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Pharmacological Insights and Clinical Challenges of Wenxin Keli in Arrhythmia Treatment

ABSTRACT

Cardiac arrhythmias remain a leading cause of cardiovascular morbidity and mortality worldwide. Although conventional antiarrhythmic drugs are effective, their use is constrained by proarrhythmic risks and extracardiac toxicity. Wenxin Keli (WXKL), a traditional Chinese medicine (TCM) formula, has demonstrated antiarrhythmic properties in preclinical and clinical studies with a reportedly favorable safety profile. This article provides a critical synthesis of WXKL's pharmacological mechanisms, including ion channel modulation (INa, ICaL, Ito), calcium handling, and calcium/calmodulin-dependent protein kinase II signaling, with explicit appraisal of translational limitations. Clinical trial evidence and meta-analyses for atrial fibrillation (AF), premature ventricular contractions, and other indications were systematically evaluated, with detailed discussion of effect sizes, heterogeneity, and methodological quality. Key challenges unique to WXKL as a TCM-derived product—formulation variability, quality control limitations, and regulatory approval pathways—are analyzed in depth. A prioritized research agenda is proposed to address evidence gaps.

Keywords: Anti-arrhythmia, clinical application, pharmacological effects, traditional Chinese medicine, Wenxin Keli

REVIEW

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INTRODUCTION

Cardiac arrhythmias affect millions of individuals worldwide and are associated with increased risks of stroke, heart failure, and sudden cardiac death.[1] Current guideline-based arrhythmia management primarily includes catheter ablation and pharmacological therapy: catheter ablation is recommended as the first-line curative option for drug-refractory arrhythmias,[1,2] while standard antiarrhythmic drugs (e.g., amiodarone, metoprolol) remain essential due to their accessibility and role as adjunctive treatment.[2,3] However, conventional antiarrhythmics are plagued by significant drawbacks: Class I agents may provoke proarrhythmia, Class III agents carry risks of QT prolongation and torsade de pointes, and many drugs exert negative inotropic effects or extracardiac toxicity.[4,5] These limitations have motivated the search for multi-targeted therapies with improved safety profiles. Wenxin Keli (WXKL), therefore, is not intended to replace first-line therapies (standard antiarrhythmics or catheter ablation); instead, it serves as a complementary or alternative option, particularly for patients who are intolerant of or refractory to conventional treatments.

Wenxin Keli is a Chinese medicine formula approved by the China National Medical Products Administration for the treatment of atrial and ventricular arrhythmias.[6] It comprises 5 herbal components: *Codonopsis pilosula*, *Polygonatum sibiricum*, *Panax notoginseng*, Amber (*Succinum*), and *Nardostachys jatamansi*. Over the past decade, more than 100 preclinical studies and several dozen clinical trials have investigated its antiarrhythmic properties. While multiple narrative reviews have summarized this literature, critical appraisal of evidence quality, discussion of conflicting findings, and examination of product-specific challenges remain scarce.

This review has 4 objectives: (1) to critically synthesize current knowledge of WXKL's pharmacological mechanisms, highlighting strengths and gaps in the preclinical evidence; (2) to systematically evaluate the design, quality, and results of clinical trials and meta-analyses involving WXKL; (3) to analyze the unique challenges of formulation consistency, quality control, and regulatory approval that affect its global translation; and (4) to propose a prioritized research agenda to address unresolved questions. By adopting an analytical rather than descriptive approach, a balanced evidence-based foundation for clinicians and researchers was intended to be provided.

LITERATURE SEARCH AND STUDY SELECTION

This review was conducted following the principles of systematic reviews where applicable. The following databases were systematically searched from inception through December 2024: PubMed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang Data, and VIP information database. Search terms included combinations of "Wenxin Keli," "Wenxin Granule," "antiarrhythmia," "atrial fibrillation," "premature ventricular contraction," "heart failure," and "arrhythmia."

Inclusion criteria were: (1) studies evaluating WXKL for any arrhythmia indication; (2) randomized controlled trials (RCTs), observational studies, systematic reviews, and meta-analyses; (3) human or preclinical studies with mechanistic relevance; and (4) articles published in English or Chinese. Exclusion criteria were: (1) case reports, commentaries, or editorials without original data; (2) duplicate publications; and (3) studies without accessible full text. Two investigators independently screened titles and abstracts, with disagreements resolved by consensus. The selection process was documented in accordance with PRISMA guidelines where applicable.

PHARMACOLOGICAL MECHANISMS: PRECLINICAL EVIDENCE AND CRITICAL APPRAISAL

Wenxin Keli has been studied extensively in isolated cardiomyocytes, animal models, and ex vivo preparations. These investigations have revealed a multi-target pharmacological profile. However, the translational relevance of many findings remains uncertain due to methodological limitations, the absence of human tissue validation, and the use of drug concentrations that may not be clinically achievable. The principal mechanisms are summarized below, along with a critical appraisal of the supporting evidence.

HIGHLIGHTS

- Provides a critical appraisal of preclinical and clinical evidence for Wenxin Keli (WXKL), identifying key translational gaps and methodological limitations.
- Systematically evaluates meta-analyses with attention to effect sizes, heterogeneity, risk of bias, and publication bias.
- Analyzes formulation variability, quality control deficiencies, and regulatory barriers that impede global acceptance.
- Proposes a prioritized research roadmap to advance WXKL toward evidence-based, internationally approved therapy.

DRUG COMPOSITION AND COMPLEXITY

Wenxin Keli contains over 71 identified compounds, including ginsenosides, steroidal saponins, alkaloids, and organic acids.[7] The proportions of the various herbs in WXKL have been meticulously formulated to optimize its overall therapeutic efficacy. As illustrated in Figure 1, the varying proportions of distinct ingredients within the formulation further augment the specificity and efficacy of WXKL. This formulation, characterized by its scientific rigor and abundant active components, collectively provides a robust basis for WXKL's multi-pathway and multi-target antiarrhythmic effects. Network pharmacology analyses have predicted 68 potentially active ingredients and 83 arrhythmia-related targets, implicating pathways involved in inflammation, oxidative stress, adrenergic signaling, and calcium homeostasis.[8,9]

While *in silico* studies generate useful hypotheses, they rely on databases of predicted interactions and often lack experimental confirmation. The actual contribution of individual compounds to antiarrhythmic effects remains undefined. Synergistic interactions between constituents have not been rigorously deconvoluted, and no studies have systematically compared the potency of the full formula vs. its individual components or combinations thereof.

MODULATION OF CARDIAC ION CHANNELS

The principal mechanism proposed for WXKL's antiarrhythmic effects is modulation of multiple ion channels on the cardiomyocyte membrane. Evidence derives largely from patch-clamp studies in isolated animal cells.

Sodium Channels (INa)

Burashnikov et al[10] demonstrated that WXKL (5-10 mg/mL) concentration-dependently inhibited peak sodium current (INa) in canine atrial and ventricular myocytes, with a greater effect in atrial cells.[10] This atrial-selective inhibition was attributed to differences in resting membrane potential and steady-state inactivation kinetics between atrial and ventricular myocytes at rapid activation rates.[11] Subsequent studies reported suppression of late sodium current (INaL), reducing early and delayed afterdepolarizations in rabbit ventricular myocytes.[12]

These experiments were conducted at supra-therapeutic concentrations (5-10 mg/mL). The peak plasma concentration of WXKL constituents after oral administration in humans has not been definitively established, but available pharmacokinetic data suggest that concentrations achieved in vivo are substantially lower.[13] Atrial selectivity has not been confirmed in human atrial myocytes or in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). No studies have examined state-dependent block or use-dependence, which are critical determinants of clinical safety and efficacy.

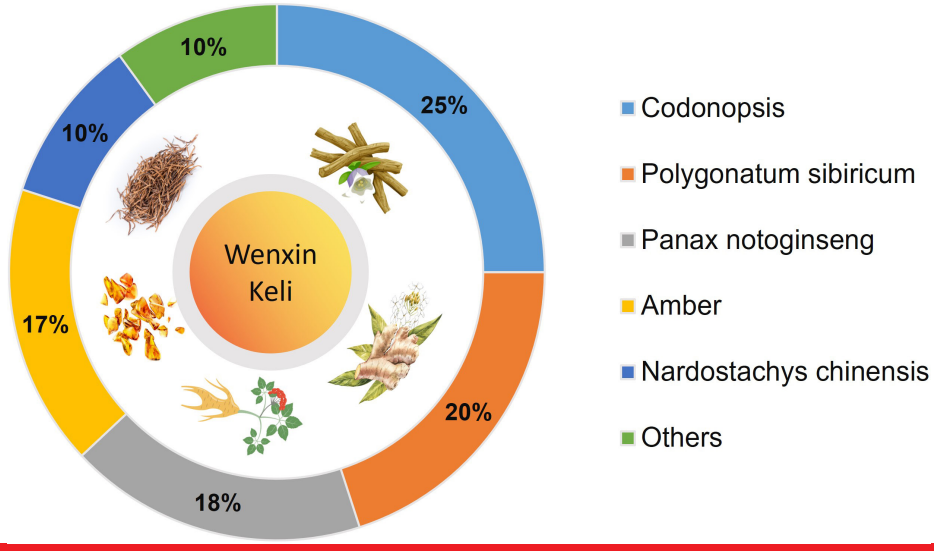

Figure 1. The composition and proportion of WXKL.

Calcium Channels (ICaL)

In post-myocardial infarction rat models, WXKL increased sarcoplasmic reticulum calcium content and reduced the incidence of early and delayed afterdepolarizations.[14] Wenxin Keli accelerated L-type calcium channel inactivation and prolonged recovery from inactivation, potentially mitigating calcium overload.[15]

These studies utilized indirect assessments of calcium handling (fluorescent indicators) rather than direct measurement of ICaL. Experiments were conducted in rodent myocytes, which differ substantially from humans in calcium handling proteins, repolarization reserve, and rate dependence. No studies have examined WXKL effects on human L-type calcium channels expressed in heterologous systems or in hiPSC-CMs.

Potassium Channels (Ito, IKr, IKs)

Wenxin Keli has been shown to reduce the transient outward potassium current (Ito) in rat ventricular myocytes and canine ventricular preparations.[16,17] Ito inhibition underlies the proposed efficacy in Brugada syndrome models.[18] Effects on delayed rectifier currents (IKr, IKs) have not been systematically characterized.

The absence of data on IKr and IKs represents a significant gap, given that inhibition of these currents is a common mechanism of drug-induced QT prolongation and proarrhythmia. Until WXKL's effects on these currents are characterized, its cardiac safety profile remains incompletely defined.

Intracellular Calcium and Signaling Pathways

Several studies have implicated the calcium/calmodulin-dependent protein kinase II (CaMKII) pathway as a key target. In rat models of transverse aortic constriction and myocardial infarction, WXKL reduced CaMKII phosphorylation, normalized calcium transients, and decreased arrhythmia susceptibility.[19,20] Gene expression studies reported downregulation of SCN5A and ADRB2 and upregulation of CHRM2 in infarcted rat hearts.[21]

These studies did not employ genetic or pharmacological CaMKII inhibition as a comparator, making it difficult to attribute antiarrhythmic effects specifically to CaMKII modulation. All experiments were conducted in rodents; confirmation in human tissues is lacking. The gene expression changes, while statistically significant, were modest (typically <2-fold) and of uncertain functional relevance.

Energy Metabolism, Oxidative Stress, and Inflammation

Additional reported effects include enhancement of glucose oxidation and branched-chain amino acid degradation during ischemia-reperfusion,[22] suppression of inflammatory cytokines (interleukin-6, tumor necrosis factor alpha),[23] inhibition of transforming growth factor beta-mediated p38/JNK signaling,[24] and attenuation of mitochondrial oxidative stress via PKC-δ/NOX2/ROS pathway modulation.[25]

These pleiotropic effects are consistent with the multicomponent nature of traditional Chinese medicine (TCM) formulas,[26] but causality is difficult to establish. Most studies are observational and lack mechanistic linkage between the metabolic/inflammatory changes and arrhythmia suppression. The contribution of individual herbal constituents to these effects has not been dissected. All studies were conducted in rodent models; human data are absent.

Regulation of miRNAs and Gap Junctions

Two studies reported that WXKL upregulated connexin 43 (Cx43) expression, increased ventricular fibrillation threshold, and modulated miR-1 and miR-133 expression in infarcted rats.[27,28]

These findings derive from single research groups with small sample sizes and no independent replication. The specificity of miRNA changes and their functional relevance to arrhythmia suppression remain speculative. The Cx43 upregulation was assessed only by Western blot; functional gap junction communication was not directly measured.

Antiplatelet Effects

One study investigated the antiplatelet activity of WXKL. Tao et al[29] demonstrated that linoleic acid, a constituent of WXKL, inhibited platelet aggregation in vitro, reduced adhesion on collagen-coated surfaces under flow conditions, and attenuated thrombus formation in a $FeCl_3$-induced carotid artery injury model. Mechanistically, linoleic acid selectively suppressed P-selectin–mediated platelet activation and disrupted the phosphorylation cascades of protein kinase B (Akt), mitogen-activated protein kinases (MAPKs), and phospholipase C β3 (PLCβ3).

This study provides rigorous mechanistic evidence for an antiplatelet effect. However, its direct relevance to arrhythmia treatment is uncertain. First, the study focused on thrombosis, not arrhythmogenesis; no experimental link was established between platelet inhibition and suppression of atrial or ventricular arrhythmias. Second, the effect was attributed to a single constituent (linoleic acid); whether the full WXKL formula exerts equivalent or synergistic antiplatelet activity, and at what clinically achievable concentrations, remains unknown. Third, the clinical implications are twofold and require caution: if WXKL possesses clinically meaningful antiplatelet effects, it could offer additional vascular protection in atrial fibrillation (AF) patients, but it may also increase bleeding risk when co-administered with anticoagulants or antiplatelet agents. Formal drug–drug interaction and pharmacodynamic studies are urgently needed.

Overall Appraisal of Preclinical Evidence

The existing preclinical literature provides plausible mechanisms by which WXKL might exert antiarrhythmic effects (Figure 2). However, the evidence is predominantly derived from non-human models, employs concentrations of uncertain clinical relevance, and lacks rigorous experimental controls (Table 1). Key limitations of the current body of research include the complete absence of investigations conducted in human cardiomyocytes or hiPSC-CMs, as well as a notable lack of pharmacokinetic-pharmacodynamic correlation studies. Moreover, there has been no systematic characterization of the effects of WXKL on the rapid (IKr) and slow (IKs) components of the delayed rectifier potassium current, and the specific contribution of individual herbal constituents to its observed therapeutic effects remains poorly defined. The reliability of the available evidence is further compromised by limited independent replication of preclinical and clinical findings, together with a substantial risk of publication bias.

Mechanistic claims should therefore be regarded as hypothesis-generating rather than conclusive.

CLINICAL APPLICATION RESEARCH AND EVIDENCE SYNTHESIS

Atrial Fibrillation

Clinical Trial Evidence

Randomized controlled trials of WXKL for paroxysmal AF are limited in both number and methodological quality. An open-label, randomized trial comparing WXKL with sotalol in 120 patients with hyperthyroidism-induced paroxysmal AF reported similar rates of sinus rhythm maintenance at 4 weeks (76.7% vs. 73.3%, $P = .67$); however, the study lacked blinding, did not include a placebo control, and was underpowered for equivalence.[30]

A meta-analysis of 8 small RCTs (n = 624) suggested that WXKL, alone or combined with conventional antiarrhythmic drugs, increased the likelihood of sinus rhythm maintenance (OR 3.21; 95% CI 2.14-4.82).[31] However, all included trials were conducted in China, none were double-blinded, allocation concealment was inadequately reported, and

Figure 2. A condensed overview of the various mechanisms and effects of WXKL.

Table 1. Key Limitations of Preclinical WXKL Studies

Domain	Limitation	Implication
Experimental models	Predominantly rodent, canine; no human cardiomyocyte data	Uncertain translational relevance
Drug concentrations	Supra-therapeutic (5-10 mg/mL); no PK/PD correlation	Clinical achievability unknown
Ion channel studies	IKr, IKs not characterized; no state-dependence assessment	Proarrhythmic risk profile incomplete
Mechanistic specificity	No genetic/pharmacological inhibitors as comparators	Attribution of effects to specific pathways uncertain
Replication	Most findings from single laboratories	Potential publication bias

heterogeneity was moderate ($I^2=52\%$). Publication bias could not be excluded due to the small number of studies. Consequently, the current evidence base is insufficient to support a definitive recommendation for WXKL as monotherapy for rhythm control in AF.

Combination Therapy Trials

Zhang et al[32] randomized 41 patients with recent-onset AF (<48 hours) to intravenous amiodarone alone or amiodarone plus oral WXKL (18 g 3 times daily). Conversion rates at 24 hours did not differ between groups (81.0% vs. 75.0%, $P=.72$). However, conversion time was significantly shorter in the combination group (291 ± 235 minutes vs. 725 ± 475 minutes, $P=.003$). No serious adverse events occurred. Limitations include open-label design, small sample size, and baseline imbalance in diabetes prevalence and QTc interval.

Premature Ventricular Contraction

Pivotal Randomized Controlled Trial

The largest trial to date randomized 1200 patients with frequent premature ventricular contractions (PVCs) (>1000/24h, no structural heart disease) to WXKL (9 g 3 times daily) or placebo for 4 weeks.[33] The primary endpoint was change in 24-hour PVC count. Wenxin Keli significantly reduced PVC burden compared with placebo (median reduction: 61% vs. 22%; $P<.001$). The proportion of patients achieving ≥90% PVC reduction was 31.5% in the WXKL group vs. 8.2% in the placebo group. PVC-related symptom scores also improved significantly.

Methodological considerations: This trial was well-designed with adequate randomization, double-blinding, and central electrocardiogram (ECG) analysis. However, 20% of randomized patients were excluded from the per-protocol analysis, raising concerns about attrition bias. The placebo run-in period was not reported. Comparative effectiveness against guideline-recommended therapy (beta-blockers) was not assessed.

Meta-Analyses

Huang et al conducted a meta-analysis of 11 RCTs (n=1243) comparing WXKL plus metoprolol vs. metoprolol alone for PVCs.[34] The combination therapy significantly improved clinical efficacy (RR 1.32; 95% CI 1.24-1.40; $P<.00001$). However, several critical limitations were identified in the included trials. All eligible studies were conducted exclusively in China. The overall risk of bias was high: only 3 of 11 studies reported appropriate randomization, and none described allocation concealment or adopted a blinded design. Substantial heterogeneity was present ($I^2=67\%$) but was not explored by subgroup or sensitivity analyses. Furthermore, asymmetry in the funnel plot indicated a potential risk of publication bias, although Egger's test was not reported to confirm this.

OTHER INDICATIONS

Cardiac Syndrome X

Only 1 clinical study has investigated WXKL for cardiac syndrome. Xu and Huang[35] reported that WXKL combined with aspirin improved angina symptoms and endothelial function markers (hs−CRP, ET-1, NO) compared with aspirin alone in a small, single-center study. However, the trial was non-randomized, open-label, did not report blinding or allocation concealment, and adverse events were not systematically assessed. The study was published in 2011 with no subsequent confirmatory trials. Therefore, the evidence for WXKL in cardiac syndrome X remains preliminary and insufficient to support routine clinical use.

Brugada Syndrome

Evidence for Brugada syndrome is limited to a single experimental study using arterially perfused canine right ventricular wedge preparations.[18] Wenxin Keli (5 mg/mL) combined with quinidine suppressed arrhythmia triggers by inhibiting Ito. No human data exist. This indication remains exploratory and should not be extrapolated to clinical practice without confirmatory studies.

Safety and Tolerability

Across clinical studies, the most commonly reported adverse events were mild gastrointestinal discomfort (2%-5%) and dizziness (1%-3%), with no severe adverse events definitively attributed to WXKL monotherapy.[33,36] However, critical gaps exist in long-term safety data, which is particularly relevant for combination therapy given that many arrhythmia patients require prolonged treatment with WXKL plus standard antiarrhythmics (e.g., amiodarone, metoprolol) or anticoagulants. To date, no clinical trials have evaluated WXKL's safety beyond 6 months, and post-marketing surveillance data are limited. Given WXKL's complex composition (over 71 identified compounds[7]), long-term administration may pose unrecognized risks, such as cumulative hepatic or renal burden—especially in elderly patients or those with pre-existing organ impairment. For combination therapy, prolonged co-administration with standard antiarrhythmics (e.g., amiodarone, which has inherent hepatic and thyroid toxicity[4]) may increase the risk of additive adverse effects, though this has not been

systematically evaluated. Further long-term, prospective studies are urgently needed to assess the safety of WXKL monotherapy and combination therapy over 12-24 months, with regular monitoring of hepatic (alanine aminotransferase, aspartate aminotransferase), renal (creatinine, estimated glomerular filtration rate (eGFR)), and thyroid function.

In addition to long-term safety concerns, herb-drug interactions represent a key safety consideration, particularly in combination therapy settings. An in vivo study in rats demonstrated that WXKL weakly inhibits the activities of CYP3A4, CYP1A2, CYP2C19, and CYP2E137, which are key enzymes involved in the metabolism of most standard antiarrhythmics (e.g., amiodarone, metoprolol), anticoagulants (e.g., warfarin), and statins.[37] This inhibition may alter plasma concentrations of co-administered drugs, increasing the risk of toxicity (e.g., amiodarone-induced QT prolongation) or reducing therapeutic efficacy, a risk that is amplified when WXKL is frequently used in combination with amiodarone or metoprolol.[32,34] No human pharmacokinetic studies have been conducted to quantify these interactions, and no dose adjustment guidelines exist for co-administered drugs. Additionally, WXKL's antiplatelet potential (attributed to linoleic acid[29]) raises concerns about increased bleeding risk when combined with anticoagulants (e.g., warfarin, novel oral anticoagulants) or antiplatelet agents (e.g., aspirin, clopidogrel)—a common scenario in AF patients requiring stroke prevention. Formal drug–drug interaction studies are critical to clarify these risks and guide clinical practice.

Compounding these safety concerns is the inadequate pharmacovigilance for WXKL, particularly in combination therapy. Current safety data are primarily derived from short-term clinical trials, which are insufficient to detect rare or delayed adverse events (e.g., long-term hepatic injury, drug-drug interaction-related proarrhythmia). For combination therapy, pharmacovigilance efforts should focus on active surveillance of adverse events specific to combination regimens, such as additive cardiac toxicity (QT prolongation) when WXKL is combined with amiodarone or bleeding events when combined with anticoagulants, as well as standardized reporting of adverse events in post-marketing settings with clear documentation of co-administered drugs to identify potential herb–drug interaction signals. The development of a dedicated pharmacovigilance registry for WXKL, particularly for patients on long-term combination therapy, would also help track long-term safety outcomes and identify high-risk subgroups (e.g., elderly patients, those with hepatic/renal impairment, or those on multiple comedications). Furthermore, healthcare providers should be educated on WXKL's potential herb–drug interactions and the need for close monitoring when used in combination with standard antiarrhythmics, anticoagulants, or antiplatelet agents, while patients should be advised to report any new symptoms (e.g., fatigue, jaundice, bruising) promptly, especially when initiating or adjusting combination therapy.

Heart Failure with Ventricular Arrhythmia

Zheng et al conducted a systematic review and meta-analysis of WXKL plus amiodarone vs. amiodarone alone for heart failure complicated by ventricular arrhythmia.[37] Thirteen trials (n = 1126) were included. The combination therapy significantly improved total effective rate (RR 1.22; 95% CI 1.16-1.29) and reduced heart rate (MD −2.25 bpm; 95% CI −2.61 to −1.88) and PVC frequency (MD −2.03; 95% CI −2.41 to −1.65).

Critical appraisal: Risk of bias was assessed as high in 3 studies and unclear in 10 studies. All trials were conducted in China; none were registered. Heterogeneity for the primary outcome was moderate ($I^2 = 46\%$). Adverse event reporting was inconsistent; pooled analysis showed no significant difference between groups (OR 0.64; 95% CI 0.39-1.07), but CIs were wide. The authors appropriately concluded that "further research is warranted, ideally involving large, prospective, rigorous trials."[38]

Critical Evaluation of Meta-Analyses

Five systematic reviews/meta-analyses evaluating WXKL for arrhythmia indications were identified.[31,34,38-40] According to the AMSTAR-2 assessment criteria, all included reviews were rated as either critically low or low quality, stemming from a series of key methodological shortcomings: all 5 reviews failed to establish a prospective a priori protocol, 4 out of 5 utilized inadequate literature search strategies with no searches of clinical trial registries or gray literature, all 5 provided no list of excluded studies accompanied by justification, 3 out of 5 included no assessment of publication bias, 4 out of 5 failed to consider risk of bias when interpreting overall results, and all 5 conducted no further exploration of heterogeneity beyond the reporting of I^2 statistics.

Detailed study characteristics, effect sizes, heterogeneity estimates, and risk of bias assessments for these meta-analyses (along with key individual RCTs) are summarized in Table 2. These methodological limitations must be considered when interpreting any pooled estimates from the available evidence.

Multiple studies have compared WXKL with conventional antiarrhythmics including metoprolol, propafenone, amiodarone, and mexiletine, generally showing comparable or superior efficacy.[31,34,39,40] However, no studies have compared WXKL with catheter ablation for any arrhythmia indication, representing an important evidence gap given ablation's established role in drug-refractory cases.

Dosing and Administration

An important practical consideration for clinicians is the appropriate dosing of WXKL. The available evidence on dosing regimens, route of administration, and adjustments in special populations or combination therapy is summarized below.

Route of Administration

Wenxin Keli is formulated as a granular preparation for oral administration. In all published clinical studies and approved indications, the granules are dissolved in warm water and taken orally. No intravenous or other parenteral formulation exists or has been studied in humans.

Standard Daily Dosing Regimens

The dosage of WXKL varies according to the condition being treated and whether it is used as monotherapy or

Table 2. Summary of Clinical Evidence for WXKL by Indication (Including RCTs and Meta-Analyses)

Indication	Study	Study Type	Design	Sample Size	Intervention	Key Outcomes	Effect Size/ Heterogeneity	Risk of Bias Summary
Paroxysmal AF	Meng et al 2015[30]	RCT	Open-label	120	WXKL vs. sotalol	Sinus rhythm maintenance: 76.7% vs. 73.3%	$P = .67$ (NS)	High (no blinding, no placebo)
Paroxysmal AF	Chen et al 2013[31]	Meta-analysis	8 RCTs	624	WXKL ± conventional vs. control	Sinus rhythm maintenance	OR 3.21 (2.14-4.82); $I^2 = 52\%$	Moderate heterogeneity; unclear allocation concealment
Recent-onset AF	Zhang et al 2018[32]	RCT	Open-label	41	Amiodarone + WXKL vs. amiodarone alone	Conversion time	291 vs. 725 min ($P = .003$); conversion rates NS	High (open-label, small sample)
Frequent PVCs	Hua et al 2015[33]	RCT	Double-blind, placebo-controlled	1200	WXKL vs. placebo	Median PVC reduction	61% vs. 22% ($P < .001$)	Low for randomization/ blinding; attrition bias concern
Frequent PVCs	Huang et al 2022[34]	Meta-analysis	11 RCTs	1243	WXKL + metoprolol vs. metoprolol alone	Clinical efficacy	RR 1.32 (1.24-1.40); $I^2 = 67\%$	High (poor randomization, no blinding)
HF with VPCs	Li et al 2017[40]	Meta-analysis	8 RCTs	748	WXKL ± conventional vs. control	VPC frequency; LVEF; 6-min walk	MD −427.08 (−526.73 to −327.43); LVEF MD 4.12 (2.97-5.27)	Low methodological quality in included trials
HF with VA	Zheng et al 2018[38]	Meta-analysis	13 RCTs	1126	WXKL + amiodarone vs. amiodarone alone	Total effective rate; AEs	RR 1.22 (1.16-1.29); AEs OR 0.64 (0.39-1.07); $I^2 = 46\%$	High/unclear risk in all 13 studies

AE, adverse event; HF, heart failure; MD, mean difference; NS, not significant; OR, odds ratio; RR, risk ratio; VA, ventricular arrhythmia; VPC, ventricular premature complex.

in combination with conventional antiarrhythmic drugs. Table 3 summarizes the dosing regimens reported in major clinical trials and registration studies.

Dose Variation by Condition and Patient Factors

The available evidence suggests that dosing may differ by indication and by whether WXKL is used alone or adjunctively. For chronic maintenance therapy in outpatient settings (e.g., PVCs, atrial premature beats), doses range from 15 to 30 g/day in divided doses, typically administered for 4 weeks or longer.[33,40] For acute conversion of recent-onset AF when combined with intravenous amiodarone, a higher loading regimen of 18 g 3 times daily (54 g/day) has been used safely for 24 hours.[32] An ongoing dose-ranging study (NCT02319603) is directly comparing 15 g/day vs. 30 g/day for atrial premature beats to establish the optimal dose, but results have not yet been published.

Notably, no studies have investigated whether dose adjustment is required based on age, body weight, renal function, or hepatic impairment. All trials to date have used fixed dosing without stratification by these factors.

Dose Adjustment with Combination Therapy

With respect to the use of WXKL in combination with other antiarrhythmic agents, existing evidence reveals no protocol-mandated dose reductions of WXKL in combination studies. In the trial evaluating WXKL combined with amiodarone, WXKL was administered at 18 g 3 times daily without any dose adjustments, and no serious adverse events were observed.[32] Similarly, in the meta-analysis of WXKL combined with metoprolol, the WXKL dose was consistently 9 g 3 times daily across all included studies, with no dose adjustments reported.[34] However, clinical trial protocols typically prohibit the concomitant use of other Class I-III antiarrhythmic agents during WXKL monotherapy studies to avoid confounding effects on efficacy and safety outcomes,[33] indicating that when WXKL is used as the primary antiarrhythmic agent, co-administration with other antiarrhythmics is generally avoided. Regarding safety, the combination of WXKL with amiodarone was associated with a shorter AF conversion time without an increase in adverse events,[32] while the metoprolol combination meta-analysis suggested a numerical reduction in adverse reactions in the combination group, though this difference did not reach statistical significance.[34]

Important Limitations and Evidence Gaps

Significant evidence gaps persist regarding optimal WXKL dosing. No pharmacokinetic dosing studies have been published to establish concentration–response relationships, leaving uncertainty about whether current fixed doses achieve therapeutic plasma concentrations of active constituents in all patients. Additionally, no dose adjustment guidelines exist for special populations, including patients with renal impairment, hepatic impairment, elderly individuals, or pediatric patients, as all trials have either excluded these groups or failed to report subgroup analyses. Furthermore, no formal drug–drug interaction studies have quantified whether WXKL affects the pharmacokinetics of co-administered antiarrhythmics (e.g., amiodarone, metoprolol) or whether these drugs alter exposure to WXKL constituents. The optimal dose for different arrhythmia subtypes also remains not definitively established; while the ongoing dose-ranging trial may help address this gap, its results are still awaited. Collectively, these evidence gaps underscore the critical need for rigorous pharmacokinetic and pharmacodynamic studies to inform evidence-based dosing recommendations for WXKL.

Critical Challenges in Development and Global Translation

Wenxin Keli, like most TCM formulas, faces inherent challenges that extend beyond those of conventional single-entity drugs. These challenges are not merely academic; they represent substantive barriers to international acceptance, regulatory approval, and evidence-based clinical integration. For WXKL to transition from a domestically approved Chinese medicine to a globally accessible therapeutic option, the following critical issues must be systematically addressed.

Formulation Variability and Quality Control

Sources of Variability

The 5 herbal components of WXKL-*Codonopsis pilosula*, *Polygonatum sibiricum*, *Panax notoginseng*, *Succinum*

Table 3. Summary of WXKL Dosing Regimens in Clinical Studies

Condition	Dosage Regimen	Duration	Key Findings	Source
Frequent premature ventricular contractions (PVCs)	9 g 3 times daily (27 g/day)	4 weeks	61% median PVC reduction vs. 22% placebo; well tolerated	Hua et al[33]
Atrial premature beats	5 g 3 times daily (15 g/day, low dose) OR 10 g 3 times daily (30 g/day, high dose)	4 weeks	Ongoing dose-ranging study; results pending	NCT02319603
Paroxysmal atrial fibrillation (monotherapy)	9 g 3 times daily (27 g/day)	4 weeks	Sinus rhythm maintenance 76.7% vs. 73.3% with sotalol (NS)	Meng et al[30]
Recent-onset AF (adjunct to IV amiodarone)	18 g 3 times daily (54 g/day)	24 hours	Shorter conversion time (291 vs. 725 min); no increased AEs	Zhang et al[32]
Heart failure with ventricular arrhythmia (adjunct to amiodarone)	9 g 3 times daily (27 g/day)	4-24 weeks	Improved total effective rate (RR 1.22); safety similar to control	Zheng et al[38]

All dosing regimens shown are derived from studies that explicitly excluded patients with significant hepatic or renal impairment. No data exist on dose requirements in these populations; extrapolation is not supported by available evidence.

(amber), and *Nardostachys jatamansi* are derived from natural botanical and mineral sources. Their phytochemical compositions and physicochemical properties can vary considerably, influenced by a multitude of interrelated factors:[41] species and chemotype differences including intraspecific genetic variation, misidentification, or adulteration with substitute species; cultivation conditions such as soil composition, climate, altitude, fertilization practices, and pesticide application; harvest time that contributes to seasonal and diurnal fluctuations in secondary metabolite accumulation; and post-harvest processing procedures including drying regimes (sun-drying vs. oven-drying), storage duration and conditions, extraction solvents, and manufacturing parameters.

Despite manufacturer specifications for marker compounds (e.g., ginsenosides Rb1, Rg1; notoginsenoside R1), these markers may not correlate with antiarrhythmic activity. Advanced analytical techniques such as high-performance liquid chromatography (HPLC) fingerprinting and liquid chromatography–tandem mass spectrometry (LC-MS/MS) multi-component quantification have been developed for research purposes, but they are not universally mandated in regulatory submissions, and batch-release specifications vary among manufacturers.

Limitations of Current Quality Control Paradigms

Current quality control for WXKL relies primarily on chemical fingerprinting—ensuring that the chromatographic profile of a production batch matches a reference standard. However, this approach has 3 fundamental limitations:

1. Analytical targets may not be bioactive. The compounds selected as markers are often abundant and chemically stable, but their contribution to antiarrhythmic efficacy is unproven. Conversely, minor, labile, or unidentified constituents may be responsible for therapeutic effects.
2. Chemical equivalence does not guarantee biological equivalence. Two batches with identical HPLC fingerprints may differ in their pharmacological activity due to undetected enantiomeric variation, differential protein binding, or synergistic interactions among unmeasured constituents.
3. No validated bioactivity assays. Unlike conventional drugs, for which potency is defined by a quantifiable biological effect (e.g., enzyme inhibition IC_{50}), no standardized, pharmacopoeial bioassay exists to assess the functional activity of WXKL batches.

Path Forward: Toward International Harmonization

For WXKL to gain acceptance in regulated pharmaceutical markets, the following quality standards must be developed and implemented:

1. Comprehensive characterization: Full phytochemical profiling using ultra-HPLC coupled with quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS) to establish a definitive chemical library
2. Multi-component quantification: Simultaneous quantification of at least 10-20 representative constituents spanning different chemical classes (ginsenosides, saponins, alkaloids, organic acids)
3. Bioactivity-linked release specifications: Development of cell-based assays [e.g., hiPSC-CM electrophysiology, ion channel Fluorescence Imaging Plate Reader (FLIPR) assays] that correlate with clinical antiarrhythmic potency and can serve as batch-release potency tests
4. Harmonization with ICH guidelines: Alignment with ICH Q3C (residual solvents), Q3D (elemental impurities), Q8 (pharmaceutical development), and Q9 (quality risk management) for eventual regulatory submission in ICH regions

Regulatory Hurdles

In China, WXKL is approved as a prescription drug under the "new drug" category by the National Medical Products Administration. However, its pathway to approval in Western jurisdictions remains ambiguous and fraught with scientific, regulatory, and evidentiary challenges.

US Food and Drug Administration Botanical Drug Pathway

The Food and Drug Administration (FDA) has established a specific guideline for botanical drug development. Key requirements and corresponding gaps for WXKL are summarized in Table 4.

To date, 4 botanical drugs have received FDA approval as prescription products under the Botanical Drug Guidance: Veregen® (sinecatechins, 2006), Mytesi (crofelemer, 2012), Filsuvez® (birch triterpenes), and NexoBrid® (anacaulase-bcdb).[42,43]The first 2 were approved as New Drug Applications, while NexoBrid® was approved as a biologics license application.[42] Neither is a cardiovascular drug. The

Table 4. Food and Drug Administration Botanical Drug Development Requirements and Current Gaps for WXKL

Requirement	Current Status for WXKL	Critical Gap
Phase 1: Chemistry, manufacturing, and controls (CMC)	Partial chemical characterization available; no validated bioassay	No defined active constituent; batch consistency not publicly demonstrated
Phase 1: Preclinical safety assessment	Limited subchronic toxicity studies; no genotoxicity, carcinogenicity, or reproductive toxicology	Non-ICH-compliant; lacks regulatory-grade GLP studies
Phase 2: Well-controlled clinical trials	Multiple RCTs conducted, all in China	Not registered; not GCP-compliant; not acceptable for FDA filing
Phase 3: Confirmatory trials	None	Pivotal trials required for approval

CMC, Chemistry, manufacturing, and controls; GCP, Good clinical practice; GLP, Good laboratory practice; ICH, International Council for Harmonization; IND, Investigational new drug; RCT, Randomized controlled trial.

FDA pathway is therefore feasible but demanding; it requires substantial investment and strategic planning.

European Medicines Agency Herbal Medicinal Products

The European Medicines Agency (EMA) Committee on Herbal Medicinal Products provides 2 registration pathways:

1. Well-established use: Requires bibliographic evidence of safety and efficacy with at least 10 years of recognized medicinal use within the EU. Wenxin Keli does not meet this criterion.
2. Traditional use registration: Requires at least 30 years of medicinal use, including 15 years within the EU. Wenxin Keli also does not meet this criterion.

Thus, WXKL would require a marketing authorization application as a full-fledged medicinal product, supported by a complete dossier of quality, preclinical, and clinical data comparable to that required for any new chemical entity.

Key Regulatory Barriers: An Analytical Summary

Despite the extensive preclinical and clinical literature on WXKL, its path to international regulatory approval is obstructed by 3 interrelated deficits that are fundamental rather than incremental.

First, the chemical complexity of WXKL and the absence of identified active constituent(s) create a cascade of scientific and regulatory ambiguities. Unlike a single-entity drug, for which absorption, distribution, metabolism, and excretion can be tracked unambiguously, WXKL contains hundreds of compounds. It remains unknown whether the antiarrhythmic effect resides in a single potent molecule, a defined combination, or the holistic synergy of the entire mixture. This uncertainty precludes rational dose optimization, prevents pharmacokinetic assessment, makes bioequivalence testing impossible, and blocks the development of mechanism-based quality control assays. Until the active principle(s) are identified—or an acceptable surrogate marker of pharmacological activity is validated—WXKL cannot satisfy the fundamental CMC and nonclinical pharmacology requirements of any ICH-aligned regulatory authority.

Second, the existing nonclinical safety package is incomplete by international standards. Although subchronic toxicity studies have been performed, they were not conducted in compliance with good laboratory practice and do not address genotoxicity, carcinogenicity, or reproductive and developmental toxicity as required by ICH S2, S1A, and S5 guidelines. Safety pharmacology assessments are limited to cardiovascular effects; central nervous system and respiratory system evaluations are absent. These gaps are not merely formalistic: without these studies, the safety of chronic WXKL administration cannot be adequately assessed, and the drug would not be approved for long-term use in any ICH jurisdiction.

Third, the clinical evidence base, while substantial in volume, does not meet the evidentiary standards expected for marketing authorization in the United States or European Union. All published RCTs were conducted in China; none were registered prospectively, and few adhered to ICH E6 Good Clinical Practice (GCP) guidelines. Deficiencies include inadequate documentation of allocation concealment, absence of independent data monitoring, unbundled or poorly described endpoint adjudication, and statistical analysis plans that were not pre-specified. Consequently, even well-conducted domestic trials cannot be used directly to support regulatory filing. A new series of international, multicenter, GCP-compliant trials will be required.

Together, these 3 barriers—unknown active constituents, incomplete regulatory-grade toxicology, and non-compliant clinical development—form a mutually reinforcing obstacle. Progress on any 1 front is contingent on progress on the others. Overcoming them will require a coordinated, strategically phased investment in analytical chemistry, nonclinical safety, and clinical trial infrastructure.

Individual Variability and Personalized Therapy

Traditional Chinese medicine is founded on the principle of bianzheng lunzhi (syndrome differentiation and individualized treatment). In theory, this allows tailoring of herbal formulas to each patient's unique constitutional and pathological state. In practice, however, WXKL is prescribed at a fixed dose (9 g 2 or 3 times daily) regardless of: age, body weight, renal function (creatinine clearance), hepatic function (Child-Pugh class), concomitant medications, and genetic polymorphisms affecting drug metabolism or arrhythmia susceptibility.

Pharmacokinetic Variability

No population pharmacokinetic studies have been published; it is unknown whether plasma concentrations of active constituents differ substantially among individuals, whether renal or hepatic impairment necessitates dose adjustment, or whether significant drug–drug interactions occur with commonly co-prescribed cardiovascular drugs such as statins, beta-blockers, anticoagulants, or antiplatelet agents.

Pharmacodynamic Variability

Response to antiarrhythmic drugs is known to be influenced by genetic polymorphisms in ion channel genes (e.g., SCN5A, KCNQ1, KCNH2), β-adrenergic receptor variants, and disease substrate such as atrial fibrosis, left ventricular hypertrophy, or ischemic burden. No studies have examined whether any of these factors predict differential response to WXKL. Consequently, there are no criteria to guide patient selection, predict therapeutic failure, or identify individuals at increased risk of adverse effects.

Toward Precision Medicine with Wenxin Keli

To realize the promise of personalized therapy, the following research priorities are identified:

1. Population pharmacokinetic modeling: Conduct dense-sampling pharmacokinetic studies in arrhythmia patients to estimate interindividual variability and identify covariates (age, renal function, genotype) that influence drug exposure.
2. Therapeutic drug monitoring: Develop and validate LC-MS/MS assays for quantification of representative

WXKL constituents in human plasma; explore concentration–response relationships.
3. Pharmacogenomic studies: Genotype patients in prospective trials for variants in drug-metabolizing enzymes (CYP2C19, CYP2D6, CYP3A4/5), drug transporters, and arrhythmia-associated genes; correlate with efficacy and safety outcomes.
4. Phenotypic stratification: Evaluate whether WXKL exhibits differential efficacy in specific arrhythmia subtypes (e.g., paroxysmal AF with high vagal tone vs. adrenergic AF, PVCs originating from outflow tract vs. fascicular).
5. Machine learning-based predictive algorithms: Integrate clinical, electrocardiographic, imaging, and -omic data to develop and validate prediction models for individualized response.

Future Research Directions

The preceding critical appraisal reveals substantial evidence gaps across the entire translational spectrum—from basic pharmacology to clinical efficacy, safety, quality control, and regulatory science. To advance WXKL from a promising TCM formula to an evidence-based antiarrhythmic therapy accepted globally, the following prioritized multi-level research agenda is proposed.

MECHANISTIC RESEARCH: FROM DESCRIPTIVE TO MECHANISTIC

Human-Based Experimental Models

A fundamental limitation of existing preclinical research is the near-exclusive reliance on non-human species (rodent, canine, rabbit) and non-cardiac heterologous expression systems. Future studies must prioritize human-relevant models.

Systematic Ion Channel Profiling

Current understanding of the ion channel-mediated effects of WXKL remains fragmentary. To address this gap, a comprehensive and unbiased ion channel profiling screen should be performed using automated patch-clamp platforms (e.g., QPatch, SyncroPatch) to enable high-throughput evaluation of all major cardiac ion channels including NaV1.5, CaV1.2, KV7.1, KV11.1, KV4.3, and HCN4, alongside state-dependent and use-dependent testing protocols to rigorously assess proarrhythmic liability. Concentration–response relationships should also be established across a concentration range relevant to human clinical exposure, with reference values derived from validated clinical pharmacokinetic studies.

Identification of Active Constituent

In the absence of clear evidence identifying the specific compounds responsible for WXKL's antiarrhythmic activity, rational dose optimization, standardized quality control, and formal regulatory approval remain unachievable. A multipronged experimental strategy is therefore required: bioassay-guided fractionation should be applied to sequentially separate WXKL extracts via preparative HPLC, with each fraction tested in electrophysiological assays using hiPSC-CMs to isolate active components and iteratively purify them to single compounds; affinity-based target deconvolution can be performed by immobilizing WXKL constituents on a solid support to pull down interacting proteins from cardiac lysates, with target identification achieved via mass spectrometry; human hepatocyte incubations and in vivo pharmacokinetic studies should be carried out to characterize circulating metabolites, and both parent compounds and metabolites should be evaluated in functional antiarrhythmic assays; finally, the full antiarrhythmic activity of WXKL should be reconstituted using defined mixtures of synthetic or purified constituents to confirm the functional contribution of individual components.

Unbiased Omics Approaches

To move beyond narrow candidate-based hypothesis testing and discover novel mechanisms, unbiased hypothesis-generating omics studies should be implemented, including transcriptomic profiling by RNA-seq in hiPSC-CMs treated with WXKL vs. vehicle, quantitative proteomic mass spectrometry to identify differentially expressed proteins and post-translational modifications, untargeted metabolomics to map metabolic pathway perturbations, and phosphoproteomics for the enrichment and quantification of phosphorylated peptides to identify activated or inhibited signaling nodes. Integration of these multi-omics datasets using systems biology approaches—including network inference, pathway enrichment analysis, and causal reasoning—can reveal previously unanticipated mechanisms of action and prioritize key molecular targets for further experimental validation.

CLINICAL RESEARCH: FROM EFFICACY TO EFFECTIVENESS

High-Quality Confirmatory Trials

Existing trials of WXKL are insufficient for regulatory approval due to methodological limitations and lack of international generalizability. A definitive phase 3 trial should enroll symptomatic paroxysmal AF patients in a double-blind, double-dummy design comparing WXKL, an active comparator, and placebo. The primary endpoint must be AF burden measured by continuous monitoring. The trial requires adequate sample size, 6-12 months treatment duration, international sites, GCP compliance, prospective registration, and independent oversight. Only evidence of this rigor can support global regulatory submission.

Patient–Reported Outcomes and Health Economics

As cardiac arrhythmias substantially diminish patient quality of life, treatment strategies and clinical trial endpoints ought to integrate patient-centered perspectives. Recent studies from Türkiye have contributed to the understanding of AF management and patient-centered outcomes in cardiovascular care.[44,45] Future clinical investigations should therefore incorporate validated disease-specific quality-of-life tools such as the Atrial Fibrillation Effect on Quality of Life (AFEQT) and Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia (ASTA) questionnaires, symptom severity grading instruments including the European Heart Rhythm Association score for AF, standardized assessments of healthcare resource utilization including hospital admissions, emergency department visits, and cardioversion procedures, as well as formal cost-effectiveness evaluations based on quality-adjusted life years.

Pragmatic and Comparative Effectiveness Studies

Following initial regulatory approval, pragmatic clinical trials implemented in routine real-world clinical settings will be essential to characterize the comparative effectiveness of WXKL in unselected patient populations, evaluate long-term treatment adherence, and detect rare or delayed adverse events. Suitable research designs may include large-scale simple trials integrated within electronic health record systems, prospective registry-based RCTs (R-RCTs), and target trial emulation approaches using large observational clinical databases.

Special Populations

Targeted clinical studies are urgently needed for patient subgroups that have been systematically excluded from most previous WXKL trials, including elderly patients aged 75 years and older, individuals with chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), those with moderate to severe hepatic impairment, pediatric patients presenting with arrhythmias, and pregnant or lactating women, for whom evidence should be accumulated through post-marketing surveillance studies.

Pharmaceutical Development: Quality by Design

Establishment of a International Reference Standard

A collaborative initiative involving the manufacturer, academic research laboratories, and official pharmacopoeial authorities including the Chinese Pharmacopoeia, United States Pharmacopoeia, and European Pharmacopoeia should be launched to establish a comprehensive international reference standard for WXKL. This standard should comprise a chemically characterized reference extract with a complete LC-MS/MS fingerprint profile, purified reference compounds corresponding to the major ginsenosides, saponins, and alkaloids present in the formulation, as well as a publicly accessible spectral library to support consistent and reliable quality control across laboratories and manufacturing sites.

Development of Bioactivity Assays

To supplement chemical fingerprint-based quality control, a validated and qualified bioactivity assay should be developed for routine batch-release testing of WXKL. Promising candidate assays include high-throughput hiPSC-CM multi-electrode array analysis for the measurement of field potential duration and beat rate, FLIPR membrane potential dye assays for the efficient assessment of ion channel modulation, and Ca^{2+} transient imaging in hiPSC-CMs to quantify drug effects on intracellular calcium handling. Any such assay must be fully validated in accordance with ICH Q2(R1) guidelines, with satisfactory demonstration of accuracy, precision, linearity, specificity, and robustness for regulatory-compliant quality assessment.

Continuous Manufacturing and Process Analytical Technology

The transition from conventional batch manufacturing to continuous manufacturing integrated with real-time release testing represents a promising strategy to minimize batch-to-batch variability in WXKL production. The implementation of process analytical technology, including near-infrared spectroscopy and Raman spectroscopy, would further enable real-time monitoring and control of critical quality attributes throughout the extraction, concentration, and granulation stages of production, thereby enhancing the consistency, stability, and reliability of the final pharmaceutical product.

Regulatory Science and Policy

Food and Drug Administration and European Medicines Agency Engagement

The sponsor should initiate formal and proactive regulatory dialogue with both the FDA and EMA to support the global clinical development of WXKL. For the FDA, a pre-investigational new drug (IND) meeting should be scheduled to present the proposed nonclinical development plan, CMC strategy, and clinical trial design, while seeking official alignment on the acceptability of the botanical IND application. For the EMA, formal scientific advice should be sought through a comparable structured process, with additional discussion regarding the feasibility of adaptive licensing pathways or eligibility for the PRIME (PRIority MEdicines) scheme to expedite development and regulatory assessment.

Development of a Global Clinical Trial Network

To conduct sufficiently well-powered international clinical trials, a dedicated academic clinical trial network focused on cardiovascular TCM research should be established. This network would develop and maintain fully standardized study protocols and case report forms, provide systematic training for participating investigators in ICH GCP, deliver centralized support for randomization, data management, and independent endpoint adjudication, and facilitate robust multi-center collaborative partnerships across Asia, Europe, and North America.

Post-Approval Commitments and Pharmacovigilance

A proactive and comprehensive pharmacovigilance plan should be designed during the pre-approval phase to support long-term safety monitoring of WXKL. This plan will encompass passive surveillance via spontaneous adverse event reporting systems, active surveillance through a prospective dedicated registry enrolling patients receiving WXKL, and systematic signal detection using advanced data mining approaches applied to electronic health records and administrative claims databases.

CONCLUSION

Wenxin Keli represents one of the most extensively studied TCM formulas for cardiac arrhythmias. Preclinical research has uncovered multiple ion channel and signaling pathway effects that plausibly underlie its antiarrhythmic activity, although the translational relevance of many findings remains uncertain due to the absence of human model validation, undefined active constituents, and incomplete ion channel profiling.

Clinical studies suggest efficacy in reducing AF burden and PVC frequency with a favorable short-term safety profile. However, the evidence base is constrained by methodological

limitations, heterogeneity, potential publication bias, and the absence of internationally conducted, regulatory-grade trials.

Crucially, WXKL's global development is hindered by fundamental challenges in formulation consistency, quality control paradigms that are not aligned with ICH standards, insufficient regulatory toxicology, and unresolved questions about its pharmacokinetics, active constituents, and drug interaction potential.

Rather than asserting therapeutic superiority, the current evidence positions WXKL as a potentially useful adjunct or alternative for selected patients—particularly those intolerant of or refractory to conventional antiarrhythmic drugs. However, this potential can only be realized through a concerted, multi-stakeholder effort involving rigorous mechanistic science, high-quality confirmatory trials, modernization of quality control, and strategic regulatory engagement.

It is hoped that this critical review provides not only a realistic appraisal of where WXKL stands today but also a constructive, actionable roadmap for where it needs to go. The path from traditional remedy to globally accepted therapy is long, but with scientific rigor and international collaboration, it is navigable.

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