Protective effects of Wenxin Keli against cardiac arrhythmias (Review)

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Abstract. Cardiac arrhythmias represent a significant problem globally. Combined traditional Chinese and Western medicine is being integrated into current therapeutic trials in continued efforts to suppress arrhythmias that are predicted to escalate in the face of increasing life expectancy and medical advances. This review highlights regulatory mechanisms and major target sites of a patented, traditional Chinese drug, Wenxin Keli (WXKL). It describes the roles of individual components of WXKL via multiple pathways in interrupting reentry, reducing automaticity and preventing arrhythmogenic substrates. It further elucidates the effects of WXKL on atrial and ventricular electrophysiology, highlighting its weaker effects on rapid sodium curent (INa), as well as its multi-channel block, apart from atrial selectivity. In addition, the present review article incorporates diverse actions of WXKL in the reduction of reactive oxygen species levels, CX43 regulation, calcium handling, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) modulation and neurohumoral system regulation. Apart from its role in managing angina and heart failure shown in experimental and clinical models, the aforementioned effects enable WXKL to maintain sinus rhythm and prevent cardiac arrhythmias and sudden cardiac death associated with multiple comorbidities. Based on the results from various studies, it has minimal side-effects and is less proarrhythmic with an efficacy that matches that of western drugs. Varying effects of WXKL on multiple ion channels, intercellular conduction, and second messenger and redox systems have opened novel doors in managing arrhythmias.

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1. Introduction

Cardiac arrhythmias pose a significant global burden, resulting in cerebrovascular accidents, myocardial infarction and sudden cardiac death (SCD) (1). The worldwide prevalence of atrial fibrillation (AF), characterized by uncoordinated atrial activation with the consequent deterioration of atrial mechanical function, is 37,574 million cases (0.51% of worldwide population) (2). The prevalence of AF is escalating in middle socio-demographic index countries, and its absolute burden is projected to increase by >60% in 2050, being one of the largest epidemics (2). The prevalence of AF is approximately 0.77% in China, with the mean age of patients being 52.5±22.4 years (3), with a lifetime risk of 1/5 among Chinese adults based on a medical insurance database involving 10 million in Southwest China (4). Premature ventricular contractions (PVCs) manifest from being asymptomatic to the development of cardiomyopathy, heart failure, sustained ventricular tachycardia (VT) or even total mortality. In Europe and North America, 50-100 unexpected SCDs occur per 100,000 population annually, half of these events owing to VT or ventricular fibrillation (VF) (5).

Although classic Western anti-arrhythmics that tend to interact with a specific or single target mostly via inhibition possess potent pharmacologic activity, they portend risks of breaking intracellular stability and have been reported to be arrhythmogenic (6). Consequently, the development of safe and effective regimens remains a major focus of contemporary cardiovascular research. With globalization, an integration of the traditional Chinese and Western medical practices has

begun in multiple medical centers (7). In recent years, network pharmacology is an effective approach which can be used to address the association between multiple TCM components and the synergistic effect of drugs on a series of targets. Modern Chinese herbal medicines manufactured according to traditional theory, play a significant role in the treatment of cardiac arrhythmias (8).

Wenxin Keli (WXKL) is a first-state sanctioned Traditional Chinese Medicine (TCM)-based anti-arrhythmic drug (8). It was officially marketed in 1995 as it received new certification issued by the Ministry of Health of the People's Republic of China (9). In China, it possesses a licensable indication for PVCs, which was incorporated in the 2009 revision of the National Reimbursement Drug List (10). As a sole anti-arrhythmic herbal extract in the 2010 revision of Chinese Pharmacopoeia, almost 5 million Asians are currently being administered WXKL for the treatment of ventricular arrhythmias (11). Wenxin Keli is composed of 5 constituents: *Nardostachys jatamansi* DC (Gansong), *Radix Notoginseng* (Sanqi), Succinum (Hupo), *Polygonatum sibricum* (Huangjing) and *Codonopsis pilosula* (Dangshen) (4,6,12-14). Dangshen, the 'monarch' in the regimen, characterized by a sweet flavor, boosts 'qi' (nutrients), tranquilizes the mind and relieves palpitations. Huangjing, the 'minister' herb, enhances the effects of Dangshen, and also possesses a sweet flavor and fortifies the spleen 'qi' to nourish the heart and lungs. The remaining 3 ingredients are assistant herbs. The bitter-flavored Sanqi removes blood stasis, relieves pain and tonifies the system. Hupo, neutral and sweet, pacifies the liver and tranquilizes the mind. Gansong is warm and sweet, relieves depression and regulates the liver and spleen 'qi'. Its indications include palpitations, dyspnea, fatigue, dizziness, chest tightness and pain, and insomnia to improve the quality of life (9,15).

In a rat model of ischemia-reperfusion (I/R) injury, pre-treatment with WXKL was shown to effectively improve cardiac hemodynamics, accelerate coronary blood flow, enhance myocardial contractility, and reduce the occurrence of arrhythmias (16,17). WXKL reportedly increases coronary blood flow, reduces myocardial oxygen consumption, enhances myocardial compliance, improves myocardial hypoxia tolerance, relieves anterior and posterior cardiac loading, and reduces arrhythmic occurrence (16). The aim of the present review article was to review the effects of WXKL on cardiac electrophysiology and how these can prevent cardiac arrhythmias.

2. Roles of individual components of WXKL

Nardostachys jatamansi DC (Gansong). Nardostachys chinensis batal extract (NcBe) at 10 g/l has been shown to inhibit both peak INa and transient outward potassium current (Ito) in rat ventricular myocytes. These actions were associated with the suppression of acetylcholine-induced AF or atrial flutter, likely by reducing both triggered activity and reentry (18,19). Additionally, it has been shown to inhibit L-type calcium currents (ICaL) and shift the current-voltage association upward without changing its activation or reversal potential (9). Calaxin, one of its components, has been predicted to be a CaV1.2 channel blocker (6). The dried roots of NcBe contain sesquiterpenoids, which can lower the incidence of ventricular arrhythmias and improve Cx43 redistribution in rats with hyper-acute myocardial infarction (MI) (20). This is probably due to the lowering of the heterogeneity of conduction (21). Moreover, NcBe contains valerian ketones that can reduce myocardial cell automaticity, extend the atrial action potential (AP) of the conduction system time and interrupt reentry (15). The volatile oil of *Nardostachys* can inhibit oxidative stress-induced cell death via reactive oxygen species scavenging and Akt activation in H9c2 cardiomyocytes (22). Since increased oxidative stress is associated with arrhythmogenesis, this may act to suppress arrhythmias (1). Nardosinone, one of the major extracts from Nardostachys, has been shown to prevent angiotensin II (AngII)-induced cardiac hypertrophy in embryonic rat hearts, particularly at a concentration of $\geq$100 μmol/l by inhibiting the phosphatidylinositol 3-kinase (PI3K)/Akt and MEK/ERK pathways (23).

Radix Notoginseng (Sanqi). Notoginseng has been reported to antagonize Na^+/K^+-ATPase activity (24) and the effect of acetylcholine on various human organs (18). This may reduce sinus node and ectopic pacemaker activity, and improve microcirculation (15). It exerts multiple cardio-protective effects, including pro-angiogenesis, anti-apoptotic, inflammatory cascade repression and endothelium-dependent vasodilation (22). It protects hypoxia-reoxygenation induced H9c2 cardiomyocyte injury at the dose of 25 μg/ml associated with apoptosis via the phosphatidylinositol 3-kinase (PI3K)/AKT and mitogen-activated protein kinases (MAPKs) pathways (25). Pre-treatment with ginsenoside, an active ingredient of *Notoginseng*, has been shown to protect rat cardiomyocytes from oxidative injury by the expression of respiratory chain complexes via the RhoA/ROCK signaling pathway (26) and through an increase in the activity of endogenous antioxidants and suppression of intracellular Ca^{2+} (27). According to a systematic review and meta-analysis of 18 randomized controlled trials (RCTs), *Notoginseng* was shown to reduce cardiovascular events, such as acute myocardial infarction (AMI), severe arrhythmia, heart failure and intractable angina pectoris (28). Through the integration of the gene interaction network, the role of *Notoginseng* in the treatment of coronary heart disease has been shown to involve the cytokine-cytokine receptor interaction pathway (29). It has also been shown to mitigate aging-induced cardiomyocyte apoptosis possibly by increasing oxidative stress, and mitochondrial function-related signaling pathways, such as the manganese superoxide dismutase (MnSOD) signaling pathway, and mitochondrial-related signaling molecules, such as peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, light chain (LC)3β and Beclin-1 (30).

Succinum (Hupo). No effect of succinum on cardiac physiology has been found to date, at least to the best of our knowledge.

Polygonatum sibiricum (Huangjing). Polygonatum sibiricum exhibits lipid-lowering and anti-atherosclerotic effects and tends to reduce blood pressure (15,20). Apart from increasing Na^+-K^+-ATP and Ca^{2+}-ATP activity in mouse brain cells, Huanjing enhances anti-aging effects by reducing lipid peroxide and B-type monoamine oxidase levels. Its anti-atherosclerotic effect may be associated with the reduction of foam cells and hypolipidemic activity (31). In addition, its protective effects
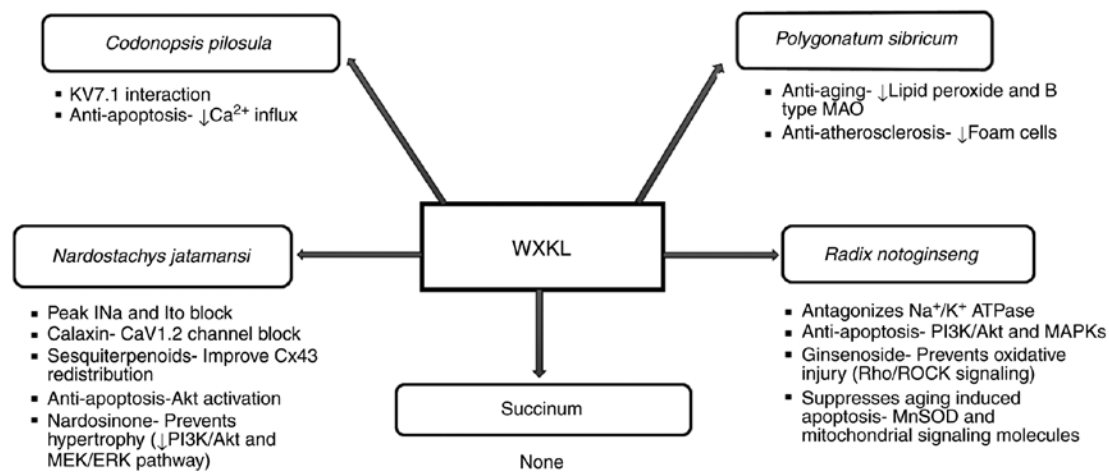
Figure 1. Diverse roles of individual components of Wenxin Keli. AKT, protein kinase B; CaV1.2, L-type voltage-dependent calcium channel 1.2; ERK, extracellular regulated protein kinases; INa, fast sodium curent; Ito, transient outward potassium current; KV7.1, voltage-activated K^+ channel 7.1; MAO, monoamine oxidase; MAPKs, mitogen-activated protein kinases; MEK, mitogen extracellular signal-regulated kinase; Mn-SOD, manganese superoxide dismutase; PI3K, phosphatidylinositol 3-kinase; Rho/ROCK, ras homolog gene/a Rho-associated coiled coil-forming proyein kinase; WXKL, Wenxin Keli.

on adriamycin-induced acute heart failure in rats may be related to its anti-inflammatory effects and to the inhibition of cardiomyocyte apoptosis (32).

Codonopsis pilosula (Dangshen). The component codonopsine is predicted to interact with KV7.1 that is significant in cardiac repolarization phases 2 and 3 (6). It contains inulin and amino acids, and exerts anti-platelet aggregation and enhances immunity (15). It attenuates calcium influx and apoptosis induced by angiotensin II in H9c2 cardiomyoblasts (22). It has been reported to induce phosphodiesterase inhibition, leading to an increase in cAMP levels in rat myocytes (24). *Codonopsis* has been shown to reverse the AngII plus Leu27 insulin growth factor II (IGFII)-induced caspase-3 activity and the apoptosis of H9c2 cardiomyoblasts (33) by reducing Ca^{2+} influx and mitochondrial outer membrane permeability (34) (Fig. 1).

3. Effects of WXKL on atrial electrophysiology

Sodium channel. The major atrial-ventricular Na channel disparities are a more negative atrial INa steady-state inactivation and a slower recovery from inactivation (35). Peak INa is responsible for phase 0 of the action potential. The density of peak INa is significantly greater in atria than in ventricles, highest in Purkinje cells (36).

The anti-AF effects of peak INa blockers are due largely to the rate-dependent reduction of excitability, the prolongation of the effective refractory period (ERP), and to the conduction block in a critical part of reentrant circuit. The reduction of peak INa can also significantly decrease intracellular sodium (Nai) and, thus, intracellular calcium (Cai), which may suppress Cai-mediated triggered activity (37). Severe structural remodeling, resulting in a small number of connections between the subendocardial and subepicardial layers of the atria, can prevent termination of AF by Na-channel block (38).

While the atrial selectivity of other INa blockers encompasses a preferential prolongation of action potential duration (APD), WXKL at 5 g/l abbreviates APD_{90} predominantly in the atria (18). It shifts the steady-state availability to more negative

potentials in atrial than in ventricular cells in a dose-dependent manner (39). Such differing atrial and ventricular effects may possibly be due to different ratios of alpha and beta subunits. WXKL binds to the inactivated state of peak I_{Na} and dissociates rapidly (39). Following ganglionated plexi (GP) ablation, it has been shown to significantly attenuate the levels of atrial natriuretic peptide (ANP), tumor necrosis factor (TNF)-α and interleukin (IL)-6 within 10 weeks of oral administration at 0.25 g/kg/day, suggesting its anti-inflammatory effects (40).

The combination of 18 g 3 times daily of WXKL and amiodarone has been shown to be safe and superior to amiodarone monotherapy in the chemical conversion of recent-onset AF, exhibiting a markedly shortened time in sinus rhythm restoration (41). In another study, the same dose of WXKL and 80 mg sotalol twice a day was shown to exhibit a similar efficacy to assist sinus rhythm reversion from hyperthyroidism-caused paroxysmal atrial fibrillation (PAF) (42).

4. Effects of WXKL on ventricular electrophysiology

Sodium channel. Late sodium channel (INaL) maintains phases 2 and 3 of cardiac AP. The rate-dependent reduction of INaL contributes to rate-dependent APD abbreviation (43). The contribution of INaL is more significant during prolonged APD and bradycardia. VT/VF most commonly occur under the conditions of prolonged APD (44). The INaL inactivation occurs in several hundreds of milliseconds and persists throughout the AP plateau.

INaL suppresses VAs by reduction of repolarization heterogeneity and intracellular Ca2+ secondary to the decrease of late INa mediated Nai (37). Increased intracellular Ca2+ alters repolarization such as T wave alternans and causes DADs (45). Its distribution is spatially heterogeneous in the ventricles (46). INaL blockers such as ranolazine effectively prevent or shorten rapid activation-induced VT and VF in non-diseased ventricles (47).

In addition to its atrial selectivity, 5 g/l WXKL has only a mild effect in reducing ventricular rapid INa. It binds very rapidly to the inactivated sodium channel and dissociates

rapidly from the closed state (39). WXKL suppresses ventricular early afterdepolarizations (EADs), delayed afterdepolarizations (DADs) and triggered activities (TAs) by the selective inhibition of late INa. The IC50 of the late INa by WXKL was approximately 3-fold higher than that of the rapid INa in the rabbit left ventricle. In addition, its weaker influence on rapid INa with little use-dependence unlike classic INa blockers renders it less proarrhythmic (48). WXKL at both 1 and 5 g/l exhibits anti-arrhythmic effects on Purkinje cells of rabbit hearts via INaL inhibition by the shortening of APD and attenuating ATX-II and ISO-induced EADs and DADs. The average magnitude of INaL in these cells exceeded by 3-fold compared to that in ventricular cells (12).

Potassium channel. Ito is the transient outward current resulting from K$^+$ efflux. It is a key regulator of phase one action potential repolarization. Ito varies in early-onset lone AF, Brugada syndrome and idiopathic VF (49). It is regulated by cold-inducible RNA-binding protein (50). Computational modeling predicts that in human ventricle, small decreases in Ito slightly increase APD, while large increases can shunt the AP and cause rapid repolarization (51).

The majority of SCD occurrences in patients with heart failure (HF) is likely secondary to VAs. Heart failure with preserved ejection fraction (HFpEF) increases the inducibility of VA as a result of delayed repolarization and multiple reentry circuits demonstrated by prolonged repolarization and Ito downregulation, contributing to arrhythmogenesis (52).

WXKL at the dose of 8 g/kg daily has been shown to prevent VAs *in vivo* following the long-term administration in a rat model of MI associated with inhibition of ICaL and Ito. It accelerates Ito inactivation without changing the activation process or the recovery of its inactivation (8). The mutual mechanism in HF and arrhythmia includes inflammation, oxidative stress and microRNA regulation. Based on a systematic review and meta-analysis on 13 studies published in Chinese, WXKL plus amiodarone combination group was shown to be superior in total effective rate, heart function and reduction in PVCs compared to amiodarone alone. WXKL downregulates genes associated with inflammation, neurohumoral system and apoptosis (53,54).

When combined with a low concentration of 5 μM quinidine, WXKL at 5 g/l inhibits Ito from epicardial and endocardial sites of coronary-perfused canine right ventricular wedge preparations in a dose-dependent manner (24). Consequently, it suppresses the substrate and trigger for VT/VF in experimental models of Brugada Syndrome (55,56).

5. Reactive oxygen species (ROS) reduction

Oxidative stress leads to repolarization and conduction abnormalities, eventually resulting in cardiac arrhythmias (57). ROS abundance increases cardiac fibrosis and hypertrophy and reduces inotropy. Defective antioxidant mechanisms in the diabetic heart (58) are mitochondrial electron leakage, NADPH oxidase and protein kinase C (PKC) activation, nitric oxide synthase uncoupling (59) and a common upstream pathway involving interaction of advanced glycation end-products (AGEs) with their receptor (RAGE) to further promote ROS synthesis (60). The mitochondrial translocator protein (TSPO)

links mitochondrial instability to lethal arrhythmias through ROS-induced ROS release (RIRR) (58).

Increased ROS production also activates the unfolded protein response (UPR) that accordingly reduces ion channel functionality and creates repolarization abnormalities (1). It decreases Cx43 protein levels in the cell and perturbs gap junction conduction, resulting in dysrhythmias and SCD. Additionally, intracellular Ca2$^+$ homeostasis alters and causes fibrosis (61).

WXKL at at a dose of 3 g/kg has been shown to improve intracellular mitochondrial membrane potential and oxygen consumption in primary atrial fibroblasts by reducing ROS in diabetic rats (62). WXKL has been shown to lead to a recovery of the level of malondialdehyde (MDA), the final product of lipid peroxidation, and superoxide dismutase (SOD) in rats/rabbits subjected to I/R (63). WXKL also improves the secretions of taurine and ketone bodies to overcome I/R-induced oxidative stress (17).

6. Gap junction modulation

Gap junction proteins, connexins, mediate action potential propagation between cells, coordinate mechanical and electrical activity of heart muscle, and ensure simultaneous cardiac electro-mechanical activity. The age-related down-regulation of atrial Cx43 can facilitate the development of AF in old guinea pig hearts (64) and cause interstitial fibrosis and collagen deposition (65). In a canine model of sympathetic AF, the low expression of Cx43 was shown to be involved in AF by influencing inter-cellular channel conduction (66). Cx43 remodeling is associated with atrial denervation following epicardial GP ablation and this is ameliorated by WXKL (40) (Table I).

Cx43 is the primary gap junction protein that is highly expressed within mammalian ventricular muscle at the intercalated disk. A potential shift in its composition in the ventricular conduction system may contribute to VAs in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) (67). Following MI, 2.7 g/kg WXKL has been shown to protect the ultrastructure of gap junctions within the intercalated disk, alleviate CX43 phosphorylation, increase PKC and miRNA-1 levels, and increase the VF threshold (22) (Table II).

7. Calcium handling

Ca^{2+} plays a key role in the excitation-contraction coupling and the activation of Ca^{2+}-dependent signaling pathways. APD prolongation as a result of cardiac hypertrophy may increase the Ca^{2+} entry via ICaL during the long plateau phase resulting in spontaneous sarcoplasmic reticulum (SR) Ca^{2+} release (68).

WXKL has been shown to block ICaL reversibly in a dose-dependent manner at 5 g/l in rabbit ventricular myocytes, in rats with transverse aortic constriction (TAC)-induced heart failure (19) and in an experimental model of Brugada syndrome (24), by causing shift of ICaL activation towards negative potentials (6). In the TAC rat model of heart failure, WXKL was shown to reduce ICaL by facilitating the steady-state inactivation and retarding its recovery (19). In cardiac myocytes from rats with MI, WXKL at 4 g/kg/day was shown to significantly increase both the SR Ca^{2+} content and the calcium transient amplitude (69). WXKL inhibits hypoxia and the hypoxia/reoxygenation-induced increase in diastolic [Ca^{2+}]$_i$ and the decrease in

Table I. Mechanisms of action of WXKL in atrial arrhythmias.

Factors	Author/(Refs.)	Model	Study characteristics	Mechanisms of action of WXKL
Peak I_{Na}	Burashnikov et al (18)	Canine right atrial preparation	Ach-induced AF	Atrial selective ERP prolongation; Increase in DTE I_{na} block; AF prevention
Mitochondrial oxidative stress	Gong et al (62)	Sprague-Dawley rats	H_2O_2 induced oxidative stress and diabetic hearts	Regulation of mitochondrial function; Reduction of mitochondrial ROS
Gap junction	Xiao et al (40)	Mongrel dogs	AF induced after epicardial GP ablation	Inhibited Cx43 remodeling; Attenuated ANP, IL-6 and TNF-α levels

I_{Na}, sodium channel; Ach, acetylcholine; AF, atrial fibrillation; ERP, effective refractory period; DTE, diastolic threshold of excitability; GP, ganglionic plexi; ANP, atrial natriuretic peptide; IL-6, interleukin-6; TNF-α, tumor necrosis factor α; H_2O_2, hydrogen peroxide; ROS, reactive oxygen species.

$\Delta[Ca^{2+}]_i$. The effect of WXKL on ICaL may be attributed to its suppressive effect on $[Ca^{2+}]_i$ transients (70). WXKL reduces the transmural dispersion of repolarization and ameliorates calcium mishandling by reducing $[Ca^{2+}]_i$ overload among Purkinje cells and in hypoxic/reoxygenated cardiomyocytes at 3 g/l in the treatment of ventricular arrhythmias (12,70). A decrease in both the expression of CaMKII and its phosphorylation at Thr-286 may be the primary mechanism through which WXKL inhibits heart failure and arrhythmia (69).

8. CaMKII signaling

CaMKII regulates SR Ca release and Ca reuptake (71). It is an upstream regulator of INaL in cardiac myocytes. The CaMKII-dependent phosphorylation of ICaL attenuates its inactivation, increasing the ICaL window current that plays a major role in the generation of EADs (72). Excess CaMKII activity due to HF results in enhanced sympathetic excitation and hyperphosphorylation of the ryanodine receptor (RyR), sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and phospholamban (PLB) proteins, which predisposes the cardiac myocytes to afterdepolarizations.

WXKL at 4 g/kg/day has been shown to significantly reduce the expression of CaMKII, p-CaMKII (Thr-286) and PLB, and to increase the expression of RyR2 and FKBP12.6 in rats with MI, to inhibit arrhythmia (69). In rats with TAC, the beneficial effects of WXKL and KN93, a pharmacologic tool used to inhibit CaMKII, is attributed to the shortening of APD90 and regulation of the CaMK II signal transduction pathway, markedly decreasing the degree of collagen deposition and improving fibrosis and hypertrophy (14).

9. Autonomic nervous system regulation

Shortened ventricular ER potential, APD, fibrillation threshold, and triggered EAD and DAD by a high sympathetic tone increase the risk of VAs (73). In canine models, the denervated myocardium becomes hypersensitive to norepinephrine indicated by the supersensitive shortening of ERP (74). In patients with long QT syndrome (LQTS), VAs are triggered following a sympathetic burst from either emotional stress or exercise. Experimentally, sympathetic stimulation induces changes in ECG repolarization and the reduction of the fibrillation threshold (75). The ischemic and infarcted myocardium becomes a substrate sensitive to arrhythmia triggers due to the heterogeneity of the sympathetic nervous system innervation contributed by nerve sprouting (76).

Parasympathetic activation, on the other hand, is considered to be anti-arrhythmogenic (77). In rodents, 100% VF episodes were shown to be terminated with vagal nerve stimulation and the efficacy was reduced in the presence of atropine (78,79). The majority of episodes of VF in patients with Brugada syndrome are observed during periods of high vagal tone, such as at rest, during sleep, or from 12 to 6 a.m. (80,81).

The positive inotropic effect exerted by WXKL in right ventricular wedge preparation is likely due principally to an increase in ICaL secondary to the release of catecholamines. The boost in ICaL also contributes to restoration of the action potential dome and suppression of phase 2 reentry and pVT. WK increases ICaL via indirect adrenergic stimulation (24).

Table II. Mechanisms of action of WXKL in ventricular arrhythmias.

Factors	Author/(Refs.)	Model	Study characteristics	Mechanisms of action of WXKL
Ion channels				
INaL	Xue et al (48)	Rabbit LV myocytes	Triggered VAs	Selective INaL block / Reduction of QT and Tp-e prolongation (1-3 mg/ml) / Suppression of EADs and DADs
	Hou et al (12)	Rabbit hearts	ATX-II and ISO induced arrhythmias in Purkinje cells	APD shortening / Suppression of EADs, DADs and TAs / Selective INaL block
	Wang et al (8)	Rats in vivo	Ischemia induced VAs	Reduced VT+VF episodes / ICaL and Ito block
Ito	Minoura et al (24)	Canine RV wedge preparation	Experimental model of Brugada syndrome	Suppression of phase 2 reentry and polymorphic VT / Ito and ICaL block
ICaL	Chen et al (76)	Male rats	TAC-induced heart failure	APD shortening / ICaL reduction by accelerating inactivation
	Minoura et al (24)	Canine RV wedge preparation	Experimental model of Brugada syndrome	Suppression of phase 2 reentry and polymorphic VT / ICaL and Ito block
	Wang et al (6)	Hartley guinea pigs	Quinidine induced arrhythmia	Alleviates prolonged QT interval / Cav1.2 channel block
	Xing et al (69)	Sprague-Dawley rats	MI induced arrhythmia	Increased SR Ca2+ content and calcium transient amplitude
	Luo et al (70)	Rabbit ventricular myocytes	Hypoxia/reoxygenation induced Ca2+ overload	Attenuation of Ca2+ overload / APD shortening
	Hou et al (12)	Rabbit hearts	ATX-II and ISO induced arrhythmias in Purkinje cells	APD shortening / Mild reduction of ICaL
	Wang et al (8)	Rats in vivo	Ischemia induced VAs	Reduced VT + VF episodes / ICaL and Ito block
CaMKII	Xing et al (69)	Sprague-Dawley rats	MI-induced arrhythmia	Reduced CaMKII and Thr-286-phosphorylated CaMKII expression / Increased RyR2 expression
	Yang et al (14)	Sprague-Dawley rats	TAC induced cardiac hypertrophy	Reduced protein level and phosphorylation of CaMKII / Reduced Type III collagen deposition
ANS	Minoura et al (24)	Canine RV wedge preparations	Experimental model of Brugada syndrome	Increases ICaL via indirect adrenergic stimulation / Positive inotropic effect
	Zheng et al (53)	Male adult rabbits	MI	Downregulated genes associated with neurohumoral system-endothelin 1 and ACE
Gap junctions	Wu et al (22)	Sprague-Dawley rats	MI	Alleviates Cx43 phosphorylation / Increases miRNA-1 and PKC

INaL, late sodium current; ATXII, anemone toxin II; APD, action potential duration; EADs, early afterdepolarizations; DADs, delayed afterdepolarizations; TAs, triggered activities; TAC, transverse aortic constriction; CaMKII, calcium/calmodulin-dependent protein kinase II; ACE, angiotensin converting enzyme; ANS, autonomic nervous system; Ito, transient outward potassium.

WXKL induces the release of catecholamines from sympathetic nerve endings at the tissue level exerting a tyramine-like effect (9). These ameliorative actions are accompanied by normalization of the repolarization defects in the epicardial AP and of the ECG by a diminution of the accentuated J waves and ST segment elevation (24). The concentration of WXKL is directly proportional to positive inotropy in wedge preparation, contradicting to that in single myocytes (24). In rabbits with MI, treatment with 817 mg/kg/day WXKL downregulates genes associated with neurohumoral system-endothelin 1 and angiotensin I converting enzyme (53).

10. Conclusion

Arrhythmia has multiple vulnerable facets that need to be addressed individually for optimal patient management. To date, WXKL has shown promising results in sinus rhythm reversion and maintenance, the reduction of PVCs and the suppression of EADs and DADs in a number of experimental and clinical models via diverse effects on channels chiefly INa, ICaL and Ito, CaMKII and its regulatory pathways, inflammatory mediators and P wave dispersion. Its efficacy in suppressing arrhythmogenesis has been compared to western drugs in several trials and the results have been satisfactory. Its safety profile as compared to severe adverse reactions and proarrhythmic tendencies of other western antiarrhythmics has further validated its promising role. With further identification of roles of gene and proteome-based therapies, second messenger systems, intercellular conduction, NCX inhibition, gating modifiers and ryanodine stabilizers, the scope of managing arrhythmias has expanded as opposed to the sole dependence of ion channel conductance-based therapies. Combining these newer approaches with actions of WXKL under diverse pathologies and circumstances could certainly fill the gaps in treating inherited as well as acquired arrhythmic syndromes.

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Availability of data and materials

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Authors' contributions

GT and TL put forward the conception and design of this review. SD, MG and SG performed the review of the literature. SD and MG contributed to the processing of the figure and tables. SD, GT and TL were major contributors to the writing and revision of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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