Heliyon 10 (2024) e35560

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Shensong yangxin, a multi-functional traditional Chinese medicine for arrhythmia: A review of components, pharmacological mechanisms, and clinical applications

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ARTICLE INFO

Keywords:
Shensong yangxin capsule
Arrhythmia
Network pharmacology
Multi-targets and multi-pathways
Mechanism of action

ABSTRACT

As a common cardiovascular disease (CVD), Arrhythmia refers to any abnormality in the origin, frequency, rhythm, conduction velocity, timing, pathway, sequence, or other aspect of cardiac impulses, and it is one of the common cardiovascular diseases in clinical practice. At present, various ion channel blockers are used for treatment of arrhythmia that include Na^+ ion channel blockers, K^+ ion channel blockers and Ca^{2+} ion channel blockers. While these drugs offer benefits, they have led to a gradual increase in drug-related adverse reactions across various systems. As a result, the quest for safe and effective antiarrhythmic drugs is pressing. Recent years have seen some advancements in the treatment of ventricular arrhythmias using traditional Chinese medicine(TCM). The theory of Luobing in TCM has proposed a new drug intervention strategy of "fast and slow treatment, integrated regulation" leading to a shift in mindset from "antiarrhythmic" to "rhythm-regulating". Guided by this theory, the development of Shen Song Yang Xin Capsules (SSYX) has involved various Chinese medicinal ingredients that comprehensively regulate the myocardial electrophysiological mechanism, exerting antiarrhythmic effects on multiple ion channels and non-ion channels. Similarly, in clinical studies, evidence-based research has confirmed that SSYX combined with conventional antiarrhythmic drugs can more effectively reduce the occurrence of arrhythmias. Therefore, this article provides a comprehensive review of the composition and mechanisms of action, pharmacological components, network pharmacology analysis, and clinical applications of SSYX guided by the theory of Luobing, aiming to offer valuable insights for improved clinical management of arrhythmias and related research.

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https://doi.org/10.1016/j.heliyon.2024.e35560
Received 30 July 2023; Received in revised form 28 July 2024; Accepted 31 July 2024
Available online 2 August 2024

1. Introduction

With the continuing development of the Chinese society, the realisation of an aging population has emerged. The prevalence and incidence of various cardiovascular diseases (CVD) continues to rise in China due to numerous factors, including the unhealthy lifestyle of the population. According to the 2021 China Cardiovascular Health and Disease Report, there are currently ~330 million patients with CVD in China, and mortality is still the leading cause of death among residents, being higher than mortality due to diseases such as cancer [1]. According to statistics, CVD deaths in both urban and rural China accounted for more than 40 % of all deaths in 2019, indicating that two out of every five deaths were due to CVD. Among these, arrhythmia is the leading direct cause of sudden cardiac death and seriously threatens the lives and health of the Chinese population.

Cardiac arrhythmia is a prevalent clinical condition characterized by abnormal heart rate and/or rhythm, which may result from abnormal excitation of the sinoatrial node or excitation originating outside the sinoatrial node, as well as slow conduction of excitation, blockage, or abnormal conduction through alternate pathways. It can be caused by various factors such as structural heart disease, electrolyte and acid-base balance disorders, and drug poisoning. Arrhythmias can be the first or the only manifestation of heart disease but can also be caused by the concomitant manifestation of other diseases. According to statistics, there are ~20 million patients with arrhythmia in China, and more than 500,000 sudden cardiac death events occur every year, of which more than 80 % are due to malignant arrhythmias. Antiarrhythmic therapy has been a popular topic in the field of CVD management [2]. Currently, antiarrhythmic drugs are the most commonly used clinical interventions that can greatly reduce the frequency of arrhythmia attacks and improve the clinical symptoms and prognosis of patients [3]. However, the safety of antiarrhythmic drugs in clinical applications has recently been questioned. Many drugs have certain limitations, including adverse reactions and many drugs have arrhythmogenic effects [4]. At this stage, the development and promotion of new and more optimised antiarrhythmic drugs is still slow. Therefore, the global pursuit of safe and effective drugs for the treatment of arrhythmia is of great significance in scientific research.

In recent years, traditional Chinese medicine (TCM) has been found to play an antiarrhythmic role in clinical practice through the integrated mechanisms of multi-target, multi-component, multi-ion channel blockage, and non-ion channel regulation. Shensong Yangxin capsule (SSYX) is an innovative Chinese medicine for the effective treatment of various arrhythmias under the guidance of the TCM-derived Luobing theory. It has the advantage of integrated regulation of "fast and slow treatment, integrated regulation" without arrhythmogenic side effects, and has been widely recognized by industry experts on the basis of evidence-based medical research [5]. Here, we review its formulation, mechanism of action, and clinical applications.

2. The theory of Luobing guides the pathogenesis and treatment of arrhythmia

In TCM, heart rhythm disorders are classified as "palpitations". According to the theory of Luobing, the heart region comprises the Qi collaterals and the vessel collateral. The Qi collaterals encompass the cardiac conduction system, the autonomic nervous system, and higher central nervous functions, while the vessel collateral refers to the coronary circulation system. The interaction between the Qi collaterals and the vessel collateral is crucial for maintaining the normal beating frequency and rhythm of the heart, promoting blood circulation, and ensuring adequate blood supply to the heart. Arrhythmia primarily results from Qi and Yin deficiency, insufficient nourishment of the vessel collateral, and vessel collateral stasis resistance in TCM. The heart governs the blood vessels, playing essential roles in the circulatory system. The Qi and blood of the heart serve as the primary motive force of the "heart-blood-vessel" circulatory system. Factors such as constitutional poor, irregular diet, and internal strain and fatigue can lead to insufficient heart Qi, resulting in weak blood circulation. Prolonged blood stagnation may lead to blood stasis and internal heat, depleting the heart's Yin, resulting in symptoms such as palpitations, shortness of breath, and chest tightness due to inadequate nourishment of the heart. Additionally, it may result in irregular pulse patterns such as "knotted," "rapid," and "intermittent" [6].

Based on the aforementioned pathological foundation, we have derived academic insights from Zhang Zhongjing's treatment of palpitations and formulated the medication guidance principles of "warming, clearing, nourishing, and promoting circulation," as well as the treatment method of "tonifying Qi and nourishing Yin, promoting blood circulation, and clearing the mind to calm the spirit". We have developed the SSYX prescription based on these principles, realizing a shift in mindset from "antiarrhythmic" to "regulating arrhythmia".

3. Shensong Yangxin capsule formulation principle and main active ingredients

The Shensong Yangxin capsule (SSYX) formulation is based on the classic formula "Shengmai SAN" that is composed of 12 herbs (See Fig. 1). Among them, Panax ginseng C.A.Mey. (Ren-Shen) tonifies heart Qi, nourishing heart veins, while Tuber of dwarf lilyturf (Mai-Dong) nourishes Yin blood, calming the spirit, eliminating irritability. Both of them together form the "monarch medicines" in this classic prescription. Taxillus chinensis Danse (Sang-Ji-Sheng), Cornus officinalis Sieb. et Zucc (Shan-Zhu-Yu). tonifies kidney function and cultivates kidney vitality; Coptis chinensis Franch. (Huang-Lian) and Salvia miltiorrhizaSieb Bge. (Dan-Shen) clear the heart and activates blood circulation: together, these four medicines are the "ministers medicines". The "adjuvant medicine" consist of Semen ziziphi spinosae (Suan-Zao-Ren) and Fructus Schisandrate Chinensis (Wu-Wei-Zi) for nourishing the heart and blood, and consolidating heart Yin; Radix Paeoniae Rubra (Chi-Shao) and Eupolyphaga sinensis Walker (Tu-Bie-Chong) for promoting blood circulation, dredging collaterals, and relieving pain; and dragon bone (Alternate name Sternum/Breastbo ne of a bird, Long-Gu) for calming the mind and tranquilizing the spirit. Radix et Rhizoma Nardostachyos (Gan-Song), an herb that enters the heart and spleen meridians, acts as the "envoy medicine" in this prescription. It both nourishes the Qi and blood in the collaterals and promotes the removal of stasis in the collaterals, thereby ensuring unobstructed collaterals, abundance of Qi and blood in the heart, a subdued spirit of the heart, leading

to the restoration of normal cardiac rhythm. The basic pathogenesis of arrhythmia is treated in TCM by a combination of warming and clearing that is both smooth and beneficial. It not only replenishes Qi Yin in the collaterals, but also clears the veins stasis, and clears the heart channel, so that the Qi Yin of the heart and collaterals is full, the veins are unobstructed, and the mind is calm, and this reflects the integrated regulation of the pathogenesis of the disease.

In TCM, ginseng saponins strengthen and protect the heart muscle and improve blood rheology [7,8]. Quercetin present in mulberry parasitica has antioxidant and inhibitory effects on fatty acid synthase [9,10]. The main components of Cornus officinalis are strychnine. Pharmacological studies have shown that strychnine has protective effects on vascular endothelial cells and cardiomyocytes as well as antiarrhythmic effects. Its mechanism of action may involve prolonging myocardial action potential (AP), increasing absolute resting potential, and decreasing the automaticity of the sinoatrial node [11–13]. The chemical components isolated from Coptis chinensis include alkaloids, flavonoids, and acidic components, such as ferulic acid. Among these, berberine is the most representative and abundant component of Coptis coptis. It has anti-cholinesterase activity, increases acetylcholine levels, antagonises adrenaline, and expands coronary arteries [14–16]. Salvia miltiorrhiza contains water-soluble components such as salvianolic acid A and B, and fat-soluble components such as tanshinone I and IIA. Modern pharmacological studies have shown that the fat-soluble and water-soluble components of salvia miltiorrhiza act by protecting organs, reducing ischaemia-reperfusion injury, anti-fibrosis, and immune regulation [17,18]. Jujube saponin A, a monomer in jujube kernel, acts as a calcium channel blocker and can affect L-type Ca^{2+} ion channels in ventricular myocytes to inhibit tachyarrhythmia [19,20]. Schisandrin is a xylan compound isolated from Schisandra chinensis that has high biological activity and can resist lipid peroxidation, thus protecting cardiomyocytes from

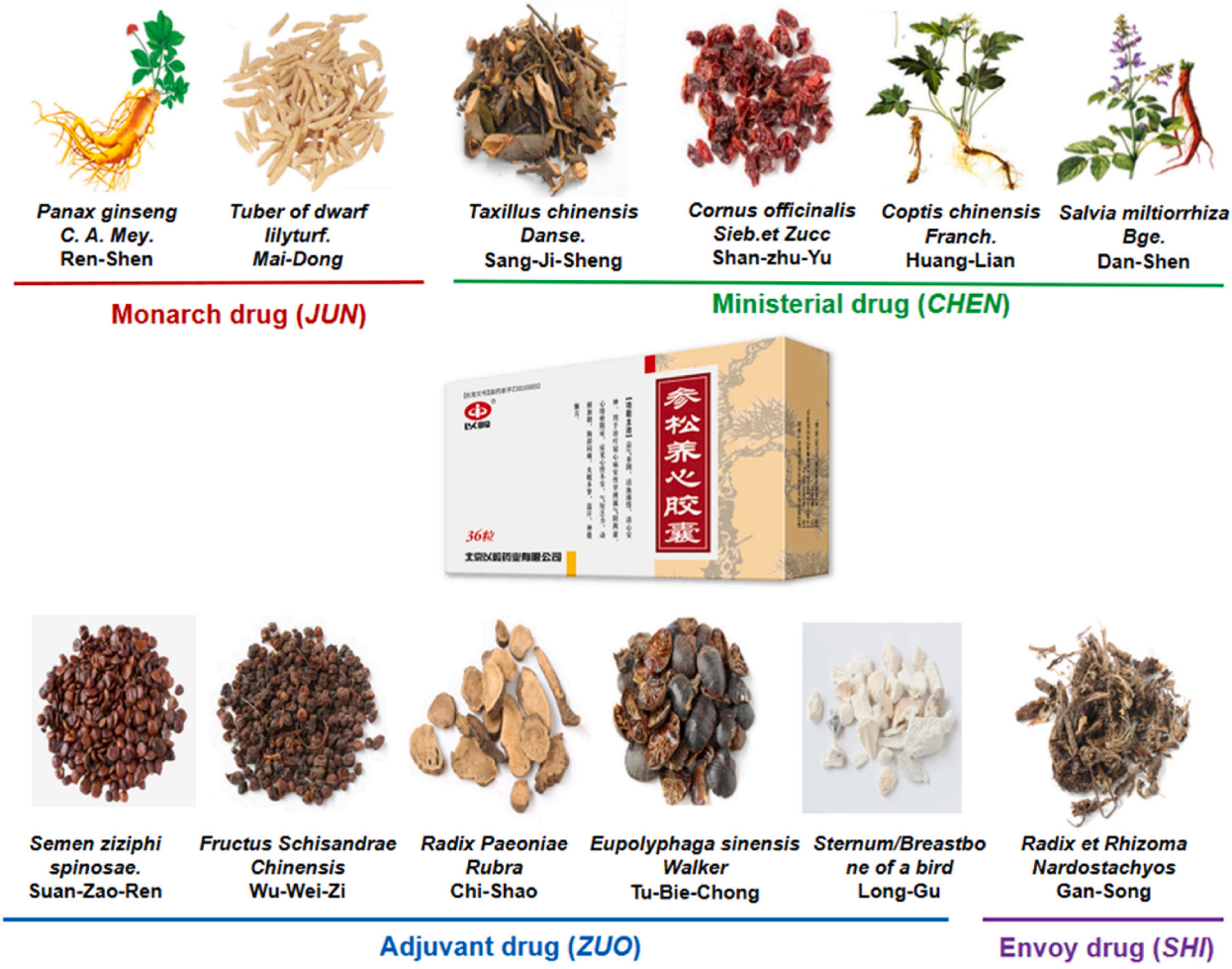

Fig. 1. The herbs included in Shensong Yangxin (SSYX) capsule and the Chinese patent for SSYX. The SSYX formulation consists of twelve herbs: two monarch drugs (JUN)- the *Panax ginseng C. A. Mey.* (Ren-Shen) and *Tuber of dwarf lilyturf.* (Mai-Dong), three ministerial drugs (CHEN)- *Taxillus chinensis Danse.* (Sang-Ji-Sheng), *Cornus officinalis Sieb.et Zucc*. (Shan-zhu-Yu), *Coptis chinensis Franch.* (Huang-Lian), *Salvia miltiorrhiza Bge.* (Dan-Shen), five adjuvant drugs (ZUO)- *Semen ziziphi spinosae.* (Suan-Zao-Ren), *Fructus Schisandrae Chinensis.* (Wu-Wei-Zi), *Radix Paeoniae Rubra.* (Chi-Shao), *Eupolyphaga sinensis Walker.* (Tu-Bie-Chong), and sternum/breastbone of a bird (Long-Gu), and one envoy drug (SHI)- *Radix et Rhizoma Nardostachyos,* (Gan-Song). SSYX is orally administered as capsules. The picture of this patented medicine has been permitted to be presented in this manuscript by Yiling Pharmaceutical, Inc.

ischaemia-reperfusion injury [21,22]. Paeoniflorin, along with its monomeric components and gallic acid derivatives, is likely the primary active compounds responsible for the diverse pharmacological effects of paeoniflorin. Paeoniflorin can treat atherosclerosis and myocardial damage through antioxidants, and reduce plaque formation via its anti-inflammatory effects [13,23]. The active components of hyalozoon have antithrombotic, anti-ischaemic, and hypoxic effects, regulate blood lipids, and enhance immune function [13,24]. Furthermore, the terpenoid compounds found in pine demonstrate antioxidative and antiarrhythmic effects by regulating cardiomyocyte function, thereby stabilizing cardiac rhythm [25].

In order to extract the active ingredients of SSYX, we employed ultra-high performance liquid chromatography-quadrupole/electrostatic field Orbitrap high resolution mass spectrometry (UHPLC-Q-Orbitrap HRMS) to conduct a qualitative analysis and rapidly identify various chemical components derived from SSYX. A total of 54 chemical components, including phenolic acids, flavonoids, terpenoids, quinones, alkaloids, and others were identified, based on their relative molecular mass, multistage fragment ion peak, retention time, reference products, and relevant reference information obtained using high-resolution mass spectrometry [13]. Phenolic acids are important secondary metabolites derived from TCMs, such as salvianolic acid A and B which exhibit anti-inflammatory, antibacterial, antioxidant, and anti-tumour effects. These natural active compounds hold significant research value and potential application [26]. Flavonoids are low molecular weight metabolites found in plant polyphenols, known for their antioxidant, anti-inflammatory, and anti-angiogenic properties [27]. Epidemiological studies have found that flavonoids play an anti-atherosclerotic role by inhibiting oxidation, preventing thrombosis, improving endothelial function, and regulating blood lipid and glucose metabolism. In addition, in recent years, an increasing number of studies have found that flavonoids have anti-tumour, anti-inflammatory, and antioxidant pharmacological effects, and can be used to treat CVD [28]. Monoterpenoids demonstrate anti-tumour, antioxidant and neuroprotective effects [29]. Alkaloids have shown outstanding anti-tumour, anti-inflammatory, anti-viral, anti-bacterial, and hypoglycaemic effects for regulating autoimmunity and treating CVDs [30]. The above-mentioned types and sources of active ingredients can play a role in multi-pathway and multi-target therapies through synergistic or complementary effects.

4. Electrophysiological mechanisms of arrhythmia

The heart regulates the rhythm, frequency, sequence, and velocity of impulses, which are crucial for maintaining the cardiomyocyte AP. The generation and differentiation of cardiac AP result from the selective permeability of various ion channels distributed across the myocardial membrane. Ion channels are proteins with hydrophilic pores on the cell membrane that play a critical role in myocardial electrophysiology [43]. These channels penetrate the phospholipid bilayer and selectively allow specific ions to pass through the cell membrane. sequential activity of cardiac ion channels generates the AP, and when the electrophysiological properties or functional expression of these ion channels are altered, the AP changes as well. Consequently, alterations in myocardial electrophysiology, induced by the stimulation or inhibition of the various cardiac ion channels, can result in arrhythmias [44,45]. This underscores that the regulation of cardiac ion channel activity is a critical mechanism of action for most antiarrhythmic drugs.

Major cardiac ion channels regulate internal ion and external electron flow. Ion-specific inward electron flow involves Na^+ ion channels (IN_a) and Ca^{2+} ion channels during depolarization, whereas non-specific inward ion flow (If) is activated by hyperpolarisation, influencing autonomous pacing activity. Outward electron flow is comprised of the outward K^+ and Cl^- currents during the repolarization phase, with outward K^+ current provides the most important contribution in the AP repolarization phase [46]. Cardiac K^+ ion channels are complex and widely distributed, the dynamic balance between the concentration gradient and electrical potential gradient of potassium ions across the membrane, combined with the inward electron flow, is crucial for maintaining the resting potential.

5. Shensong Yangxin capsule "fast and slow treatment and integrated regulation" role

5.1. Blocking effect of shensong yangxin capsule on multiple ion channels

Research has indicated that the formation of bioelectricity in biological cells necessitates the presence of multiple ions and their channels to uphold cellular excitability. Information transmission between and within cells occurs through ion channels on the cell membrane. The main channels present on the cardiac muscle cell membrane are those for calcium, potassium, and sodium ions. The dynamic equilibrium among these ions constitutes a highly coordinated and complex network system that underpins the maintenance of normal heart rhythm. As a complex system, it inherently demonstrates a certain level of "robustness," indicating its ability to maintain functionality in the event of random node failures or deliberate attacks within the network. The conventional approach to antiarrhythmic drug development has historically emphasized highly selective single-target interventions while overlooking the "holistic" regulation of the electrophysiological processes underlying arrhythmia formation as a "complex system." Traditional antiarrhythmic drugs excessively perturb the physiological homeostasis within cardiac muscle cells in one or more specific aspects (targets), surpassing the threshold required for maintaining robust stability. This ultimately leads to electrophysiological disturbances, culminating in arrhythmias, and contributing to clinical treatment bottlenecks. By contrast, TCM has emerged as a significant regulator of cardiac rhythms. The composite constituents of Chinese herbal medicine exhibit rational synergistic interaction with ion channel targets, imparting them with the ability to block multiple ion channels. This feature confers the advantage of minimal side effects and low toxicity during clinical application [47].

As an antiarrhythmic drug commonly prescribed in China, SSYX has been demonstrated in evidence-based medicine research to safely and effectively regulate various types of arrhythmias. Most of the pharmaceutical components in SSYX have demonstrated

significant antiarrhythmic effects [48]. Studies have found that SSYX exerts varying degrees of blocking effects on the Na^+ channel current, L-type calcium channel current, slow activation delayed rectification K^+ current, and inward rectification K^+ current in cardiac ventricular muscle ion channels. It plays a broad-spectrum antiarrhythmic role without inducing adverse reactions associated with arrhythmias [49]. We elucidated the mechanism of action of SSYX on each ion channel.

5.1.1. Na + channels in cardiac ventricular myocytes

The voltage-gated sodium channel (INa) is the main ion channel in the myocardial cell membrane and plays an indispensable role in ventricular myocyte excitation and conduction. The Na+ channel is the first channel that can be activated by stimulation, and its ion current (INa) is the primary current for the depolarization of phase-0 (AP phase-0) in fast-response cells. This depolarization directly the amplitude of the AP overshoot in cardiomyocytes and the rate of increase in the ascending phase-0. Blocking IN_a reduces both action potential amplitude (APA) and maximum velocity (Vmax), thereby the AP threshold. It also exhibits antiarrhythmic effects by delaying re-entry impulse or re-entry circuits. In addition, an overload of cellular sodium ions can induce the sodium-calcium ion exchange, potentially elevating intracellular calcium ion concentrations and leading to calcium overload [50]. Therefore, the inhibition of Na^+ inflow and Na^+ overload contributes to arrhythmia inhibition and myocardial protection to a certain extent. Li et al. utilized whole-cell patch clamp technique to investigate the effects of SSYX on Na^+ channel and L-type calcium channel currents ($I_{Ca\text{-}L}$) in guinea pig single ventricular myocytes [51–53]. In that study, Li et al. observed that SSYX reduced the Na^+ current density of guinea pig ventricular myocytes in a dose-dependent manner, resulting in an upward shift in the current density-voltage curve. However, SSYX did not alter AP, peak potential, reversal potential, or curve morphology, suggesting that SSYX inhibited I_{Na} across various membrane potential levels. In conclusion, SSYX plays a Class I antiarrhythmic role by blocking the Na^+ channels.

5.1.2. Ca^{2+} ion channels in cardiomyocytes

T- and L-type channels are the major cardiac Ca^{2+} ion channels. Both are voltage-dependent channels that play a crucial role in regulating the intracellular calcium ion levels, and contribute to the formation of the relative equilibrium plateau phase. L-type Ca^{2+} ion channels determine the duration and plateau of the AP and interact with outward K^+ currents to establish an ion flow balance crucial for the AP plateau in cardiomyocytes.Increased sensitivity of L-type Ca^{2+} ion channels prolongs the duration of cardiomyocyte AP, leading to Early After depolarization(EAD) and resulting in arrhythmia [54]. Simultaneously, Ca^{2+} influx affects the excitation and contraction of cardiomyocytes, which is closely associated with the occurrence of arrhythmia. Under normal circumstances, Ca^{2+} inflow and outflow are balanced. When the outflow decreases or the inflow increases, a condition termed Ca^{2+} overload arises that triggers elevated Ca^{2+} ion levels in the sarcoplasmic reticulum until the overload leads to the spontaneous release of Ca^{2+}, resulting in delayed afterdepolarization that is the central cause of myocardial ischaemia-reperfusion injury and arrhythmia [55,56]. Therefore, inhibiting L-type Ca^{2+} ion channels ($I_{Ca\text{-}L}$) can not only treat arrhythmia but may also protect the myocardium.

Zhao et al. utilized ligation of the anterior descending branch of the coronary artery to induce an acute myocardial infarction (AMI) model. The patch clamp technique was used to measure action potentials of rat myocardium, and laser scanning confocal microscopy was used to detect intracellular Ca^{2+} concentration in myocardial cells. The results indicated that SSYX significantly prolonged the AP duration of rat myocardial cells and inhibited KCl-induced elevation of Ca^{2+} in myocardial cells. These findings suggest that SSYX might prevent the onset of ischemic arrhythmias. The potential mechanism underlying this effect may involve the prolongation of action potentials and relief of Ca^{2+} overload [57]. SSYX may prevent the onset of ischaemic arrhythmias by prolonging AP and alleviating Ca^{2+} overload. Futhermore, cell experiments have shown that SSYX can reduce spontaneous calcium release through various mechanisms, thereby achieving antiarrhythmic therapy [58]. Other studies have shown that SSYX can inhibit the $I_{Ca\text{-}L}$ channel and K^+ current in rat ventricular myocytes, shift the $I_{Ca\text{-}L}$ current-voltage (I–V) curve upward, reduce the V1/2 of the inactivation curve, and prolong the recovery time after inactivation. This occurs through the gating effects of the voltage-dependent inactivation and time-dependent activation of the L-type channels [59,60]. In addition, Lian et al. [61], Zhou et al., and Liang et al. [62,63] demonstrated that SSYX inhibit $I_{Ca\text{-}L}$ to reduce the frequency of arrhythmia attacks and protect the myocardium through *in vivo* and *in vitro* experiments using different experimental animal models. This reflects the mechanism of action similar to class IV antiarrhythmic drugs.

5.1.3. K^+ ion channels of cardiomyocytes

In cardiomyocytes, K^+ ions are crucial for maintaining the resting membrane potential, as well as AP repolarization. Hence, blocking potassium ion channels plays an extremely important role in inhibiting arrhythmia. Potassium ion channels are classified into several types, including voltage-gated potassium channels (Kv), calcium-dependent potassium channels (K_{Ca}), acetylcholine-sensitive potassium channels ($I_{K(ACh)}$), and ATP-sensitive potassium channels ($I_{K(ATP)}$). Among voltage-gated potassium channels (Kv channels), the transient outward potassium channel (I_{to}), the delayed rectifier potassium channel (I_K), and the inward rectified potassium channel (I_{K1}) play crucial roles in cardiac repolarization.

In the process of repolarization, the transient outward potassium channel Ito constitutes the primary current responsible for early repolarization of cardiomyocytes, including the onset of rapid repolarization phase-1 and the plateau phase-2 of the action potential. Activation and deactivation of Ito directly influence the morphology and duration of AP in cardiomyocytes, playing a crucial role in early AP repolarization and plateau potential [64]. Zhang et al. employed patch-clamp technique to investigate alteration in Ito density and the Ito inactivation curve in epicardial (Epi), endocardial (Endo), and intermediate (M) ventricular myocytes from the border zone of left ventricular infarction induced by SSYX [65]. The results demonstrated SSYX markedly suppressed the Ito-derived repolarization current in the epicardial region of the infarction border, leading to an extension of the APD in ventricular myocytes and mitigating repolarization heterogeneity, thereby lowering the risk of phase-2 reentry (a local arrhythmogenic phenomenon). Delayed rectifier

Table 1
The chemical ingredients of Shensong Yangxin (SSYX) capsule.

Reference	Compound	Count
[15]	**Dan-Shen**: Tanshinone II A **Huang-Lian**: Berberine Hydrochloride **Nan-Wu-Wei-Zi**: Schisandrin A **Shan-Zhu-Yu**: Strychnine	4
[7]	**Ren-Shen**: Ginsenoside Re; Ginsenoside Rg1	2
[8]	**Ren-Shen**: Ginsenoside	1
[22]	**Nan-Wu-Wei-Zi**: Schisandrin A; Schisantherin A	2
[16]	**Chi-Shao**: Paeoniflorin **Dan-Shen**: Salvianolic acid B **Huang-Lian**: Berberine **Shan-Zhu-Yu**: Strychnine	4
[18]	**Dan-Shen**: Cryptotanshinone; Dihydrotanshinone I; Tanshinone I; Tanshinone II A	4
[31]	**Dan-Shen**: Protocatechualdehyde	1
[32]	**Ren-Shen**: Ginsenoside Rb1	1
[13]	**Chi-Shao**: Apigenin; Baicalin; Calyx isoflavone; Catechin; Ellagic acid; Kaempferol; Paeoniflorin; Paeoniflorin; Baicalin; Protocatechuic acid; Gallic acid **Dan-Shen**: Baicalin; Protocatechuic acid; Cryptotanshinone; Danshensu; Dihydrotanshinone I; Hydroxyttanshinone II A; Rosemary acid; Salvia miltiorrhiza cryptospironolactone; Salvianolic acid A; Salvianolic acid B; Salvianolic acid C; Salvianolic acid D; Salvianolic acid F; Salviol A; Sodium danshensu; Tanshinone I; Tanshinone V; Rutin; Caffeic acid; Tanshinone II A; Protocatechualdehyde; Quercetin **Gan-Song**: Geranium lignin; Luteolin; Luteolin; Robinin; Caffeic acid; Tanshinone II A; Chlorogenic acid; Protocatechuic acid; Gallic acid **Huang-Lian**: Chlorogenic acid; Berberine; Coptisine; Corydine; Emodin; Ferulic acid; Jatrorrhizine/Tetrandrine; Jatrorrhizine/ Tetrandrine; Magnolia alkaloid; Palmatine; Protocatechualdehyde; Betaine **Nan-Wu-Wei-Zi**: Hyperoside; Schisantherin A; Schisandrin A; Schisandrin B; Rutin **Ren-Shen**: Ginsenoside Re; Ginsenoside Rg1 Sang-Ji-Sheng: Quercetin **Shan-Zhu-Yu**: Betaine; Strychnine; Gallic acid **Tu-Bie-Chong**: 5,4′- dihydroxy-7-methoxyflavone	54
[19]	**Chi-Shao**: Paeoniflorin* **Nan-Wu-Wei-Zi**: Schisandrin A* Suan-Zao-Ren: Spinozol*	3
[33]	**Chi-Shao**: Paeoniflorin **Dan-Shen**: Salvianolic acid A; Salvianolic acid B **Huang-Lian**: Berberine hydrochloride; Palmatine chloride **Nan-Wu-Wei-Zi**: Schisandrin A **Shan-Zhu-Yu**: Strychnine Suan-Zao-Ren: Spinozol	8
[34]	**Ren-Shen**: Ginsenoside Rb1	1
[35]	**Shan-Zhu-Yu**: Strychnine	1
[36]	**Nan-Wu-Wei-Zi**: Schisantherin A	1
[37]	**Ren-Shen**: Ginsenoside Rb1	1
[38]	**Chi-Shao**: Apigenin; Baicalin; Calycosin; Catechin; Ellagic acid; Kaempferol; Paeoniflorin; Paeoniflorin; Baicalin; Protocatechuic acid; Gallic acid **Dan-Shen**: Baicalin; Protocatechuic acid; Cryptotanshinone; Danshensu; Dihydrotanshinone I; Hydroxyttanshinone II A; Rosemary acid; Salvianolic acid A; Salvianolic acid C; Salvianolic acid D; Rutin; Caffeic acid; Tanshinone II A; Protocatechualdehyde; Quercetin **Gan-Song**: Protocatechuic acid; Gallic acid; Diosmetin; Luteolin; Robinin; Caffeic acid; Tanshinone II A; chlorogenic acid **Huang-Lian**: Chlorogenic acid; Berberine; Emodin; Magnolia alkaloid; Palmatine; Violadine; Protocatechualdehyde; Betaine **Nan-Wu-Wei-Zi**: Hyperoside; Schisandrin A; Schisandrin B **Sang-Ji-Sheng**: Ferulic acid; Quercetin **Shan-Zhu-Yu**: Betaine; Gallic acid; Strychnine	39
[10]	**Chi-Shao**: Calycosin; Paeoniflorin **Dan-Shen**: Quercetin **Gan-Song**: Chlorogenic acid **Sang-Ji-Sheng**: Ferulic acid	5
[39]	**Nan-Wu-Wei-Zi**: Schisantherin A **Shan-Zhu-Yu**: Strychnine	2
[12]	**Chi-Shao**: Paeoniflorin **Dan-Shen**: Salvianolic acid B; Tanshinone I; Tanshinone II A **Nan-Wu-Wei-Zi**: Schisandrin A; Schisantherin A **Shan-Zhu-Yu**: Strychnine; Morroniside	8
[40]	**Chi-Shao**: Paeoniflorin#; Huang-Lian: Berberine#; Coptisine#; Epiberberine#; Palmatine#; **Nan-Wu-Wei-Zi**: Deoxyschizandrin#; Schisantherin#; Shan-**Zhu-Yu**: Loganin#; Morroniside#; **Suan-Zao-Ren**: Spinosin#	10
[41]	**Chi-Shao**: Benzoylpaeoniflorin; Galloylpaeoniflorin; Paeoniflorin **Dan-Shen**: Cryptotanshinone; Danshensu; Dihydroisotanshine; Ginsenoside Re; Lithospermic acid; Protocatechualdehyde; Protocatechuic acid; Rosmarinic acid; Salvianolic acid A; Salvianolic acid B; Salvianolic acid C; Salvianolic acid D; Salvianolic acid E; Salvianolic acid H/I; Salvianolic acid H/I; Tanshinone I; Tanshinone IIA; Tanshinone IIB **Gan-Song**: 7-Deoxyloganic acid; Kanshone F; Linarin; M14; M16; Nardoaristolone B; Nardosinone **Huang-Lian**: 13-Hydroberberine; 13-Hydroxyberberastine; 13-Hydroxypalmatine; 13-Methylberberine; 13-Methylepiberberine; Berberastine; Berberine; Berberrubine; Columbamine; Coptisine; Dehydrocorydaline; Demethyleneberberine; Demethyleneepiberberine;	99

(*continued on next page*)

Table 1 (*continued*)

Reference	Compound	Count
[42]	Epiberberine; Jatrorrhizine; M15; M27; M32; M9; Palmatine; Worenine **Mai-Dong**: M89; Ophiopogonin B; Ophiopogonin D **Nan-Wu-Wei-Zi**: (?)-Anwulignan; Deoxyschizandrin; Epigomisin O; Gomisin G; Gomisin J; Pregomisin; Schisandrol A; Schisandrol B; Schisanhenol; Schisantherin A; Schisantherin B/C; Schisantherin B/C; Schisantherin D; Schizandrin B **Ren-Shen**: 20(R)-ginsenoside Rh1; 20(S)-ginsenoside Rh1; 20R-ginsenoside Rg2; 20R-ginsenoside Rg3; 20S-ginsenoside Rg2; 20S-ginsenoside Rg3; Ginsenoside F1; Ginsenoside F5; Ginsenoside Rb1; Ginsenoside Rb2; Ginsenoside Rc; Ginsenoside Rd; Ginsenoside Rf; Ginsenoside Rg1; Ginsenoside Rh4; Ginsenoside Ro; Notoginsenoside R1 **Sang-Ji-Sheng**: Avicularin; Ferulic acid; Quercetin **Shan-Zhu-Yu**: Cornuside I; Loganin; Morroniside; Oleanic acid; Sweroside; Ursolic acid **Suan-Zao-Ren**: Jujuboside A; Jujuboside B; Spinosin **TBD**: Chlorogenic acid; Gallic acid; Loganic acid; Neochlorogenic acid **Chi-Shao**: Paeoniflorin△ **Dan-Shen**: 3-Hydroxytanshinone IIB△; Cryptotanshinone△; Dihydrotanshinone I△; Methyl tanshinonate△; Neocryptotanshinone△; Protocatechuic aldehyde△; Tanshinol B△; Tanshinone I△; Tanshinone V△; Tashinone IIA△ **Gan-Song**: 7-deoxonarchinol A△; Aristolone△; Kanshone H△; Nardosinonedio△l; Nardostachone△ **Huang-Lian**: Berberine△; Palmatine△ **Nan-Wu-Wei-Zi**: Angeloylgomisin O△; Angeloylgomisin P△; Benzoylgomisin O△; Deoxyschisandrin△; Kadsuric acid△; Nigranoic acid△; Schisandrin△; Schisandrol B△; Schisandronic acid△; Schisanhenol△; Schisantherin A△; Schisantherin B△; Schisantherin C△; Schisantherin D△; Tigloylgomisin O△; Tigloylgomisin P△ **Ren-Shen**: Ginsenoside Rb1△; Ginsenoside Rb2△; Ginsenoside Rc△ **Sang-Ji-Sheng**: Quercitrin△ **Shan-Zhu-Yu**: 7-O-ethylmorroniside△; Loganin△; Morroniside; Sweroside△ **Suan-Zao-Ren**: Ceanothic acid△; Epiceanothic acid△; Magnoflorine△ **TBD**: 19-Hydroxyschisantherin B▲; 19-Hydroxyschisantherin C▲; 21-Hydroxyschisantherin B▲; 21-Hydroxyschisantherin C▲; 25, 26-Dihydroschisandronic acid–O-gluA▲; 3-Hydroxyschisandronic acid-O-gluA▲; Cryptotanshinone catechol glucuronide▲; Cryptotanshinone catechol glucuronide isomer▲; Dehydrocryptotanshinone▲; Dehydroneocryptotanshinone▲; Dehydrotanshinone V▲; Demethylated dihydroangeloylgomisin O▲; Demethylated dihydroangeloylgomisin P▲; Demethylated dihydroschisantherin A▲; Demethylated dihydroschisantherin B▲; Demethylated dihydroschisantherin C▲; Demethylated dihydrotigloylgomisin O▲; Demethylated dihydrotigloylgomisin P▲; Demethylated hydroxytanshinone V▲; Demethylated schisandrin-O-glucuronide▲; Demethyleneberberine-2-O-glucuronide▲; Demethylpalmatine-O-glucuronide▲; Demethylpalmatine-O-glucuronide isomer▲; Demethylschisandrin-O-glucuronide isomer I▲; Demethylschisandrin-O-glucuronide isomer II▲; Demethylthalifendine-10-O-glucuronide▲; Didehydrotanshinone V▲; Dihydrotanshinone I catechol glucuronide▲; Hydrated and Decarbonylated of Dihydrotanshinone I▲; Hydrated demethylneocryptotanshinone▲; Hydroxyschisanhenol▲; Hydroxyschisanhenol isomer I▲; Hydroxyschisanhenol isomer II▲; Kadsuric acid O-glucuronide▲; Methyltanshinone V▲; Neocryptotanshinone-O-glucuronide▲; Nigranoic acid-O-glucuronide▲; Schisandronic acid-27-O-glucuronide▲; Schisanhenol-O-glucuronide▲; Schisanhenol-O-glucuronide isomer▲; Tanshinone I catechol glucuronide▲; Tanshinone I catechol glucuronide isomer▲; Tanshinone IIA catechol glucuronide▲; Tanshinone IIA catechol glucuronide isomer▲; Tanshinone V–O-glucuronide▲; Thalifendine▲; Thalifendine-10-O-glucuronide▲	92

potassium currents (I_K) contribute to phase-2 activation of cardiomyocyte action potentials (APs) and constitute the primary outward current during the plateau phase. These channels encompass I_{Kr}, I_{Ks}, and I_{Kur}. I_{Kr} primarily mediates the repolarization current crucial for maintaining action potential duration (APD) stability during repolarization in large mammalian ventricular myocytes, including humans [66]. I_{kr} exhibits an outward rectification characteristic at negative potential and strong inward rectification at positive potential. Its inactivation kinetics are faster than its activation dynamics and play an crucial role in cardiac repolarization [67,68]. I_{Ks} plays an important role during the late repolarization phase of cardiac AP, as it is an important target for the sympathetic nervous system (SNS) to regulate cardiac electrophysiology, and plays an important role in the repolarization of myocardial AP in phase-3 [69]. The SSYX formulation exhibited a voltage-dependent inhibitory effect on I_{KS},and this blocking effect on I_{KS} resulted in a therapeutic benefit for treating arrhythmia during tachycardia, thus showing a class III antiarrhythmic effect. These experiments also revealed that SSYX can accelerate the deactivation rate of the channel and slightly reduce the peak current and tail current density of I_{Kr}, thereby avoiding the adverse frequency-dependent side effects of QT interval prolongation caused by other class III drugs that block I_{Kr} [52]. I_{K1} plays an crucial role in stabilizing the resting membrane potential and facilitating both the initial depolarization and final repolarization of AP. The permeability of K^+ decreased with an increase in the degree of depolarization. I_{K1} overexpression can lead to a short QT interval, whereas inhibition of I_{K1} can lead to a long QT phenotype. Thus, the regulation of I_{K1} significantly impacts cardiac excitability and arrhythmia [70,71]. Li et al. used whole-cell patch-clamp recordings to observe the effects of SSYX dry powder-derived solution on the inward-rectified potassium current (I_{K1}) in rat single ventricular myocytes and delayed rectified potassium current (I_K) in guinea pig cardiomyocytes [52,72]. Studies have shown that SSYX inhibits the inward current component of I_{k1},which contribute to the maintenance of phase-4 depolarization and a reduction in delayed afterdepolarization. Additionally, SSYX affects phase-3 repolarization of the action potential, leading to enhanced cell membrane stability, eliminating early afterdepolarization, and of arrhythmias arising from triggered. In summary, the distribution of potassium channels is complex, and each potassium channel has a different influence on the process of AP repolarization. Hence, the electrophysiological effects of blocking each of these channels will also be different. Multidirectional regulation and inhibition of the K channels by SSYX treatment may be an important mechanism of action for its antiarrhythmic effects.

5.1.4. hHCN4 cation channel in ventricular muscle

The hyperpolarisation-activated cyclic nucleotide-gated cation channel (HCN) serves as the molecular basis for enhancing the

pacing current I_f, which primarily contributes to the generation of phase-4 automatic depolarization. Particularly in the early phase of automatic depolarization, it theoretically reduces the risk of arrhythmia under normal electrophysiological conditions without affecting the AP repolarization duration.Conversely, in pathological conditions, upregulation of hHCN4 mRNA and protein expression occurs in the heart, leading to an increase in pacemaker current, which is particularly prominent in patients with ischemic heart disease. The elevated expression of hHCN4 mRNA and protein results in a more than twofold increase in pacemaker current in ventricular myocytes of patients with end-stage ischemic heart disease, which represents one of the significant contributors to malignant arrhythmias.Studies have shown that modulating the expression of HCN4 through electrophysiological remodelling techniques may emerge as a crucial mechanism for antiarrhythmic therapy [73–75].

Sun et al. used SSYX dry powder to prepare a 0.5 % concentration solution with using extracellular fluid as a solvent. This solution was then used to transfect hHCN4 cDNA (a human hyperpolarisation-activated cation channel [If] gene) into a human embryonic kidney (HEK293) cell for recording hyperpolarisation-activated cation flow using the whole-cell patch-clamp technique. The results demonstrated the inhibition of the peak current density in HEK293 cells. In addition, this inhibition is reversible and can be restored to a certain percentage of the original current after elution, representing bidirectional regulation [76]. It can be seen that the hHCN4-derived pacing current is reversibly inhibited by SSYX dry powder solution, thus providing a new hypothesis for the mechanism involved in the SSYX treatment of arrhythmia.

5.2. Regulating effect of shensong yangxin capsule on non-ion channels

5.2.1. Improvement of myocardial electrophysiological structure

The cardiac cell population comprises the intrinsic myocardium and specialized myocardium. Conduction cells such as the sinoatrial node, atrioventricular node, and Purkinje fibers are responsible for transmitting electrical impulses to individual working muscle cells. Upon receiving these electrical impulses, the working myocyte generates excitatory contractions. Disruption in the link between conduction cells and myocytes can affect excitability, and conductivity, leading to arrhythmia. This sinus node, among the conduction cells, acts as the pacemaker that generates a normal sinus rhythm. Dysfunction of the sinus node can lead to abnormalities in conduction and pacemaker functions, subsequently affecting heartbeat frequency and rhythm. Several studies have shown that SSYX can improve the sinus heart rate, shorten the sinus node conduction time, recovery time, and atrioventricular conduction time in adult Chinese miniature pigs, resulting in enhanced sinus node and heart conduction functions, thereby playing a therapeutic role in chronic arrhythmia [77].

It is widely recognized that the action potential durations (APD) of cardiomyocytes is generated by the transmembrane movement of various ions. APD of cardiomyocytes is determined by the interplay between inward and outward currents during repolarization. An increase in inward current or a suppression of outward current leads to prolongation of the APD, and conversely. Studies have indicated that excessive prolongation of APD and shortening of effective refractory period (ERP) are crucial indicators of electrical remodelling resulting from electrophysiological abnormalities. These changes may give rise to conduction and reentrant abnormalities, which constitute the primary mechanism of ventricular arrhythmias [78]. During their study on electrical remodelling in metabolic syndrome (MetS)-induced Wistar rats, Yang et al. [79] found that rats exposed to a high-carbohydrate, high-fat diet to induce metabolic syndrome showed increased susceptibility to ventricular arrhythmia. This was linked to both shortened ERP and prolonged APD. The electrophysiological changes induced by MetS, as described above, were reversed following intervention with SSYX. An additional electrophysiological study conducted on a rabbit model of heart failure, as confirmed by Wang et al. [80], demonstrated that SSYX can modify the cardiac electrophysiological changes resulting from increased pre and post load. This was evidenced by SSYX's ability to shorten atrial muscle APD and bring the atrial electrophysiological characteristics closer to a physiological state. In this experiment, SSYX was also observed to exert an antiarrhythmic effect by reducing transmural dispersion of repolarization (TDR) and elevating the ventricular fibrillation threshold (VFT). Furthermore, other studys [81,82]have also confirmed that SSYX can prolong the ERP and VFT, while shortening RDR in a ventricular remodelling model induced by left coronary artery ligation. These findings align with the previously discussed experimental outcomes. Taken together, these studies suggest that SSYX exerts antiarrhythmic effects by influencing electrophysiological outcomes through multiple pathways.

5.2.2. Inhibition of myocardial fibrosis

Physiologically, fibroblasts are typically in a dormant state, while collagen formation and degradation in the extracellular matrix are dynamically balance. However, under pathological conditions, a set of cytokines such as angiotensin II and TGF-β and external factors such as mechanical stress stimulate fibroblasts to proliferate and differentiate into myofibroblasts that have an enhanced ability to synthesise and secrete extracellular matrix components and alter the balance of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). Studies have shown that the balance of MMP/TIMP is key to maintaining the balance between collagen synthesis and its metabolic degradation in cardiac fibroblasts. An elevation in MMP activity or a serious imbalance in the MMP/TIMP ratio leads to ventricular remodelling and cardiac fibrosis [83]. However, an increased MMP activity can degrade normal collagen that is replaced by fibrous interstitial tissue, resulting in serious destruction of the cardiac collagen network. This is one of the main factors leading to heart rhythm fluctuations [84,85]. In a rat model of ventricular remodelling induced by aortic constriction [86], it was observed that SSYX altered the pathological morphology, decreased cardiac fibrosis in rats undergoing concentric remodelling, notably enhanced the ventricular fibrillation threshold, and reduced the duration of ventricular fibrillation.

TGF-β1 can stimulate collagen synthesis and upregulate MMP expression, thereby contributing to cardiac fibrosis. Ma et al. discovered that SSYX reduces left atrial fibrosis, downregulates the expression of TGF-β1, MMP-9, TIMP-I, type I and III collagen, inhibits the transformation of cardiac fibroblasts into myofibroblasts, improves left atrial conduction function, and decreases the

induction of atrial fibrillation following myocardial infarction [87]. Another study revealed the involvement of the TGF-β1/Smad signalling pathway in the progression of cardiac fibrosis in diabetic cardiomyopathy. SSYX can diminish cardiac fibrosis and collagen deposition in type 2 diabetes mellitus rats, subsequently delaying the onset of malignant arrhythmias through inhibition of the TGF-β1/Smad signalling pathway [88].

Cardiac fibrosis often results in remodelling of cardiac gap junctions, which is a significant factor in the progression of CVD, including arrhythmia and heart failure. Gap junctions are the main mode of connection for cardiomyocytes, maintaining their normal electrical coupling, and are made up of connexin (Cx) 43 and Cx40. Cx40 is expressed in atrial myocytes, whereas Cx43 is present in both the ventricular and atrial myocytes. Studies have shown that the release of TNF-α by myoblasts after myocardial infarction can induce the pathogenic condition known as atrial fibrosis in mice via the TGF-β signalling pathway and other pathways. In this process, Cx40 and Cx43 expression is altered, and these changes are associated with the occurrence and development of arrhythmia [89–91]. Studies on the mechanism of arrhythmia after myocardial infarction have demonstrated that SSYX can enhance Cx43 expression in myocardial tissue, decrease collagen fibre deposition and collagen volume fraction, the development of cardiac fibrosis, and reduce the incidence of fatal arrhythmia [92–94]. Similarly, SSYX induces Cx40 expression in the atrial muscle of diabetic rats but has little effect on its spatial distribution: these findings require further study [95].

5.2.3. Regulation of cardiac autonomic nervous function

Under normal circumstances, the autonomic nervous system regulates the heart by maintaining a balance between vagus and sympathetic nerve activity, while neurotransmitters regulate the physiological characteristics of cardiomyocytes. Stimulation of the sympathetic nerve leads to the excitation of cardiomyocytes, whereas signals from cardiomyocyte induce activation of the vagus nerve. An imbalance in the regulation of these two systems can lead to abnormal electrophysiological effects, resulting in arrhythmias [96].

Heart rate variability (HRV) is a common index used to evaluate the influence of sympathetic and vagus nerve balance on the cardiovascular system and is often used to reflect the regulatory function of the autonomic nerves. HRV increases when there is an increase in vagal nerve activity and a decrease in sympathetic nerve activity [97]. In HRV, the low-frequency (LF) component of heart rate variability represents sympathetic nerve activity, while the high-frequency (HF) components reflects vagal nerve activity. Consequently, the LF/HF ratio serves as an index for assessing the balance between sympathetic and vagal nerve activity.

By observing the electrophysiological effects of SSYX on Chinese miniature pig hearts and isolated guinea pig ventricular myocytes, Feng et al. demonstrated that SSYX could increase the heart rate and improved the conduction capacity of the heart. If the autonomic nervous system was experimentally inhibited, SSYX had no effect on the intrinsic heart rate [78]. Another study on atrial electrical remodelling and paroxysmal atrial fibrillation found that SSYX inhibited atrial electrical remodelling and susceptibility to atrial fibrillation after 8 weeks of long-term intermittent atrial pacing in mutants, reducing LF and LF/HF. The LF/HF ratio, serving as an indicator of the interplay between sympathetic and vagal nerve activity, increases following the induction of long-term intermittent atrial pacing, leading to heightened sympathetic nerve activity and reduced vagal nerve activity [98]. Thus, SSYX can inhibit sympathetic remodelling during long-term intermittent atrial pacing by modulating autonomic nerve activity. Additionally, the above study showed that not only TNF-α but also other inflammatory cytokines were inhibited by vagus nerve stimulation or administration of α7nAChR antagonists. The cholinergic anti-inflammatory pathway inhibits inflammation by activating the vagus nerve. It was also revealed that SSYX inhibited the atrial decrease in Ach and α7nAChR protein expression. This impliess that SSYX exerts antiarrhythmic effects by modulating imbalances in autonomic nerve activity, increasing vagus nerve activity, consequently boosting the cholinergic anti-inflammatory pathway, lowering inflammatory cytokines levels, and providing protection against atrial fibrillation.

In another study that administered SSYX post-coronary artery ligation in New Zealand rabbits, a significant correlation was discovered between autonomic nerve remodelling following myocardial infarction and the incidence of arrhythmia. By inhibiting inflammatory factors and NGF signaling pathway, SSYX is capable of decreasing nerve density in experimental animals post-myocardial infarction, suggesting that intervening in autonomic nerve remodelling may be a crucial way to prevent arrhythmia [99].

5.2.4. Inhibiting inflammation

In cardiomyocytes, the inflammatory response induced by the release of inflammatory factors can cause myocardial cell damage, often leading to arrhythmia after myocardial ischaemia-reperfusion injury. Studies have shown that inflammation is directly related to the induction of atrial fibrillation, and inflammatory cytokines such as TNFα and IL-6 may be related to fibrosis and the expression of current channel subunits, and the abnormal expression of these subunits has a substantial impact on the electrical remodelling of atrial fibrillation [100,101].

Zhao et al. demonstrated that SSYX could inhibit the elevation of TNFα and IL-6 levels following long-term intermittent atrial pacing in dogs, while also preventing the decrease in acetylcholine levels. Consequently, we postulated that the impact of SSYX on inflammatory cytokine levels could be linked to enhanced vagus nerve activity [98]. Endothelial dysfunction is a pivotal factor in vascular inflammation, characterized in part by the heightened surface expression of adhesion molecules. Macrophages produce pro-inflammatory cytokines, such as iNOS, TNF-α, MCP-1 and IL-1β, and macrophage activation significantly contributes to inflammation induced by endothelial injury. Macrophages residing in heart tissue can promote electrical conduction by forming gap junctions with cardiomyocytes. Macrophage polarisation can affect the gap junction structure of cardiomyocytes, resulting in arrhythmia. Zhang et al. found that SSYX not only increased the protein expression and NO levels of eNOS in heart tissue of db/db mice, but also reduced the expression of ET-1 mRNA and directly improved endothelial function in a study on susceptibility to arrhythmia in db/db mice [102]. Likewise, SSYX decreased inflammatory cell infiltration in mouse heart tissue, suppressed the mRNA expression of inflammatory cytokines TNF-α, IL-1β, IL-6, MCP-1 and CCR-2, as well as the polarisation of macrophages, consequently reducing the susceptibility to arrhythmia in db/db mice. Therefore, the study confirmed the endothelial protective effects of SSYX in db/db mice. In

addition, *in vitro* experiments and electrophysiological studies under whole-heart Langendorff perfusion conditions found that, on the premise of improving atrial electrical remodelling, SSYX on the one hand reduced the levels of serum markers of oxidative damage and increased the serum levels of antioxidant enzymes SOD and GSH-Px in diabetic rats. Additionally, SSYX decreased the levels of serum inflammatory markers TNF-α and IL-6 in diabetic rats, thereby alleviating atrial fibrosis caused by diabetes through anti-inflammatory and antioxidant effects [103].

In addition, C-reactive protein (CRP/hs-CRP), TNF-α, IL-6, and IL-1β are the signature factors of systemic inflammatory response that can activate inflammatory cells to cause hypoxia and vasospasm, and independently regulate cardiac function. It is apparent that they are important clinical indicators of inflammatory changes in CVD such as coronary heart disease and arrhythmia. Several clinical studies have demonstrated that SSYX, either alone or in combination with metoprolol and amiodarone, can effectively inhibit the expression of inflammatory markers including CRP (hs-CRP), TNF-α, IL-6, and IL-1β in patients with coronary heart disease and arrhythmia. This leads to a reduction in systemic inflammation, better control of arrhythmia symptoms, and improved overall outcomes [104–106].

5.2.5. Improving mitochondrial energy metabolism

Mitochondria are the main sites of ATP production via the tricarboxylic acid cycle. Mitochondria must have a constant need to synthesise ATP in order to fulfill the energy demands of cardiomyocytes, ensure proper cardiac contractile function, and stabilize myocardial electrical activity. Impaired mitochondrial function results in inadequate ATP production within cardiomyocytes, disrupting ion homeostasis and ultimately causing arrhythmia [107]. The mitochondrial biosynthesis of ATP is governed by a complex regulatory system that includes various steps, such as glucose and fatty acid substrate utilisation, oxidative phosphorylation, and the formation and transfer of mitochondrial ATP. Among these, peroxisome proliferator activating receptor coactivator 1α (PGC-1α) is a key regulatory factor involved in mitochondrial biosynthesis of ATP and cardiac oxidative metabolism. Some reports suggest that elevation of PGC-1α levels can enhance ATP concentration and improve mitochondrial dysfunction [108,109]. AMP-activated protein kinase (AMPK) plays a critical role in regulating lipid metabolism and energy balance. It is rapidly activated when ATP levels decline to maintain energy balance [110,111]. Studies have demonstrated that SSYX can activate AMPK and significantly up-regulate the expression of PGC-1α. Simultaneously, SSYX can promote the oxidation of fatty acids and glucose by upregulating the expression of crucial factors involved in their metabolism, namely carnitine palmitoyltransferase-1 (CPT-1) and glucose transporter-4 (GLUT-4). This leads to enhanced oxidative phosphorylation and improved energy metabolism [112]. This study provides a new approach for the future treatment of myocardial metabolic diseases, implying that SSYX increases the oxidative phosphorylation capacity of cells in cardiac hypertrophy, improves cardiac function, and slows or even reverses cardiac hypertrophy progression to heart failure. These results provide support for the development of new treatments for cardiac hypertrophy and heart failure.

5.2.6. Improving microvascular endothelial function and promoting angiogenesis

Microvascular dysfunction plays a crucial role in left ventricular remodelling following acute myocardial infarction (AMI) [113]. Acute occlusion of coronary artery lead to local myocardial cell ischaemia, causing microvascular injury, such as capillary and myocardial reperfusion injuries. This can eventually result in oedema and microvascular endothelial dysfunction [114]. The vascular endothelium is a vital endocrine and paracrine organ involved in immune regulation and atherosclerosis in the human body. Research has demonstrated that vascular endothelial injury is a significant factor influencing restenosis following percutaneous coronary intervention [115]. Vascular endothelial cells regulate the coronary artery blood flow through the release vasoactive factors. Nitric oxide (NO) is a primary vasodilator produced by the endothelium [116], whereas endothelin-1 (ET-1) is an endogenous vasoactive peptide with potent and sustained vasoconstrictor effects on coronary arteries [117]. NO and ET-1 are closely linked with vascular endothelial function. Impaired endothelial function leads to a significant decrease in NO levels and a significant increase in ET-1 levels. Under physiological conditions, endothelial cells synthesise von Willebrand factor (vWF), which mediates platelet adhesion to damaged vascular endothelium. However, under pathological conditions, activated platelets release vWF, facilitating platelet aggregation at the site of vascular injury, thereby promoting thrombosis [118]. Studies have shown that SSYX can increase microvascular density in the peri-infarction zone in infarcted rabbit hearts while decreasing ET-1 and vWF levels and increasing NO levels in plasma [119]. It is apparent that SSYX can improve cardiac microcirculation after myocardial infarction, and the mechanism may be related to the ability of SSYX to promote capillary angiogenesis in the peripheral area of myocardial infarction and balance endothelium-derived vasodilator and vasoconstrictor factors. In addition, Zhang et al. have demonstrated that SSYX can potentially attenuate endothelial cell damage and subsequent inflammatory responses through the eNOS pathway, thus lowering the risk of arrhythmia [102]. *In vitro* experiments demonstrated that SSYX effectively enhanced the viability of endothelial cells impaired by high glucose and lipid levels. It also prevented the decrease in mitochondrial membrane potential, regulated mitochondrial fusion and fission function, attenuated endoplasmic reticulum stress, reduced the inflammatory response, and inhibited the expression of adhesion molecules. It was further confirmed that SSYX has a protective effect on endothelial cells induced by high glucose and fat. These results suggests that microvascular endothelial cell injury and the subsequent inflammatory response contribute to an increased susceptibility to arrhythmia. By inhibiting endothelial cell damage and the associated inflammatory response, SSYX can mitigate the susceptibility to arrhythmia.

The process of enhancing the blood supply to the ischaemic myocardium by promoting collateral circulation through drugs has been termed therapeutic angiogenesis. In recent years, this therapy has become popular in the clinical treatment of vascular diseases. Therapeutic angiogenesis can enable the ischaemic myocardium to release a set of proangiogenic factors to promote the generation of new micro-blood vessels, thereby establishing collateral circulation that can restore the blood supply to ischaemic myocardium, and improve the symptoms and prognosis of patients [120,121]. Vascular endothelial growth factor (VEGF), a member of the platelet-derived growth factor family, is a potent endothelial cells mitogen that strongly promotes angiogenesis [122]. Studies have

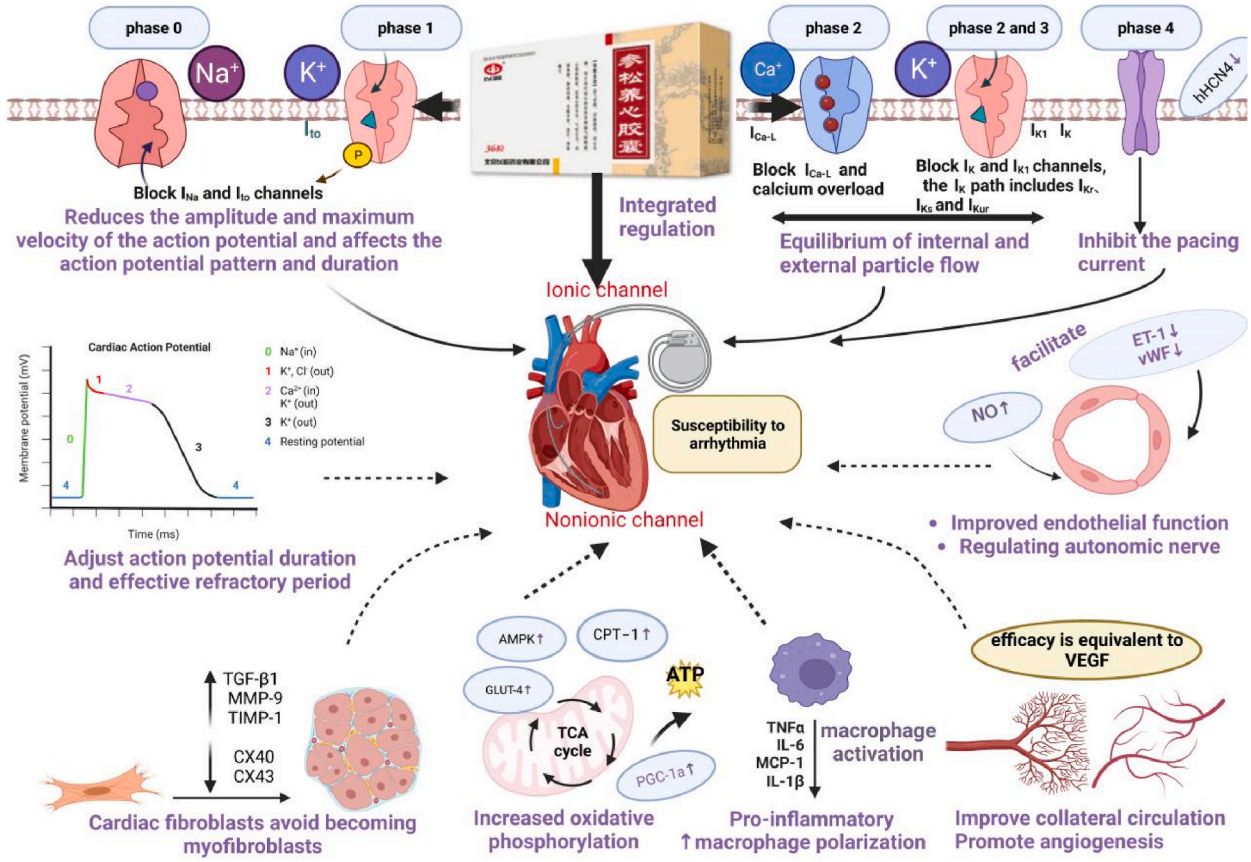

Fig. 2. Schematic showing the mechanism of action of SSYX. In this figure, → represents the SSYX ion channel mechanism of action, ⇢represents the SSYX non-ion channel mechanism of action.

demonstrated that SSYX promotes blood vessel in the chorioallantoic membrane of chicken embryos, leading to a significant increase in the total number of blood vessels. Its efficacy in this regard is comparable to that of VEGF [123]. *In vitro* studies have indicated that SSYX enhances the proliferation of human umbilical vein endothelial cells, resulting in an increase in the number of endothelial cell.

In addition to the aforementioned mechanisms, SSYX has also been studied in other systems. Studies have revealed that a combination of SSYX and simvastatin can significantly reduce serum cholesterol and low-density lipoprotein levels and prevent atherosclerosis-related diseases [124]. In terms of immune function, studies have shown that serum anti-β1-adrenoceptor autoantibody (β1-AAB) levels increase in patients with ventricular arrhythmia, and this may be related to immune dysfunction and T lymphocyte proliferation. Among the various ingredients of SSYX, pine, Cornus officinis, jujube kernel, and schisandra chinensis can ameliorate immune dysfunction of the body to a certain extent. Additionally, SSYX can decrease serum β1-AAB levels in ventricular arrhythmia and improve the distribution of T lymphocyte subgroups, which may be one of its antiarrhythmic mechanisms [125,126]. In addition, abnormal NR1 expression may be a critical molecular mechanism of post-MI depression, and SSYX can ameliorate depression-like behaviour in post-MI depressed rats by regulating NR1 subunit expression [127].

In conclusion, SSYX has extensively investigated the mechanisms of treating arrhythmia based on the theory of Luobing. It exhibits unique advantages through multi-ion channel blockade and non-ion channel regulation (Fig. 2 and Table 2). These mechanisms provide a cardiac electrophysiological basis for its clinical bidirectional regulatory effects in treating both rapid and slow arrhythmias, highlighting the advantage of "integrated regulation" during collateral dredging intervention. These findings lay the foundation for understanding the scientific implications of the shift from an "anti-arrhythmic" approach to "arrhythmia regulation." They also provide valuable insights for further research on arrhythmia drugs aimed at improving clinical efficacy.

6. Studies on the mechanism of Shensong Yangxin capsule in treating arrhythmia based on network pharmacology

TCM has multiple components, targets, and pathways [128]. In recent years, network pharmacology has been widely accepted as an effective research strategy for exploring TCM from the perspective of biological network balance [129–131]. In this review, we explored the molecular mechanism of action of SSYX in the treatment of cardiac arrhythmia (CA) using a network pharmacological approach that combines chemical and therapeutic properties. Using "cardiac arrhythmia" or "cardiac arrhythmias" as the search term, we retrieved genes associated with arrhythmia from six bibliographic databases, including DisGeNET [132], the Open Target Platform

Table 2
Studies on pharmacological mechanism of action of Shensong Yangxin (SSYX) capsule based on different models.

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref
1	Guinea-pig ventricular cells, rats' ventricular cells, HEK293 cell: cardiac arrhythmia model	↓: L-type calcium channel current (I(Ca-L)), sodium channel current(I_(Na)), potassium channel current(I_(K))	–	Reduce the depolarization amplitude of myocardial cells	[52]
2	Guinea-pig ventricular cells: cardiac arrhythmia model	↓: I(Ca-L), I_(Na)	–	Cardiac ion channel	[53]
3	Guinea-pig ventricular cells, rats' ventricular cells: cardiac arrhythmia model	↓: IK1, Ito, I_(K)	–	Cardiac ion channel	[72]
4	Chinese miniature pig: cardiac arrhythmia model	↑: Sr; ↓: SNRT, SACT, Pr	–	Myocardial electrophysiology	[77]
5	SD rats: ventricular remodelling model	–	–	Cardiac remodelling; Cardiac fibrosis	[86]
6	HEK293 cell: cardiac arrhythmia model	–	–	Myocardial AP	[76]
7	SD rats: ventricular remodelling model	–	–	Cardiac remodelling	[81]
8	Rabbit: cardiac arrhythmia model	↑: APD; ↓: TDR	–	Myocardial AP	[79]
9	SD rats	↓: I(Ca-L), Ito	–	Myocardial electrophysiology	[59]
10	Japanese Large-Ear Rabbit: myocardial infarct model	↑: MAPD_ (90); ↓: ERP	–	Myocardial electrophysiology	[82]
11	SD rats	↓: I(Ca-L), Ito	–	Cardiac ion channel	[60]
12	SD rats: diabetes model	↑: SOD, GSH-Px; ↓: Cav1.2, TNF-α, IL-6, MDA	–	Cardiac remodelling; Cardiac fibrosis	[103]
13	New Zealand Rabbit: myocardial infarct model	↑: CX43, NCX, RYR2	–	Cardiac ion channel	[94]
14	SD rats: myocardial infarct model, depression model	↓: NR1	–	Myocardial electrophysiology	[127]
15	Japanese Large-Ear Rabbit: myocardial infarct model	↑: SERCA2ATPase, RYR2, PLB, NCX1, VEGF, CX43; ↓: TGF-β, MMP-2	–	Cardiac remodelling; Cardiac fibrosis	[92]
16	SD rats: cardiac arrhythmia model	↓: I(Ca-L), Ito	–	Cardiac ion channel	[61]
17	SD rats: diabetes model	↑: Cx40	–	Cardiac fibrosis	[95]
18	Spontaneously hypertensive rats	↑: Cx43, MMP-2	–	Cardiac fibrosis	[93]
19	Patients with arrhythmia after coronary intervention surgery	↓: hs-CRP, TNF-α, IL-6	–	Myocardial inflammation	[106]
20	Patients with coronary heart disease and arrhythmia	↓: CRP, VEGF, BNP	–	Myocardial inflammation	[105]
21	Patients with coronary heart disease and arrhythmia	↓: MMP-2, hs-CRP	–	Myocardial inflammation	[104]
22	HEK293 cell: cardiac arrhythmia model	↓: The incidence and frequency of spontaneous calcium release	–	Cardiac ion channel	[58]
23	Patients with chronic heart failure and arrhythmia in coronary heart disease	↓: MMP-2, hs-CRP	–	Myocardial inflammation; Vascular endothelial cell function	[123]
24	VA patients	↓: β1-AAB	–	Myocardial inflammation	[125]
25	ACS patients with arrhythmia	↓: TNF-α, IL-1β, hs-CRP	–	Myocardial inflammation; Vascular endothelial function	[147]
26	Elderly patients with coronary heart disease and arrhythmia	↓: TC, TG, LDL-C	–	Vascular endothelial function	[148]
27	Ventricular myocytes	↓: I(Ca-L), I_(Na)	–	Cardiac ion channel	[53]
28	Human induced pluripotent stem cell-derived cardiomyocytes	↓: I(Ca-L)	–	Myocardial electrophysiology	[62]
29	Rabbit pulmonary vein cardiomyocytes	↓: $I_{(Ca-L)}$, IK1, Ito	–	Cardiac ion channel	[63]
30	Rats: cardiac arrhythmia model	↓: Ca^{2+} overload	–	Myocardial electrophysiology; Myocardial AP	[57]

Notes: ↑: Increased/activated/up-regulated by SSYX at the level of gene and/or protein expression, or enzyme activity content; ↓: Decreased/inhibited/down-regulated by SSYX at the level of gene and/or protein expression, or enzyme activity, or active substance content. SSYX, Shensong Yangxin capsule; HEK293 cell, human embryonic kidney 293 cells; SD rats, Sprague Dawley rats; VA, ventricular arrhythmias; ACS, acute coronary syndrome; ADP, action potential duration; CHF, chronic heart failure; BNP, brain natriuretic peptide; Cav1.2, cardiac L-type calcium channel; CRP, C-reactive protein; Cx40, connexin-40; CX43, connexin-43; ERP, effective refractory period; GSH-Px, glutathione peroxidase; hs-CRP, hypersensitive C-reactive protein; IL-1β, interlenkin-1 beta; IL-6, interlenkin-6; I(Ca-L), L-type calcium channel current; I_(Na), sodium channel current; I_(K), potassium channel current; IK1, Inward rectifying potassium channel; Ito, transient outward potassium current; LDL-C, Low-Density Lipoprotein Cholesterol; MAPD, monophasic action potential duration; MDA, malondialdehyde; MMP-2, matrix metalloproteinase-2; NCX, Na^{+}-Ca^{2+} exchanger; NCX1, Na^{+}/Ca^{2+} exchange protein 1; NR1, N-methyl-D-aspartate receptor 1 subunit; PLB, phospholamban; Pr, atrioventricular conduction time; RYR2, ryanodine receptor 2; SACT, sino-atrial conduction time; SERCA2ATPase, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; SNRT, sinus node recovery time; SOD, superoxide dismutase; Sr, sinus rhythm; TDR, transmural dispersion of re-polarisation; TC, total cholesterol; TG, triacylglycerol; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; β1-AAB, β1-adrenoceptor autoantibody.

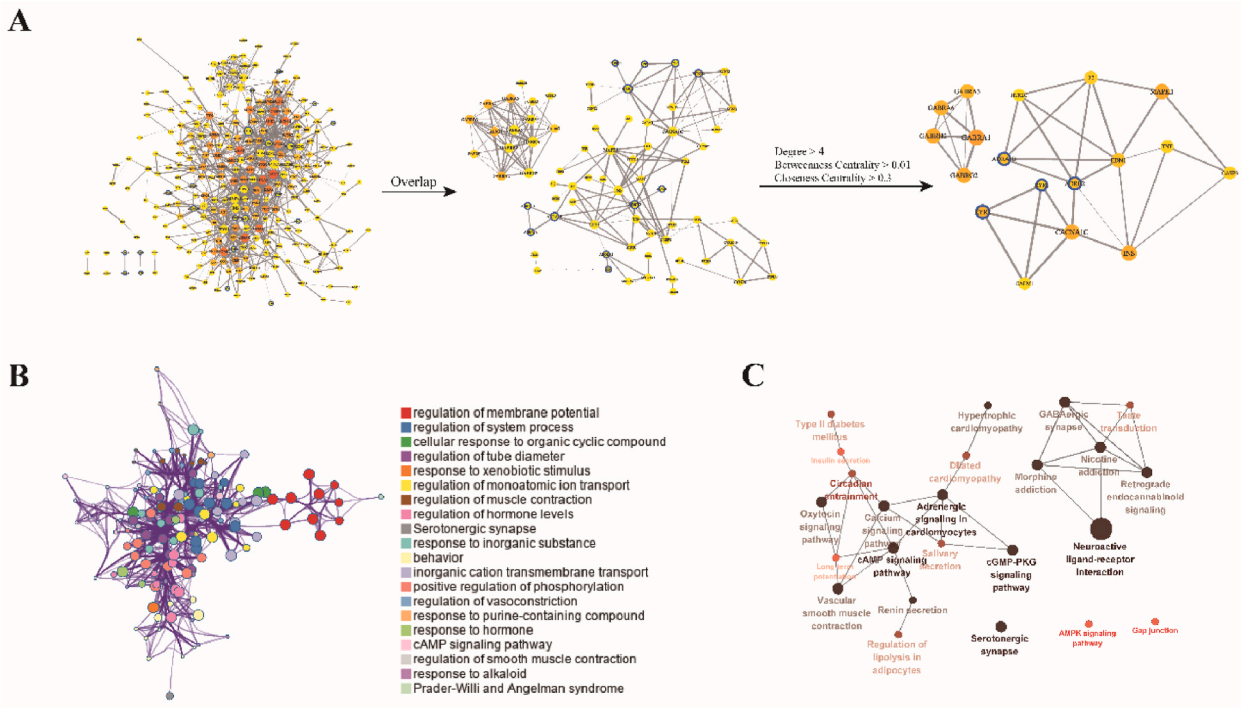

Fig. 3. Arrhythmia protein-protein interaction (PPI) network and mechanism of action of Shensong Yangxin (SSYX) for exerting antiarrhythmic effects. (**A**) PPI network of arrhythmia and key targets for SSYX antiarrhythmic effects. (**B and C**) Enrichment analysis of biological processes and KEGG pathways for targets regulated by SSYX for exerting antiarrhythmic effects.

[133], MalaCards [134], CTD [135], GeneCards, and mined the retreived texts [136]. The Database for Annotation, Visualisation, and Integrated Discovery (DAVID) v6.8 (https://david.abcc.ncifcrf.gov/) was used to standardise gene names [137]. To ensure data reliability, only the genes that appeared in more than three databases were retained as the core gene set for arrhythmia. The genes related to arrhythmia were analysed to identify the functional targets of SSYX for preventing and treating arrhythmia. The target data were then submitted to STRING Version 11.5 (https://cn.string-db.org/) to construct the a protein-protein interaction (PPI) network (confidence 0.7) [138]. The PPI network was visualised using Cytoscape v3.8.1 [139]. A comprehensive target spectrum of SSYX is essential to study its substantive basis and mechanism of action in the treatment of CA. The compounds listed in Table 1 were standardised using the PubChem database, and 65 compounds were obtained for subsequent analysis. We collected targets from DrugBank [140], TTD [141], ChEMBL [142], and PubChem and standardised their names using UniProt [143–145]. To probe the role of the key active compounds of SSYX and their target proteins in the treatment of the HF parameter of HRV, we collected the literature on SSYX chemical ingredients and their therapeutic targets from the PHARMACODIA database (https://www.pharmacodia.com/). To systematically explore the mechanism of action of SSYX in CA therapy, we performed gene ontology (GO) and KEGG pathway enrichment analyses using Metascape (https://metascape.org) and the ClueGO plugin in Cytoscape [146].

Based on the pathogenic genes reported in the arrhythmia literature and the therapeutic targets of approved drugs, a PPI molecular network of arrhythmia-specific pathogenesis was constructed, and the underlying mechanism was explored. We found 87 protein targets that were regulated by SSYX and selected 18 key targets through network parameters. These included RYR1, RYR2, CALM1, CACNA1C, ADRA1B, ADRB2, MAPK, INS, and END1 (threshold: degree>4, between centrality>0.01, closeness centrality>0.3) (Fig. 3A). The key biological processes regulated by SSYX included regulation of membrane potential, regulation of monoatomic ion transport, regulation of muscle contraction, regulation of hormone levels, Serotonergic synapse response to inorganic substance behavior, inorganic cation transmembrane transport positive, regulation of vasoconstriction, CAMP signaling pathway, and regulation of smooth muscle contraction (Fig. 3B). The neuroactive ligand-receptor interaction, cAMP signaling pathway, circadian entrainment, the cGMP-PKG signaling pathway, adrenergic signaling in cardiomyocytes, and the AMPK signaling pathway are the key signaling pathways regulated by SSYX that exert antiarrhythmic effects (Fig. 3C).

7. Clinical applications of Shensong Yangxin capsule

We conducted searches in databases including PubMed, China Journal Full-Text Database (CNKI), Wanfang Database, VIP Chinese Science and Technology Journal Database (search date: May 2023), as well as other Chinese and English databases. For our searches, we used Chinese terms such as "Shensong Yangxin capsule", "arrhythmia", "mechanism", "clinical efficacy", etc. In English, we used terms such as "Shensong Yangxin capsule", "SSYX", "curative effect", "mechanism". We used subject words combined with free words in these searches. We identified a total of 1646 clinical research articles, of which 1591 were relevant to the treatment of arrhythmias, including tachyarrhythmias such as ventricular premature beat, atrial fibrillation, supraventricular tachycardia, sinus bradycardia, sick sinus syndrome, atrioventricular block, and others. Some of the retrieved studies also investigated arrhythmias in conjunction with conditions like coronary heart diseases, heart failure, myocarditis, and valvular heart disease.

7.1. The effect of shensong yangxin capsule "fast and slow treatment" in the treatment of arrhythmia

7.1.1. Clinical effect of shensong yangxin capsule on tachyarrhythmia

Tachyarrhythmia is an independent factor that influences the development and prognosis of CVD, and it is also one of the common complications of CVD, which includes premature beat, ventricular tachycardia, atrial fibrillation, paroxysmal supraventricular tachycardia, atrial flutter, etc [149]. The etiology of tachyarrhythmia is closely linked to myocardial electrophysiological abnormalities [150]. Currently, the main treatment for tachyarrhythmia is drug therapy; however, most antiarrhythmic drugs cause adverse reactions such as sinus bradycardia after long-term use, and this limits their clinical application to a certain extent [151]. Therefore, the development of a safe and effective anti-tachyarrhythmia drug is crucial for alleviating clinical symptoms and enhancing the quality of life of patients.

SSYX is often used to treat premature ventricular beats and can improve the symptoms of palpitations caused by premature beats. The combination therapy of SSYX with other drugs demonstrates significant therapeutic efficacy in treating tachyarrhythmia associated with diverse conditions, including hypertension, coronary heart disease, and heart failure. Moreover, it has been deemed safe for clinical administration. Presently, the relevant guidelines recommend SSYX for treating premature ventricular beats [152]. In a study conducted by Cao et al., a randomised, double-blind, multi-centre, placebo-controlled trial was carried out in 22 Chinese hospitals. The study included 859 patients with frequent premature ventricular beats but normal heart function, who were randomly assigned to either a non-organic heart disease group or an organic heart disease group (ventricular arrhythmia accompanied by hypertension, coronary heart disease, and other related diseases). After 8 weeks of intervention with SSYX, placebo, and mexiletine, a 24-h Holter electrocardiogram was used to monitor and calculate the number of premature ventricular beats as the main evaluation index. The secondary evaluation criteria consisted of the improvement in clinical symptoms associated with premature ventricular beats and the safety evaluation of SSYX. The results showed that in the non-organic heart disease group, the total effective rates of SSYX and placebo for the treatment of premature ventricular beats were 74.2 % and 28.9 %, respectively. In Comparison to the placebo group, SSYX demonstrated a significant reduction in symptoms associated with premature ventricular beats, such as palpitations, chest tightness, insomnia, fatigue, and night sweats. For the organic heart disease group, the overall response rates for ventricular tachycardia treatment were 65.8 % with SSYX and 50.7 % with mexiletine. In addition, SSYX effectively decreased the frequency and symptoms of supraventricular tachycardia in patients, regardless of the presence of organic heart disease. It is apparent that SSYX has a significant effect on tachyarrhythmia and related symptoms such as premature ventricular beats, ventricular tachycardia, and supraventricular tachycardia [153].

7.1.2. Clinical effect of shensong yangxin capsule on bradycardia

Chronic arrhythmia is a cardiovascular disease characterised by a slow heart rate caused by myocardial conduction dysfunction or autonomic impairment due to various factors. Clinically, a ventricular rate of less than 60 beats/min is the standard, including sinus bradycardia, heart block, sick sinus syndrome, and other diseases. It is frequently associated with organic heart diseases, such as coronary heart disease and chronic heart failure, and is also influenced by these comorbid conditions. Currently, anticholinergic drugs, pacemaker implantation, and cardiac nerve ablation are the main therapeutic methods in modern medicine and have achieved some clinical success [154]. Nevertheless, the current treatment lacks specificity, and oral administration of Western medicine for arrhythmias is often associated with numerous side effects. In addition, the surgical indications for bradycardia are relatively strict, the postoperative complications are more severe, and this is unfavourable for a population with more underlying diseases. Consequently, patient acceptance of surgery for bradycardia is low [155].

To evaluate the efficacy and safety of SSYX in the treatment of chronic arrhythmias, Pu et al. conducted a randomised, double-blind, multi-centre, placebo-controlled study in 11 Chinese hospitals. They randomly divided 219 patients with bradyarrhythmia into an SSYX treatment group (SSYX, four capsules/time, three times/day) and a placebo treatment group (placebo, three times/day) for 4 weeks, with average heart rate, fastest heart rate, and slowest heart rate as the main evaluation indices. Palpitation, shortness of breath, fatigue, chest tightness, insomnia, and night sweats were the secondary therapeutic indices. After 4 weeks of treatment, the clinical symptoms of palpitation, shortness of breath, fatigue, chest tightness, insomnia, and night sweats were significantly improved in the SSYX treatment group. The SSYX treatment group showed a significantly higher overall efficacy (total effective rate of 63.5 %) and better symptom scores compared to the placebo group (total effective rate of 22.1 %). Additionally, no obvious adverse reactions were observed. In terms of improving heart rate, through 24-h Holter ECG monitoring and evaluation, the SSYX treatment group showed an increase in the average ventricular rate of patients by 7.09 beats/min, and the improvement in the fastest and slowest heart rate was significantly higher than that of the control group [156]. In addition, patients with severe sinus bradycardia may experience

sympathetic-vagal balance disruptions. Jin et al. Investigated the effects of SSYX on patients with sinus bradycardia and their cardiac autonomic nervous function. Their findings revealed that SSYX increased heart rate in patients with sinus bradycardia. Additionally, SSYX decreased the HF parameter of HRV and the standard deviation of all NN intervals (SDNN), while increasing the LF parameters of HRV and LF/HF ratio [157]. Therefore, we speculate that SSYX can improve heart rate and symptoms in patients with sinus bradycardia by suppressing vagal tone and increasing sympathetic tone to restore balance in the autonomic nervous system.

7.1.3. Clinical effects of shensong yangxin capsule on "fast and slow treatment and integrated regulation"

Bradycardia syndrome, also referred to as bradycardia-tachycardia syndrome, is a specific pathological sinus syndrome that manifests as sinus bradycardia, sinus arrest, or sinus block combined with supraventricular tachycardia, atrial flutter, or atrial fibrillation. It is a commonly occurring and difficult to treat syndrome using conventional Western medicine [158]. Th e treatment of slow sinus heart rate combined with tachyarrhythmia remains a difficult problem. The usual treatment is to use drugs that inhibit tachyarrhythmia in addition to pacemaker protection. However, for some patients who cannot receive pacemaker therapy or radiofrequency ablation, we consider that there are some contraindications in conventional antiarrhythmic drugs for this group of people, and the option of treatment with Chinese patented medicines is worth exploring.

Recent clinical research has provided evidence that SSYX not only possesses efficacy in treating tachyarrhythmia but also reduces the incidence of various tachyarrhythmias, such as ventricular precontraction, atrial precontraction, atrial tachycardia, atrial flutter, and junctional rhythm in patients with chronic arrhythmias. This effect observed in conjunction with an increase in the 24 h average heart rate measured by Holter electrocardiogram recordings. Zhang et al. confirmed the clinical efficacy of SSYX in the treatment of sinus bradycardia accompanied by premature ventricular beats through a multi-centre, randomised, double-blind, placebo-controlled clinical trial. A total of 333 patients with frequent symptomatic premature ventricular beats and sinus bradycardia were randomly assigned to the SSYX treatment or placebo group. Following an 8 weeks treatment period, the SSYX group exhibited notable improvements in terms of maximum heart rate, average heart rate, and total stroke count as measured by the Holter electrocardiogram recordings. The average heart rate increased significantly by 10.9 % in the SSYX group, compared to a 4.7 % increase in the placebo group. In terms of regulating premature ventricular beats, SSYX reduced the premature ventricular beats load by 68.2 %, and this was statistically significant, compared to 32.2 % in the placebo group [159]. In addition, Yang et al. collected research articles related to randomised controlled trials of SSYX in the treatment of chronic arrhythmias combined with premature arrhythmias for a meta-analysis, where the key indicators reflecting SSYX clinical efficacy for bradycardia therapy included the average heart rate, bradycardia response rate, and clinical response rate. A total of nine studies involving 706 patients were included in this meta-analysis: SSYX significantly increased the mean heart rate of patients with bradycardia complicated with premature ventricular beats and the effective rate of premature ventricular beats, bradycardia, and the clinical response rate were significantly improved while no significant adverse reactions were observed [160].

7.2. Clinical studies involving shensong yangxin capsule for the treatment of premature ventricular beats complicated by abnormal heart function

Premature ventricular beats are the most frequently encountered arrhythmia in clinical practice. When heart failure is accompanied by premature ventricular beats, it exacerbates haemodynamic disturbances, deteriorates patient conditions, and raises mortality rates. Premature ventricular beats and heart failure can interact to create a vicious cycle. Currently, most antiarrhythmic drugs used to treat premature ventricular beats negatively affect cardiac function and increase mortality. Non-drug therapies, such as implantable radiofrequency catheter ablation and cardiac resynchronisation, have been widely used in the clinical treatment of premature ventricular beats complicated by cardiac dysfunction. However, a considerable number of patients cannot obtain effective intervention. Therefore, it is particularly important and urgent to identify alternative drugs for the treatment of chronic heart failure complicated by premature ventricular beats.

Wang et al. conducted a randomised, double-blind, placebo-controlled, multi-centre study involving 465 patients with chronic heart failure and frequent premature ventricular beats who were randomly assigned to the SSYX (n = 232) and placebo (n = 233) groups for 12 weeks. The number of premature ventricular beats monitored by employing a 24 h Holter electrocardiogram was designated as the primary therapeutic index. The left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter, N-terminal brain natriuretic peptide (NT-proBNP) level, New York Heart Association (NYHA) grade, 6-min walking distance (6 MWD), Minnesota Heart Failure Life Questionnaire (MLHFQ) score, and complex cardiac events (CCEs) were used as secondary therapeutic indices. The results showed that the total number of premature ventricular beats induced by SSYX was significantly lower than that in the placebo group, with a decreasing trend in monomorphic, polymorphic, multifocal, paired, dizymoid, and trinomial premature ventricular beats. Among the secondary outcome measures, SSYX treatment improved NYHA grade and increased LVEF. SSYX also helped to reduce plasma NT-proBNP levels and improve 6 MWD and quality of life scores. All data showed that SSYX performed better than the placebo, with no significant adverse effects. Therefore, SSYX inhibited premature ventricular beats and improved cardiac function [161].

7.3. Clinical effects of shensong yangxin capsule in the treatment of other cardiovascular diseases

Liu et al. used the Cochrane systematic evaluation method to conduct a systematic review of randomised controlled trials using SSYX for the treatment of cardiac neurosis. In this study, it was found that SSYX could improve the clinical symptoms of chest tightness, shortness of breath, insomnia, and irritability in patients with cardiac neurosis and reduce the number of premature ventricular beats

measured via Holter electrocardiography monitoring. Its overall effectiveness was found to be superior to conventional Western medicine [162]. Liu et al. compared and observed the efficacy of SSYX treatment and Western medicine control groups, such as ribavirin, Coenzyme Q10, and vitamin C, in the treatment of viral myocarditis using a random plus extended control method. This study found that the improvements in chest tightness, shortness of breath, fatigue, and spontaneous sweating symptoms in the SSYX treatment group were greater than those in the control group. Moreover, it significantly improved AST, LDH, CPK, and CPK-MB levels, indicating that SSYX has a significant effect on viral myocarditis [163]. Li et al. found that SSYX combined with edaravone significantly improved the efficacy of cerebrovascular diseases complicated by cerebrocardiac syndrome, improved the levels of norepinephrine, epinephrine, dopamine, serum malondialdehyde, and superoxide dismutase, and did not increase the incidence of adverse reactions [164]. In addition, SSYX has also been reported to improve the efficacy of menopausal depression [165], perimenopausal syndrome [166], insomnia, and hypotensive vertigo [167–169].

7.4. Safety evaluation of shensong yangxin capsule in clinical applications

In a basic science study [170], an acute toxicity test demonstrated that the maximum tolerated dose of oral SSYX in mice was 129.6 g of crude drug per kg of body weight that was 524 times that in clinical patients. Futhermore, a 3-month experimental toxicity study revealed that SSYX did not have significant effects on 10 biochemical indicators, including body weight, food intake, electrocardiogram, blood image, liver and kidney function, and did not result in any histologically pathological changes in organs. Huang et al. conducted large-scale randomized controlled evidence-based clinical studies on coronary heart disease, arrhythmia, and chronic heart dysfunction. Studies have demonstrated that, compared with other antiarrhythmic Chinese patented drugs, SSYX has fewer clinical side effects in the treatment of various CVDs, such as occasional dizziness, rash, and abdominal distension [171–173]. Compared with Western antiarrhythmic drugs, a meta-analysis of the safety of SSYX in the treatment of arrhythmias found that the incidence of SSYX-induced arrhythmia was significantly lower than that of amiodarone and arrhythapine, suggesting that SSYX offers the advantages of multi-target therapy and superior safety over current conventional antiarrhythmic drugs.

8. Conclusions

The clinical effect of traditional antiarrhythmic single-ion channel blocking drugs is often not ideal, while multi-ion channel blocking drugs can reduce the electrical dispersion of the myocardium to a certain extent; however, significant side effects are commonly observed with long-term use. SSYX can paly a crucial role in the treatment of arrhythmias, both at the level of symptoms and root causes by the application of the TCM principle of “multiple links-multiple targets to inhibit the occurrence of arrhythmias and improve patient prognosis. The clinical effect of treating arrhythmias with SSYX is positive, with fewer side effects. Clinical studies have proven that SSYX can treat tachyarrhythmia, premature ventricular beats, and paroxysmal atrial fibrillation as well as improve the ventricular rate of chronic arrhythmia and has a measurable clinical effect. Furthermore, SSYX has unique advantages over Western drugs in clinical studies of the treatment of cardiac dysfunction combined with premature ventricular dysfunction. Mechanistic studies have shown that SSYX can inhibit multiple ion channels such as Na^{+}, Ca^{2+}, and K^{+} channels, and has a broad-spectrum antiarrhythmic effect. In addition, SSYX can improve SA node function and cardiac conduction by improving SA node conduction and shortening the APD. Simultaneously, it exhibits various effects such as inhibition of myocardial fibrosis, regulation of cardiac autonomic nervous function, attenuation of myocardial inflammatory response, improvement of mitochondrial energy metabolism, enhancement in microvascular endothelial function, promotion of angiogenesis and modulation of non-ion channel mechanisms. These collectively contribute to a novel therapeutic strategy of "fast and slow treatment with integrated regulation" for managing arrhythmias. This further realises the transformation of the therapeutic thinking concept from "resisting law" to "regulating law". However, arrhythmia is a pathological process involving multi-factor interactions, and its mechanism has not been fully elucidated.

SSYX, a TCM formulation, is utilized for treating arrhythmia. However, further research is needed to investigate the material basis and mechanism of action underlying its pleiotropic activity. Network pharmacology provides the possibility to reveal the mechanism of action characteristics of SSYX in the treatment of arrhythmia and other heart diseases through "multi-component, multi-target and multi-pathway" approaches at the system level [128]. In this study, we inferred that the key targets of its therapeutic effects, including RYR1, RYR2, CALM1, CACNA1C, ADRA1B, ADRB2, MAPK, INS, and END1, are worthy of investigation in subsequent studies. Therefore, further expansion of the research field is required to conduct in-depth theoretical studies, aiming to elucidate the pharmacodynamic basis, including the multi-component, multi-target, multi-pathway effects,as well as the underlying interaction mechanisms of SSYX *in vivo*. Concomitantly, based on multi-centre, large-sample, randomised controlled clinical studies that have been carried out in accordance with evidence-based medicine, the overall therapeutic effects of SSYX on CVDs, especially arrhythmia, need to be explored further.

Funding

This research was supported by the National Key Research and Development Program (Grant Number: 2017YFC1700500), the National Natural Science Foundation of China (Grant Number: 81973692) and the Scientific Research Project of Hebei Provincial Administration of Traditional Chinese Medicine (Grant Number: 2022216).

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this paper is a review article. Ethics committees and Informed consent are not involved.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Xuan Lu: Writing – original draft, Software, Methodology, Data curation. **Tongxing Wang:** Writing – original draft, Software, Methodology, Data curation. **Bin Hou:** Writing – original draft, Software, Methodology, Data curation. **Ningxin Han:** Visualization, Investigation. **Hongrong Li:** Visualization, Investigation. **Xiaoqi Wang:** Visualization, Investigation. **Jingjing Xin:** Visualization, Investigation. **Yanling He:** Visualization, Investigation. **Dan Zhang:** Visualization, Investigation. **Zhenhua Jia:** Writing – review & editing, Conceptualization. **Cong Wei:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We wish to extend our thanks to all individuals for their assistance in conducting this study.

Abbreviations

SSYX	Shensong Yangxin capsule
CVD	cardiovascular disease
HRMS	high resolution mass spectrometry
APA	action potential amplitude
AP	action potential
APD	action potential duration
ERP	effective refractory period
Vmax	maximum velocity
SNS	sympathetic nervous system
HCN	hyperpolarisation-activated cyclic nucleotide-gated cation channel
MMPs	matrix metalloproteinases
CX43	connexin 43
CX40	connexin 40
LF	low frequency
HF	high frequency
GLUT-4	glucose transporter-4
AMI	acute myocardial infarction
ECG	Electrocardiograph
SDNN	standard deviation between sinus beats
6 MWD	6-min walking distance
MLHFQ	Minnesota Heart Failure Life Questionnaire
CCEs	complex cardiac events; METS, metabolic syndrome

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