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Review

Therapeutic potential of *Ziziphora clinopodioides* in cardiovascular diseases: a review

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ABSTRACT

Cardiovascular diseases (CVDs) are driven by intricate and multifactorial pathophysiological mechanisms, presenting substantial challenges for the development of effective therapeutic strategies. Recent studies have highlighted the therapeutic potential of various traditional Chinese medicines (TCMs), which exert vasodilatory, anti-inflammatory, and antioxidant effects that may alleviate clinical symptoms and slow CVD progression. *Ziziphora clinopodioides*, a traditional herbal medicine, contains primarily flavonoids, phenolic acids, and essential oils. These compounds contribute to its pharmacological activities, including inhibition of apoptosis inhibition, inflammation reduction, oxidative stress mitigation, mitochondrial function improvement, and vasodilation promotion, all of which are relevant to CVD treatment. This review comprehensively examines the pathophysiological basis of CVDs, elucidates the molecular mechanisms and signaling pathways involved in the cardioprotective actions of *Ziziphora clinopodioides*, and summarizes its emerging clinical applications in cardiovascular therapy. The findings aim to inform future research and promote the rational development of this medicinal plant as a complementary or adjunctive treatment for CVDs.

1. Introduction

Cardiovascular disease (CVD) encompasses a group of conditions affecting the heart and vascular system, including coronary heart disease (CHD), atherosclerosis (AS), hypertension (HTN), arrhythmias, and heart failure (HF) [1]. Pathological processes, such as AS and thrombosis, represent significant risk factors CVDs. In traditional Chinese medicine (TCM), these conditions are often conceptualized as manifestations of "heart Qi deficiency" and "blood stasis" [2, 3]. According to global health statistics, CVDs accounted for approximately 19.05 million deaths in 2020, making them the leading cause of mortality worldwide [4-7]. This high burden, driven by rising incidence and multifactorial risk profiles, underscores the urgent need for effective strategies to reduce CVD incidence and improve patient outcomes—an area of critical importance for future research.

Current clinical treatment of CVDs primarily relies on pharmacological interventions and surgical procedures. However, these approaches often produce significant side effects, elevated treatment risks, and substantial costs, thereby compromising overall therapeutic outcomes [8, 9]. TCM employs acupuncture, Tui Na (Chinese therapeutic massage), and herbal remedies for cardiovascular conditions [10]. However, considerable patient variability and extended treatment cycles limit the broader application of TCM. A pressing need exists for cardiovascular medications that demonstrate effective pharmacological action, consistent quality, and minimal side effects. The development of effective therapeutic strategies for CVDs holds both significant clinical value and broader social implications.

As an ethnopharmacological herbal medicine, *Ziziphora clinopodioides* treats CVDs through multiple components with cardiovascular protective effects, and its volatile oil components reduce patient anxiety, providing certain clinical advantages compared to alternative therapeutic drugs [11-13]. Additionally, *Ziziphora clinopodioides* is frequently combined with other herbal medicines for cardiovascular conditions, including Tianxiangdan, compound *Ziziphora clinopodioides* Granule, Ningxin-Tongbi Capsule, and compound Xinta Flower. Although these herbal combinations have demonstrated therapeutic potential in the management of CVDs, several limitations hinder their clinical translation, including poor formulation stability, prolonged treatment durations, limited clinical trial data, and incomplete safety evaluations. Specifically, *Ziziphora clinopodioides* has shown promise as a cardioprotective agent; however, current research on its role in CVD treatment remains fragmented and insufficient. To date, no comprehensive systematic review has been conducted to evaluate its pharmacological mechanisms or clinical applications in cardiovascular therapy.

This review examines CVDs, the primary chemical constituents of *Ziziphora clinopodioides* and their associated pharmacological effects as main keywords. Literature searches will be conducted across PubMed, Web of Science, CNKI, and VIP databases. Beyond these key terms, the search will encompass signaling

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pathways related to CVD mechanisms. The review aims to systematically summarize chemical composition analyses, mechanisms of action against CVDs, and research progress regarding synergistic applications with various traditional Chinese medicinal herbs. This comprehensive review seeks to promote further investigation into *Ziziphora clinopodioides* applications in CVD treatment, providing valuable insights for the development of this ethnopharmacological herbal medicine.

2. Chemical constituents of *Ziziphora clinopodioides*

Ziziphora clinopodioides contains a variety of bioactive compounds, including flavonoids, terpenoids, and phenolic acids, which can be broadly categorized into volatile and non-volatile constituents. Researchers have focused on extracting and isolating these active chemical components from the floral buds of *Ziziphora clinopodioides* establishing foundations for investigating potential pharmacological effects, mechanisms and clinical applications of these constituents. Table 1 presents the main chemical constituents of *Ziziphora clinopodioides*.

2.1. Non-volatile constituents

Research has demonstrated that extracts from *Ziziphora clinopodioides* contain non-volatile compounds, primarily flavonoids and phenolic acids. Flavonoids represent a class of natural polyphenolic compounds that antioxidant response element (ARE) widely distributed in plants and show significant potential in CVD prevention and treatment [14-16]. Characterized by a C6-C3-C6 backbone structure, flavonoids can be categorized based on their chemical structures into flavones, flavanones, flavanols, isoflavones, biflavonoids, and other groups. These compounds exist as secondary metabolites in plants and exhibit diverse biological activities, including apoptosis inhibition, lipid regulation, vasodilation induction, and antioxidative and anti-inflammatory properties [17, 18]. Research has identified more than twenty flavonoid compounds within *Ziziphora clinopodioides*.

Yang et al. employed thin-layer chromatography (TLC) tracking, repeated silica gel column chromatography, Sephadex LH-20 column chromatography, and additional chromatographic techniques for separation and purification. Their analysis of *Ziziphora clinopodioides* yielded 6 flavonoid compounds, including kaempferol, quercetin, and hyperoside [19]. He et al. utilized silica gel column chromatography, high-performance liquid chromatography (HPLC), and LC-MS/MS to isolate and extract 29 flavonoid compounds, with 12 showing relatively high peak areas during the plant's flowering period. These primary flavonoids include rutin, luteolin, quercetin-7-*O*-rutinoside, and others, establishing a foundation for the medicinal application of *Ziziphora clinopodioides* aerial parts [20]. Zhang et al. identified 16 flavonoid compounds using HP-20 resin separation and purification, UPLC-Q-TOF-MS, and other methods, including rutin, baicalein, quercetin, luteolin, kaempferol, chrysin, and hyperoside [21].

Phenolic acids demonstrate lipid-lowering, antihyperglycemic, cardioprotective, and vasodilatory activities. They protect against CVDs through mechanisms including inflammation inhibition, antioxidation, apoptosis reduction, and vasodilation promotion [22-24]. Multiple phenolic acids have demonstrated anti-inflammatory and antioxidative mechanisms, leading to their application in CVD treatment [25-28]. Research indicates that various phenolic acids can be isolated and identified from the entire *Ziziphora clinopodioides* plant using techniques such as silica gel column chromatography and HPLC. These compounds include protocatechuic acid, rosmarinic acid, caffeic acid, 5-hydroxymethyl-2-furfural, umbellulone, *β*-D-glucopyranose, and clinopodic acid B [29]. The non-volatile constituents also include steroidal compounds and fatty acids. Yang et al. extracted and analyzed steroidal compounds, including carotene glycoside, *β*-sitosterol, *α*-spinasterol, and *α*-spinasterol-3-*O*-*β*-D-glucopyranoside, from the roots and stems of *Ziziphora clinopodioides* using repeated silica gel column chromatography, Sephadex LH-20 column chromatography, and recrystallization techniques [30]. Li and colleagues extracted fatty acid components using a Soxhlet extractor and analyzed the separated compounds through GC-MS, identifying palmitic acid, oleic acid, linoleic acid, and others [31]. Tian et al. confirmed the presence of triterpenoids, specifically oleanolic acid and ursolic acid, through HPLC analysis [32]. These findings provide crucial references for understanding the material basis and mechanisms of its therapeutic effects.

2.2. Volatile constituents

Essential oils are aromatic, oily liquids produced by plants, recognized for their diverse biological activities and pharmacological effects, including antibacterial, antiviral, antioxidant, and anti-inflammatory properties [33-39]. Studies demonstrate that essential oils can ameliorate symptoms of CVDs and offer potential benefits for cardiovascular risk factors [40-43]. *Ziziphora clinopodioides* contains a high concentration of essential oils, particularly during the flowering period, comprising components such as phenols, ketones, and terpenoids. Due to the widespread distribution of *Ziziphora clinopodioides*, the chemical composition and content of its essential oils vary by region. For example, *Ziziphora clinopodioides* from Xinjiang, China, analyzed by Ding et al. using GC and GC-MS, revealed 18 chemical constituents, with pulegone as the predominant component, along with p-menthanone, *trans*-isopulegone, D-limonene, and eucarvone [44]. Liu et al. identified 29 compounds through TLC and GC-MS, including pulegone, p-menthone, 3-carvomenthenone, limonene, acetone, *cis*-menthone, and 3-methyl-6-(1'-methyl-ethyl)-2-cyclohexen-1-ketone, with pulegone being the predominant compound [45]. Omer et al. identified pulegone as the principal constituent in *Ziziphora*

Table 1 The major chemical components in *Ziziphora clinopodioides*.

Chemical constituents	Category	Major constituents	Extraction techniques and analysis methods
Non-volatile constituents	Flavonoids	Kaempferol (1); quercetin (2); hyperoside (3); rutin (4); luteolin (5); quercetin-7-*O*-rutinoside (6); baicalein (7); chrysin (8); apigenin (9); diosmin (10); linarin (11).	TLC; Sephadex LH-20 column chromatography; silica gel column chromatography; HPLC, LC-MS/MS; HP-20 resin purification; UPLC-Q-TOF-MS.
	Phenolic acids	Protocatechuic acid (1); rosmarinic acid (2); caffeic acid (3); 5-hydroxymethyl-2-furfural (4); umbellulone (5); *β*-D-glucopyranose (6); clinopodic acid B (7).	Silica gel column chromatography; HPLC.
	Steroidal compounds	Carotene glycoside (1); *β*-sitosterol (2); *α*-spinasterol (3); *α*-spinasterol-3-*O*-*β*-D-glucopyranoside (4).	Silica gel column chromatography; Sephadex LH-20; recrystallization.
	Fatty acids	Palmitic acid (1); oleic acid (2); linoleic acid (3).	Soxhlet extraction; GC-MS.
	Triterpenoids	Oleanolic acid (1); ursolic acid (2).	HPLC
Volatile constituents	Essential oils	Pulegone (1); *p*-menthanone (2); *trans*-isopulegone (3); D-limonene (4); eucarvone (5); *p*-menthone (6); 3-carvomenthenone (7); limonene (8); acetone (9); *cis*-menthone (10); 3-methyl-6-(1'-methyl-ethyl)-2-cyclohexen-1-ketone (11); geraniol (12); carvacrol (13); *α*-terpineol (14); 4-terpineol (15); borneol (16); *γ*-terpinene (17); neomenthol (18); menthone (19); *p*-menth-3-en-8-ol (20); piperitenone (21); piperitone (22).	GC; GC-MS; TLC.

clinopodioides collected from the Kurdistan region of northern Iraq [46]. Ajourloo et al. identified geraniol, carvacrol, *α*-terpineol, 4-terpineol, borneol, and *γ*-terpinene in *Ziziphora clinopodioides* collected from the mountains of Kermanshah Province in Iran [47]. Sharopov et al. identified 45 constituents in *Ziziphora clinopodioides* collected from Tajikistan using GC-MS, with major components being pulegone, neomenthol, menthone, p-menth-3-en-8-ol, piperitenone, and piperitone [48].

3. Cardiovascular protective effects of major chemical components in *Ziziphora clinopodioides*

Several bioactive constituents of *Ziziphora clinopodioides*, including apigenin, quercetin, baicalin, and luteolin, have demonstrated significant therapeutic potential in the prevention and treatment of CVDs. These chemical components exhibit various properties, including antioxidant, anti-inflammatory, and antithrombotic activities, as well as regulation of lipid metabolism, all of which effectively interfere with CVD development. Furthermore, these compounds improve vascular endothelial function, reduce blood lipid levels, and effectively delay CVD progression. The following sections detail the specific mechanisms and pharmacological effects of these compounds in *Ziziphora clinopodioides* for cardiovascular protection.

3.1. Cardiovascular protective effects of non-volatile constituents in Ziziphora clinopodioides

3.1.1. Cardiovascular protective effect of apigenin

Apigenin is a natural flavonoid exhibiting pharmacological effects, including anti-inflammatory, antioxidant, and antithrombotic properties. Apigenin alleviates dysfunction through its antioxidative properties, protecting low-density lipoprotein cholesterol (LDL-C) from oxidative stress. It regulates cholesterol metabolism by enhancing absorption and transformation, accelerating reverse cholesterol transport, and reducing lipid levels [49]. Apigenin increases ATP-binding cassette transporter A1 (ABCA1) expression in a dose-dependent manner, decreases pro-inflammatory cytokine secretion, and inhibits AS development [50]. Zhu et al. administered 50–100 $mg \cdot kg^{-1}$ of apigenin for four weeks to rats with renal vascular HTN-induced myocardial hypertrophy. Results demonstrated reduced blood pressure, heart weight, heart weight index, cardiomyocyte cross-sectional area, serum angiotensin II (AngII), and free fatty acids in both serum and myocardium [51]. These findings indicate that apigenin may regulate AS, alleviate HTN and its complications, and provide cardiovascular protection.

3.1.2. Cardiovascular protective effect of quercetin

Quercetin, a naturally occurring flavonoid, exhibits diverse pharmacological effects, particularly in CVDs. Quercetin's distinctive ability to lower blood pressure has been demonstrated in studies where it downregulates the sirtuin 3/poly (ADP-ribose) polymerase 1 (SIRT3/PARP-1) signaling pathway in spontaneously hypertensive rats [52]. Kim et al. discovered that quercetin activates AMP-activated protein kinase (AMPK) and myosin light chain kinase (MLCK) pathways, modulating vascular smooth muscle cell contraction and producing a hypotensive effect [53]. AngII, a principal fibrogenic factor causing myocardial fibrosis, is inhibited by quercetin, thus reducing myocardial fibrosis and hypertrophy [54]. Clinical trials have demonstrated that chronic coronary artery disease (CAD) patients show elevated serum levels of interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and IL-10, which decrease with quercetin treatment. This effect stems from reduced inhibitor of *κ*B alpha (*IκBα*) gene expression, resulting in decreased levels of IL-1β, IL-10, and TNF-α, thereby supporting CHD treatment [55].

3.1.3. Cardiovascular protective effect of baicalin

Baicalin, a flavonoid compound, has emerged as a significant focus in cardiovascular research and shows promise as a therapeutic agent for CVDs. Research indicates that baicalin dose-dependently inhibits tert-butylhydrogen peroxide-induced decreases in myocardial viability and increases in apoptosis, while enhancing superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities [56]. Baicalin additionally ameliorates myocardial hypertrophy, cellular disarray, and interstitial fibrosis, reducing myocardial injury and apoptosis induced by AngII [57]. In myocardial infarction rats, baicalin markedly improves cardiac function and myocardial fibrosis, potentially *via* p38 phosphorylation and transforming growth factor beta 1/mothers against decapentaplegic homolog 2 (TGF-β1/Smad2) pathways [58]. Baicalin inhibits myocardial remodeling in essential HTN rats, through suppressing nuclear factor kappa B (NF-*κ*B) signaling pathway-induced inflammatory responses [59]. Furthermore, baicalin reduces oxidative stress in myocardial ischemia-reperfusion injury rats, likely by enhancing the endogenous antioxidant nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) signal transduction pathways, thus increasing myocardial tissue antioxidant capacity [60].

3.1.4. Cardiovascular protective effect of luteolin

Luteolin, a natural flavonoid, has been utilized to treat HTN, inflammatory diseases, and central nervous system diseases. Current research emphasizes luteolin's effectiveness in preventing and treating CVDs, establishing it as a promising candidate drug. Hypercholesterolemia negatively impacts myocardial ischemia-reperfusion injury, compromising cardioprotective effects [61]. Luteolin improves myocardial tissue viability and ventricular systolic function in hypercholesterolemic I/R mice, increases phosphorylated protein kinase B (p-Akt) and phosphorylated glycogen synthase kinase 3 beta (p-GSK3β) expression, inhibits Fyn nuclear translocation, reduces mitochondrial permeability transition pore opening, and activates Nrf2, thereby inhibiting AS [62]. Through inhibition of transforming growth factor beta receptor 1 (TGFβR1) signaling pathway activation, luteolin prevents vascular smooth muscle cell proliferation and migration and vascular intima hyperplasia, effectively treating vascular restenosis and related diseases [63].

3.2. Cardiovascular protective effects of volatile constituents in Ziziphora clinopodioides

Ziziphora clinopodioides contains abundant essential oil components that demonstrate cardiovascular protective effects, including D-limonene, geraniol, *α*-terpineol and borneol. These compounds exhibit significant antioxidant and anti-inflammatory properties. They effectively eliminate reactive oxygen species (ROS) in the body and mitigate oxidative stress and inflammatory damage to cells and tissues. D-limonene reduces serum LDL-C levels, thereby preventing AS [64]. Geraniol and borneol enhance the activity of SOD and GPx, while inhibiting the NF-*κ*B signaling pathway and decreasing pro-inflammatory cytokine production [65, 66]. Additionally, *α*-terpineol reduces chronic inflammation and maintains vascular endothelial function. Regarding vascular protection, D-limonene prevents abnormal blood vessel formation and AS progression [67]. Geraniol activates nitric oxide synthase (NOS), promoting NO production and vascular smooth muscle relaxation, thus reducing blood pressure, an important factor in preventing HTN and its complications [68]. Borneol acts directly on coronary arteries to relax vascular smooth muscle, increase coronary blood flow, improve myocardial oxygen supply, and enhance microcirculation [69]. Furthermore, geraniol improves

cardiomyocyte energy metabolism efficiency, maintains mitochondrial function, and prevents hypoxia or reperfusion-induced apoptosis, thereby reducing myocardial injury risk [70]. Borneol helps maintain normal cardiac function and reduces cardiac event risk by decreasing heart rate, reducing cardiac workload, increasing cardiac output, and improving heart efficiency [71]. D-limonene protects the heart from doxorubicin-induced cardiotoxicity and arrhythmias [72].

4. The pathological mechanisms of CVDs

CVDs develop through multiple interrelated factors, including endothelial dysfunction, AS, thrombosis, and HTN. These factors collectively contribute to heart and vascular damage. A systematic examination of CVD pathogenesis provides both deeper insight into the protective effects of *Ziziphora clinopodioides* and new perspectives for its clinical application in CVDs. The pathological mechanism of CVDs is shown in Fig. 1.

4.1. Endothelial dysfunction

Endothelial cells, the primary components of blood vessel inner walls, serve crucial functions in regulating vascular tension, blood flow, and preventing thrombosis [73]. Endothelial dysfunction initially manifests as endothelial cell injury or apoptosis, potentially triggered by various factors including hyperglycemia, HTN, smoking, and oxidative stress. Oxidized low-density lipoprotein (ox-LDL) plays a crucial role in CVD pathogenesis [74]. Low-density lipoprotein (LDL) accumulates in the vascular wall and generates ox-LDL through oxidation. These oxidation products directly damage endothelial cells and induce local inflammatory responses by binding to endothelial cell surface receptors, significantly increasing pro-inflammatory factor secretion [75].

4.2. AS leads to cardiovascular damage

AS, the primary pathological basis of CVDs, is characterized by vascular wall lipid accumulation, smooth muscle cell proliferation, inflammatory response, and fibrous tissue proliferation, ultimately forming atherosclerotic plaques [76]. The migration and proliferation of vascular smooth muscle cells represent a crucial step in plaque formation [77]. During this process, smooth muscle cells increase vascular wall thickness and enhance plaque stability and hardness by secreting collagen and other extracellular matrix (ECM) components [78]. While stable plaques typically resist rupture, unstable plaques may lead to vascular rupture and trigger acute myocardial infarction or stroke [79].

4.3. Thrombosis leads to vascular embolism

Thrombosis is primarily influenced by three factors: vascular wall injury, hemodynamic changes, and abnormal blood composition. When the vascular endothelium sustains damage, the exposed subendothelial matrix components activate platelets and promote their adhesion and aggregation [80]. Furthermore, damaged endothelial cells reduce the production of anticoagulant substances, increase the expression of procoagulant factors, and enhance thrombosis formation [81]. Simultaneously, abnormal activation of coagulation factors accelerates fibrin formation and creates a stable thrombus. Additionally, diminished function of the fibrinolytic system impedes thrombus dissolution, facilitating its progression to a chronic state [82].

4.4. Changes of cardiac structure and function

The burden of HTN on the heart and vascular system induces multiple pathophysiological changes. The heart responds to elevated blood pressure by enhancing contractility through muscle layer thickening. Ventricular structural remodeling, cardiomyocyte proliferation, fibrosis, and expansion may result in cardiac function deterioration [80]. Myocardial fibrosis represents a significant pathological process in CVDs, characterized by abnormal cardiac interstitial fibroblast proliferation and excessive ECM component accumulation [83]. HTN promotes adverse cardiac structural changes while accelerating myocardial fibrosis and increasing both cardiovascular event incidence and mortality risk.

5. Mechanisms of action of *Ziziphora clinopodioides* in treating CVDs

A systematic analysis of the flavonoids, terpenoids, phenolic acids, and other bioactive components abundant in *Ziziphora*

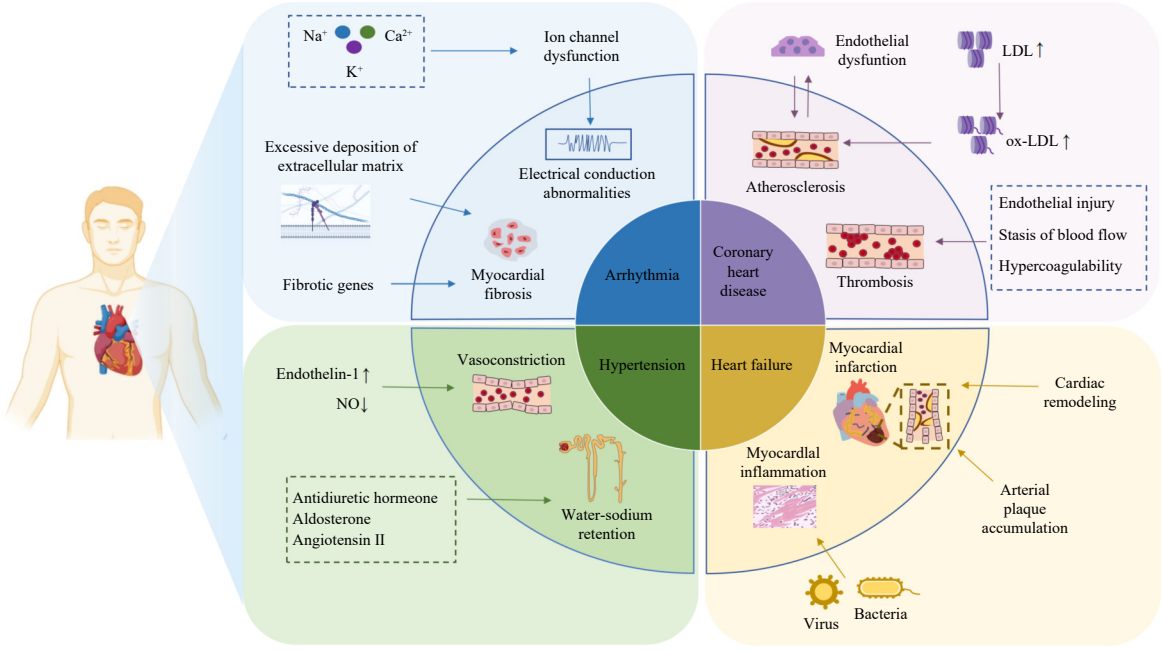

Fig. 1 The pathological mechanism of CVDs.

clinopodioides reveals that these constituents not only exhibit a wealth of pharmacological characteristics and mechanisms but are also pivotal in the herb's therapeutic role in CVDs. To comprehensively elucidate the therapeutic potential of *Ziziphora clinopodioides* in CVD treatment, extensive research has demonstrated that the herb exerts its cardioprotective effects through multiple pharmacological actions, including inhibiting apoptosis, mitigating oxidative stress, reducing inflammation, and improving mitochondrial dysfunction. Additionally, the regulation of key signaling pathways such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/Akt, Nrf2, and NF-κB further underscores the multifaceted nature of the cardiovascular protection offered by *Ziziphora clinopodioides.* Therefore, understanding the relationship between the chemical constituents of *Ziziphora clinopodioides* and its pharmacological effects on CVD not only aids in unraveling its potential therapeutic mechanisms but also provides crucial references for the development of new drugs and therapeutic strategies derived from this herb, thus facilitating its application in clinical practice.

5.1. Inhibition of apoptosis

Apoptosis represents a form of programmed cell death essential for maintaining normal development, tissue homeostasis, and immune system function in multicellular organisms [84]. This highly ordered process involves changes in cellular morphology, deoxyribonucleic acid (DNA) fragmentation, and cellular content packaging and clearance without triggering inflammatory responses [85]. The apoptotic process is regulated by complex signaling pathways involving multiple protein interactions and activity changes. Apoptosis initiation occurs through two primary pathways: intrinsic and extrinsic. Cardiomyocytes utilize multiple protective mechanisms against apoptosis [86]. Research demonstrates that *Ziziphora clinopodioides* extracts inhibit apoptosis by interfering with lipopolysaccharide (LPS) binding to Toll-like receptor 4 (TLR-4) and myeloid differentiation factor 2 (MD-2) on the cell surface. LPS binding to the TLR-4/MD-2 complex initiates downstream signaling events, including Akt and MAPK pathway activation. MAPK induces c-Jun *N*-terminal kinase 1 and 2 (JNK1/2) phosphorylation, activating c-Jun and enhancing transcription-dependent apoptotic signals, while activating pro-apoptotic protein Bim increases B-cell lymphoma 2 (BCL2)-associated X protein (Bax) expression, ultimately promoting apoptosis [87].

Research demonstrates that following treatment of endothelial cells (HUVEC) with extracts of *Ziziphora clinopodioides* for 24 h, the protein levels of vascular endothelial growth factor receptor 2 (VEGFR-2) decreased significantly compared to the H_2O_2-treated group, while p-Akt/Akt levels increased significantly relative to the H_2O_2 group [88]. VEGF binding to VEGFR-2 induces receptor dimerization and activation of its tyrosine kinase domain, resulting in autophosphorylation. The phosphorylated VEGFR-2 then recruits and activates downstream signaling molecules, including PI3K. Activated PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), subsequently activating Akt [89]. Endothelial cell apoptosis compromises vascular wall integrity, exposing underlying collagen fibers and procoagulant substances, thereby activating platelets and coagulation factors and promoting thrombosis [90]. Extracts of *Ziziphora clinopodioides* reduce PI3K expression in atherosclerotic models while activating the Akt pathway, enhancing Akt expression. The activated Akt inhibits the MAPK signaling pathway and reduces MAPK expression, thereby suppressing apoptosis [91]. MAPK activates p38 MAPK phosphorylation, which disrupts BCL2 activity and stimulates Bax translocation to mitochondria, altering mitochondrial outer membrane permeability and triggering the release of cysteinyl aspartate-specific proteinase 3 (caspase-3), caspase-9, and apoptotic factors into the cytoplasm, thus initiating the apoptotic cascade and disturbing the balance between antiapoptotic and pro-apoptotic proteins, ultimately promoting apoptosis [92]. The extract from *Ziziphora clinopodioides* exhibits its pharmacological effects through modulation of intracellular signaling pathways to inhibit apoptosis, while providing cardiomyocyte protection and enhancing cardiac function. The mechanism diagram is shown in Fig. 2.

5.2. Antioxidant activity

Oxidative stress significantly influences CVDs, affecting cardiomyocyte function and exacerbating conditions such as myocardial infarction [93]. Studies demonstrate that the primary chemical constituents of *Ziziphora clinopodioides*, including quercetin, thymol, and rosmarinic acid, exhibit potent antioxidant properties in both *in vitro* and *in vivo* experiments. These compounds effectively neutralize ROS, which are major contributors to oxidative stress and can damage cellular membranes, proteins, and DNA, while also inhibiting lipid peroxidation [46]. Research indicates that extracts of *Ziziphora clinopodioides* markedly improve oxidative stress conditions in H9c2 cells treated with H_2O_2. The mechanism involves enhanced activity of antioxidant enzymes, including SOD, HO-1, NAD(P)H: quinone oxidoreductase 1 (NQO1), and NQO2, which collectively eliminate ROS and oxygen radicals, protecting cells from oxidative stress-induced damage [94].

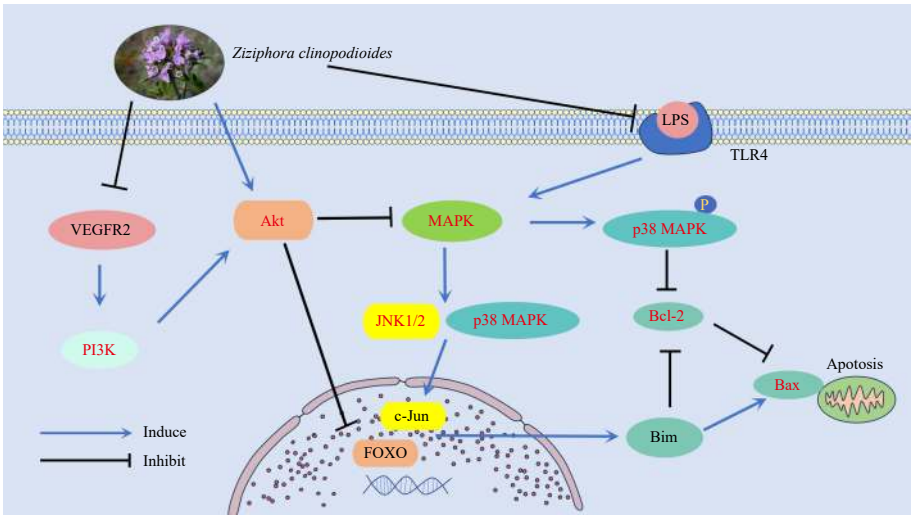

Fig. 2 *Ziziphora clinopodioides* exerts its therapeutic effect on CVDs by inhibiting apoptosis.

Moreover, the extracts enhance catalase (CAT) activity, facilitating hydrogen peroxide decomposition into water and oxygen, thereby reducing intracellular oxidative stress [88]. They also increase GPx activity, strengthening cellular antioxidant capacity by reducing lipid peroxides and hydrogen peroxide, thus lowering ROS levels. Furthermore, studies have shown that extracts of *Ziziphora clinopodioides* significantly reduce serum levels of creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), and malondialdehyde (MDA) in rat models. CK-MB, predominantly found in cardiomyocytes and brain tissue, is most abundant in the heart. Cardiomyocyte damage results in CK-MB release into the bloodstream, serving as a myocardial injury marker [95]. During oxidative stress, cellular damage and increased lipid peroxidation elevate LDH and MDA levels [19]. In early oxidative stress stages, cells increase inducible nitric oxide synthase (iNOS) expression, promoting NO production. As a crucial signaling molecule, NO reduces radical toxicity by reacting with superoxide anions to form peroxynitrite, while also protecting against myocardial ischemia-reperfusion injury through vascular function modulation [96]. Additionally, oxidative stress reduction inhibits excessive fibroblast activation and abnormal collagen deposition, effectively decreasing myocardial fibrosis and slowing myocardial remodeling. This process holds significant importance in the development of cardiovascular conditions, including arrhythmia, HF, and CHD [97]. The antioxidant properties of *Ziziphora clinopodioides* extract demonstrate remarkable efficacy in combating oxidative stress-induced cellular damage, thereby reducing CVD risk. The mechanism diagram is shown in Fig. 3.

5.3. Anti-inflammatory effects

Inflammation represents a fundamental physiological defense mechanism of the body. Upon experiencing injury, infection, or irritation, the body initiates an inflammatory response to facilitate damage clearance and tissue healing [98]. This response plays a crucial role in the pathogenesis of CVDs [99]. Research demonstrates that *Ziziphora clinopodioides* extracts activate AMPK, subsequently inhibiting the downstream NF-κB signaling pathway and NLRP3 inflammasome activation, thereby attenuating inflammatory responses and oxidative stress induced by pro-inflammatory cytokine release in endothelial cells [100]. The deactivation of NLRP3 results in decreased levels of inflammation mediators, including IL-1β, IL-6, and TNF-α, thus preventing inflammatory reactions. These inflammatory factors directly influence cardiac ion channels and action potential duration, altering the heart's electrical conduction properties. NF-κB functions as a key transcription factor in inflammatory responses, orchestrating the inflammatory process. Upon immune cell infection or injury, NF-κB activation induces pro-inflammatory cytokine synthesis, triggering inflammatory responses that recruit immune cells for pathogen clearance or tissue repair, thereby mediating anti-inflammatory effects. Furthermore, NF-κB regulates T cell and B cell development, activation, and function, indirectly modulating inflammatory responses through these cellular activities. Research indicates that *Ziziphora clinopodioides* extracts activate intercellular adhesion molecule-1 (*ICAM-1*) and vascular cell adhesion molecule-1 (*VCAM-1*) gene expression through NF-κB activation, inducing their surface expression and providing adhesion sites for intercellular interactions [101]. These interactions involve the binding of leukocyte integrins, specifically lymphocyte function-associated antigen 1 (LFA-1) and very late antigen 4 (VLA-4), to their respective endothelial ligands, thereby facilitating leukocyte rolling, adherence, and migration. Through modulation of these adhesion molecules, the extracts enhance leukocyte migration to inflammatory sites, achieving anti-inflammatory effects and potentially offering therapeutic approaches for inflammatory conditions. Studies further demonstrate that *Ziziphora clinopodioides* extracts inhibit iNOS activity, reducing NO production, which can cause cellular damage when excessive [95]. Additionally, by inhibiting cyclooxygenase-2 (COX-2) activity, prostaglandin production decreases. NO and prostaglandins regulate inflammatory responses through complex mechanisms, producing anti-inflammatory effects. NO also maintains blood pressure homeostasis through vasodilation and peripheral resistance reduction. The extract demonstrates significant capacity to reduce inflammatory factors and damage while enhancing cardiac function, presenting a promising therapeutic approach for CVDs. The mechanism diagram is shown in Fig. 4.

5.4. Improving mitochondrial dysfunction

Mitochondria are essential organelles within cells that regulate ATP generation, calcium homeostasis, oxidative stress responses, and apoptosis [102]. These organelles maintain a dynamic equilibrium through fusion and fission activities in response to environmental stimuli. Under normal conditions, mitochondrial fission produces one healthy and one damaged mitochondrion. While healthy mitochondria can undergo fusion with other mito-

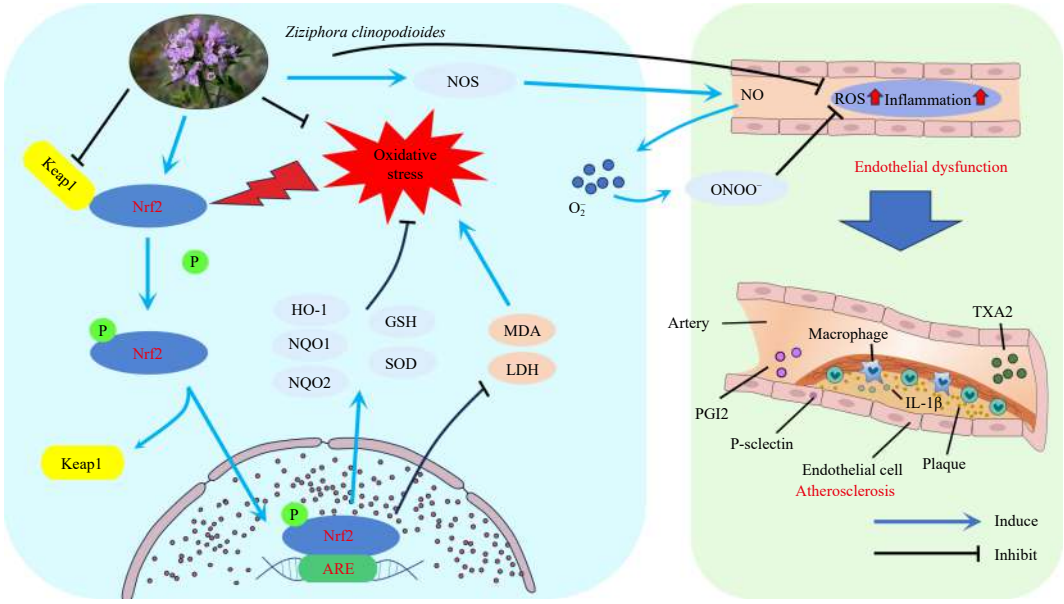

Fig. 3 *Ziziphora clinopodioides* exerts its therapeutic effect on CVDs by antioxidant stress.

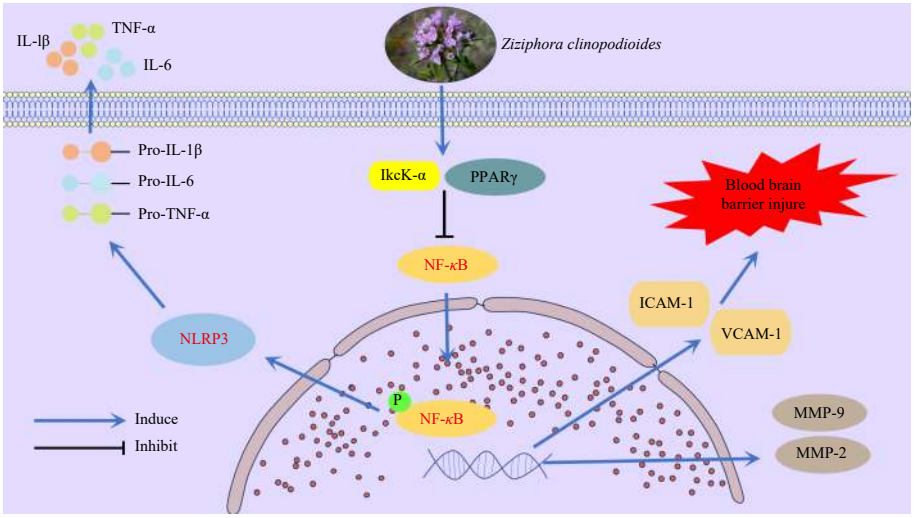

Fig. 4 *Ziziphora clinopodioides* exerts its therapeutic effect on CVDs by anti-inflammatory.

chondria, damaged ones undergo selective degradation. Mitophagy, the selective removal of damaged mitochondria, plays a crucial role in maintaining mitochondrial quality control [103]. Disruptions in mitophagy can lead to deteriorating mitochondrial function, contributing to various pathological conditions. The mitophagy process involves specific steps, including labeling, isolation, and degradation of damaged mitochondria. Maintaining proper mitochondrial function is therefore vital for cellular health and has significant implications for CVDs [104]. When mitochondrial function becomes impaired, it disrupts calcium homeostasis and ion channel function, resulting in altered cardiac electrophysiology, contractile dysfunction, and apoptosis, which can initiate or exacerbate cardiovascular conditions [105]. The flavonoids present in *Ziziphora clinopodioides*, particularly quercetin, enhance the expression of mitophagy-related proteins like E3 ubiquitin-protein ligase Parkin (Parkin) and PTEN induced kinase 1 (PINK1), which are essential for identifying damaged mitochondria and initiating autophagy [106]. Extracts of *Ziziphora clinopodioides* preserve mitochondrial membrane potential in H9c2 cells under oxidative stress conditions while effectively reducing ROS generation and simultaneously enhancing myeloperoxidase (MPO) activity in experimental mouse inflammatory bowel disease (IBD) [94]. MPO, an enzyme predominantly found in neutrophils, serves important functions in antimicrobial defense and autoimmune diseases. The ROS generated by MPO can indirectly impact mitochondrial function [107]. Excessive ROS can cause damage to mitochondrial DNA, proteins, and lipids, resulting in mitochondrial dysfunction. Elevated mitochondrial ROS can trigger mPTP opening, leading to decreased mitochondrial membrane potential and further mitochondrial impairment [108]. Mitochondrial dysfunction can also increase oxidative stress and ROS production, causing additional damage to vascular endothelial cells, promoting vascular smooth muscle cell proliferation and migration, and contributing to vessel wall thickening and hardening, thereby affecting CVD progression [109]. Research demonstrates that *Ziziphora clinopodioides* extracts maintain mitochondrial membrane stability. Furthermore, they reduce serum matrix metalloproteinase-9 (MMP-9) concentrations and downregulate MMP-2 expression, minimizing mitochondrial membrane potential damage and improving mitochondrial function [101]. The extract demonstrates significant efficacy in maintaining mitochondrial function, thereby enhancing cellular energy metabolism and reducing oxidative stress-induced mitochondrial damage. The mechanism diagram is shown in Fig. 5.

6. Therapeutic effects of Chinese herbal compounds containing *Ziziphora clinopodioides* on CVDs

Pharmacological investigations have shown that *Ziziphora*

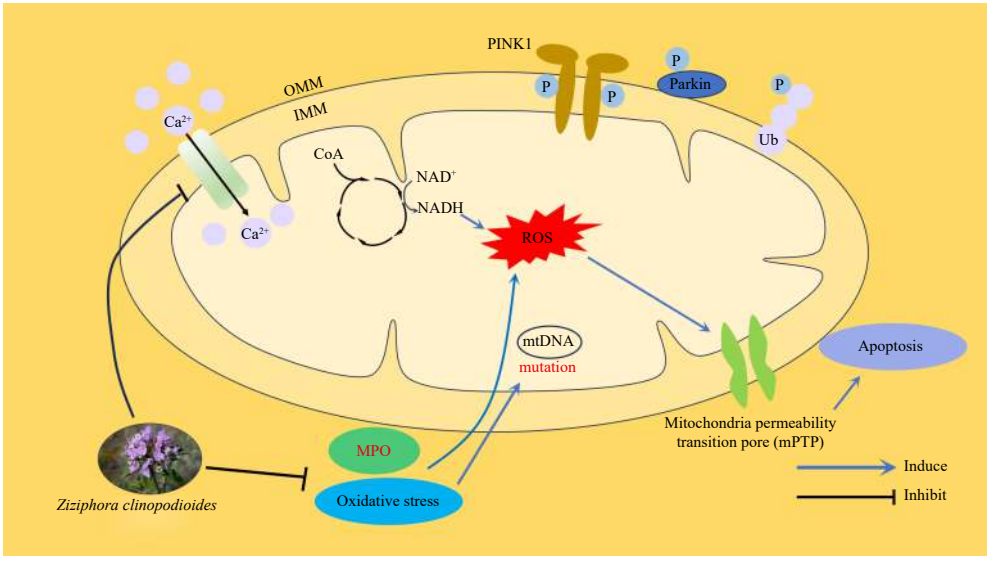

Fig. 5 *Ziziphora clinopodioides* exerts its therapeutic effect on CVDs by improving mitochondrial dysfunction.

clinopodioides exerts multiple beneficial effects in the context of CVDs, including the inhibition of cardiomyocyte apoptosis, enhancement of cardiac function, and anti-inflammatory and antioxidant activities. However, its clinical efficacy is influenced by multiple factors, particularly its compatibility with other TCMs. TCM theory emphasizes the interrelationships among herbs, where appropriate combinations can enhance therapeutic effects while reducing adverse effects and improving treatment outcomes. Therefore, investigating the compatibility effects of *Ziziphora clinopodioides* with other TCMs in CVD treatment provides crucial insights for effective clinical application. The following discussion examines specific applications of combining *Ziziphora clinopodioides* with other TCMs for CVD prevention and treatment, aiming to provide comprehensive guidance for clinical practice. The summary diagram is shown in Fig. 6.

6.1. Tianxiangdan

Tianxiangdan, composed of *Rhodiola rosea*, *Ziziphora clinopodioides*, *Salvia miltiorrhiza*, and *Dalbergia odorifera*, is utilized clinically for treating CHD by regulating Qi and blood circulation while enhancing cardiac function. Research demonstrates that Tianxiangdan modulates the Nrf2/ARE signaling pathway to ameliorate microcirculatory disturbances in coronary arteries [110]. Furthermore, Tianxiangdan Granule reduces inflammatory cytokine expression of IL-1β and TNF-α, while inhibiting the activation of NF-κB p65 and p38 MAPK signaling pathways [111]. During cellular oxidative stress or pathological stimuli, modification of cysteine residues in Keap1 induces Nrf2 phosphorylation. The phosphorylated Nrf2 dissociates from the Keap1 complex and translocates to the nucleus. Inside the nucleus, Nrf2 forms a heterodimer with Maf proteins and binds to the ARE. This Nrf2/ARE pathway enables cellular resistance to oxidative stress and protection from oxidative damage, serving a crucial role in CVDs, inflammatory conditions, and various pathological processes [112].

It has been shown to improve ischemic myocardial energy metabolism by enhancing ATPase activity, preserving mitochondrial integrity, and maintaining cardiomyocyte ultrastructure, thereby exerting protective effects against myocardial ischemia. By reducing myocardial tissue damage and mitigating cellular injury, Tianxiangdan offers critical cardioprotective benefits. Experimental studies have revealed that Tianxiangdan decreases the expressions of guanine nucleotide-binding protein G(i) subunit alpha-2 (GNAI2), tropomyosin 3 (TPM3), and myosin heavy chain 10 (MYH10) proteins in myocardial ischemia models, suggesting its involvement in modulating mitochondrial function and energy homeostasis [113]. Moreover, Tianxiangdan has been reported to regulate the integrity and maturation of epicardium-derived mesenchymal cells, contributing to its therapeutic efficacy in CVDs.

6.2. Compound *Ziziphora clinopodioides* Granule

Compound *Ziziphora clinopodioides* Granule represents a TCM formulation developed for CVD treatment. Its principal components include *Ziziphora clinopodioides*, *Agrimonia pilosa*, *Sophora flavescens*, *Rhodiola rosea*, *Sinomenium acutum*, and *Pueraria lobata*. Pharmacological studies have shown that tthis multiherb formulation exerts anti-inflammatory effects by downregulating the mRNA expression of *IκK-β* and *NF-κB* while elevating *IκBα* mRNA expression [114]. Furthermore, the granule increases the expression of peroxisome proliferator-activated receptor gamma (PPARγ) in atherosclerotic plaques, contributing to their stabilization.

PPAR activation promotes anti-inflammatory cytokine production while inhibiting pro-inflammatory cytokines and inflammation-related transcription factors, thereby reducing inflammatory factor expression. Additionally, PPAR activation enhances endothelial function, reduces blood pressure, modulates macrophage and T cell functions, inhibits smooth muscle cell proliferation and migration, and decelerates arteriosclerosis progression. Furthermore, the granules reduce serum MMP-9 concentration, decreasing plaque instability and rupture risk [115]. They also enhance coronary artery blood flow and decrease endothelin release, maintaining normal vascular contractility and relaxation functions while reducing platelet aggregation.

In summary, compound *Ziziphora clinopodioides* Granule demonstrate antiatherosclerotic effects through multiple mechanisms targeting the AS pathological process, thereby reducing cardiovascular event incidence.

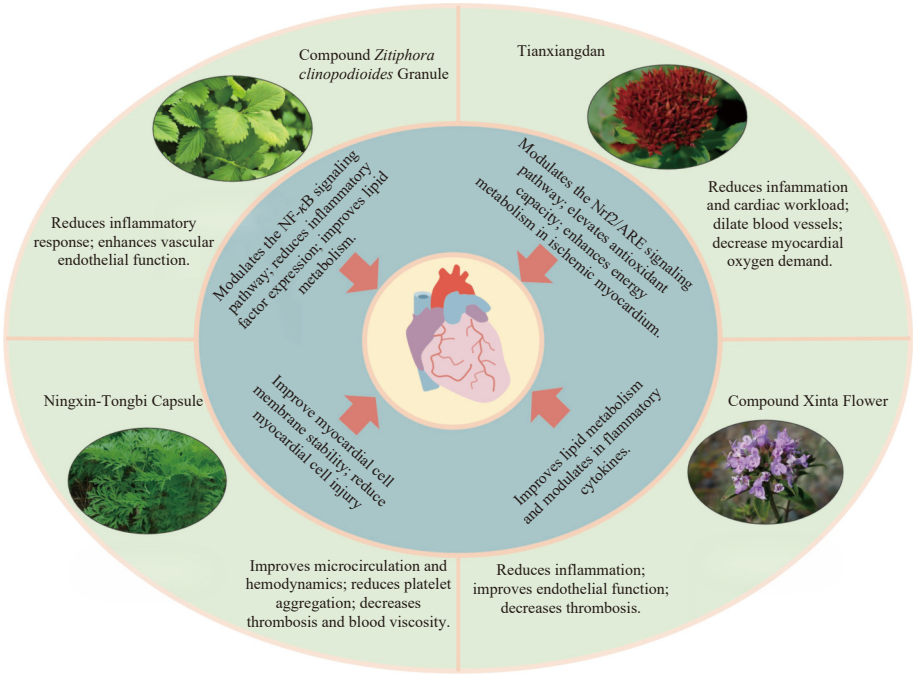

Fig. 6 Pharmacological effects and mechanisms of *Ziziphora clinopodioides* in combination with other herbal medicines.

6.3. Ningxin-Tongbi Capsule

Ningxin-Tongbi Capsule, comprising 9 herbs including *Ziziphora clinopodioides*, *Ligusticum chuanxiong* and *Corydalis yanhusuo*, is formulated to alleviate arthralgia and calm the heart, specifically targeting angina pectoris and HF resulting from phlegm and blood stasis interaction [116]. Platelets represent one of the most active blood components and are crucial in thrombosis. Platelet hyperactivity can increase blood viscosity, alter hemodynamics, and subsequently lead to microcirculatory disorders, manifesting as blood stasis syndrome [117].

Nie et al. conducted a study using a blood stasis syndrome model in rats to evaluate hemorheology and coagulation function indicators. Their observations revealed a significant decrease in vascular contraction rates and capillary network intersection frequency. The capsule demonstrated significant reductions in whole blood viscosity and hematocrit levels in mice, while also decreasing platelet aggregation rates and extending thrombin time in rats [118]. Using a canine model of acute myocardial ischemia, they evaluated myocardial infarct size, electrocardiograms, hemodynamics, and enzymatic indices. The findings indicated that the capsule substantially reduced the mass-to-infraction area ratio in the ischemic zone and produced significant thoracic aorta dilation [119].

In conclusion, Ningxin-Tongbi Capsule enhances microcirculation and decreases platelet aggregation, thus improving hypercoagulable, hyperviscous, and hyperaggregable blood conditions. This mechanism facilitates blood stasis dissolution and thrombosis reduction, effectively supporting CHD treatment.

6.4. Compound Xinta Flower

The combination of *Ziziphora clinopodioides*, *Origanum vulgare* and *Hyssopus officinalis* demonstrates clinical efficacy in treating CVDs. In AS, lipid peroxidation and LDL oxidation promote disease progression. LDL, a heterogeneous lipoprotein particle, functions as the primary cholesterol carrier to target cells. Its structure comprises a hydrophobic core containing triglyceride (TG) and cholesterol esters, enclosed by a hydrophilic surface layer of phospholipids, free cholesterol, and apolipoproteins. Cholesterol esters facilitate LDL particle binding to specific cell surface receptors. Modified LDL acts as a primary AS pathogen, stimulating endothelial cells to produce inflammatory markers, causing cytotoxic effects, and inhibiting NO-induced vasodilation. Research demonstrates that the Compound Xinta Flower formula effectively reduces AS severity by decreasing serum TC, TG, and LDL levels while increasing high-density lipoprotein (HDL) levels, thereby enhancing lipid metabolism. Moreover, the formula reduces pro-inflammatory cytokine levels, including IL-1β, IL-6, and TNF-α, while increasing anti-inflammatory cytokine IL-10 levels [120-121]. The formula maintains vascular stability, enhances endothelial function, and reduces thrombus formation, supporting CVD treatment.

7. Summary and outlook

Clinical practice increasingly recognizes the pharmacological activities of natural plant extracts, particularly flavonoid compounds, which show significant potential in CVD prevention and treatment due to their extensive therapeutic effects [122]. These compounds contribute to cardiovascular health through diverse mechanisms, effectively reducing the risk of CVDs. The chemical constituents of *Ziziphora clinopodioides* include well-characterized bioactive compounds, primarily flavonoids such as luteolin, quercetin, hyperoside, baicalin, kaempferol, apigenin, and rosamarinic acid. Most of these compounds exhibit multiple mechanisms of action, including anti-inflammatory, antioxidative, and antiproliferative properties. Additionally, essential oils and phenolic compounds, including menthone, iso-menthone, rosmarinic acid, and caffeic acid, represent significant components of *Ziziphora clinopodioides*, contributing to these mechanisms [123-126].

We comprehensively analyzed the pharmacological effects and mechanisms of *Ziziphora clinopodioides* on CVDs, including anti-inflammation, antimicrobial activity, immunomodulation, neuroprotection, and antioxidant effects. The abundance of these chemical components in *Ziziphora clinopodioides* makes it a potential therapeutic agent for CVDs. The plant operates through multiple mechanistic pathways to improve and treat CVDs. These mechanisms demonstrate close interconnections, particularly among inflammation, oxidative stress, and apoptosis, forming cascade relationships. Inflammatory processes trigger ROS release, leading to oxidative stress. This stress activates apoptotic signaling pathways and induces apoptosis through cellular structural damage. These interacting mechanisms form a complex regulatory network governing cell and tissue damage and repair processes.

A comprehensive literature review reveals that while *Ziziphora clinopodioides* demonstrates multiple potential mechanisms in treating CVDs, clinical research remains limited. This review innovatively summarizes the clinical applications of *Ziziphora clinopodioides* in cardiovascular medicine, primarily through compound preparations including Tianxiangdan, Compound *Ziziphora clinopodioides* Granule, Ningxin-Tongbi Capsule, and Compound Xinta Flower. These preparations demonstrate significant therapeutic potential in CVDs, incorporating diverse active ingredients and enhancing therapeutic efficacy through synergistic effects, thus offering novel approaches for cardiovascular treatment. These findings may provide valuable guidance for future research and clinical applications of *Ziziphora clinopodioides*.

Literature analysis indicates that current research predominantly focuses on the effects of *Ziziphora clinopodioides* extract or its major compounds on CVDs, lacking detailed investigation of individual extract components. While studies demonstrate that *Ziziphora clinopodioides* can address CVDs through multiple pathways, its effects and mechanisms in related conditions remain incompletely understood. Although this review details the pharmacological effects and mechanisms of its combination with other Chinese herbal medicines in cardiovascular treatment, specific synergistic mechanisms require further investigation. Three key research directions emerge: 1. Component-specific efficacy: although *Ziziphora clinopodioides* contains numerous bioactive compounds, the lack of standardized extraction protocols has limited the investigation of the individual therapeutic effects of its isolated constituents. Future research should focus on characterizing the pharmacological activities of single components. 2. Multi-disease therapeutic potential: beyond cardiovascular diseases, the potential benefits of *Ziziphora clinopodioides* in treating comorbid conditions, such as cerebrovascular and metabolic disorders, remain largely unexplored and warrant further investigation. 3. Mechanisms within compound formulations: the specific pharmacological role of *Ziziphora clinopodioides* in multi-herb formulations, including its synergistic interactions and mechanisms of action in cardiovascular therapy, requires systematic elucidation. These considerations suggest new directions for investigating the pharmacological effects and clinical applications of *Ziziphora clinopodioides*.

Chemical pharmaceuticals often present various side effects [127]. *Ziziphora clinopodioides* demonstrates fewer adverse effects compared to conventional medications [95]. Beyond common benefits such as antiatherosclerotic properties and myocardial protection, its volatile oil components, including pulegone, provide additional therapeutic effects such as sedation and anxiety relief [128]. As an ethnic Chinese herbal medicine, *Ziziphora*

clinopodioides is extensively cultivated in Xinjiang, China, offering abundant, cost-effective raw materials and established clinical applications in cardiovascular treatment [48]. However, its blood circulation-promoting and stasis-removing properties may potentially affect coagulation and wound healing [100]. Additionally, high doses may induce liver dysfunction, central nervous system toxicity, gastritis, nephrotoxicity, pulmonary toxicity, and cytotoxicity [12].

The limited fundamental research on the active ingredients of *Ziziphora clinopodioides* presents a significant constraint for advanced studies. Despite increasing research efforts in recent years, the complex mechanisms of these components remain insufficiently explored through comprehensive and systematic investigation. Furthermore, the absence of standardized cultivation practices for *Ziziphora clinopodioides*, combined with varying environmental factors and harvest timing, affects its medicinal properties, biological characteristics, and therapeutic efficacy. The current limitations in extraction and separation methodologies result in impure extracts containing various contaminants, which impedes further research and applications [129]. Future research should prioritize toxicological evaluation of *Ziziphora clinopodioides*. While standardized large-scale cultivation of ethnic Chinese medicinal materials presents challenges, advancing drug analysis and extraction technologies enables the establishment of rigorous quality control systems, potentially facilitating the clinical application of *Ziziphora clinopodioides*. These developments may expand its therapeutic applications beyond cardiovascular and cerebrovascular diseases.

This review aims to increase awareness among researchers regarding the effects of *Ziziphora clinopodioides* on CVDs. Additional research may address current knowledge gaps and establish a more robust scientific foundation for its application in both cardiovascular and other diseases, while providing direction for future investigations.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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