Herbs for Atrial Fibrillation

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Abstract

Herbal medicines show much promise for helping patients with atrial fibrillation (AF). Nǎo Xīn Tōng Náng (Brain and Heart Connected Capsule) formula with aspirin, lumbrokinase, and nattokinase are all natural anticoagulants, with varying degrees of evidence supporting their use or potential use in AF patients. The modern Chinese herbal formula Wen Xin Ke Li looks promising for maintaining sinus rhythm in paroxysmal AF patients, as does Shēn Sōng Yǎng Xīn Capsule. Anti-arrhythmic herbs, both for heart rate and for heart rhythm control (as well as preventing paroxysmal AF from recurring), generally used historically and not studied in clinical trials but with substantial supporting preclinical information on their actions, include *Leonurus cardiaca* (motherwort), *L. japonicus* (Chinese motherwort), *Lycopus virginicus* (sweet bugleweed) and related species, *Corydalis yanhusuo* (Chinese corydalis, yán hú suǒ), *Stephania tetrandra* (fēn fáng jǐ, hàn fáng jǐ, stephania), *Rauvolfia serpentina* (Indian snakeroot, rauwfolia), *Crataegus* spp (hawthorn), and *Cinchona* spp. (Peruvian bark). The isolated herbal alkaloids berberine and tetrahydropalmatine have shown promise for AF or related conditions. Further research is needed to determine the full potential of these herbs.

Keywords: atrial fibrillation, herbal medicine, berberine, lumbrokinase, Nao Xin Tong Nang, *Leonurus cardiaca*

Introduction

Atrial fibrillation (AF) continues to be the most common sustained arrhythmia in the developed world. It becomes increasingly common with older age, reaching a prevalence of almost 10% in people >70 years of age.[1] It is moderately more common in men than in women and in people of European descent than in any other ethnic group. Many conventional therapies exist for AF, ranging from electrical or drug cardioversion to various anti-arrhythmic drugs to anticoagulants. While it has become clear from head-to-head trials that lowering heart rate and using anticoagulants is safer (the so-called rate control approach) and just as effective as anti-arrhythmic drugs (the so-called rhythm control approach), neither approach resolves the majority of cases, and often lifelong therapy is required with potential expensive and hazardous agents.[2,3] Here, alternative and adjunctive herbal therapies will be considered for the prevention and treatment of AF.

Anticoagulation: Adjuncts and Alternatives

Preventing the turbulent flow in the atria from creating clots is a major goal of therapy in AF patients. Warfarin used to be the drug of choice for this purpose, but it often came with the advice to avoid eating a high vitamin K–containing diet, which functionally meant eating a diet low in vegetables. The actual problem is that patients often eat highly variable amounts of vitamin K in their diets. When they exceed 150 µg/day (which is rare), interference can occur. Many studies confirm that dietary stability, not overall vitamin K intake, is the real issue.[4] Nevertheless, most patients are still told to eat diets low in green leafy vegetables that are high in vitamin K, and the large majority follow this advice.[5] This results in a unhealthy diet for the heart that may exacerbate AF and aggravate arterial calcification.[6,7] There is some evidence that consuming a vegetable-rich Mediterranean diet helps reduce vascular events in AF patients without interfering with warfarin efficacy.[8,9] Increasingly, studies show that the old standby aspirin as well as the newer drug dabigatran are more or just as effective as warfarin with less toxicity, at least in low- to moderate-risk patients.[10] Dabigatran, however, is dramatically more expensive. Aspirin also reduces stroke risk in AF patients, but not as effectively as warfarin.[11]

One clinical trial randomized 151 Chinese patients with nonvalvular AF and high thromboembolism risk to 100 mg of aspirin and 1.6 g three times a day (t.i.d.) of the herbal formula Nǎo Xīn Tōng Náng (Brain and Heart Connected Capsule) or warfarin (dose adjusted to achieve INR 2–3) for 12 months.[12] The contents of Brain and Heart Connected Capsule are listed in Table 1. All patients had variants in the vitamin K epoxide reductase gene associated with strong susceptibility to warfarin's effects. The majority of patients had hypertension and were taking a range of antihypertensive drugs, notably beta-blockers, which were also useful for rate control for their AF. There was no difference in the rate of ischemic strokes, deaths, or minor bleeding episodes between the groups. Episodes of severe bleeding were significantly more common in the warfarin group. A previous study using a slightly modified version

Table 1. Components of Nǎo Xīn Tōng Náng (Brain and Heart Connected Capsule)[a]

Latin name	Common names	Part used	Percent in formula
Astragalus membranaceus	Astragalus, huáng qí	Root	16%
Paeonia lactiflora	Red peony, chì sháo	Root with bark	7%
Angelica sinensis	Dong quai, dāng guī	Prepared root	7%
Salvia miltiorrhiza	Red sage, dān shēn	Root	7%
Ligusticum chuanxiong	Szechuan lovage, chuān xiōng	Root	7%
Morus alba	Mulberry twig, sāng bái pí	Branch	7%
Pheretima spp.	Earthworm, dì lóng	Whole animal	7%
Hirudo spp.	Leech, shuǐ zhì	Whole animal	7%
Prunus persica or *P. davidiana*	Peach pit, táo rén	Seed	7%
Achyranthes bidentata	Achyranthis, niú xī	Root	7%
Spatholobus suberectus	Spatholobus, jī xuè téng	Root and vine	5%
Cinnamomum cassia	Cassia cinnamon, guì zhī	Branch	5%
Boswellia carterii	Frankincense, rū xiāng	Resin	4%
Carthamus tinctorius	Safflower, hóng huā	Flower	4%
Commiphora myrrha	Myrrh, mò yào	Resin	4%
Buthus martensii	Scorpion, quán xiē	Whole animal	4%

[a]Ma XH, Lv B, Li P, et al. Identification of "multiple components-multiple targets-multiple pathways" associated with Naoxintong Capsule in the treatment of heart diseases using UPLC/Q-TOF-MS and network pharmacology. Evid Complement Altern Med 2016;2016:9468087.

of this formula found it effective compared to clopidogrel in patients undergoing percutaneous coronary procedures.[13]

Brain and Heart Connected Formula is based on the traditional Chinese herbal formula called Bǔ Yáng Huán Wǔ Tāng (Tonify the Yang to Restore the Five-Tenths Decoction) developed by Wáng Qīng-Rèn in his book *Yī Lín Gǎi Cuò* (*Correction of Errors Among Physicians*) written in 1830 CE. Tonify the Yang to Restore the Five-Tenths Decoction use was associated with reduced mortality in stroke patients according to an epidemiologic study in Taiwan.[14]

An interesting component of the Brain and Heart Connected Capsule formula is *Pheretima* spp. (earthworm, dì lóng). Earthworms are organisms in Class Oligochaeta. *Pheretima* is a Southeast Asian genus of earthworms in the family Megascolecidae. *Lumbricus* is a holoarctic (Northern European, Northern Asian, and Canadian) genus of earthworms in the family Lumbricidae. *Lumbricus* spp. were introduced to the United States by European invaders and have naturalized there, being the familiar earthworms now seen in most locales. Both of these genera of earthworm, as well as related Lumbricidae family worms *Eisenia* spp., contain fibrinolytic serine proteases.[15–17] These proteins are closely homologous in structure and activity, though lumbrokinase is the most widely known and available.[18] Despite its name, lumbrokinase is not a kinase-type enzyme but a protease. Besides directly lysing fibrin, these proteins generally also activate plasminogen. This action is very similar to that of streptokinase derived from *Streptococcus pyogenes*, a widely-used fibrinolytic for ST-elevation myocardial infarction when percutaneous coronary intervention is not available or not an option.[19] Oral use of crude earthworm powder is a very well established part of Chinese medicine, having been discussed in the *Shén Nóng Běn Cǎo Jīng* (*Divine Husbandman's Classic of the Materia Medica*; a foundational text written somewhere between 300 BCE and 200 CE). Animal studies confirm that oral administration of powdered *Pheretima aspergillum* can resolve ischemic strokes.[20]

Though no studies were identified on use of lumbrokinase or earthworm extracts as anticoagulants in AF patients, other studies of lumbrokinase are promising. Two small human studies initially reported on use of oral lumbrokinase. One single-blind trial randomized 51 Chinese patients having acute ischemic strokes to 400 mg t.i.d. of lumbrokinase plus dextran or dextran alone for one month.[21] The lumbrokinase used was not further characterized in the paper, in terms of either activity units or whether enteric-coated capsules were used. There was no difference between the groups in relieving stroke symptoms. Fibrinogen levels fell, while tissue plasminogen activator (tPA) activity rose significantly in the treatment group compared to controls. A case series of 10 Indonesian patients with angiographically confirmed stable angina found that 300,000 units t.i.d. of lumbrokinase (enteric coating not stated) improved symptoms in six patients and improved average nuclear stress test scores 37–39%.[22] All patients were simultaneously taking 81 mg of aspirin per day in this case series.

In one open trial, 310 Chinese patients who had suffered an ischemic stroke or transient ischemic attack (TIA) in the preceding six months were randomized to 600,000 units t.i.d. of lumbrokinase 30 minutes before a meal or placebo for one year.[23]

Lumbrokinase powder was packaged in enteric-coated capsules. All patients received standard post-stroke supportive therapies. Total vascular events including repeat strokes or TIA as well as myocardial infarctions were significantly reduced in the lumbrokinase group compared to controls. There was no effect on clotting factors and no difference in mild adverse effects between the groups (transient dizziness, nausea, and vomiting). Fibrinogen, D-dimer, and blood viscosity levels fell significantly, while tPA activity rose significantly in the lumbrokinase group compared to controls. Oral lumbrokinase (490 mg t.i.d.) was safe in a double-blind trial in 20 healthy Indonesian adults that lasted 14 days.[24] Large, double-blind, randomized trials appear warranted for stroke prevention; a preliminary trial in AF patients also appears warranted. Any AF patient who chooses to use lumbrokinase in place of anticoagulants that have been proven effective is taking a significant risk, as there is simply no evidence as to whether it will be effective in this setting.

Nattokinase is a similar protease complex isolated originally from nattō, a traditional Japanese soy food that is made with the bacterium *Bacillus natto*.[25] Black soybeans fermented with specific strains of *Bacillus subtilis* and other species are a staple food in China, known as dòuchǐ in Mandarin, and also produce nattokinase.[26] Batch culture and recombinant production of nattokinase are now more common ways of producing the product for encapsulation.[27,28] Nattokinase is clearly fibrinolytic and thrombolytic based on preclinical studies.[29,30]

A single dose of 2000 units of a nattō-derived nattokinase to healthy American volunteers resulted in measureable levels of nattokinase in their blood.[31] This extract has vitamin K deliberately removed from it, unlike most nattō. In an open trial, 45 Chinese adults (some healthy, some with cardiovascular risk factors, and some undergoing hemodialysis) took 4000 units of nattokinase daily for two months.[32] Fibrinogen, factor VII, and factor VIII levels fell significantly compared to baseline in all groups (by 7–19% depending on the parameter and the subgroup).

No clinical trials were identified on the use of nattokinase or nattō for prevention of stroke or other thromboembolic complications of AF. One trial randomized 204 Italian adults to take a combination of pine bark extract and 300 mg of nattokinase two hours before six hours into a long-duration airplane flight or placebo.[33] Blinding was not described in the study, and the details including potency units for the nattokinase were not disclosed. Edema, episodes of superficial or deep vein thrombosis, and D-dimer levels were all improved significantly with the treatment compared to placebo. The treatment was extremely safe. This provides preliminary evidence that oral nattokinase is an active fibrinolytic, but of course larger trials specifically in AF patients are required to determine its utility in this setting.

At least two trials have shown that nattokinase lowers blood pressure. In the first, 73 Korean hypertensive adults were randomized to 2000 units of nattokinase (the same vitamin K–free extract mentioned above) or placebo daily for eight weeks in a double-blind fashion.[34] Systolic and diastolic blood pressure was lowered significantly more by nattokinase than placebo, though the absolute changes were small (6/3 mmHg, respectively). Adverse effects were minimal. An essentially identical trial performed in 79 American patients with hypertension found similar results.[35] Men had a larger blood pressure benefit in this trial than women did.

Anticoagulants only address the complications of AF, however. The remaining herbs discussed below are used to attempt to deal with AF directly.

Mother the Heart

In a previous review by the author of anti-arrhythmic herbs in this journal 13 years ago, one of the most important highlighted was the European native herb *Leonurus cardiaca* (motherwort).[36] This herb has withstood the test of time, with its affinity to the heart attested by its Latin name (*cardiaca*) and its use for tachyarrhythmias and other heart problems since antiquity.[37] As the common name of this herb suggests, it has another strong historical use as a uterine tonic. It is also used clinically as a nervine to help with mild insomnia and anxiety. Surprisingly, given its long continuous use for arrhythmias, there are still no clinical trials assessing its efficacy for AF or any other arrhythmia.[38] Clinically, it seems most helpful for tachyarrhythmias, functional palpitations, and tachycardia due to hyperthyroidism. *Leonurus japonica* (yì mǔ cǎo, literally "mother the heart herb," Chinese motherwort), formerly *L. heterophyllus* or *L. artemisia*, is used for almost identical purposes as European motherwort, with even better support for its uterine tonic effects.[39] The close similarity even of their common names is striking.

Since our original description of this plant in 2003, several pharmacological studies have been published investigating the chemistry and mechanism of the anti-arrhythmic effect of both these species of motherwort. In one of the most complete, a complex dichloromethane, aqueous, and ethanolic extract of motherwort was shown to lengthen the duration of action potentials in isolated cardiac pacemaker cells.[40] This was strongly related to increasing inward depolarizing sodium and potassium channels, which is very similar to the mechanism of action of class III anti-arrhythmic drugs. Although class III anti-arrhythmics are indicated in AF, particularly when there is tachycardia, they also carry the risk of provoking ventricular arrhythmias by prolonging the Q-T interval. There are absolutely no historical or modern case reports of any adverse effects from motherwort consistent with such problems, so it is possible that it operates either differently or less potently in humans, but caution is warranted combining it with drugs that can lengthen the Q-T interval until safety is proven. Animal studies only show a maximum of a 29% prolongation of the Q-T interval with high doses of motherwort extracts.[41] This may explain the lack of observation of ventricular arrhythmias being induced by the herb. The anti-ischemic and cardioprotective effects seen with Chinese motherwort in preclinical research is comforting and may offset this theoretical toxicity issue.[42,43] Though one study found that intravenous injection of a Chinese motherwort extract reduced platelet aggregation and had other anticoagulant effects, it is unclear if this is relevant to oral use of the herb.[44]

Other research has shown that the pseudoalkaloid leonurine acts as a very weak L-type calcium channel blocker, like class IV anti-arrhythmic drugs.[45] This could offset the Q-T interval prolongation caused by motherwort. A fairly recent chromatographic analysis of *Leonurus* species found that only *L. japonica*'s aerial parts (not the fruit) contains leonurine, not *L. cardiaca*.[46] This is intriguing, as another paper found that leonurine accounted in part for the non-benzodiazepine $GABA_A$ receptor agonist effects of *L. japonica* but not for extracts of *L. cardiaca*.[47] However, *L. cardiaca* extracts still had activity in this model, despite the absence of leonurine. The mere absence of one compound does not rule out a calcium channel blockade effect for *L. cardiaca*. An earlier study found the phenylethanoid glycoside lavandulifolioside from *L. cardiaca*, as well as crude butanolic extracts of the herb, also lengthened the Q-T interval while slowing heart rate and reducing blood pressure in rats.[40] This same research group earlier found that an aqueous extract of motherwort had similar effects.[48] Clinical trials are needed to determine if any species of *Leonurus* has a clinically relevant calcium channel blocking effect or any anti-arrhythmic effects.

Motherwort and Chinese motherwort are extremely safe. One study in adult rats found no observable adverse effects at up to 1 g/kg/day for 13 weeks using freeze-dried powder of Chinese motherwort.[49] Since *Leonurus* spp. are all bitter, they may occasionally upset patients' stomachs. They are best taken with food to prevent this problem.

Bugleweeds

Lycopus virginicus (sweet bugleweed) and closely related species found in Eurasia and North America, such as *L. europaeus* (gypsywort), *L. lucidus* (zé lán, shiny bugleweed), *L. americanus* (American bugleweed), *L. asper* (rough bugleweed), and *L. uniflorus* (northern bugleweed), are akin to *Leonurus* in that they are bitter members of the Lamiaceae family with calming, anti-arrhythmic properties. The aerial parts of all species are used. They are all perhaps most famous as effective remedies for Graves' disease, but also useful as a mild hemostatic.[50,51] The famous Eclectic physician Harvey Wickes Felter, MD, wrote of bugleweed as being primarily effective for "vascular excitement, with rapid, tumultuous action of the heart, but lacking power."[52]

Unfortunately, only one modern study of any of these herbs could be located related to AF. In an ex vivo study, shiny bugleweed ethanol extract blocked L-type calcium channels.[53] The triterpenoids oleanolic and ursolic acids, both of which are found in many herbs, including *Lycopus* spp., have been shown to reduce heart rate in insulin-resistant, salt-sensitive, hypertensive rats by an unknown mechanism, though further evaluation in preclinical studies strongly suggested that at least oleanolic acid was acting as a β-adrenergic antagonist.[54,55] If confirmed, this would be a highly unusual action and most useful in AF patients, but clinical trials are needed to determine whether this is true. In the meantime, bugleweed tincture is recommended as an empirically effective treatment for AF patients at a dose of 1–2 mL t.i.d. Bugleweed tinctures are generally quite safe at this dose and do not cause hypothyroidism in euthyroid patients (as their main action in Graves' disease is to prevent the causative thyroid stimulating antibodies from activating the thyrotropin receptor, not through any direct thyrosuppressive action[56]).

Alkaloids and Herbs That Contain Them

Isoquinoline, quinoline, and aporphine alkaloids are a group of important, related, medicinal compounds including berberine, tetrahydropalmatine, papaverine, morphine, protopine, boldine, emetine, tetrandrine, sanguinarine, yohimbine, reserpine, and ajmaline. Many of these have been reported to affect potassium and calcium channels (see Table 2) and thus may have anti-arrhythmic effects.

Berberine is a good example and one of the best studied of the anti-arrhythmic isoquinoline alkaloids. Like most of these alkaloids, it appears to act primarily by inhibiting a range of potassium channels, but most specifically the human ether-à-go-go related gene (hERG; see sidebar) and thus the inward-rectifying potassium channel (IRK; see citations in Table 2). In rabbits, both oral and intravenous berberine has been shown to correct acetylcholine-induced AF rapidly.[57] This did not occur from inhibition of acetylcholine receptors but instead through IRK inhibition.

Though no clinical trials appear to have been done on berberine in patients with AF, several others show it does have anti-arrhythmic effects in humans. In a study of 156 Chinese patients with congestive heart failure (CHF) and ventricular tachycardia or premature complexes, patients were randomized to either 1.2–2 g of berberine once a day or placebo for 8 weeks.[58] All patients were simultaneously taking angiotensin-converting enzyme inhibitors, digoxin, diuretics, and nitrates. CHF symptoms were significantly reduced, exercise capacity significantly increased, and mortality significantly decreased by berberine compared to placebo. Frequency and severity of ventricular premature complexes were significantly reduced by berberine versus placebo as well. No adverse effects were associated with berberine. Berberine's well-documented antidiabetic, antithrombotic, and anti-atherosclerotic effects also all recommend it at least as an adjunct therapy in AF patients.[59–61] A typical dose is 300–500 mg t.i.d. with meals. It is not known if whole plant extracts of herbs that contain berberine are effective; they have no clear traditional history of use for AF or other arrhythmias.

Corydalis yanhusuo (Chinese corydalis, yán hú suǒ) is in the Papaveraceae family, and its isoquinoline alkaloids have many anti-arrhythmic effects. Tetrahydropalmatine exhibits class IV anti-arrhythmic activity (see Table 2). Allocryptopine and benzyltetrahydropalmatine are two additional alkaloids found in this species as well as other closely related species (e.g., *C. ambigua*) that inhibit hERG in vitro.[62] In other in vitro models, allocryptopine and protopine (another corydalis alkaloid) have shown a range of anti-arrhythmic effects.[63,64]

Tetrahydropalmatine has been evaluated in two low-quality case series. In one, 24 Chinese AF patients were given 60 mg

Table 2. Preclinical Anti-Arrhythmic Effects of Isoquinoline, Quinoline, and Aporphine Alkaloids

Alkaloid (and major herbal source)	Model	Effect	Reference
Tetrandrine (from *Stephania tetrandra*)	Bovine chromaffin cells	Blocks all types of CCs	Weinsberg 1994[a]
	Rat cardiac myocytes and neurons	L- and T-type CC blocker; K_{Ca} inhibitor	Wang 1995[b]
	Rat aortic smooth muscle cells	L-type CC inhibitor	Wu 1997[c]
	Bovine aortic endothelial cells	IRK inhibitor	Liu 2000[d]
Tetrahydropalmatine (from *Corydalis yanhusuo*)	Guinea pig cardiac myocytes	Blocks L-type CC	Huang 1999[e]
	Isolated perfused rat heart	Inhibited CC	Chan 1999[f]
Berberine (from *Berberis* spp., *Mahonia* spp., *Coptis* spp., and *Hydrastis canadensis*)	Rats with MI and DM	Inhibited IRK; alleviated clinical arrhythmias	Wang 2011[g]
	Guinea pig cardiac myocytes	Inhibited IRK, hERG and ODRK	Li 2001[h]
	Human embryonic kidney cells, *Xenopus* oocytes	Inhibited hERG and KCN	Rodriguez-Menchaca 2006[i]
Ajmaline (from *Rauvolfia serpentina*)	Human embryonic kidney cells, *Xenopus* oocytes	Inhibited hERG	Kiesecker 2004[j]
	Frog myelinated neurons	ODRK, sodium channel inhibitor	Khodorov 1983[k]
Reserpine (from *Rauvolfia serpentina*)	Hamster ovary cells	Inhibited hERG	Xia 2011[l]
	Xenopus oocytes	Inhibited hERG	Schramm 2014[m]
Protopine (from *Eschscholzia californica*, *Corydalis yanhusuo*)	*Xenopus* oocytes	Inhibited hERG	Schramm 2014[m]
	Rat aorta	CC inhibitor	Ko 1992[n]
Boldine (from *Peumus boldo*)	*Xenopus* oocytes	Inhibited hERG	Schramm 2014[m]

[a]Weinsberg F, Bickmeyer U, Wiegand H. Effects of tetrandrine on calcium channel currents of bovine chromaffin cells. Neuropharmacology 1994;33:885–890.
[b]Wang G, Lemos JR. Tetrandrine: A new ligand to block voltage-dependent Ca2 + and Ca(+)-activated K + channels. Life Sci 1995;56:295–306.
[c]Wu SN, Hwang TL, Jan CR, Tseng CJ. Ionic mechanisms of tetrandrine in cultured rat aortic smooth muscle cells. Eur J Pharmacol 1997;327:233–238.
[d]Liu WB, Liu GQ, Xiao H, et al. Tetrandrine inhibits inward rectifying potassium current in cultured bovine aortic endothelial cells. Acta Pharmacol Sin 2000;21:1115–1118.
[e]Huang K, Dai GZ, Li XH, et al. Blocking L-calcium current by l-tetrahydropalmatine in single ventricular myocyte of guinea pigs. Zhongguo Yao Li Xue Bao 1999;20:907–911.
[f]Chan P, Chiu WT, Chen YJ, et al. Calcium influx inhibition: Possible mechanism of the negative effect of tetrahydropalmatine on left ventricular pressure in isolated rat heart. Planta Med 1999;65:340–342.
[g]Wang LH, Yu CH, Fu Y, et al. Berberine elicits anti-arrhythmic effects via IK1/Kir2.1 in the rat type 2 diabetic myocardial infarction model. Phytother Res 2011;25:33–37.
[h]Li BX, Yang BF, Zhou J, et al. Inhibitory effects of berberine on IK1, IK, and HERG channels of cardiac myocytes. Acta Pharmacol Sin 2001;22:125–131.
[i]Rodriguez-Menchaca A, Ferrer-Villada T, Lara J, et al. Block of HERG channels by berberine: Mechanisms of voltage- and state-dependence probed with site-directed mutant channels. J Cardiovasc Pharmacol 2006;47:21–29.
[j]Kiesecker C, Zitron E, Lück S, et al. Class Ia anti-arrhythmic drug ajmaline blocks HERG potassium channels: mode of action. Naunyn Schmiedebergs Arch Pharmacol 2004;370:423–435.
[k]Khodorov BI, Zaborovskaya LD. Blockade of sodium and potassium channels in the node of Ranvier by ajmaline and N-propyl ajmaline. Gen Physiol Biophys 1983;2:233–268.
[l]Xia MH, Shahane SA, Huang RL, et al. Identification of quaternary ammonium compounds as potent inhibitors of hERG potassium channels. Toxicol Appl Pharmacol 2011;252:250–258.
[m]Schramm A, Saxena P, Chlebek J, et al. Natural products as potential human ether-a-go-go-related gene channel inhibitors - screening of plant-derived alkaloids. Planta Med 2014;80:740–746.
[n]Ko FN, Wu TS, Lu ST, et al. Ca(2 +)-channel blockade in rat thoracic aorta by protopine isolated from *Corydalis* tubers. Jpn J Pharmacol 1992;58:1–9.
CC, calcium channel; DM, diabetes mellitus; hERG, human ether-à-go-go related gene; K_{Ca}, calcium-activated potassium channel; KCN, potassium voltage-gated channel; IRK, inward-rectifying potassium channel; MI, myocardial infarction; ODRK, outward delayed rectifier potassium channel.

of oral tetrahydropalmatine.[65] In patients with a left atrial diameter <45 mm, 80% had reversal or improvement of AF (compared to just 30% when the left atrium was larger than this). In patients with chronic AF, 3/8 (38%) improved, while 8/10 (80%) patients with short-term AF improved or were converted to normal rhythm. Another study showed that 2 mg/kg tetrahydropalmatine given intravenously (i.v.) was effective for 14 Chinese patients with pre-excitation syndromes such as Wolf-Parkinson-White syndrome.[66] This syndrome can be associated with problems including sudden cardiac death if AF-related dysrhythmic waves propagate into the ventricles through the abnormal accessory conduction pathway that has developed connecting the atria to the ventricles. Only mild adverse effects occurred in this study. Clearly, more research is needed, but corydalis and its alkaloids look promising for treating AF and other arrhythmias.

Stephania tetrandra (fěn fáng jǐ, hàn fáng jǐ, stephania) of the Menispermaceae family is an intriguing vine, the root of which has been used for a very long time in Chinese medicine. Its isoquinoline alkaloids, most notably tetrandrine, as documented in Table 2, inhibit calcium and potassium channels, giving this herb type III and IV anti-arrhythmic activity. Unfortunately, it has been confused with the completely unrelated herb *Aristolochia fangchi*, which is also called fáng jǐ (but more correctly,

Human Ether-à-go-go-Related Gene

This gene, more systematically called the potassium voltage-gated channel subfamily H member 2 (*KCNH2*) gene on chromosome 7q36.1, codes for the protein Kv11.1 or alpha subunit. Four subunits together form the rapid delayed inward-rectifying potassium channel (IRK) in cardiac myocytes. This channel is one of the main targets of many of the anti-arrhythmic herbal compounds that have been studied, and accounts for these compounds and the herbs that contain them, acting at least somewhat like class III anti-arrhythmic drugs (which more potently inhibit IRK). Inhibition of IRK prolongs the Q-T interval on the electrocardiogram (producing a syndrome known as torsades de pointes), and if it either prolongs it too far or prolongs it in a patient who has a congenital mutation in IRK channels or other areas causing them to have a prolonged Q-T interval anyway, ventricular fibrillation and sudden cardiac death can result. Numerous pharmaceuticals prolong the Q-T interval, including chloroquine, fluoroquinolones, macrolide antibiotics, many tricyclic antidepressants, azole antifungals, haloperidol, ondansetron, triptan antimigraine drugs, and many others.[a] hERG is also associated with some leukemias. It is considered a negative drug target when developing agents other than class III anti-arrhythmics: something to test and make sure a drug does not inhibit so as to avoid the rare but catastrophic complications of an overly prolonged Q-T interval. Berberine has been shown in vitro to enhance significantly the Q-T prolongation caused by clarithromycin.[b] It also inhibited breakdown of clarithromycin by CYP3A4, thereby increasing the amount of the drug available for Q-T prolongation in another model in this same study. Caution is warranted when combining berberine with Q-T prolonging drugs clinically, though no clinical reports of toxicity have been published or observed in practice.

[a]Kao LW, Furbee RB. Drug-induced q-T prolongation. Med Clin North Am 2005;89:1125–1144, x.

[b]Zhi D, Feng PF, Sun JL, et al. The enhancement of cardiac toxicity by concomitant administration of berberine and macrolides. Eur J Pharm Sci 2015;76:149–155.

and to distinguish it properly, guǎng fáng jǐ; known as birthwort or aristolochia in English). Birthwort contains the dangerously nephrotoxic, carcinogenic compound aristolochic acid, and inadvertent use of that herb when people thought it was stephania resulted in a number of deaths and serious harm.[67] Stephania does not contain aristolochic acid and is very safe, but it has become so politically problematic (due to ongoing fears that inadvertent mistakes might be made despite heightened awareness of this problem) that it is mostly unavailable.

Crude extracts of stephania containing 7% tetrandrine were shown to be anti-arrhythmic in rats to a very similar degree to the calcium channel blocking-drug verapamil.[68] Intriguingly, a similar complex extract with 9% tetrandrine was more effective than anti-arrhythmics in rats than isolated tetrandrine or a combination of tetrandrine and fangchinoline, another isoquinoline alkaloid from stephania.[69] As is so often the case, this demonstrates synergy among constituents in the whole plant extract and argues against use of the isolated constituent. However, much study on the isolated compound shows certain effects. Human studies are warranted on extracts of this herb to determine for certain if it could be useful in patients with AF.

Indian Snakeroot

Rauvolfia serpentina (Indian snakeroot, rauwolfia) is a famous traditional medicine from South Asia, as its name suggests. It is interchangeable with its close cousin, the unfortunately named *R. vomitoria* (African rauwolfia).[70] Both herbs contain the alkaloids reserpine and ajmaline, which have diverse anti-arrhythmic actions, as summarized in Table 2. Unfortunately, there is a lack of clinical research on the whole herb or extracts of Indian snakeroot for patients with AF, but if the person is tachycardic, then these are empirically helpful at doses delivering 0.05–0.1 mg of reserpine per day. Whole rauwolfia extracts frequently cause a stuffy nose and sometimes an upset stomach (transiently), but are otherwise very safe at this dose. In particular, the fear that reasonable doses of rauwolfia cause depression are not only unfounded, but clinical trials have actually shown that they are helpful in treating depression.[71]

Purified ajmaline (given i.v. in a hospital), though not widely available, has been shown to be preferable over flecainide for diagnosis of Brugada syndrome, a genetic arrhythmia that agents such as flecainide can unmask before it causes sudden cardiac death.[72] Ajmaline i.v. has also been shown, in a head-to-head clinical trial of 31 German patients, to be superior to lidocaine at terminating persistent ventricular tachycardia.[73] In this study, ajmaline lengthened the QRS duration, unlike lidocaine, an effect that strongly suggests it would help with AF. A similar trial found ajmaline i.v. as effective as propafenone at terminating AF in nine German patients.[74] Older research suggests ajmaline is more effective and is certainly much safer than quinidine for AF.[75] However, doses >300 mg orally or >10 mg/min infusion ajmaline can be lethal due to heart block, dysrhythmia, and respiratory depression.[76] Neutropenia may occur with ajmaline use, and there are also isolated cases of agranulocytosis and hepatitis due to ajmaline.[77] There are no reports of crude rauwolfia causing such symptoms.

Miscellaneous Asian Herbal Formulas

Wen Xin Ke Li is a modern Chinese herbal formula developed at Guanganmen Hospital, Chinese Academy of Chinese Medical Sciences, containing unknown ratios of *Nardostachys jatamansi* = *N. chinensis* (nardostachys, gān song) root, *Codonopsis pilosula* (codonopsis, dǎng shēn) root, *Polygonatum sibiricum* (Siberian Solomon's seal, huáng jīng) rhizome, *Panax notoginseng* (tienchi ginseng, sān qī) root, and amber (hǔ pò). The total daily dose is 5–10 g. In ex vivo canine heart tissue, it inhibited sodium channels in atrial tissue, prolonging

atrial contraction, with minimal effects on ventricular function.[78] It was able to maintain normal rhythm and prevent recurrence of AF in this model.

A meta-analysis of 14 clinical trials of the formula, all conducted in China, for patients with paroxysmal AF, found that overall the quality of trials was low.[79] P-wave dispersion was significantly improved in patients taking Wen Xin Ke Li alone or combined with conventional medications compared to patients taking such medications alone. The same was true when looking at the outcome measure of maintaining sinus rhythm/preventing recurrent AF. In those trials reporting adverse effects, they were all mild and generally appeared to be due to the effects of concomitant conventional medications being used. Wen Xin Ke Li needs to be tested in a large, high-quality clinical trial, but has promise for helping patients with paroxysmal disease stay out of AF.

Another modern herbal formula named Shēn Sōng Yǎng Xīn Capsule, roughly translating to ginseng pine cultivating the heart, has been studied in patients with paroxysmal AF. It contains undisclosed ratios of *Panax ginseng* (bái rén shēn, white ginseng) root, *Ophiopogon japonicus* (mài dōng, mondo grass) rhizome, *Cornus officinalis* (shān zhū yú, Asiatic Cornelian cherry) fruit, *Salvia miltiorrhiza* (dān shēn, red sage) root, *Ziziphus jujube* (suān zǎo rén, jujube) fruit, *Taxillus chinensis* (sāng jì sheng, mulberry mistletoe) whole plant, *Paeonia lactiflora* (chì sháo, red peony) root with bark, *Eupolyphaga sinensis* (tǔ biē, wingless cockroach) body, nardostachys, *Coptis chinensis* (huáng lián, goldthread) root, *Schisandra sphenanthera* (nán wǔ wèi zǐ, southern schisandra) fruit, and *Elephas americanus* (lóng gǔ, dragon bone, which is fossilized mastodon bone). A meta-analysis of 22 randomized clinical trials conducted in China, all of low or poor quality (only one described any kind of blinding, for example), compared this formula combined with anti-arrhythmic drugs and/or "routine treatment" (usually not defined) to these treatments by themselves.[80] The doses used were 1.2 or 1.6 g t.i.d. of the herbal formula. Shen Song Yang Xin capsules were significantly superior to "routine treatment" for improving P-wave dispersion and reducing frequency of AF attacks. It was not clear whether Shen Song Yang Xin capsules combined with anti-arrhythmic drugs alone were superior to anti-arrhythmic drugs alone. Only a few studies reported on adverse effects, and they were all mild and less common than with anti-arrhythmic drugs. While promising, a rigorous, large-scale clinical trial is needed to confirm these reports. Note that this formula has also been shown in a similar meta-analysis with similarly low-quality clinical trials to be useful for premature ventricular contractions and in a modern, higher-quality, placebo-controlled, randomized trial for bradycardia.[81,82]

Other Potential Herbal Therapies

Many other herbs have shown promising actions in preclinical research, suggesting they might help patients with AF but are lacking clinical trials to prove this. *Crataegus* spp. (hawthorn) leaf, flower, and fruit have a strong history of use as cardiac tonics in general. In vitro research shows that extracts of hawthorn can inhibit IRK.[83] There is some concerning research that it may exacerbate development of arrhythmias after ischemia, but the relevance of such in vitro models to actual practice is highly dubious.[84] It does not appear to have β-blocking effects, but its flavonoids do inhibit cAMP phosphodiesterase in vitro in myocytes.[85]

As the botanical source of the anti-arrhythmic drug quinidine, *Cinchona* spp. (Peruvian bark) is feasibly active as an

Table 3. Probable Anti-Arrhythmic Classes of Natural Products Relevant to Atrial Fibrillation

Singh-Vaughn Williams class and main use	Mechanism(s) of action	Natural product
1a (prevention of PAF)	Sodium channel blockade (intermediate association/ disassociation); also exhibit class III activity (block IRK)	Ajmaline from *Rauvolfia serpentina* (Indian snakeroot)
		Quinidine from *Cinchona* spp. (Peruvian bark)
		Wen Xin Ke Li[a]
III (maintenance of normal rhythm)	IRK blockade; also exhibit class IV (CCB) activity	*Leonurus cardiaca* (motherwort), *L. japonica* (Chinese motherwort)
IV (reduce ventricular rate)	CCB; most also exhibit class III (IRK blockade) activity	Tetrandrine from *Stephania tetrandra* (stephania)
		Tetrahydropalmatine from *Corydalis yanhusuo* (corydalis)
		Berberine from *Berberis* spp. (barberry), etc.
		Lycopus spp (bugleweed)[a]
		Shen Song Yang Xin[b]
V (prevent ventricular fibrillation)	Parasympathomimetic at AV node	Digoxin from *Digitalis* spp. (foxglove), other cardiac glycosides

[a]No known class III activity.
[b]Class I and IV activity shown in preclinical research. (Li N, Huo YP, Ma KJ, et al. Effects of solution of dry powder of Shen Song Yang Xin capsule on sodium current and L-type calcium current in ventricular myocytes: experiment with guinea pig [in Chinese]. Zhonghua Yi Xue Za Zhi 2007;87:995–998.)
AV, atrioventricular; CCB, calcium channel blockade; PAF, paroxysmal atrial fibrillation.

anti-arrhythmic in crude extracts.[86] This has not been formally tested in any clinical trial that could be located. Such an effect of Peruvian bark is not mentioned by any of the major Eclectic writers, though this herb was widely used by them for many other purposes. Given the known adverse effects of quinidine and whole Peruvian bark, this treatment should be withheld for AF patients until rigorous research can be conducted and its place in therapy determined.

Conclusion

Arguably, herbal medicine has long provided many of the mainstays in treatment of AF, ultimately being the source of amiodarone (semi-synthetically from *Ammi visnaga* or khella), quinidine, ajmaline, and digoxin to name just a few. While other treatments have superseded many of these, they have never completely gone out of use and may be seeing a resurgence. Given all this, it should not be surprising then that whole herbs and herbal extracts, as well as other compounds from them, could and do play a role in helping patients with AF as well (see Table 3).

Numerous European, American, and Asian plants show great promise in helping AF patients. Here, those that have been studied clinically have been highlighted, including as anticoagulants, heart rate and heart rhythm control agents, and for preventing recurrence of paroxysmal AF. The range of research is wide, and most have not been rigorously proven effective, but they are generally safe enough for use with careful monitoring. Further clinical trials on these herbs and their constituents alone and, preferably, in combination are eagerly awaited to determine fully their place in therapy. ■

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