mitochondrial function impairment, disturbances in mitochondrial membrane stability, and cellular demise [55]. The preservation of operational mitochondria is contingent upon a consistent and regulated provision of mitochondrial proteins, which are initially furnished by transcriptional factors that bind to the promoters of nuclear mitochondrial genes. YY1, which binds DNA via four C-terminal zinc finger domains, can act as either an activator or repressor of mitochondrial gene expression [56, 57].

The protective effect of pretreatment with TAN-IIA on myocardial cell function and cell apoptosis in obese rats was studied. The obese rats were generated through a high-fat diet for eight weeks. The TAN-IIA at the dose of 10 mg/kg/day was given intraperitoneally (IP) to obese rats. After two weeks, renal I/R was induced by ligation to induce acute myocardial injury. The pretreatment with TAN-IIA reduced heart injury and the percentage of damaged mitochondria. It also decreased apoptosis by the reduction in caspase-3 and caspase-9 activity. It was concluded that TAN-IIA inhibits myocardial cell apoptosis by modulating mitochondrial function in obese rats [58].

In a study conducted by Yan et al., the effect of TAN-IIA on oxidative stress and cardiac function was investigated. A suture around the aorta of mice induced oxidative stress. After four weeks of surgery, mice were given TAN-IIA intravenous (IV) at the dose of 10 mg/kg/day for four weeks. The treatment with TAN-IIA caused a reduction in LV diameter in diastole (LVIDd) and LV diameter in systole (LVIDs). It also improved the fractional shortening (FS) percentage. Due to the reduced expression of caspase-3 and caspase-9, the apoptosis index was decreased. Additionally, ROS levels were measured due to the possible relation between ROS and apoptosis in failing hearts. Treatment with TAN-IIA reduced ROS level. The authors concluded that TAN-IIA has a mitochondrial protection effect due to the elevation of Nrf2 expression, which was confirmed by *in vitro* and *in vivo* experiments [54].

Cardiovascular Structure and Function

Certain factors are measured to investigate the effect of damage on the structure and function of the heart, and based on the changes of these factors, the effect of the wound and the effective substance can be understood. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), LVEF, left ventricular fractional shortening (LVFS), and dP/dt(max) ratio are critical factors in the evaluation of cardiac function and structure. Left ventricular end-diastolic diameter, known as a common indicator in echocardiography, reflects the size of the heart and left ventricular function [59–62]. The left ventricular ejection fraction, used to measure the left ventricular systolic function, represents the fraction of chamber volume ejected in systole (stroke volume) to the volume of blood in the ventricle at the end of diastole (end-diastolic volume) [63]. Additionally, dP/dt(max) refers to the maximal rate of rise of left ventricular pressure and is an important factor to consider in assessing left ventricular systolic function [64, 65]. Regulation of these factors by TAN-IIA plays a vital role in improving cardiac function and structure. Furthermore, Studies have demonstrated that TAN-IIA can decrease myocardial apoptosis, cardiac fibrosis, collagen deposition levels, infarction size in myocardial infarction (MI) models, and cardiac necrosis and splitting of muscle bundles, ultimately improving widespread myocardial structure disorder [66, 67].

In the Sun et al. study, cardioprotective effects of TAN-IIA were conducted via kinin B_2 receptor-Akt-GSK-3β dependent pathway in experimental diabetic cardiomyopathy. After administration of TAN-IIA, an increase in LVEF along with a decrease in myocardial apoptosis, cardiac fibrosis, and collagen deposition levels, show improvement in cardio function. Moreover, TAN-IIA enhanced Akt and GSK-3‘ phosphorylation and inhibited the nuclear factor kappa B (NF-κB) phosphorylation, leading to decreased tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and myeloperoxidase (MPO) activities [67].

Effects of TAN-IIA on viral myocarditis (VMC) induced by IP injecting Coxsackie virus B3 (CVB3) in mice were investigated by Guo et al. Mice were treated with 20 mg/kg/day (i.p.) TAN-IIA for 14 days. The result demonstrated that TAN-IIA treatment could significantly decrease the heart weight (HW)/BW ratio, alleviate CVB3-caused myocardial injury, and enhance survival rate. It could remarkably decrease heart rate (HR), and the values of LVFS, LVESD, and LVEDD, and also elevation in systolic blood pressure (SBP) value and cardiac function improvement can be established by this treatment. Furthermore, the serum levels of lactate dehydrogenase, creatine kinase, and T helper-1 (Th1) cytokines in the TAN-

IIA group were significantly improved. In inflammation responses, TAN-IIA treatment significantly decreased serum levels of interferon-gamma (IFN-γ) and IL-2 and increased serum expression of IL-4 and IL-10 [68].

A study by Wei et al. presented to elucidate the cardioprotective effects of sodium TAN-IIA sulfonate (STS) on the MI model driven by isoproterenol (ISO) in rats. Treatment with 4, 6, and 8 mg/kg of STS ameliorates cardiac dysfunction and variation of myocardial zymogram. Evaluating cardiac marker enzymes showed that STS treatment downregulated the level of creatine kinase-myocardial band (CK-MB), aspartate transaminase (AST), and lactate dehydrogenase (LDH). Furthermore, significant improvement in the activities of ATPases, including Na^+/K^+ATPase, Ca^{2+}-ATPase, and Mg^{2+}-ATPase. Treatment with STS upregulates antioxidant systems via upregulation of glutathione peroxidase (GPx) and SOD and maintains the levels of circulating lipids by decline in MDA level and elevation in glutathione (GSH) level. Moreover, expressions of nuclear factor erythroid 2–related factor 2 (Nrf2) and Heme oxygenase-1 (HO-1) and the ratio of phosphor-extracellular signal-regulated kinase (ERK) to ERK dramatically increased, which shows that STS restores the impaired cardiac ERK/Nrf2/HO-1 signaling pathway in ISO-treated rats. On the lipid profile, STS treatment reduced the level of total cholesterol (TC), triglycerides (TG), and FFAs in serum. Additionally, a significant reduction in the adenosine monophosphate (AMP)-activated protein kinase (AMPK) phosphorylation level and subsequently improvement of acetyl CoA carboxylase (ACC) was observed; these alterations would decrease carnitine palmitoyl transferase (CPT1) protein production, deteriorating the heart damage by enhanced fatty acid β-oxidation. This treatment could also elevate the mean arterial blood pressure (MABP) level, decrease left ventricular end-diastolic pressure (LVEDP), and improve heart rate in MI rats. Using STS improved widespread myocardial structure disorder, area of infarction with edema, inflammatory infiltration, cardiac necrosis, and splitting of muscle bundles caused by ISO [66].

A study by Li et al. investigated the effects of TAN-IIA on myocardial I/R injury in rats. Oral administration of TAN-IIA (15 mg/kg) for seven days enhanced left ventricular contraction movement, LVEF, and LVFS and, conversely, decreased myocardium infarct volume, inflammatory infiltration, CK, CK-MB, and LDH, demonstrating protective cardiac function effects. Regulation of CD4 + T cell differentiation via nucleotide-binding domain and leucine-rich repeat (NLR) family pyrin domain containing 3 (NLRP3) inflammasome was evaluated in this study; results showed that TAN-IIA treatment remarkably reduced the value of Th17 cells and Th17/Treg cells ratio by inhibition of NLRP3 inflammasome activation [69].

In an *in vivo* study, the anti-inflammatory and anti-oxidative effect of TAN-IIA on atherosclerotic vessels was investigated. One hundred twenty female $apoE^{-/-}$ mice were ovariectomized and fed a high-fat diet. The TAN-IIA was administered intramuscularly at doses of 30 and 60 mg/kg/day for three months. It was observed that lipid deposition occurred in the treatment group. It also decreased blood fat factors such as TG, TC, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). The treatment with TAN-IIA elevated the blood SOD activity and decreased MDA concentration and inflammatory factors such as NF-κB and activated protein-1 (AP-1) [70].

Ischemia

The term ischemia refers to the reduction of blood flow to tissues due to arterial occlusion [71]. Both the amount of blood flow reduction and the duration of ischemia affect cell dysfunction or death [71–73]. Also, different organs show different vulnerability to ischemia. In addition, depending on the organ in which they are placed, the cells can survive ischemia for a short period [72]. Excessive production of ROS and inflammatory cascades are the main factors of ischemia [74, 75]. Oxidative stress can not only cause cell damage by itself, but by increasing the release of calcium and the participation of calcium in pathways, it causes further cell destruction [76]. According to this information, drugs that improve the antioxidant system can limit ischemic injury [77]. Restoring blood flow and reperfusion as quickly as possible remains the mainstay of treatment for ischemia [71].

The protective effect of pretreatment and treatment of TAN-IIA against myocardial I/R was investigated by Wei et al. via an *in vivo* study. The LAD-ligation was performed on rats to induce an ischemia model. The pretreatment was the administration of TAN-IIA IV injection at the dose of 8 mg/kg 15 min before the ischemia. The treatment significantly reduced the infarct area, and it was demonstrated that the protective effect of TAN-IIA decreased over time. Also, it decreased CK-MB, LDH, and AST activity. Additionally, it reduced MDA content and enhanced antioxidant enzymes such as SOD, GPx, and GSH. The TAN-IIA improved cardiac function, including left ventricular developed pressure (LVDP), work index, heartbeat, and LVEDP [77].

In another study, the effect of TAN-IIA on myocardial I/R injury was investigated. A total of 88 rats were included in the study. The left main coronary artery was ligated to induce ischemia. The TAN-IIA was injected IV at 5, 10, and 20 mg/kg doses. It was observed that the infarct size of tissue was reduced with medium and high doses of TAN-

IIA. Also, the expression of p-Akt and p-eNOS was measured. The p-Akt and p-endothelial nitric oxide synthase (eNOS) levels were increased. The authors concluded that TAN-IIA had a protective effect against I/R injury through the Akt-eNOS pathway [78].

Myocardial Calcium Regulation and Rhythm

The regulation of calcium in the cardiac system is intricately connected to the process of cardiac contraction [79]. Calcium is essential for ATP synthesis in mitochondria. Augmented calcium uptake by mitochondria enhances ATP generation, resulting in better energy metabolism and supply to contractile proteins during systolic and diastolic actions [80]. The sarcoplasmic reticulum serves as the primary supplier of calcium for myocardial contraction [79]. Sodium-calcium exchanger (NCX), Ca^{2+}-ATPase, and sodium–potassium ATPase (Na^{+}/K^{+}-ATPase) are calcium regulatory proteins. These proteins regulate calcium ion transport across the cell membrane, controlling both the uptake and release of these ions [81]. The activation of the NCX is initiated by a decrease in intracellular Na^{+}, which results in an influx of Na^{+} into the cell in exchange for Ca^{2+} [81].

Conversely, the uptake of Ca^{2+} into cells and the sarcoplasmic reticulum is regulated by the sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase (SERCA) [79]. Elevated intracellular diastolic Ca^{2+} levels in heart failure impede ventricular relaxation and blood refill [82, 83]. In addition, during cardioplegic arrest, KATP channel activation preserves myocardial Ca^{2+} by inducing sarcoplasmic reticulum Ca^{2+} release and altering NCX to maintain Ca^{2+} homeostasis [84]. By regulating the myocardial calcium, TAN-IIA plays a crucial role in cardiac function, both systolic and diastolic.

Fang et al. conducted an *in vitro* and *in vivo* study on the anti-apoptotic effect of TAN-IIA on an animal model of myocardial I/R and myocardiocytes. In the *in vivo* study, the LAD-ligation was performed on rats to induce myocardial I/R. It was administered 10 mg/kg orally for 20 days. Treatment with TAN-IIA decreased LVESD, LVEDD, and infarction ratio. Also, it elevated LVEF, LVES, and dp/dt factors. Moreover, results demonstrated that TAN-IIA treatment had anti-apoptotic effects on myocardial cell protein expression, such as upregulation of Bcl-2 and Bcl-xL expression and downregulation of caspase-3, cyto c, and Apaf-1 expression. In the *in vitro* study, H_2O_2-induced myocardiocytes showed an increase in cell viability after administration of TAN-IIA dose-dependently. Also, it upregulated anti-apoptotic protein expression and downregulated pro-apoptotic protein expression. Finally, it was observed that TAN-IIA treatment reduced oxidative stress and intracellular calcium in myocardiocytes [85].

Oxidative Stress

Oxidative stress occurs when the production of ROS increases and the body's antioxidant defense system is unable to control it [86]. The elevated ROS plays an important role as second messengers in many intracellular signaling cascades that keep the cell in homeostasis. If these species' levels increase, they can damage the molecules and eventually cause the cell to lose its function or even die [87]. The body's defense system, including enzymatic and non-enzymatic defenses, inhibits the oxidant attack. In enzymatic defense, they all have a metal core that can take different amounts of electrons during the detoxification of oxygen species. One example of enzymatic defense is GPx, whose function depends on the presence of GSH [88]. Non-enzymatic defense includes vitamin C and vitamin E. Reactive oxygen species can be produced in many pathways, including mitochondria, endoplasmic reticulum (ER), and enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidases 2 (NOX2) [89]. Intervention in the antioxidant system can be a treatment against oxidative stress.

Zhu et al. investigated the antioxidative effect of TAN-IIA on atherosclerosis. The atherosclerosis model was induced by feeding apolipoprotein E-deficient mice. The mice were divided into four groups, and three of them had high-fat and cholesterol-rich (HFC) diets. Two groups were administered IP with TAN-IIA at 10 and 20 mg/kg/day doses for four weeks. The HFC diet developed atherosclerosis lesions. It also increased TC, TG, and low-density lipoprotein-cholesterol (LDL-C) levels. Treatment with TAN-IIA reduced all those indexes in both doses. It also decreased TNF-α and IL-6 expression. Additionally, it improved SOD and GSH activity and reduced MDA and glutathione disulfide (GSSG) concentration. The *in vitro* study showed that the H_2O_2-treated human umbilical vein endothelial cells (HUVECs) had lower SOD and GSH activity, and treatment with TAN-IIA improved antioxidant activity. Also, HUVECs treated with TAN-IIA had lower TNF-α and IL-6 concentrations. Overall, it was observed that TAN-IIA had an antioxidative and anti-inflammatory effect that ameliorated atherosclerosis [90].

Chen et al., in an *in vivo* and *in vitro* study, explored the effect of TAN-IIA on atherosclerosis. The apolipoprotein E-deficient mice were fed the HFC diet for 20 weeks. The TAN-IIA was injected IP at the dose of 10 mg/kg once a day. In the end, the macrophages were isolated from the aorta. It was observed that TAN-IIA downregulated significantly the plasma TG, total cholesterol (CHO), and LDL, while the level of high-density lipoprotein (HDL)

was upregulated. The intimal lesion area was reduced by treatment with TAN-IIA. The macrophages treated with TAN-IIA had reduced CD197 expression, while the expression of CD206 was improved. Also, lipid accumulation was reduced in macrophages. The results demonstrated treatment with TAN-IIA reduced inflammatory response and attenuated atherosclerosis [91].

Vascular Smooth Muscle Cell (VSMC) Proliferation

The inflammation and division of VSMCs are important factors in the pathogenesis of numerous proliferative vascular diseases, including atherosclerosis and restenosis [92–95]. A complicated network of growth, pro-inflammatory, and transcription factors coordinates and harmonizes the expression of inflammatory and proliferative genes [96]. For example, multiple growth stimuli released during arterial injury activate intimal hyperplasia, which includes VSMC proliferation, migration, and transition to a secretory phenotype [92–95, 97]. Previous studies have shown that vascular remodeling is strongly linked to endothelial cell oddities, VSMC proliferation, and vascular inflammation [98]. Hence, therapeutic interventions that constrain VSMC proliferation may be valuable in preventing restenosis. It has been found that using TAN-IIA could withhold the progression of atherosclerosis by constraining vascular inflammation. It also showed that it could reduce the levels of MMP-2 and MMP-9, VSMC proliferation, and migration and downregulate the TLR4/TAK1/NF-κB signaling pathway [99] (Fig. 2).

In an *in vivo* and *in vitro* study conducted by Qin et al., the protective effect of TAN-IIA against VSMC inflammation was investigated. The common carotid artery was ligated to induce the neointimal hyperplasia model in mice. It was administered IP at 10 mg/kg doses for seven days before ligation and 21 days after ligation. The TAN-IIA ameliorated neointimal formation and inflammation induced by carotid artery ligation. In addition, it could also inhibit VSMC inflammation by a reduction in IL-1β, IL-6, and TNF-α. It was concluded that TAN-IIA inhibited inflammation by suppressing miR-712-5p expression through TNF-α. Because the expression of miR-712-5p increased dose-dependently with TNF-α concentration, and treatment with TAN-IIA decreased TNF-α concentration and miR-712-5p expression [100].

In another study, Du et al. investigated the effect of TAN-IIA on intima hyperplasia in mice. The ligated-carotid-induced hyperplasia mice were administered TAN-IIA orally at 0.3 and 0.6 g/kg doses for four weeks. After four weeks of treatment, the intimal area and ratio of intima were significantly reduced. Also, the treatment decreased proliferating cell nuclear antigen (PCNA), a particular marker for cellular proliferation found in most cell phases during proliferation. It is distinguished as VMSC proliferation in injured arteries. Hence, TAN-IIA had an inhibitory effect on intimal hyperplasia by inhibiting the proliferation of VMSC [101].

Vascular Endothelial Growth Factor (VEGF)

One of the key regulators of angiogenesis during embryonic and muscle development is VEGF, which plays a role in the angiogenesis associated with tumors [102–107]. Furthermore, its activities include the ability to grow and multiply endothelial cells branched from arteries, veins, and lymphatic vessels [103–108]. Also, VEGF is considered a survival factor for endothelial cells. Further studies have shown that VEGF increases the expression of anti-apoptotic proteins such as Bcl-2 [109–111]. Endothelial cells that are newly formed show dependence on VEGF, and by inhibiting VEGF, apoptosis is concomitantly induced [111, 112]. Two receptor tyrosine kinases (RTKs), VEGFR-1 and VEGFR-2, are important in VEGFR function and significantly differ in signaling pathways [113, 114]. Also, coreceptors such as neuropilin (NRP1 and NRP2) regulate the RTK pathway [115]. Inhibition of VEGF is a strategy used to treat malignant tumors by stopping tumor angiogenesis and preventing tumor growth [116].

In an *in vitro* study, Xu et al. investigated the cardioprotective effect of TAN-IIA against myocardial ischemia injury in rats. The LAD-ligation myocardial-induced rats were divided into three groups. The TAN-IIA was administered at a dose of 30 mg/kg for seven days. The hemodynamic measurements demonstrated that TAN-IIA improved ventricular function, including increasing LV systolic pressure (LVSP) and reducing LVEDP and LV/BW. Also, the infarct size was significantly reduced. The treatment with TAN-IIA had anti-oxidative effects, such as improving SOD and GPx activity and reducing MDA concentration. The administration of TAN-IIA enhanced VEGF expression in the heart, leading to angiogenesis that inhibits ischemic damage. It was concluded that TAN-IIA had beneficial effects and improved myocardial cells through angiogenesis [117].

In another study, TAN-IIA improved MI injury by inhibiting myocardial necrosis, modulating inflammation, and promoting angiogenesis. The animal model was LAD-ligation MI-induced mice. TAN-IIA was administered IP at 20.8 mg/kg/day for 28 days. The mice treated with TAN-IIA showed improvement in hemodynamic indexes, including cardiac function and scar size. Treatment significantly reduced infiltration of inflammatory cells, plasma levels of LDH, and eosinophil necrosis. Also, the VEGF level was enhanced in TAN-IIA-treated mice [118].

Tanshinone and Effects on Signaling Pathways

AMPK

Cells constantly coordinate their metabolism to meet their energy necessities and respond to nutrient consumption. Eukaryotic organisms have evolved a complicated and adaptable complex, AMPK, to sense low levels of cellular ATP [119]. In circumstances of deficient energy, AMPK is activated upon binding with AMP or ADP [119]. When activated, AMPK moderates metabolic processes like protein synthesis (e.g., phosphofructokinase [120] and mammalian target of rapamycin complex [121, 122]), lipid homeostasis (e.g., ACC) [123, 124], and mitochondrial homeostasis (e.g., peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α)) [125] by phosphorylating crucial proteins across multiple pathways. Furthermore, AMPK can continuously control intracellular metabolism by moderating transcriptional regulators (e.g., forkhead box O3) [126]. Activated AMPK sustains energy balance by upregulating ATP synthesis or lessening ATP consumption (Fig. 2). Because of its critical role in intracellular metabolic processes, dysregulation of AMPK is widespread in cancer, obesity, cardio-metabolic diseases, and diabetes. It is also known as an auspicious pharmacological target [127–132], predominantly for the treatment of type 2 diabetes [133–135].

In a study performed by Zhang et al., the protective effect of TAN-IIA on heart failure post-myocardial infarction was investigated. The heart failure (HF) model was induced by LAD ligation in rats, and TAN-IIA was administered orally at a dose of 1.5 mg/kg for 28 days. The study showed that TAN-IIA administration significantly reduced the LVIDs and LVIDd factors, and EF and FS were upregulated in the HF rat model. Administration of TAN-IIA also reduced the apoptotic rate by a significant margin, and this was confirmed by downregulation of Bcl-2, Bax, cleaved caspase-3, and cleaved caspase-7, and upregulation of Bcl-2/Bax ratio of expression. The expression of LC3 and Beclin1 proteins was also upregulated, and p62 expression was inhibited following the treatment. For further analysis of TAN-IIA treatment on cell injury, a hydrogen peroxide-induced H9C2 cell injury model was established. It was concluded that TAN-IIA at 1 μM could increase cell viability, LC3, and AMPK phosphorylation and reduce the mammalian target of rapamycin (mTOR), p62, and S6K1 proteins' expression [136].

Chi et al. studied the effect of TAN-IIA on the development of diabetic cardiomyopathy. Diabetes mellitus (DM) was induced by Streptozotocin in Wistar rats, and TAN-IIA was administered through IP injection at a dose of 5 mg/kg for four weeks. It was concluded that TAN-IIA could decrease LVEDd and LVEDs and increase LVEF of DM rats significantly. The results of ELISA analysis of cytokines showed a substantial decrease in TNF-α, IL-6, and IL-1β levels, meaning that TAN-IIA treatment inhibits the inflammatory response. The study also showed that TAN-IIA decreased DM-induced myocardial fibrosis. It also increased the expression of MMP-2/9 and did not affect the expression of TIMP-1/2. The effect of TAN-IIA on the mTOR pathway was also analyzed, and it was revealed that treatment with TAN-IIA could decrease the expression of p-mTOR and P70S6K and, therefore, partly inhibit the activation of the mTOR pathway [137].

Bcl-2/Bax

The Bcl-2 protein family's constituents function as significant regulators of programmed cell death pathways, with individual members capable of either suppressing or promoting apoptosis [138–140]. In particular, Bcl-2 has been shown to possess potent abilities in suppressing the programmed cell death process [141]. The main programmed cell death pathway in most tissues involves mitochondria [142]. Several Bcl-2 family proteins are located in the mitochondrial outer membrane. Proteins that cause apoptosis, such as Bax and Bak, increase the permeability of the mitochondrial outer membrane and cause the release of proteins that activate caspase and other mediators of cell death. Meanwhile, anti-apoptotic proteins such as Bcl-2 protect the outer membrane and control its permeability [143–145]. Also, during cellular stress, the ER can initiate a molecular cascade that ultimately causes cell death, which is both caspase-dependent and non-caspase-dependent [146]. Due to this, the accumulation of unfolded proteins stimulates the molecular cascade [147, 148]. It has been shown that overexpression of Bcl-2 anti-apoptotic proteins prevents cell death caused by ER stress (Fig. 2). Such apoptotic proteins are necessary to perform apoptosis resulting from ER [149, 150]. Overexpression of Bcl-2 and other anti-apoptotic proteins inhibits cell death due to various stimuli such as growth factor depletion, environmental oxygen depletion, and oxidative stress. Bcl-2 anti-apoptotic proteins can also prevent normal cell death and protect against the toxic effects of anti-cancer drugs. Therefore, most traditional anti-cancer drugs depend on the Bcl-2/Bax pathway [151, 152].

Wang et al. study observed the regulation of TAN-IIA in doxorubicin (DOX)-Induced Cardiotoxicity zebrafish (20 μM), mice (10 mg/kg), and H9C2 models (1 μM). Results revealed that TAN-IIA significantly improved heart function by upregulating EF and FS levels and downregulating LVEDD and LVESD. Moreover, TAN-IIA decreased LDH and CK-MB, increasing the mice's body

weight. They showed that the anti-apoptotic effects were promoted by the reduction of the BAX/Bcl-2 ratio. Furthermore, this treatment restored autophagic flux by promoting autolysosome degradation and autophagosome formation, demonstrating that these effects were mediated through the upregulation of Beclin1 and LAMP1. The mTOR agonist MHY1485 was shown to nullify the impact of TAN-IIA via the UNC-51-like kinase 1 (ULK1)-Beclin1/TFEB-LAMP1 signaling pathway [153].

In another study conducted by Pan et al., the cardioprotective effects of STS were evaluated in I/R-induced cardiac injury in rats. Results demonstrated that STS pretreatment in doses of 15, 30, and 70 mg/kg IP remarkably reduced the percentage of myocardial infarct size and improved cardiac function. It was also concluded that STS pretreatment can significantly downregulate the levels of Caspase-3 and Bax protein and upregulate the level of Bcl-2. Moreover, the change in autophagy-related protein beclin-1 and Lc3B/Lc3A was increased, and the level of HMGB1 significantly decreased. Overall, STS ameliorates I/R-induced myocardial injury and shows a cardioprotective effect by reducing inflammation and apoptosis while enhancing autophagy [154].

eNOS/NO

Nitric oxide (NO) is produced by nitric oxide synthase (NOS) from arginine. NOS has three subtypes, including eNOS, inducible nitric oxide synthase (iNOS), and neuronal nitric oxide synthase (nNOS) [155]. In physiological terms, most of the NO is produced by eNOS, which oxidizes arginine nitrogen. Endothelial-derived NO is an important molecule in various signaling pathways. It reduces the production of ROS and lipid peroxidation [156]. In addition, eNO prevents the adhesion and accumulation of platelets and the migration of inflammatory cells [157]. The eNO pathway participates in the PI3K/Akt/eNOS pathway, and disruption of eNO production causes endothelial dysfunction and disease [158, 159] (Fig. 2).

In a study conducted by Pan et al., the cardiac protective effects of TAN-IIA, one of the major components in Danshen, were analyzed. A LAD-induced myocardial infarction model of mice, an *ex vivo* micro-artery system, and a HUVECs model were used. Treatment of MI mice with 20 mg/kg of TAN-IIA reduced the infarction size and post-infarction hypertrophy, as apparent by the observed impact on the heart-to-body weight ratio. It also resulted in a reduction of left ventricular dilatation, shown by the significant decrease in LVEDV and LVESV. The treatment also meaningfully increased LVFS and LVEF in the mice, improving cardiac function post-MI. In the *ex vivo* micro-artery system model, Pan et al. concluded that TAN-IIA induces its vasodilatory effect through the eNOS/NO and PI3K pathways. Using an $eNOS^{-/-}$ mice model, they also determined that the eNSO-related TAN-IIA-induced vasodilation may be endothelium-dependent. In the cultured HUVECs, TAN-IIA improved eNOS phosphorylation, and results also suggested the involvement of the PI3K/Akt pathway in eNOS phosphorylation. The HUVECs models also showed that TAN-IIA considerably increased NO production and L-arginine uptake in endothelial cells. The results of quantitative PCR showed that TAN-IIA also upregulates CAT-1 and CAT-2B mRNA levels [160].

In a 2012 study by Zhou et al., the effects of TAN-IIA on high glucose-induced eNOS uncoupling in the EA.hy926 human endothelial cell line was investigated. After incubation of the cells for 24 h of 48 h in the high glucose culture media, the cells were cultured in 1-10 μM of TAN-IIA, and the effects were reported. The researchers found that TAN-IIA significantly inhibited the high glucose-induced superoxide production in a concentration-dependent manner. They also observed that TAN-IIA drastically increased the NO generation, which was lowered due to the high glucose culture. It was concluded that TAN-IIA improves eNOS function weakened by oxidative stress. The effect of TAN-IIA on NOX expression was also investigated, and it was perceived that the expression level of NOX4 had decreased extensively. The change in the eNOS forms (monomer and dimer) and the ratio of Tetrahydrobiopterin4 (BH4) to BH2 was also examined, and it was observed that the treatment could recover the eNOS dimer/monomer ratio and increase the BH4/BH2 ratio markedly, which was lowered by the high glucose exposure. The TAN-IIA treatment also increased GTPCH1, DHFR, and HSP90 expression and decreased PI3K expression significantly. This study demonstrated that high glucose-induced eNOS uncoupling in HUVECs can be restored by TAN-IIA treatment [161].

ERK1/2

The ERK1/2 pathway includes the activation of downstream kinases by means of a series of phosphorylation events. Particularly, reticular activating system (RAS) GTPase stimulates the activity of rapidly accelerated fibrosarcoma (RAF) kinase, which sequentially phosphorylates mitogen-activated protein kinase kinase 1/2 (MEK1/2). These kinases then trigger ERK1/2, which then phosphorylate a variation of intracellular targets in both the cytoplasm and nucleus. Among the roughly 70 cytoplasmic substrates are SOS, EGFr, cPLA2, RSK1, phosphodiesterase 4D (PDE4), and p70 S6 kinase [162]. In the nucleus, ERK1/2 phosphorylates several transcription factors that cause reprogramming of cardiac gene expression (Fig. 2). The literature holds many reports supporting the

valuable role of ERK1/2 signaling in the heart. For instance, RAF-1 null mice present left ventricular systolic dysfunction and heart dilatation without cardiac hypertrophy, along with increased cardiomyocyte apoptosis [163]. Likewise, transgenic mice expressing a dominant negative form of RAF-1, especially in the heart, display diminished hypertrophic remodeling, high levels of cardiomyocyte apoptosis, and increased mortality as a result of pressure overload [164]. In addition, transgenic mice expressing activated MEK1 in cardiomyocytes develop stable concentric hypertrophy free of interstitial cell fibrosis [165]. In another study, Erk1 null and Erk2 − / + heterozygous mice exhibit heart decompensation and failure after long-term pressure overload because of increased cardiomyocyte apoptosis [166].

The protective effects of TAN-IIA on DOX-induced HF were assessed in a study by Xu et al.. An *in vitro* model of H9C2 and HL-1 cells was used, treated with DOX and TAN-IIA for 24 h, and an in vivo model of DOX-induced HF in C57BL/6 mice. The mice were treated with TAN-IIA (2.5, 5, and 10 mg/kg/day), and the results were as follows. In the in vitro model, TAN-IIA significantly increased cell viability and inhibited DOX-induced apoptosis. Death-domain associated protein (DAXX) expression was upregulated, and the TAN-IIA-mediated protection was eliminated after silencing the expression of DAXX using RNA interference, which suggests the association with ERK1/2 and MEK expression. The in vivo study showed that TAN-IIA treatment improved myocardial function and inhibited myocardial structure alteration and myofibril disruption. Also, TAN-IIA increased the expression of DAXX, p-ERK1/2, and p-MEK and decreased apoptosis by reducing cleaved caspase-8, p-P38, and cleaved caspase-3 expression levels. Xu and colleagues concluded that TAN-IIA may be a viable strategy for the treatment of HF through the DAXX/MEK/ERK1/2 pathway [167].

Zhou et al. investigated the effects of X-ray irradiation on primary rat cardiac fibroblasts (CFs) its potential mechanisms, and the protective effects of STS. The CFs were isolated from neonatal rats and were radiation-treated with a single dose of 4 Gy of X-rays. After the radiation treatment, the cells were cultured in different concentrations of STS for 24 h or 48 h. It was observed that STS increased cell viability concentration-dependently. It was also observed that STS pretreatment decreased LDH release following radiation exposure and prevented radiation damage. STS also inhibited ROS formation and increased SOD activity in CFs after irradiation. It was also noted that after STS treatment, angiotensin II (ANG II) and brain natriuretic peptide (BNP) levels were markedly elevated, BNP levels were decreased, and STS did have a noteworthy impact on VEGF levels. Flow cytometric analysis indicated STS significantly reduced S phase cell cycle arrest in a concentration-dependent manner compared with the radiation group. It was also perceived that STS treatment drastically decreased the X-radiation-induced apoptotic rate. Next, the levels of apoptosis-related molecules and P38 mitogen-activated protein kinase (MAPK) pathway-related molecules were measured and it was observed that the levels of p-P38/P38, cleaved caspase-3, caspase-3 and the ratio of cleaved caspase3/caspase-3 were downregulated and the levels of p-ERK 1/2/ERK 1/2 and Bcl-2/Bax were upregulated significantly following the STS treatment [168].

Endothelin (ET)-1 Receptor

The role of Endothelin (ET) has been studied lengthily in numerous physiological and pathophysiological processes across multiple systems [169]. The ET family includes 21 amino acid peptides that occur in three distinct isoforms, namely ET-1, ET-2, and ET-3. ET is a highly effective vasoconstrictor that induces slow and continuous contraction. Although originally identified as the source of ET-1, endothelial cells are not the only cells that produce this peptide, as various other cell types containing pulmonary VSMC also synthesize it [170, 171]. ET-1 has been associated with the development of chronic pulmonary hypertension (CPH). Overexpression of the peptide has been detected in endothelial cells of pulmonary arteries in patients with secondary and idiopathic forms of pulmonary hypertension [172]. Additionally, arterial-to-venous ratios of ET-1 protein were found to be upregulated above the normal range in patients with pulmonary hypertension [173]. Many studies have linked heightened expression of ET-1 to the progression of hypoxia-induced CPH in rats [174, 175]. The use of ET-1 receptor antagonists has been shown to prevent disease progression and help recovery [176–178].

In a study performed by Wang et al., the protective effects of TAN-IIA treatment on chronic intermittent hypoxia (CIH)-induced hypertension were investigated. The CIH-triggered left ventricular dysfunction was used in adult male rats to mimic CIH in obstructive sleep apnea (OSA) patients; then, after three weeks of modeling, the rats were treated with a single dose of TAN-IIA (20 mg/kg). After the treatment, It was observed that the tail artery pressure was significantly lowered. Also, TAN-IIA administration lowered plasma ET-1 levels and increased serum NO levels notably. Echocardiographic measurements revealed that the LVSD, LVPWd, LVSP, and $\pm$ dp/dt_{max} factors were reduced, and FS was increased dramatically. The study also showed that TAN-IIA treatment prevented myocardial interstitial fibrosis caused by exposure to CIH. Further analysis of ET-1, $ET_{A,}$ and ET_B receptor expression revealed that the ET-1 and ET_A

expression levels were downregulated while the expression of the ET_B receptor was upregulated significantly. Significantly higher levels of eNOS expression were also observed. The authors concluded that TAN-IIA boasts protective effects on cardiovascular risk induced by CIH, including systolic blood pressure elevation [179].

The role of ER signaling in mediating the protective effects of TAN-IIA on insulin-like growth factor II receptor (IGF-IIR)-induced myocardial hypertrophy was investigated in a study conducted by Weng et al.. H9C2 cell line and neonatal rat cardiomyocyte models were used. Actin filament organization was partially inhibited by TAN-IIA treatment. Significant inhibition of atrial natriuretic peptide (ANP), BNP induction, and markedly lower levels of ANP and IGF-IIR mRNAs were also observed after TAN-IIA treatment. Also, it was concluded that the PI_3K/Akt signaling pathway plays a role in the cardioprotective effects of TAN-IIA. In conclusion, the results from this study suggest that TAN-IIA can mitigate Leu27IGF-II-induced hypertrophy in cardiomyocytes [180].

JNK

Protein phosphorylation is a very important regulatory step in many signaling pathways. Among the MAPK family, c-jun N-terminal kinase (JNK) is an important member of this family [181, 182]. This serine-threonine protein kinase is involved in regulating several cellular processes, including cell cycle progression, proliferation, and apoptosis [183, 184]. Several members of the JNK signaling pathway are sensitive to TNF-α, indicating that JNK promotes cell survival [185]. Although JNK indirectly cooperates with NF-κB and causes the expression of genes effective in survival [185], it also plays an essential role in apoptosis [186–188] (Fig. 2). It can cause the phosphorylation of pro-apoptotic proteins that inhibit the activity of anti-apoptotic proteins. Also, JNK facilitates the release of Cyt c, which promotes the progress of apoptosis [186]. In addition, it regulates apoptosis through p53 phosphorylation during DNA damage [189].

Yang et al. performed both an *in vitro* and an *in vivo* study to investigate the anti-oxidative effect of STS. In the *in vivo* study, rats were LAD-ligated to induce the MI model. They used STS at doses of 1, 3, 10, and 30 mg/kg 15 min before surgery. The pretreatment with STS reduced infarct size and the level of LDH in blood dose-dependently. In the *in vitro* study, the cardiomyocytes were pretreated with STS and then were administered H_2O_2 for 24 h. The pretreatment increased cell viability and reduced apoptotic cells. The JNK phosphorylation was investigated to find out the STS cardioprotective effect signaling pathway. It was observed that STS pretreatment inhibited the activation of JNK [190].

Wu et al. also demonstrated that STS treatment inhibited JNK activation. In an *in vitro* study, the anti-apoptotic effects of STS on H9C2 cardiomyocytes were investigated against injury induced by oxygen–glucose deprivation/recovery (OGD/R) or TNF-α. The STS treatment decreased caspase-3 and caspase-8 activity and apoptosis. Also, it upregulated Bcl-2 expression and downregulated Bax expression. The NF-κB activation was reduced with STS treatment dose-dependently. Also, it was observed that STS increased Akt activation but had no significant effect on MAPK activation. Moreover, STS reduced JNK phosphorylation. Results suggested that STS showed cardioprotective effects against injury [191].

NF-κB

NF-κB regulates a wide range of cellular processes. Also, various signaling pathways stimulate the NF-κB pathway [192]. The NF-κB family consists of five proteins, all formed as homodimers or heterodimers with similar structural features [193]. In most dormant cells, NF-κB dimers are bound to an inhibitor called Inhibitor of kappa B (IκB) [194]. In addition, NF-κB is involved in various cellular pathways, including cell division, apoptosis, response to infection, and inflammation [195] (Fig. 2). The two main NF-κB pathways include the canonical and non-canonical pathways. In the canonical pathway, signals are received from receptors such as tumor necrosis factor receptor (TNFR), interleukin-1 receptor (IL-1R), and toll-like receptors (TLRs). This pathway includes IκB phosphorylation and its degradation [193, 194]. When a signal activates the NF-κB pathway, it causes the cell to make proteins called the inflammasome. Inflammasomes are multi-unit protein complexes composed of danger-sensitive proteins activated during microbial attack and free radicals. These inflammasomes induce an inflammatory response by producing inflammatory proteins [196–198]. In chronic inflammation, due to free radicals, the DNA of the cell is greatly damaged [199]. Also, due to numerous and continuous inflammatory signals, it produces a lot of NF-κB, which causes the DNA repair system and apoptosis to be turned off [195, 200]. As a result, cancerous cell accumulations are created. Selective inhibition of NF-κB pathway in cells can be a suitable treatment for various diseases.

In a study performed by Mao et al., a monomethoxy-poly (ethylene glycol)-poly (lactic acid)-D-a-Tocopheryl polyethylene glycol 1000 succinate (mPEG-PLA-TPGS) nanoparticle incorporating TAN-IIA (tanshinone IIA-NPs) was developed to study its efficacy in post-infarction LV in mice. This mixture contained 40 mg copolymers (mPEG-PLA-TPGS) and 1 mg TAN-IIA dissolved in acetone. The treatment with TAN-IIA-NP prevented left ventricle dilation, improved cardiac function by reduction of LVEF and

LVFS, and limited infarct expansion. Moreover, TAN-IIA-NP treatment significantly reduced apoptosis via reduction of cleaved caspase-3 and Bax levels and increase of Bcl-2 level. Cardiomyocyte inflammation factors such as TNF-α, IL-1β, IL-6, MCP1, and IL-18 were remarkably reduced, similar to myocardial fibrosis, by suppressing levels of transforming growth factor-beta1(TGF-β1), SMAD3, and MMPs expression. Inhibition of IκB protein phosphorylation and NF-κB activation were also shown in this study, which led to suppression of proinflammatory cytokine expression [201].

A study conducted by Long et al., aimed to elucidate the effects of STS in coronary no-reflow (CNR) induced by I/R. With STS treatment, 4 and 8 mg/kg IV in rats, no-reflow and infarct areas decreased. Since the reduction of LVIDd and LVIDs levels and increase of EF and FS were established in this study, improvement of cardiac function can be concluded. The *in vivo* and *in vitro* studies demonstrated that this treatment also suppressed the Fibrinogen-like protein 2 (FGL2) expression with thrombin generation inhibition, which affected the downregulation of protease-activated receptor-1 (PAR-1). Furthermore, STS in CNR models improved Akt phosphorylation and abrogated NF-κB expression in activated MECs, which can be the possible pathway in inhibition of FGL2. Additionally, administration of STS downregulated fibrin deposition and inflammatory response via reduction of MPO and CD68 expression [202].

NOD-Like Receptor protein 3 (NLRP3)

NOD-like receptor protein 3 (NLRP3) is a critical pattern recognition receptor that is capable of detecting both pathogen-associated molecular patterns (PAMPs) and endogenous danger signals, also known as danger-associated molecular patterns (DAMPs), thereby initiating the formation of a multi-protein complex referred to as the NLRP3 inflammasome [203, 204]. The canonical activation of the NLRP3 inflammasome involves two sequential steps. The first signal, also known as the priming signal, is provided by PAMPs or the activation of cytokines, which activates NF-κB and induces the expression of NLRP3, pro-IL-1β, and pro-IL-18, all of which are integral components of the NLRP3 inflammasome (Fig. 2). The second signal, also known as the activation signal, is provided by a wide range of stimuli, including particulates, crystals, and ATP. Upon activation, the assembly of the NLRP3 inflammasome activates caspase-1, which subsequently cleaves pro-IL-1β and pro-IL-18. The activity of the NLRP3 inflammasome has been implicated in numerous diseases, including cardiovascular, and therefore, its activity must be tightly regulated [203].

The role of NLRP3 inflammasome in the pathogenesis of MI injury and the effects of STS was investigated by Hu et al. The MI model was established in Beagle dogs by LAD occlusion, and STS (2.6 and 5.2 mg/kg) was administered IV 15 min after the surgery. It was observed that infarct size was reduced dose-dependently following the STS administration, and the increase in CK-MB levels was lessened. The rise in ROS production was also dampened significantly. The NLRP3, apoptosis-associated speck-like protein containing (ASC), and Caspase-1 cardiac protein expression levels and the levels of pro-inflammatory cytokines, including IL-1β and IL-18, were also meaningfully downregulated in the STS-treated group. It was also observed that the STS treatment significantly decreased p-JAK2, p-STAT3, and SOCS3 expression levels. Furthermore, the phosphorylation levels of cardiac Akt and ERK1/2 were returned nearly back to normal after being lowered following MI. Treatment of STS markedly elevated the decreased levels of peroxisome proliferator-activated receptor α (PPAR-α) and lowered the elevated levels of TC and TG in a dose-dependent manner, therefore meaningfully reducing lipid accumulation in the ischemic heart [205].

Chen et al. studied the effect of STS on endotoxin-induced cardiomyopathy. The endotoxemic model was established in mice by lipopolysaccharide (LPS) injection. STS was administered 10 mg/kg 2 h and 12 h after endotoxin injection. Firstly, a significant promotion in the survival rate of STS-treated septic mice was observed. Echocardiographic results revealed a significant improvement in stroke volume (SV), LVFS, and LVEF and a meaningful decrease in LVESD and LVEDD in septic mice. Also, it was shown that the BNP expression levels were lowered considerably after STS treatment. Additionally, ELISA and immunohistochemical analysis results demonstrated that the elevation in expression levels of TNF-α, IL-1β, IL-6, and IL-18 was significantly decreased by STS. A meaningful reduction in the over-expression of caspase-1, NLRP3, GSDMD, and TUNEL-positive cells following the STS treatment was also detected. In conclusion, the results of the study suggest that STS enhances autophagy and suppresses NLRP3 inflammasome activation via AMPK [206].

Nuclear Factor erythroid 2-Related Factor 2 (Nrf2)

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor of significant importance, expressed in a majority of tissues, and is known to play a crucial role in amplifying antioxidant pathways associated with myocardial enzymes [207–209]. The binding of Nrf2 with antioxidant response element (ARE) is recognized as a key mechanism for regulating gene expression of oxidants and

antioxidants [210, 211]. Nrf2 is instrumental in coordinating cellular processes and safeguarding sensitive cellular components such as proteins and DNA from oxidative damage. Cardiovascular diseases are associated with various risk factors, including diabetes, inflammation, and smoking, where ROS is a central and shared factor [212, 213]. The activation of the Nrf2 receptor can be facilitated by increased ROS generation and PI3K-Akt signaling [214] (Fig. 2). The expression of antioxidant genes regulated by Nrf2 may play a protective role in endothelial cells against atherosclerosis, as excessive ROS production is linked to its development [215].

A 2018 study investigated the role of Nrf2 signaling and its underlying mechanisms in TAN-IIA's protection against DOX-induced cardiotoxicity. The acute cardiotoxicity model was induced in male mice using DOX (18 mg/kg) IP injection. To assess its effects, TAN-IIA (15 and 30 mg/kg) pretreatment was administered through IP injection. The H9C2 rat myoblast cell line model was also used. The cells were cultured with 1 μM DOX and pretreated with 1, 3, 5, and 10 μM TAN-IIA. It was observed that TAN-IIA pretreatment considerably dampened the increase in AST, LDH, CK, and CK-MB enzyme levels. The effect of TAN-IIA on the antioxidant capacity of mice hearts was also determined, and it was revealed that TAN-IIA pretreatment upregulated GSH, SOD, and catalase (CAT) levels and downregulated MDA levels significantly and in a dose-dependent manner. Further analysis showed that TAN-IIA pretreatment considerably increased Nrf2, HO-1, NQO1, and GCLC levels and reduced MRP2 expression. The *in vitro* model revealed that TAN-IIA pretreatment reversed the inhibition of cell viability following DOX treatment. It was also discovered that TAN-IIA pretreatment lowered the ROS levels and increased GSH levels in the in vitro model significantly and dose-dependently. Moreover, the expression levels of Nrf2, HO-1, NQO1, and GCLC were increased, and the levels of P-gp and MRP2 were lowered meaningfully [216].

In a 2021 study conducted by Wu et al., the effect of TAN-IIA on oxidative stress and oxidative stress–induced cardiomyocyte apoptosis was investigated *in vivo* and *in vitro*. TBHP-induced H9C2 cell apoptosis and ISO-induced myocardial injury in mice were used as the *in vitro* and *in vivo* models, respectively. Significant reductions in ROS levels and MDA production with considerably higher SOD activity were observed in the *in vitro* study. Furthermore, H9C2 cell viability was enhanced, expression of Bax and cleaved caspase-3 was inhibited, and Bcl-2 expression was upregulated in a dose-dependent manner. SPR assay showed that TAN-IIA could directly bind to Nrf2, which strongly suggests that Nrf2 signaling plays a role in the protective effects of TAN-IIA. Moreover, immunofluorescence analysis revealed that TAN-IIA treatment significantly upregulated the expression of Nrf2 in a dose-dependent manner and lowered the phosphorylation of P38 MAPK, ERK1/2, and SAPK/JNK dose-dependently. In the *in vivo* study, significantly lower levels of p-ROS and heart/body weight ratio were observed. Also, echocardiographic results revealed that LVEF and LVFS were increased, and LVEDD and LVESD were decreased meaningfully in the TAN-IIA-treated group. It was further revealed that collagen formation also decreased considerably with TAN-IIA treatment. Also, TAN-IIA treatment decreased apoptotic cell count and Bax and caspase-3 expression and increased Bcl-2 expression significantly in the *in vivo* study. Further research showed significantly higher Nrf2 expression and lower p-P38 MAPK, p-ERK1/2, and p-SAPK/JNK expression, which demonstrates that TAN-IIA inhibits ISO-induced myocardial injury through the Nrf2/MAPK signaling pathway [217].

PI_3K/Akt

The PI_3K-Akt signaling pathway has been related to various diseases such as cancer, diabetes mellitus, and autoimmunity [218–220]. Several forms of cellular stimuli or toxins activate the PI_3K/Akt signaling pathway and control fundamental cellular functions, including transcription, translation, proliferation, growth, and survival [218, 221] (Fig. 2). PI3K, a lipid kinase, generates phosphatidylinositol-3,4,5-trisphosphate (PIP_3), a potent second messenger necessary for survival signaling and insulin action [222]. And Akt, a Ser/Thr kinase, translocates and binds to PIP_3, which was previously produced. The interaction between the PH domain of Akt and PIP_3 is believed to stimulate conformational changes in Akt, leading to the exposure of its two primary phosphorylation sites [223]. PDK1, which is believed to be constitutively activated, phosphorylates Akt at Thr308, resulting in the stabilization of the active conformation [224]. The activation of Akt necessitates the phosphorylation of Thr308, while the full activation of the kinase requires phosphorylation of the residue site. Following this, active Akt relocates to the cytoplasm and nucleus [225]. The function of various substrates that regulate cell proliferation, including glycogen synthase kinase-3 (GSK3) [226, 227], membrane translocation of the glucose transporter (GLUT4) [228], and mTOR [229, 230], are modulated by activated Akt protein. In many cell types, overexpression of Akt has an anti-apoptotic effect, leading to resistance or delay of cell death [231]. Indeed, the p53 protein acts as a sensor of cellular stress and induces apoptosis. Akt indirectly regulates the tumor suppressor p53 protein [232].

The protective effects of TAN-IIA against acute ethanol-induced cardiac damage were investigated by Deng et al. study. An *in vivo* study presented that the use of 5 and

10 mg/kg IP once a day for two weeks on mice can significantly improve heart function by increasing EF and FS and decreasing LVESD. In addition, this treatment can block myocardial apoptosis by significantly inhibiting cleaved caspase-3 expression and increasing the Bcl-2/Bax ratio. An *in vitro* study was conducted on acute ethanol-induced H9C2 cells. Cell apoptosis was abrogated by TAN-IIA Treatment, 0.1, 0.3, 1, 3, 10, and 30 μM for 24 h, through downregulating the programmed cell death protein 4 (PDCD4) expression and activating the PI_3K/Akt pathway. It was also revealed in this study that the PI_3K inhibitor (LY294002) application significantly attenuated the main protective effects of TAN-IIA [233].

Another Study conducted by Zhang et al. investigated the *in vitro* and *in vivo* protective effects of STS in I/R-induced rats with MI. Administrating 20 mg/kg of STS for 15 days remarkably upregulated the myocardial function by increasing the dp/dt_{max} ratio, LVDP, and coronary flow at different reperfusion time stages and reduction of myocardial infarct size. In addition, STS remarkably decreased the rate of apoptotic cells, caspase-3 activity, and expression of pro-apoptotic gene BIM and increased the phosphorylation of Akt and its downstream target, FOXO3A. In conclusion, the protective effects of STS are via activation of Akt/FOXO3A/BIM-mediated signal pathway [234].

TGF-β

The misregulation of TGF-β signaling in humans has been linked to the advancement of CVDs and vascular pathologies, inclusive of aneurysms, arteriovenous malformations (AVMs), retinopathy, atherosclerosis, valvular heart disease, and cardiac fibrosis. Moreover, TGF-β signaling has been linked to the formation of endothelial tumors such as hemangiomas [235, 236]. The importance of TGF-β signaling pathways in cardiovascular homeostasis, as well as the regulation of heart and blood vessel morphogenesis, is apparent from the phenotypic analysis of mice missing components of the TGF-β signaling cascade [237, 238] (Fig. 2). However, the multifunctional and context-dependent activities of TGF-β, as well as its interactions with nonvascular cells such as immune cells, complicate the understanding of its *in vivo* roles in cardiovascular biology.

Mao et al. investigated the effects of STS on post-infarct cardiac remodeling in LAD-induced MI mice. 10 mg/kg of STS was administered through IP injection after LAD ligation, and the results were as follows. The LVFS and LVEF factors were increased, and LVESD and LVEDD were lowered significantly. Also, STS treatment significantly reduced HW/BW, interstitial myofibroblasts, and fibrotic tissue post-MI. Further investigation revealed that STS treatment completely reversed the MI-induced increase in ANP and BNP levels. Moreover, a significantly lower count of TUNEL-positive cells was present, and further investigation showed that STS reduced the levels of cleaved caspase-3 and Bax and increased the levels of Bcl-2 meaningfully. The authors also observed significantly higher levels of LC3 and a notably higher LC3II/LC3I ratio while the p62 levels were decreased. It was also observed that the STS treatment markedly boosts the expression of Sirt1 and significantly lowers the levels of TGF-β1 and Smad3. Western blot and immunohistochemistry analysis revealed that STS treatment inhibits MMP2 and MMP9 expression while upregulating the levels of TIMP1. It was also observed that the levels of p-AMPK were upregulated and p-mTOR and phosphorylated P70/S6K downregulated in the hearts of STS-treated mice [239].

The inhibitory effect of TAN-IIA on inflammatory responses following MI and its potential mechanisms were investigated by Ren et al.. In the *in vivo* study, the MI model was established through permanent LAD coronary artery ligation in rats, and TAN-IIA at 60 mg/kg/day was administered intragastrically. In the *in vitro* study, cardiomyocyte and cardiac fibroblast isolated from neonatal rats were cultured with 0.5 to 8 mM of TAN-IIA for 24 h. TAN-IIA retained LV dp/dt_{max} and LV dp/dt_{min} and enhanced LVEDP and LVSP. The infarct size and collagen deposition were considerably lower. The MCP-1 positive cell count and NF-κB-p65 were markedly lowered. The treatment also inhibited the increase in MCP-1 and TGF-β_1 mRNA expression levels and of TGF-β_1 and CD68 protein levels, and the level of TNF-α was significantly lowered. TAN-IIA meaningfully enhanced the viability of cardiac fibroblasts. Also, it was observed that TAN-IIA reduced the expression of MCP-1 and TGF-β_1 in cardiac fibroblasts significantly and dose-dependently [240].

TLR4/MyD88/NF-κB/NLRP3

Cellular patterns activate TLRs and DAMPs. Among the primary TLRs expressed in cardiomyocytes are TLR2, TLR3, and TLR4 [241], with TLR4 being implicated in myocardial injury caused by MI. Activation of TLR4 by DAMPs triggers an inflammatory response in myocardial tissue, leading to additional damage to already compromised cardiomyocytes [242, 243]. Previous studies have demonstrated that inhibition of the TLR4/Myd88/NF-κB pathway reduces myocardial inflammation, thereby improving cardiac function. Specifically, inhibiting TLR4 expression reduces NLRP3-mediated inflammation and proinflammatory cytokine expression [244], reduces the size of the myocardial infarction [245], alleviates myocardial tissue remodeling, and protects cardiac function [246]. Therefore, to develop drugs that effectively

reduce the loss of cardiomyocytes and improve the prognosis of MI patients, it is necessary to investigate the involvement of the TLR4/Myd88/NF-κB/NLRP3 pathway in mediating pyroptotic cell death (Fig. 2).

In a 2022 study, Li et al. investigated the effect of TAN-IIA on coronary microembolization (CME) and its underlying mechanism. The CME model was established in rats by injection of polyethylene microspheres. The rats in TAN-IIA groups were pretreated with TAN-IIA IP injection for seven days before CME. The echocardiographic evidence demonstrated that TAN-IIA pretreatment boosted LVFS and LVEF and lowered LVESd and LVEDd. The data also revealed decreased levels of LDH and CK-MB in the TAN-IIA-treated groups. Furthermore, the MI size was significantly lowered following TAN-IIA pretreatment. Additionally, the GSDMD-N, caspase-1 p20, IL-18, and IL-1β expression levels were downregulated in the treated rats. The researchers also revealed that the TLR4, NLRP3, MyD88, p-NF-κB p65, and ASC levels were considerably lower, which suggested that the TLR4/MyD88/NF-κB/NLRP3 cascade plays a role in delivering the effects of TAN-IIA on CME-induced cardiomyocyte pyroptosis [247].

The role of TAN-IIA in MI and the underlying mechanism involving the TLR4/MyD88/NF-κB signaling pathway was investigated by Wu et al. The MI model was induced in rats via LAD ligation, and IP was administered to TAN-IIA (5 and 20 mg/kg). Echocardiography showed a significant decrease in LVEDD and LVESD and a notable increase in LVEF and LVFS in TAN-IIA-treated groups. Also, MAP, LVESP, + dP/dt, and -dP/dt increased, and LVEDP decreased observably. The BW of rats in TAN-IIA-treated groups increased while the HW/BW and HW reduced meaningfully. Moreover, myocardial infarct size, LVWT, IVST, and fibrosis area were significantly lowered following the TAN-IIA treatment. Furthermore, the TLR4, NF-κB-P65, and MyD88 mRNA expression levels were meaningfully lowered, demonstrating the role of the TLR4/MyD88/ NF-κB signaling pathway in the effect of TAN-IIA. Also, the proinflammatory cytokines IL-2, IL-6, IL-8, and TNF-α levels were notably lowered. Additionally, the degree of infiltration of ED-1-positive macrophages was significantly decreased, and the degree of cell apoptosis was notably lessened by the TAN-IIA treatment in MI rats [248].

Tumor necrosis factor α (TNF-α)

Tumor necrosis factor α (TNF-α) is an inflammatory cytokine whose neutralization is one of the most suitable drugs for the treatment of inflammatory and autoimmune diseases. It has been found that TNF-α causes inflammatory response directly through the expression of inflammatory genes and indirectly through inducing cell death and stimulating inflammatory immune reactions [249] (Fig. 2). Anti-TNF-α drugs work by blocking the binding of TNF-α to its receptor (TNFR1) and TNFR2. The binding of TNF-α to its receptor directly activates the MAPK pathway and the canonical NF-κB pathway, which ultimately increases the expression of inflammatory genes. Also, the binding of TNF-α to TNFR1 indirectly increases the inflammatory response by inducing cell death. Cell death causes intracellular components to release, which induces an inflammatory response in nearby cells [250–252].

In a study presented by Gao et al., LAD-induce myocardial ischemia mice were treated with 0.3 mg/20 g of TAN-IIA along with puerarin 0.3 mg/20 g orally, respectively, on 3d, 7d, 14d, and 28d, to study on cardiac function and inflammatory response. The result revealed that the ejection fraction of the model group, the shortening rate of the short axis of the left ventricle, and the flow rate of the outflow tract were significantly decreased, and the structure of the ventricle was changed considerably. This treatment can substantially inhibit $F4/80^{+}Ly6c^{+}$ macrophages and $CD11b^{+}Ly6c^{+}$ monocytes, which leads to an effective reduction in inflammation. In the early stage of inflammation, TAN-IIA and puerarin treatment inhibited the expression of M1 macrophages and promoted the expression of M2 macrophages; this was reversed in the end. In addition, IL-6, IL-1β, and iNOS levels were remarkably downregulated; in contrast, the level of IL-10 was upregulated. TAN-IIA and puerarin significantly decreased cardiac index and the serum TGF-β. Furthermore, the *in vitro* study suggested that this treatment can regulate inflammation by inhibiting the expression of TLR4 protein but regulating the expression of C/EBP-β protein [253].

Wu et al. '*s* study aims to investigate the effects of STS on cardiac function improvement and myocardial remodeling prevention in LAD-induced MI mice. Mice were treated with 30 mg/kg/day through IP injection of STS for three weeks. The result showed improvement in the motion of the left ventricular anterior wall, LVEF, LVFS, and VEGF expression by STS treatment. Fibrosis and collagen deposition significantly lessened in the STS group. Additionally, expression levels of inflammatory cytokines such as TNF-α, IL-1β, and TGF-β were reduced considerably. In the anti-oxidant effects of STS, results demonstrated that this treatment can upregulate SOD and GSH degrees while downregulating MDA degrees. Moreover, the reduction in expressions of apoptosis-related protein Bax and increase in Bcl-2 can be concluded that STS can resist myocardial apoptosis [254].

Conclusion and Future Perspectives

Salvia miltiorrhiza, a member of the *Lamiaceae* family, genus Salvia, is a prized in Chinese medicine. Danshen, its dried root, has been used for hundreds of years in China and other Asian countries to treat cardiovascular conditions. Tanshinone, namely tanshinone I and tanshinone IIA, are a group of pharmacologically active constituents isolated from the roots and rhizome of *S. miltiorrhiza* and are currently used in China and neighboring countries to treat patients with diabetes, cardiovascular system conditions, sepsis, arthritis, apoplexy, and other diseases.

The reviewed articles studied the effects of tanshinone on rats, mice, and multiple cell lines. In a number of in vivo studies, a wide range of 1.5–120 mg/kg body weight of tanshinone was administered in C57BL/6J and SD rats and significant increases in MAP, Bcl-2, and Bax signaling and HR, LVEF, and LVFS factors and decreases in NF-κB, SOD, CK, NLRP3, LDH, IL-18, IL-1β, LVEDD, and LVESD was observed. In other studies, on mice, from 0.3 up to 120 mg/kg body weight of tanshinone was administered, and it was observed that the tanshinone administration increased Nrf2, Akt, AMPK, eNOS/NO, and SOD activity and IL-10 concentration and decreased oxidative stress, IL-6, IL-1β, TNF-α, TGF-β1, and IFN-γ concentration meaningfully. In in vitro studies on multiple cell lines, including H9C2, HL-1, HUVEC, RAW 264.7, and many other cell lines, a range of tanshinone concentrations was administered, and noteworthy increases in cell viability, ERK1/2, PI_3K/Akt and Bcl-2 expression and decreases in Apoptotic rate, SOD and JNK were observed.

The reviewed studies revealed that tanshinone induces cardioprotective effects through multiple pathways, including the AMPK, Bcl-2/Bax, ERK1/2, ET-1 receptor, PI_3K/Akt, and other pathways. Since activated AMPK plays a crucial role in maintaining energy balance in cells, its dysregulation can cause cardio-metabolic diseases, and tanshinone plays a cardioprotective role by enhancing intracellular AMPK levels. The Bcl-2 family of proteins are significant regulators of cell apoptosis, and tanshinone has shown the ability to reduce the Bax/Bcl-2 ratio in treated cells, therefore playing an anti-apoptotic role. The ERK1/2 signaling pathway has been demonstrated in a number of studies to have a beneficial role in the heart, and tanshinone improves myocardial function by inducing ERK1/2 signaling in the heart. The role of ET has been studied broadly, and it has been demonstrated that the ET family comprises 21 amino acid peptides, namely ET-1, ET-2, and ET-3, which are highly potent vasoconstrictors. ET-1 has been linked to the development of CPH, and tanshinone has been shown to downregulate the ET-1 receptor expression and, therefore, has a significant protective effect on cardiovascular risk. The PI_3K-Akt signaling pathway has been linked to the development of several diseases, including cardiovascular disease. PI_3K is a lipid kinase that produces PIP_3, a required second messenger for survival, and it has been demonstrated that tanshinone activates the PI_3K/Akt signaling pathway, thus producing cardioprotective effects.

In conclusion, through many signaling pathways, tanshinone has shown promising protective effects against cardiovascular system conditions. Several studies have also demonstrated that tanshinone boasts vasodilatory effects, improves cardiac function, and inhibits inflammation, oxidative stress, and apoptosis, making it a potential therapeutic agent in treating and preventing cardiovascular diseases. However, further research on its optimal dosage, potential drug interactions, and long-term safety is needed. Nevertheless, the collected evidence indicates that tanshinone could be a critical addition to the collection of therapies for cardiovascular diseases. With more research on tanshinone and its therapeutic effects, it may prove to be a substantial asset in enhancing cardiovascular health and reducing the impact of cardiovascular diseases on the global economy.

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Declarations

Conflicts of interest The authors declare no competing interests.

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