



A review on plants and herbal components with antiarrhythmic activities and their interaction with current cardiac drugs

Ahmad Beik ^a, Siyavash Joukar ^{b, a, c, *}, Hamid Najafipour ^b

^a Physiology Research Center, Institute of Basic and Clinical Physiology Sciences, Department of Physiology and Pharmacology, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran

^b Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Department of Physiology and Pharmacology, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran

^c Neuroscience Research Center, Institute of Neuropharmacology, Department of Physiology and Pharmacology, Afzalipour School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

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ABSTRACT

This paper aimed to compile information on plants or their compounds which have experimentally shown antiarrhythmic effect and to scrutinize the efficacy and potency of them and their potential interaction with conventional cardiac drugs.

Literature searches were accomplished by using numerous electronic databases, and the available knowledge on different parts of herbs and their ingredients with antiarrhythmic effects up to 2019 were identified and collected.

The results indicate that 36 herbs or their derivatives can be effective in the treatment of arrhythmias, especially in animal and cellular models. They affect various ionic channels in different action potential phases. The alterations in ionic currents lead to changing in the amplitude and duration of the action potential, effective refractory period, maximum velocity, resting membrane potential, channel trafficking, or intracellular calcium concentration. The agents that prolong action potential duration and effective refractory period such as dauricine and sophocarpine seem to be more beneficial if more comprehensive studies confirm their efficacy and safety. It is noteworthy that the consumption of some herbal agents for cardiovascular (e.g. Hawthorn and Ginseng) or other (e.g. Ginseng and Licorice) therapeutic purposes may boost the pro-arrhythmogenic effect of current cardiovascular drugs such as cardiac glycosides.

This study accentuates known plants or their derivatives with anti-arrhythmic effects, potential interaction with other cardiac drugs, and the possible mechanisms involved. It can assist clinicians and scientists in research and therapeutic approaches to the management of cardiac arrhythmias.

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1. Introduction

Cardiovascular diseases (CVDs) are considered a major global health challenge in the modern era. Despite the advancement in diagnostic and therapeutic methods over the past decades, they continue to be the most common cause of morbidity and mortality. The mortality rate due to CVD is estimated to be more than 24

million worldwide by 2030. Cardiac arrhythmias are one of the leading causes of death from CVD and are also responsible for at least half of sudden cardiac arrests. Cardiac arrhythmias or dysrhythmias are disturbances in the electrical activity of the heart, which include irregular rate or rhythm that they can appear as tachycardia or bradycardia.^{1,2} Major cardiac arrhythmias are including **A**: Supraventricular arrhythmias; such as premature atrial contraction (PAC), Atrial Flutter (AFL), Atrial fibrillation (AF), paroxysmal atrial tachycardia (PAT) and so on, **B**: Ventricular arrhythmias; such as premature ventricular contraction (PVC), ventricular tachycardia (VT), ventricular fibrillation (VF), etc. **C**: Cardiac blocks; such as first, second and third degree blocks, bundle branch blocks and etc. Generally, the mechanisms causing cardiac

* Corresponding author. Department of Physiology and Pharmacology, School of Medicine, Kerman University of Medical Sciences, P.O.Box 7616914115, Kerman, Iran.

E-mail addresses: sjokar@gmail.com, jokar@kmu.ac.ir (S. Joukar).

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Abbreviation			
AADs	Antiarrhythmic drugs	IKto	Transient outward potassium current
AF	Atrial fibrillation	INa	Sodium current
AFL	Atrial flutter	IV	Intravenous
AP	Action potential	LA	Left atrial
APD	Action potential duration	LAD	Left anterior descending
AV	Atrioventricular	LV	Left ventricle
CVD	Cardiovascular disease	l-NAME	N (gamma)-nitro-L-arginine methyl ester
DAD	delayed afterdepolarization	MDA	Malondialdehyde
EAD	Early afterdepolarization	NO	Nitric oxide
ECG	Electrocardiogram	PAC	Premature atrial contraction
ERP	Effective refractory period	PO	Orally
HERG	Human ether -a-go-go-related gene	PVC	Premature ventricular contraction
HCN channels	Hyperpolarization-activated cyclic nucleotide-gated channels	QTc	Corrected QT interval
ICa-L	L-type calcium current	RA	Right atrial
If	Funny current	RV	Right ventricle
IK1	Inwardly rectifier potassium current	SA	Sino atrial
IKr	Rapid delayed rectifier potassium current	SOD	Superoxide dismutase
IKs	Slow delayed rectifier potassium current	TDP	Torsade de points
		Vmax	Maximal depolarization velocity
		VF	Ventricular fibrillation
		VT	Ventricular tachycardia

arrhythmias can be classified into two categories, abnormal impulse generation, abnormal impulse propagation or a combination of both (Table 1).³ An important part of treating cardiac arrhythmias is with anti-arrhythmic drugs (AADs). These drugs mainly act to affect membrane ionic currents, alter the electrical conduction velocity or block trigger activity.⁴ The newest classification divided AADs into 8 classes. Class 0 such as ivabradine block HCN channel-mediated pacemaker current. Class 1 such as quinidine and flecainide act through blockade of fast inward sodium current. This current is responsible for rapid depolarization and conduction of action potential in the heart. Class 1 in turn include 4 subclasses 1a, 1b, 1c, and 1d. Class 2 comprises autonomic inhibitors and activators such as propranolol, timolol, metoprolol, atropine, and pilocarpine that place in 2a, 2b, 2c, 2d, and 2e subclasses. Class 3 such as amiodarone, sotalol, nicorandil, and vernakalant are K⁺ channel blockers and openers that are divided into 3a, 3b and, 3c subclasses. Class 4 such as verapamil, diltiazem, and bepridil are Ca²⁺ handling modulators. Class 5 are mechanosensitive channel blockers, while Class 6 are gap junction channels inhibitors. Class 7 such as captopril, valsartan, and statins are upstream target modulators.⁵ The development and prescription of AADs and monitoring of antiarrhythmic drug therapy require an understanding of the fundamental knowledge of cardiac electrophysiology. However, due to volume limitations, it is not possible to address them in this article. On the other hand, the narrow therapeutic windows of AADs and their potential for induction of fatal pro-arrhythmia is a clinical challenge. For example, some antiarrhythmic drugs in classes 1 and 3, such as quinidine, disopyramide, procainamide, dofetilide, ibutilide, and sotalol can worsen preexisting arrhythmias and lead to torsade de points.⁵ Therefore, finding new anti-arrhythmic drugs with more therapeutic effects and fewer side effects is inevitable.

Plants continue to play a vital role in health care and are a rich source of medicines. Estimates show that a large number of people in many developing countries heavily rely on traditional herbs and traditional practitioners to resolve their primary health needs. In developed countries also, despite the availability of modern medications, the trend towards alternative therapies is on the rise.⁶ In addition, many modern drugs available in drug stores such as morphine, ephedrine, paclitaxel, digitoxin, aspirin, pilocarpine,

reserpine, and vinblastine originate from plants directly or indirectly. Some herbal remedies like quinidine have antiarrhythmic effects and some of them such as opium can have arrhythmogenic effects.⁷ The current review was prepared and highlights plants or herbal compounds indicating antiarrhythmic properties, particularly in experimental models, and also points to some plants or some herbal components with arrhythmogenesis effects and their potential interactions with cardiovascular drugs. It keeps up-to-date and be a source of quick access for medical science researchers, clinicians and those interested in this area of knowledge to find more effective anti-arrhythmic compounds for treatment of patients.

2. Methods

We searched for the following electronic databases to collect articles related to the subject: Web of Science, Google Scholar, Pub Med, Science Direct, EMBASE, Springer Link and Scopus. The searched terms were: herbs, plants, medicinal plants or herbs, flavonoids, polyphenols, alkaloids, herbal compounds, phytochemicals plus the plants affecting the cardiovascular system along with arrhythmia, antiarrhythmic, dysrhythmia, atrial or ventricular fibrillation, torsade de points, ventricular tachycardia, cardiovascular, cardioprotective and other related terms. In this document, literature from 1986 to November 2019 was included.

3. Plants and their ingredients with antiarrhythmic properties

3.1. *Crocus sativus* (saffron)

Crocus sativus is a perennial stemless herb belonging to the Iridaceae family. Its cardioprotective effect against isoproterenol-induced cardiac injury⁸ led us to investigate the effect of saffron on ischemia-reperfusion induced arrhythmias. In an experimental study, saffron showed a significant reduction in the incidence and duration of VF, the incidence of VT/VF, duration of VT and VT/VF as well as the severity of lethal arrhythmias and mortality rate. The anti-arrhythmic effects of saffron with a dose of 100 mg/kg were comparable to amiodarone.⁹ In another research on rats, orally administration of aqueous extract of saffron for one week

Table 1
Mechanisms of cardiac arrhythmias, their resultant arrhythmias and predisposing factors.

Mechanism	resultant arrhythmias	Predisposing factors
Disorders of impulse generation		
1) Automaticity		
Altered normal automaticity	Sinus bradycardia: HR < 60 beat/min	Sleep, Athlete, Sick sinus syndrome, Myocardial infarction, Hypothyroidism, Jaundice, Increased intracranial pressure, Beta-blockers, etc.
	Sinus tachycardia: HR > 100 beat/min	Fever, Hyperthyroidism, Exercise, Anxiety, Increased sympathetic nervous system activity, etc.
Abnormal automaticity (Ectopic foci)	PAC, PVC, Bigeminy, Trigeminy, Salvo, AF, AFL, Atrial tachycardia, VT, VF	Myocardial infarction, Myocardial Ischemia, Hypertension, Myocarditis, Cardiomyopathies, Valvular heart diseases, Digitalis toxicity, etc
2) Triggered activity		
Early afterdepolarization	TDP	Prolongation of QT interval due to: Congenital, Hypokalemia, Hypoxia, Hypocalcemia, Hypomagnesemia, Acidosis, Some drugs such as class1a, 1c and 3 antiarrhythmic drugs, Phenothiazines, Tricyclic and tetracyclic antidepressants, Amiloride, Erythromycin, Antihistamines, etc.
Delayed afterdepolarization	Atrial tachycardia, digitalis toxicity-induced tachycardia, accelerated ventricular rhythms, some forms of repetitive monomorphic VT, reperfusion-induced arrhythmias, exercise-induced VT	Calcium overload due to: digitalis, catecholamines, hypokalemia, hypercalcemia, cardiac hypertrophy, heart failure, etc.
Disorders of impulse propagation		
1) Blocks		
	Atrioventricular blocks, bundle branch blocks, and fascicular blocks	Congenital, coronary artery diseases, cardiomyopathy, right and left ventricular hypertrophy, some drugs, etc
2) Re-entry		
Anatomic or Functional re-entry	AF, AFL, Atrial tachycardia, VT, VF	Shortening of refractory period, slow conduction and heart cavities dilation, hypertension, myocardial ischemia, cardiomyopathies, myocardial infarction, myocarditis, scarring due to cardiac surgery, etc.
Anatomic re-entry	atrioventricular re-entrant tachycardia (wolff-parkinson-white syndrome (WPW)) atrioventricular nodal re-entrant tachycardia	Congenital

AF; Atrial fibrillation, AFL; Atrial flutter, HR; Heart rate, PAC; Premature atrial contraction, PVC; Premature ventricular contraction, TDP; Torsade de points, VF; Ventricular fibrillation, VT; Ventricular tachycardia.

significantly decreased cardiac conductivity, especially at a dose of 200 mg/kg/day.¹⁰ These findings are consistent with another study on isolated A-V node preparations of rabbit in which aqueous extract of saffron increased the nodal conduction time and refractoriness secondary to electrical stimulations.¹¹ Some active components of saffron have also shown an anti-arrhythmic effect. In a study, pretreatment of rats with crocin (20 mg/kg/daily/i.p for 3 weeks) decreased cardiac reperfusion-induced arrhythmias. Reductions in the number of PVC, the number of VT episodes, and the incidence of VF were significant compared with the control group.¹² The calcium channel inhibiting effect of saffron may be involved in its antiarrhythmic property.^{10,13}

3.2. *Zingiber officinale* (ginger)

Zingiber officinale is a perennial herb belonging to the Zingiberaceae family. Ginger is one of the ingredients of Zhigancao, a cardioprotective decoction with a long history in traditional Chinese medicine.¹⁴ Karbalaei et al. showed that orally pretreatment with ginger during 15 days (100 mg/kg/daily) had a cardioprotective effect against CaCl₂ induced arrhythmia in rats. In this research, the percentage of PVC, VT, and VF significantly diminished compared to the control group, and intermittent fasting every other day enhanced the anti-arrhythmic effect of ginger.¹⁵ In another study on rat ventricular myocytes, application of 6-gingerol, the main bioactive constituent of Ginger, decreased I_{Ca-L} of normal and ischemic cells as well as their contractility in a dose-dependent manner.¹⁶

3.3. *Crataegus* (Hawthorn)

Crataegus is a large genus of bushes from the Rosaceae family. Previous studies addressed the protective effect of *Crataegus oxyacantha* against agents or ischemia induced arrhythmias in rats. The venous infusion of digoxin at a dose of 40 µg/kg/min, *Crataegus oxyacantha* at a dose of 4 mg/kg/min were started simultaneously and lasted for 1 h. In this study, the duration of PAC, VT, and VF in the experimental group were significantly shorter than in the vehicle group. However, arterial blood pressure significantly decreased in the experimental group.¹⁷ In another study, Garjani et al. investigated the effects of the different extracts of *Crataegus meyeri* on ischemic induced arrhythmias in rats. The venous infusion of the extracts (1 mg/kg) was started 5 min before the left coronary artery occlusion and was continued until the end of the occlusion (30 min). Hydro-alcohol and chloroform extracts significantly reduced the number of PVC compared to the control group. Also, a significant drop in the duration of VF was observed by hydro-alcohol and ethyl acetate extracts.¹⁸ Veveris et al. showed that orally pretreatment with 100 mg/kg hydroalcoholic *Crataegus* extract (7 days) significantly lowered the ST-elevation level, the occurrence of VF, VT, and mortality in rats subjected to heart ischemia-reperfusion.¹⁹ According to electrophysiological studies done by Muller et al., the methanolic extract of *Crataegus* suppressed both the delayed and inward K⁺ rectifier currents in guinea-pig ventricular myocytes respectively by 25% and 15% but did not affect I_{Ca-L}.²⁰ Conversely, in another study, the pretreatment of rats with 1% *Crataegus oxyacantha* extract (8 weeks) had no anti-arrhythmic property during ischemia or reperfusion periods,

neither in the isolated nor in situ hearts.²¹ Furthermore, in a study on healthy volunteers, an orally single dose of 160 mg *Crataegus oxyacantha* made no changes in ECG parameters.²² Some studies reported that Hawthorn can increase the activity of digitalis and hence its potential toxicity and pro-arrhythmic effect and it has been recommended precautions about using this plant with digitalis.²³

3.4. *Sophora flavescens*

Sophora is a large genus from the Fabaceae family. In an experimental study, *Sophora flavescens* 120 mg/kg significantly reduced the number of VT and delayed the onset of VT during the ischemia period when compared with the control group in rats. In mice, cardiac arrhythmias were evoked by aconitine infusion. Intravenous administration of *Sophora flavescens* 180 or 240 mg/kg significantly delayed the onset of VT and initial cardiac arrhythmia compared with the control group.²⁴ As well, some of the alkaloids of *Sophora flavescens* such as oxymatrine, matrine, and sophocarpine have indicated an antiarrhythmic property.^{25–28} In one study on rats, cardiac arrhythmias were developed by left anterior descending (LAD) coronary artery ligation. Intravenous pretreatment with 10 or 20 mg/kg oxymatrine delayed the onset of ventricular arrhythmia and lessened the scores of arrhythmias. Moreover, oxymatrine 10 mg/kg shortened the time of ventricular arrhythmias. Examination on cardiac myocytes showed that oxymatrine likely exerts its useful effects by shortening of action potential time via the alleviation of I_{Ca-L} and potentiation of I_{to} .²⁵ The outcomes of a study signified that long term treatment of rats with matrine 30 mg/kg/po before and after ligation of LAD coronary artery significantly decreased arrhythmias durations, arrhythmias scores and mortality rate than the untreated group. In addition, matrine bettered the hemodynamic function of the hearts. In ventricular cells, the prolongation of AP induced by ischemia was significantly shortened by matrine and was restored to the normal level compared with the untreated group. Also, reduced I_{to} , I_{K1} and intracellular calcium concentration $[Ca^{2+}]_i$ following ischemia in rat ventricular myocytes were recovered by matrine.²⁶ Another study on guinea-pigs proved the ameliorating effect of matrine on arrhythmias induced by ouabain. Intravenous injection of 5, 10, 15 mg/kg matrine before starting the ouabain infusion significantly and dose-dependently raised the doses ouabain required to produce arrhythmias and decreased the duration of arrhythmias. In cardiomyocytes, matrine shortened the duration of AP and impeded the increase of calcium currents induced by ouabain.²⁷ Yang and coworkers found that sophocarpine, the other component of *Sophora flavescens* is an antiarrhythmic agent. At first, the guinea-pig hearts were transferred to the Langendorff system and were perfused with an Isoprenaline containing solution for induction of arrhythmias. After adding sophocarpine to the solution, VF and tachyarrhythmias were inhibited. Furthermore, in the examination of the sinus node, papillary muscles, and ventricular cells, sophocarpine could decrease the amplitude and the maximal depolarization velocity (V_{max}) of the fast AP and Na^+ current (I_{Na}), as well as, could prolong the effective refractory period (ERP). Also, sophocarpine reduced the amplitude and V_{max} of slow AP and I_{Ca-L} . These effects were comparable to amiodarone.²⁸

3.5. *Melissa officinalis* (lemon balm)

Melissa officinalis is a perennial herb from the Lamiaceae family. *Melissa officinalis* has both cardioprotective and suppressing effects on ventricular arrhythmias induced by ischemia and reperfusion of the rat hearts.^{29,30} Intra-peritoneal pretreatment with various doses of aqueous extract of *Melissa officinalis* caused partial

prolongation of PR and QTc, a reduction in the number of VF and the diminution of arrhythmia severity during reperfusion stage.²⁹ Another laboratory study reported that the intake of the aqueous extract of *Melissa officinalis* at doses of 50,100, and 200 mg/kg for a week significantly prolonged QRS, QTc, TpTe, and JT intervals in rats. Some of these effects were similar to class 1 or 3 antiarrhythmic drugs that slow ventricular conductivity.³¹ Akhondali and colleagues demonstrated the antiarrhythmic effect of *Melissa Officinalis* on $CaCl_2$ -induced arrhythmias in rats. Orally pretreatment with hydroalcoholic extract of *Melissa Officinalis* at doses of 100 and 200 mg/kg/day for 2 weeks significantly decreased the incidence of VT, VF, and PVC than the control group.³²

3.6. *Stephania tetrandra*

Stephania tetrandra is a perennial plant belonging to the Menispermaceae family. Yu et al. compared the cardioprotective effects of the extract of radix *Stephania tetrandra* and tetrandrine, one of the active components derived from its root, in isolated rat heart preparations. Regional ischemia was produced by ligation of the left coronary artery for 30 min and was followed by 120 min reperfusion. The extract and tetrandrine significantly repressed arrhythmia score and infarct size than the control group. These effects were comparable to that of verapamil, a calcium channel blocker.³³ In a similar in vivo study, ischemia/reperfusion was created in the same way. Treatment with the extract of Radix *Stephania Tetrandra*, tetrandrine and verapamil led to a considerable reduction in arrhythmia scores and infarct size. Inhibition of I_{Ca-L} , I_{Ca-T} , Ca^{2+} -activated K^+ current, and I_{Na} are mechanisms that have been suggested for the anti-arrhythmic action of Tetrandrine.^{34,35}

3.7. *Allium sativum* (garlic)

Allium sativum is a bulbous plant belonging to the Alliaceae family. According to a study data in anesthetized dogs, injection of garlic extract after induction of arrhythmias by ouabain decreased the incidence of PVC and VT. As well, in isolated atria of rat, garlic extract suppressed ectopic rhythms developed by aconitine and isoprenaline as well as prolonged ERP and sinus node recovery time in a dose-dependent pattern.³⁶ Sungnoon et al. examined the effect of garlic on defibrillation efficacy in pigs. VF was made by electrical shock with an alternating current of 60 Hz. The IV infusion of 40 mg/kg garlic significantly lowered the defibrillation threshold in comparison with the control group with a reduction of 13% in peak voltage and 25% in total energy.³⁷ In another work by the same researchers on anesthetized pigs, garlic extract could not alter the ventricular fibrillation threshold in comparison to the control group after the induction of VF by electrical stimuli, however dose-dependently pulled down the upper limit of vulnerability.³⁸ Sheep were treated with 50 mg/kg hydro-ethanol extract of garlic before and after taking a lethal dose (100 mg/kg, orally) of dried leaves of oleander. Pretreatment or treatment with garlic extract decreased fatality from 100% to 25% and 33%, respectively. Furthermore, the extract delayed the onset time of arrhythmias and animals death.³⁹ Huang and colleagues surveyed the antiarrhythmic effects of allicin, a component of Garlic, in diabetic rats. Three days after STZ injection, the animals received different doses of allicin (i.p) daily for 4 weeks. Then, the rats were anesthetized, and $BaCl_2$ was injected for the induction of arrhythmia. Prolonged RR, QT, and QTc due to $BaCl_2$ injection were restored to normal in allicin group than the untreated group in a dose-dependent manner. Meanwhile, allicin delayed the onset of arrhythmias and alleviated the score of them. Experiment on cardiomyocytes displayed the allicin mediated shortening of APD via inhibition of I_{Ca-L} and potentiation of I_{K1} .⁴⁰ In

another investigation on mouse ventricular cells, allicin significantly suppressed I_{to} current in a dose-dependent manner. Likewise, a high concentration of allicin ($\geq 100 \mu\text{mol/l}$) enhanced the voltage-dependent inactivation of I_{to}.⁴¹ A recent study on rat cardiomyocytes revealed that allicin disrupts Cav1.2 channel traffic, which this may be another its antiarrhythmic mechanism.⁴²

3.8. *Leonurus cardiaca* (motherwort)

Leonurus cardiac is a perennial herb of the Lamiaceae family. Ritter and coworkers accomplished a study on the electrophysiological effects of *Leonurus cardiaca* extract. They displayed that the perfusion of the isolated rabbit hearts with 1 and 2 mg/ml *Leonurus cardiaca* extract in a Langendorff system prolonged the PR interval, cycle length, and activation recovery interval. In the experiment on different cell models, *Leonurus cardiaca* had various activities including the blockade of the I_{Ca-L}, reduction of I_{Kr}, as well as prolongation of both the APD and the activation time constant of I_f.⁴³ The examination of two components from *Leonurus cardiaca*, Lavandulifolioside, and Ferulic acid verified some of the above effects. In rat ventricular myocytes, these two agents inhibited I_{Ca-L} and shortened APD, while did not affect I_{Na}. Also, the application of the Ferulic acid in rabbit perfused hearts through the Langendorff system induced the rise of the cycle length and the drop of the left ventricular pressure.⁴⁴

3.9. *Magnolia officinalis*

Magnolia Officinalis is a perennial plant from the Magnoliaceae family. Magnolol and honokiol are two main active compounds of *Magnolia* stem bark. The remedial effects of honokiol and magnolol against the arrhythmias induced by coronary ligation have been reported. Pretreatment with honokiol and magnolol 15 min before coronary ligation significantly depressed the incidence and duration of VT and stopped VF compared with the untreated group. Besides, pretreatment with L-NAME, a NOS inhibitor, abolished the antiarrhythmic effects of honokiol and magnolol in the acute phase of coronary ligation. Accordingly, it was suggested that cardioprotective effects of honokiol and magnolol against arrhythmias during myocardial ischemia are mediated by the upregulation of the NOS.⁴⁵

3.10. *Arctium lappa*

Arctium lappa is a biennial plant belonging to the Asteraceae family. In an aconitine-induced arrhythmia model on rats, pretreatment with arctigenin, a lignin found in the dried fruit of *Arctium lappa*, significantly delayed the onset of VT, PVC, and mortality compared to the untreated ones in a dose-dependent pattern. In ventricular myocytes, aconitine prolonged AP and decreased resting potential, while arctigenin restored them to nearly normal. Also, arctigenin could significantly recover aconitine induced abnormality in I_{Na}, I_{Ca-L}, and I_{to} by depressing the I_{Na}, I_{Ca-L} and amplifying the I_{to}.⁴⁶ A recent study by Yang et al. revealed the protective effect of arctigenin against arrhythmia in coronary artery ligated rats. Orally pretreated rats with arctigenin daily for a week before coronary ligation showed a significant reduction in the number and duration of VT, VF, PVC, and arrhythmia score during the ischemia phase. Moreover, the number and duration of VT, infarct size and arrhythmia score reduced during the reperfusion phase as well as VF was disappeared. The severity of the ventricular arrhythmia decreased during both phases, too. Biochemical data suggested arctigenin exert at least a part of its effects through repressing oxidative stress.⁴⁷

3.11. *Berberis vulgaris* (Barberry)

Berberis vulgaris is a shrub from the Berberidaceae family. Results of an investigation on chronic diabetic rats indicated that orally pretreatment with berberine for 7 days before coronary ligation could markedly decrease the duration and severity of arrhythmias during ischemia and could reverse the prolonged QTc interval in compare to untreated diabetic rats. Furthermore, in ventricular myocytes of berberine-treated diabetic rats, diminished I_{to} and I_{Ca-L} currents were recovered compared with the untreated diabetic ones.⁴⁸ Another research conducted by Wang addressed the effects of berberine on delayed afterdepolarizations. In isolated ventricular papillary muscle of guinea-pigs, delayed afterdepolarizations were induced by ouabain or post-hypoxic reoxygenation. berberine diminished the incidence and amplitude of delayed afterdepolarizations in a concentration-dependent manner and inhibited ensuing triggered activity. In the second series of experiments on rabbit left ventricular muscles, subsequent to evoking delayed afterdepolarizations by ouabain and calcium gluconate, berberine lowered their amplitude and repressed ventricular arrhythmia. In this study, the antiarrhythmic action of berberine was partly ascribed to a reduction in Na⁺ influx.⁴⁹ Data of a clinical trial on congestive heart failure patients demonstrated treatment with berberine (0.3 g, 4 times/day, for 8 weeks) significantly reduced the incidence of PVC, VT, and mortality than the placebo group during 24 months follow-up. Besides, berberine improved the mechanical functions of the hearts.⁵⁰ To justify the antiarrhythmic mechanisms of berberine, Wang et al. examined the effects of berberine on ionic currents responsible for the repolarization phase of action potentials in isolated ventricular myocytes of guinea-pigs. They found that berberine significantly and dose-dependently prolonged APD, an effect that was mainly due to the blockade of I_{Ks} and potentiation of I_{Ca}.⁵¹ In a recent study, oral pretreatment of rats with berberine diminished aconitine-evoked arrhythmias and mortality rate. Additionally, berberine increased PR, QRS and QT intervals as well as aconitine dosage for the induction of arrhythmia compared with the untreated group. Histopathological and enzymatic examinations showed the decrease of the heart tissue congestion and the improvement of the cardiac function indices mediated by berberine.⁵² A study addressed the protective effect of berberine on acetylcholine-induced AF in rabbit. For AF induction, a multipole electrode was advanced into the right atrium via the right jugular vein. Then, high-frequency electrical stimulation was performed during intravenous acetylcholine (Ach) infusion. The simultaneous infusion of berberine and Ach significantly decreased the rate of sustained AF compared with the vehicle and stopped the majority of AFs. In isolated atrial myocytes, berberine recovered the shortening of APD due to Ach, as well as increased the RR interval and ERP.⁵³ Examination on rabbit sinoatrial node cells showed that berberine depresses spontaneous activity through reduction in action potential amplitude, maximal diastolic potential, diastolic depolarization rate, pacemaker firing rate, and increase in APD. In *Xenopus* oocytes, berberine concentration-dependently inhibited hHCN currents and slowed the kinetics of them.⁵⁴ In other experimental studies using 100 and 200 mg/kg of *Berberis* fruit extract for two weeks showed cardioprotective effect and prolonged the depolarization phase and shortened the repolarization phase of ventricular muscle in rat.^{55,56}

3.12. *Dracocephalum moldavica* (Moldavian balm or dragonhead)

Dracocephalum moldavica is an annual herbaceous herb belonging to the Lamiaceae (Labiatae) family. In one report, the antiarrhythmic capacity of *Dracocephalum moldavica* on isolated rat hearts was addressed. After mounting the hearts on the

Langendorff apparatus, the (LAD) coronary artery was occluded for 30 min and followed by 120 min reperfusion. The results of this study revealed that *Dracocephalum moldavica* significantly reduces the duration of VT and VF, the number of VT and PVC, and incidence of VT during both ischemia and reperfusion phases in comparison with the control group.⁵⁷

3.13. *Scutellaria baicalensis*

Scutellaria baicalensis is a flowering herb in the Lamiaceae family. Based on the findings of a study on aconitine-poisoned patients, intravenous infusion of 450 mg baicalin, one of the major components of *Scutellaria baicalensis*, could significantly inhibit atrial flutter and sinus bradycardia as well as could improve all clinical manifestations and blood pressure in all patients during a short time. In the untreated group, however, these factors were recovered with a long delay.⁵⁸

3.14. *Aloe vera*

Aloe vera is a perennial plant from the Aloaceae family. In one study on rabbit ventricular myocytes, application of barbaloin, a constituent obtained from *Aloe*, decreased APD and the maximum depolarization velocity (V_{max}) in a dose-dependent manner as well as repressed early and delayed afterdepolarizations. Again, barbaloin dose-dependently blocked I_{Ca-L} and in Langendorff mounted hearts significantly inhibited aconitine-induced ventricular arrhythmias.⁵⁹ It is reported that *Aloe vera* may increase the chance of hypokalemia and causing digitalis toxicity and arrhythmia.²³

3.15. *Cinnamomum* genus

Various *Cinnamomum* species are the members of the Lauraceae family that their dried bark is known as cinnamon. A survey by Sedighi and colleagues demonstrated the antiarrhythmic potential of *Cinnamomum zeylanicum* (*Cinnamomum Verum*) bark extract after ischemia-reperfusion in rats. Orally pretreatment with the extract for two weeks before the ligation of the LAD coronary artery showed the marked reduction of the number of PVC, VT and duration of VT in the treated group than the control group during 30 min of ischemia. The extract also normalized QTc shortening and ST-segment changes and decreased the infarct size. Because of useful alterations in oxidative stress indices, the researchers suggested that the cardioprotective effects of the extract may be due to oxidative stress repressing.⁶⁰ In another study, cinnamophilin derived from *Cinnamomum philippinense* had an antiarrhythmic effect on rat isolated hearts. After ligation of the left coronary artery, application of cinnamophilin in Langendorff-perfused hearts, dose-dependently converted VT to normal sinus rhythm. In the experiment on rat ventricular cells, cinnamophilin led to the prolongation of AP time, suppression of V_{max} , as well as inhibition of I_{Na} , I_{Ca} , and I_{to} in a dose-dependent manner.⁶¹

3.16. *Citrus bergamia* (Bergamot)

Citrus bergamia is a plant from the Rutaceae family. A study investigated the effect of bergamottine, an active compound of bergamot, on arrhythmias in guinea-pigs and rats. The application of bergamottine could ameliorate the electrocardiographic signs of the coronary arterial spasm and the occurrence of the cardiac arrhythmias evoked by pitressin or ouabain in anesthetized guinea-pigs. Likewise, bergamottine raised the dose of ouabain needed for inducing arrhythmias and death as well as restored sinus rhythm. In rat isolated hearts, in addition to the dilation of the coronary artery

and reduction of initial perfusion pressures, bergamottine lessened the duration and severity of arrhythmias during the reperfusion phase. These effects were compatible with verapamil.⁶² The same researchers in another study found that bergamottine significantly increased the atrioventricular node conduction time, the corrected sino-atrial conduction time, and the corrected sinus-node recovery time in anesthetized rabbits. In isolated guinea-pig atria, bergamottine had a negative inotropic effect in a dose-dependent manner that raising extracellular calcium concentration reversed it. According to these data, the researchers suggested that bergamottine acts via blocking calcium channel.⁶³

3.17. *Salvia miltiorrhiza* (Danshen)

Salvia miltiorrhiza is a deciduous perennial herb in the Lamiaceae family. Pretreatment with danshensu (salvianic acid), an active component of *Salvia miltiorrhiza*, during 4 days before the ligation of the LAD coronary artery had cardioprotective effects against ischemia-reperfusion injuries. Danshensu significantly recovered electrocardiographic and functional changes to nearly normal levels as well as lowered the incidence of VT and VF during pre-ischemia, ischemia, and reperfusion stages compared with the untreated ones.⁶⁴ There is a study related to the antiarrhythmic effects of dimethyl lithospermate B, a compound found in the root of *Salvia miltiorrhiza*, on Brugada syndrome induced arrhythmias. The Brugada syndrome was developed in canine arterially perfused right ventricular preparations by using either terfenadine or verapamil for suppressing I_{Na} and I_{Ca} or pinacidil for enhancing I_{K-ATP} . In this study, application of dimethyl lithospermate B abolished PVC, VT and VF in all of the preparations.⁶⁵

3.18. *Menispermum dauricum* (Moonseed)

Menispermum dauricum is a woody liana in the Menispermaceae family. A study determined the damping effect of dauricine, a bioactive component of *Menispermum dauricum*, against ischemia-reperfusion induced arrhythmias in dogs. During the occlusion period of the LAD coronary artery, dauricine significantly decreased the number of PVC, VT, and VF than the control group.⁶⁶ In situ procedure done on rabbit revealed that dauricine prolonged the effective refractory period (ERP) and repolarization period, and depressed the amplitude of action potentials.⁶⁷ Electrophysiological experiments using the patch-clamp technique suggested that the antiarrhythmic effect of dauricine is exerted through K^+ current blockade. In guinea-pig ventricular myocytes, dauricine dose-dependently inhibited both rapidly (I_{Kr}) and slowly (I_{Ks}) activating components of the delayed rectifier K^+ current. Also, it repressed I_{K1} as well as decreased I_{Kr} and I_{Ks} tail currents.⁶⁸ Another research performed on HEK293 cell line was indicative of HERG potassium channel blockade by dauricine in a concentration-dependent manner. I_{Kr} channels are coded by human ether α -go-go-related gene (HERG), hence, they are known as HERG channels, and potassium efflux via them determine APD in cardiomyocytes.⁶⁹ Guo et al. reported which dauricine inhibited I_{Ca-L} in ventricular myocytes of guinea-pig.⁷⁰ In another study on the papillary muscles of rabbits with cardiac hypertrophy induced by partial ligation of the abdominal aorta, the application of dauricine decreased APD and repressed EADs. In rabbit ventricular cells also dauricine inhibited EADs evoked by hypokalemia, hypomagnesemia and dofetilide (an I_{Kr} blocker).⁷¹

3.19. *Vitis* genus (Grape)

Vitis is a genus with more than 60 species belonging to the Vitaceae family. Niroomand et al. addressed the effects of grape

juice on QT interval in human volunteers. They found that QTc was significantly prolonged 4 h after grape juice drinking. More examinations on HEK cells and *Xenopus* oocytes displayed that several flavonoids of grape including naringenin, hesperetin, morin, flavone, kaempferol, quercetin, methoxsalen, scopoletin, umbelliferone, and 7-ethoxycoumarin significantly blocked HERG channels.⁷² In another study, grape seed proanthocyanidin extracts also had a protective effect against ischemia reperfusion-induced arrhythmia in rabbits. Three weeks pretreatment before LAD coronary artery ligation significantly lessened the number of VF and infarct size than the control group during the reperfusion period.⁷³ In an experiment on rat ventricular myocytes and recombinant tsA201 cells, grape extract and three its derivatives, quercetin, catechin, and resveratrol significantly inhibited I_{Na} in a concentration-dependent pattern. Also, resveratrol prevented and reversed overloads in diastolic Ca^{2+} developed by ATXII, a specific toxin for voltage-gated sodium channels (VGSC) as well as delayed contractile dysfunction and decreased the incidence of abnormal contractions.⁷⁴ Application of hydro-alcoholic extract of grape seed in rat isolated hearts pointed out an antiarrhythmic effect. Infusion of the extract (1 μ g/ml) before and during ischemia and reperfusion led to a significant reduction in the number, incidence, and duration of VT in both phases as well as attenuation in infarct size. As well, the number of PVC decreased during the reperfusion phase.⁷⁵

3.20. *Gynostemma pentaphyllum*

Gynostemma pentaphyllum is a wild perennial liana belonging to the Cucurbitaceae family. Some studies reported the antiarrhythmic effects of *Gynostemma pentaphyllum* Makino in anesthetized guinea pigs. Treatment with the aqueous extract of leaves significantly attenuated the electrocardiographic signs of coronary arterial spasm induced by pitressin injection such as ST-elevation, PQ/QT prolongation, and the incidence of arrhythmias. Also in ouabain receiving guinea-pigs, the extract repressed VT and restored a normal rhythm in a concentration-dependent pattern. In both experimental models the extract significantly raised the dose of agents required to produce VT, PVC, and lethality. Gypenosides derived from *Gynostemma pentaphyllum* had a similar effect in both experimental models too.⁷⁶

3.21. *Evodia rutaecarpa*

Evodia rutaecarpa that is now classified in the genus *Tetradium* as *Tetradium rutilcarpum* is a plant from the Rutaceae family. In a study on guinea-pig cardiomyocytes, dehydroevodiamine, one of the active principles isolated from the dried fruits of *Evodia rutaecarpa*, prolonged APD in both atrial and ventricular myocytes. AP prolongation was due to the inhibition of outward K^+ current (delayed rectifier, I_K) and the Na-dependent inward current (I_{Na}) at a low concentration of dehydroevodiamine as well as was due to the moderate inhibition of the L-type Ca^{2+} current (I_{Ca-L}) at high its concentrations. Furthermore, in low-K (1 mM) and high- Ca^{2+} (9 mM) media, dehydroevodiamine ameliorated the delayed afterdepolarizations (DAD) and the transient inward current induced by Strophanthidin.⁷⁷ In another investigation on isolated human atria and ventricles, dehydroevodiamine could decrease the amplitude of AP and upstroke velocity in slow and fast response action potentials. Likewise, pretreatment with dehydroevodiamine depressed triggered activities induced by strophanthidin and dose-dependently suppressed the Na^+ and Ca^{2+} currents.⁷⁸ In a recent study, dehydroevodiamine and hortiamine (another alkaloid from *Evodia rutaecarpa*) inhibited I_{Kr} in human embryonic kidney cells (HEK 293) as well as dehydroevodiamine dose-dependently increased APD and evoked EADs in dog ventricular myocytes. In

human cardiomyocytes, dehydroevodiamine and hortiamine dose-dependently prolonged the APD and evoked EADs. A study on rabbits and dogs demonstrated that the prolongation of the QT interval subsequent to dehydroevodiamine usage could lead to the development of torsade de points.⁷⁹

3.22. *Glycyrrhiza uralensis* (Licorice)

Glycyrrhiza uralensis is an herbaceous perennial herb from the Fabaceae family. *Glycyrrhiza radix* is one ingredient of the antiarrhythmic Chinese decoction named Zhigancao.¹⁴ The cardioprotective effects of licorice are ascribed more to a bioactive derivative named glycyrrhetic acid. According to the results of a study, glycyrrhetic acid dose-dependently blocked both rapidly activating (I_{Kr}) and slowly activating (I_{Ks}) components of delayed rectifier potassium current (I_K) in guinea-pig ventricular myocytes and HERG K channel in human HEK 293 cells. The inhibition of these currents predisposes the prolongation of AP and ERP that cause arrhythmias prevention.⁸⁰ Another survey on human atrial myocytes and *Xenopus* oocytes indicated that 18 β -glycyrrhetic acid inhibits both the peak Na^+ current and the late Na^+ current in a dose-dependent pattern. These effects suggest that 18 β -glycyrrhetic acid can have antiarrhythmic potential.⁸¹ Licorice may potentiate the effects of digoxin and increase the risk of hypokalemia and leads to increase the susceptibility for ventricular arrhythmia.^{23,82}

3.23. *Panax pseudoginseng* (sanchi)

Panax pseudoginseng or notoginseng that is known as the king of herbs is a deciduous perennial plant belonging to the Araliaceae family. Trilinolein, a triacylglycerol having Linoleic Acid as the unsaturated fatty acid, is isolated from ginseng (the root of *Panax pseudoginseng*). Intravenous injection of trilinolein 15 min before the left coronary ligation resulted in a significant and dose-dependent suppression in the total number of PVC, incidence and duration of VT and duration of VF during 30-min heart ischemia in rat. Also, the total number of PVC and duration of VT and VF markedly reduced during the reperfusion phase. Additionally, the infarct zone decreased in trilinolein treated rats subjected to 4 h of coronary occlusion.⁸³ In strophanthidin induced arrhythmia model, pretreatment of guinea-pigs with trilinolein considerably alleviated ventricular extrasystoles during strophanthidin infusion. However, the administration of trilinolein after induction of arrhythmias did not repress VT.⁸⁴ It should be noted that the co-administration of Ginseng and digitalis may increase the plasma level of digoxin and its pro-arrhythmic effect.²³

3.24. *Potentilla reptans*

Potentilla reptans is an herbaceous perennial plant belonging to the Rosaceae family. Pretreatment with its rhizome extract via the Langendorff system 40 min before regional ischemia could significantly decrease the arrhythmia score, VF incidence, infarct size, and apoptotic indices compared with the control group in a concentration-dependent manner. These effects were relatively abolished by L-NAME, a NO synthesis inhibitor. In addition, the extract enhanced SOD and catalase activity and attenuated MDA level.⁸⁵

3.25. *Scrophularia frigida*

The genus *Scrophularia* from the Scrophulariaceae family consists of approximately 300 species. The perfusion of the hearts with methanolic extract of *Scrophularia frigida* caused a significant

reduction in the number and duration of VT during the ischemia phase and significant reductions in single and total arrhythmia during the reperfusion phase. Also, the extract decreased the infarct size.⁸⁶

3.26. *Cynodon dactylon*

Cynodon dactylon is a Perennial grass from the Poaceae family. In isolated rat heart, rhizome extract of *Cynodon dactylon* exhibited a cardioprotective effect against ischemia/reperfusion-induced arrhythmias. Regional ischemia was achieved by the ligation of the LAD coronary artery. The perfusion of the hearts with hydro-methanolic extract at doses of 25 and 50 µg/ml profoundly lessened the total number of PVC, as well as the incidence and duration of VT/VF during both ischemia and reperfusion phases. The extract as well caused a strong positive inotropic effect in these hearts.⁸⁷

3.27. *Bauhinia variegata* (camel's foot)

Bauhinia variegata belongs to the Leguminosae family. A study assayed the cardioprotective efficacy of *Bauhinia variegata* against CaCl₂ induced arrhythmias in rats. Pretreatment with 400 mg/kg aqueous and ethanolic extract of *Bauhinia variegata* root entailed a significant reduction in atrial and ventricular fibrillations compared with the control group.⁸⁸

3.28. *Ligusticum wallichii*

Ligusticum wallichii is a medicinal herb from the Umbelliferaeaceae family. Tetramethyl pyrazine is the main constituent derived from the rhizomes of *Ligusticum wallichii*. In a report, rats received tetramethylpyrazine (i.p, 12 mg/kg/day) for 7 days. Then the hearts were isolated and regional ischemia was induced by the ligation of the left coronary artery for 15 min. Pretreatment with tetramethyl pyrazine caused a significant reduction in the incidence of VF and VT during both ischemia and reperfusion phases.⁸⁹

3.29. *Fissistigma glaucescens*

The genus *Fissistigma* is from the Annonaceae family. Whose main constituents are alkaloids such as liriodenine. In a Langendorff-perfused heart model, after occlusion of the LAD coronary artery of rats, liriodenine was able to convert polymorphic VT to normal sinus rhythm. Liriodenine as well exerted a positive inotropic effect in rat myocardial strips. Experiments on rat isolated ventricular myocytes exhibited that liriodenine prolonged APD and decreased V_{max} and resting membrane potential. The whole-cell voltage-clamp study specified that the suppressive effect of liriodenine on arrhythmias is due to the inhibition of the I_{Na} and I_{to} currents.⁹⁰

3.30. *Marrubium crassidens*

Marrubium is a genus of the Lamiaceae family. Rameshrad and colleagues studied the effect of the methanolic extract of *Marrubium crassidens* on ischemia-reperfusion induced arrhythmias in isolated rat heart. The hearts were perfused with an extract containing solution via Langendorff apparatus from before LAD ligation until the end of reperfusion. Data analysis showed that the extract made a significant reduction in the number of PVC during ischemia and reperfusion phases, in the number of VT during ischemia and in the infarct size after reperfusion.⁹¹

3.31. *Camellia oleifera*

The genus *Camellia* is from the Theaceae family. There is one study about the cardio-protective effects of sasanquasaponin, a saponin obtained from *Camellia oleifera*. The intravenous administration of sasanquasaponin 10 min before ligation of LAD could considerably diminish the incidence of VT, VF, and salvos during both ischemia and reperfusion stages in mice. The injection of sasanquasaponin after arrhythmias appearance also reduced arrhythmias during reperfusion. Sasanquasaponin made similar antiarrhythmic effects in isolated mice hearts, too. Furthermore, in isolated ventricular papillary muscle, it caused hyperpolarization and APD shortening.⁹²

3.32. *Tinospora cordifolia*

Tinospora cordifolia is a perennial shrub belonging to the Menispermaceae family. In a CaCl₂-induced model of arrhythmia in rats, intravenous administration of different doses of *T. cordifolia* alcoholic extract normalized atrial and ventricular fibrillation compared with the untreated group.⁹³

3.33. *Corydalis yanhusuo*

Corydalis yanhusuo is a perennial herb from the Papaveraceae family. Protopine is an isoquinoline alkaloid extracted from *Corydalis yanhusuo*. In guinea-pig isolated ventricular myocytes, Protopine in addition to the marked abbreviation of APD, V_{max}, amplitude and overshoot of AP, caused a considerable hyperpolarization in the resting membrane potential. Furthermore, Protopine significantly reduced the amplitude of the I_{Ca-L} and suppressed the inward rectifier (I_{K1}) and delayed rectifier (I_K) potassium currents and sodium current (I_{Na}). All of these effects were dose-dependent.⁹⁴

3.34. *Fluggea virosa*

Fluggea virosa is a wilding shrub or tree in the Phyllanthaceae family. One study asserted the antiarrhythmic effects of bergenin, a compound isolated from *Fluggea virosa*, on rats and rabbits. Cardiac arrhythmias in rats were induced by either BaCl₂ injection or LAD coronary artery ligation. Bergenin significantly accelerated the restoration of the sinus rhythm in rat arrhythmia induced by BaCl₂ as well as shortened the duration of PVC, VT, and VF following ischemia/reperfusion. Also, bergenin raised the threshold of the electrical stimulation for inducing atrial fibrillation in rabbits.⁹⁵

3.35. *Camellia sinensis* (tea)

Camellia sinensis is an evergreen shrub from the Theaceae family. Three main types of tea can produce based on the processing method; green (non-fermented or non-oxidized), oolong (semi-fermented or semi-oxidized), and black (fermented or oxidized). In a study, rats received black tea brewed instead of drinking water for four weeks. Then, animals were anesthetized and the intravenous infusion of aconitine 1.5 mg/min was done for 10 min for arrhythmia induction. The utilization of black tea caused a significant reduction in the duration of VT + VF, but a significant increase in the number of PVC. Besides, black tea delayed the onset of arrhythmias and diminished the score of their severity.⁹⁶ In addition, black tea increased heart rate variability and improved sympatho-vagal balance.⁹⁷ In a case-control study, Liu and coworkers assess the relation between green tea consumption and AF incidence in a Chinese population. They showed that low doses of green tea had a significant protective effect on the incidence of paroxysmal and persistent AF.⁹⁸

3.36. Polyphenols

Polyphenols are natural compounds finding largely in the fruits, vegetables, cereals, and beverages that the most prominent action of them is free radical scavenging. phenolic acids, flavonoids, stilbenes, and lignans are the main classes of polyphenols.⁹⁹ Research on rats pointed out that hesperidin, the major flavonoid in citrus fruits, can protect the heart against ischemia/reperfusion-induced injuries. Isolated hearts were perfused with Hesperidin containing solution through the Langendorff apparatus from 5 min before the ligation of the LAD coronary artery until the end of reperfusion. Hesperidin significantly reduced the incidence of PVC and VT during both ischemia and reperfusion phases.¹⁰⁰ Resveratrol is a polyphenolic compound that is found in a variety of plants. Daily pretreatment of rats with resveratrol from a week before coronary artery ligation had a protective role against arrhythmia. During the first 24-h after regional ischemia, the incidence of VT/VF and mortality rate was significantly lower in the resveratrol group compared to the control group. Cellular recordings by Patch-clamp method specified that resveratrol produced I_{Ca-L} blockade and ATP sensitive K^+ current (I_{K-ATP}) augmentation in a concentration-dependent manner.¹⁰¹ Another study assessed resveratrol effects on three models of animal arrhythmias. In aconitine-induced arrhythmias, rats received resveratrol (i.v) 10 min before aconitine infusion. Resveratrol significantly and dose-dependently raised the doses of aconitine required to induce PVC, VF, and VT. In the second model, arrhythmias were evoked by ouabain infusion in guinea-pigs that pretreatment with Resveratrol showed similar outcomes. In the third model, arrhythmias were induced by ligation of the LAD coronary artery. The pretreatment of rats with resveratrol decreased the ventricular arrhythmias duration, VT incidence, arrhythmia score and mortality in a dose-dependent pattern. Experiment on guinea-pig ventricular myocytes also revealed that Resveratrol dose-dependently shortened APD via I_{Ca} blockade and I_{Ks} potentiation.¹⁰² Chronic administration of resveratrol in diabetic rats also had a preventing effect on arrhythmia. Two days after induction of diabetes, daily pretreatment of rats with resveratrol for 6 weeks attenuated the arrhythmia score, the arrhythmic period and the incidence of types of arrhythmias compared to the untreated group.¹⁰³ A study clarified that acacetin, a flavone that is widely distributed in plant pigments, prolonged ERP without influencing the corrected QT interval, and prevented AF induced by bilateral stimulation of vagus nerve in dogs. In human atrial myocytes, acacetin suppressed ultrarapid delayed rectifier K^+ current (I_{Kur}) and I_{to} , and prolonged APD. Additionally, it inhibited the Acetylcholine-activated K^+ current in guinea-pig atrial myocytes.¹⁰⁴ Another study displayed the considerable inhibition of small conductance Ca^{2+} -activated K^+ channels (S_{K-Ca}) in the HEK 293 cells by acacetin that suggests this action likely contribute to its anti-AF effect.¹⁰⁵ Orally pretreatment of rats with total flavonoids of *Choerospondias axillaris* for seven days significantly delayed the onset time of PVC, VF, VT and heart arrest following induction of arrhythmias by i.v injection of aconitine.¹⁰⁶ Ellagic acid is a polyphenol substance found in many plants such as pomegranate, grapes, blackberry, strawberries and walnuts. Dianat et al. treated rats with ellagic acid 15 mg/kg/daily/p.o for ten days. After three weeks, they induced arrhythmias by i.v injection of 140 mg/kg $CaCl_2$ in anesthetized animals. Pretreatment with ellagic acid decreased the incidence of VT, VF, and PVC in comparison with the untreated group. Moreover, ellagic acid had a similar effect on animals that are restrained 6 h a day for 21 days.¹⁰⁷ In a study, troxerutin or vitamin P4, a derivative of glucosidal natural bioflavonoid, indicated antiarrhythmic efficacy. Rats received troxerutin 150 mg/kg/daily/p.o for a month then the hearts were transmitted to the Langendorff system. The number of PVC and VF as well as the

duration of VF markedly reduced in the treated group than the control group during ligation of the LAD coronary artery. In chronic diabetic rats also troxerutin had similar effects.¹⁰⁸

4. Arrhythmogenesis plants and drug interactions

It was explained above that the prescription of Aloe vera, Ginseng, Hawthorn, Sanchi and Licorice along with digitals can increase their adverse effects and the risk of arrhythmia.^{23,82} In addition, usage of dehydroevodiamine, one of the active principles isolated from the dried fruits of *Evodia rutaecarpa*, could lead to the development of torsade de points.⁷⁹ The arrhythmogenic effects of some other medicinal plants or their derivatives such as aconitum, Bitter orange, Echinacea, Ginkgo biloba, Guarana, Horny goat weed (Epimedium), Lily of the valley (Convallaria majalis), Night-blooming cereus, Oleander, Rhodiola and St. John's wort (Hypericum perforatum) has also been reported.^{23,109,110} The Lily of the valley, Night-blooming cereus, Oleander, and Strophanthus are using to treat congestive heart failure. The Lily of the valley increases the effects of calcium-channel blockers, beta-blockers, digitalis, and quinidine. Night-blooming cereus enhances the effects of cardiac glycosides, angiotensin-converting enzyme inhibitors, beta-blockers, calcium-channel blockers, and other antiarrhythmics. Oleander increases the risk of heart block, hyperkalemia, arrhythmia, and death. Strophanthus amplifies the effects of cardiac glycosides.²³

St. John's wort is one of the top-selling herbs used to treat ulcerative colitis, some viral infections, and some neuropsychiatric conditions such as depression, anxiety, and sleep disorders. However, it can interact with different classes of cardiovascular and antiarrhythmic drugs.¹¹¹ For example co-administration of this herb reduces the plasma concentration of digoxin,¹¹² simvastatin¹¹³ and ivabradine,¹¹⁴ increases the required dose of atorvastatin to treat patients with hypercholesterolemia,¹¹⁵ reduces the efficacy of rosuvastatin,¹¹⁶ and decreases the bioavailability of R and S-verapamil¹¹⁷, talinolol¹¹⁸ and nifedipine.¹¹⁹ These interactions are mediated through the induction of cytochrome P450 enzymes (CYP) and P-glycoprotein transporter (P-gp), and therefore, affects the pharmacokinetics of the mentioned drugs.^{119,120} A study on healthy volunteers showed that green tea reduces plasma concentration of nadolol, a beta-1-blocker, by 85% possibly through inhibition of OATP1A2-mediated uptake of nadolol in the intestine.¹²¹ In addition, some of the herbal medicine which mentioned above such as danshen, garlic, ginger, ginkgo, licorice, aloe vera and bitter orange can increase bleeding risks of the anticoagulant/antiplatelet drugs.¹²²

5. Summary and conclusion

Given the variety of arrhythmias, understanding the mechanism behind each arrhythmia is necessary to treat it. Current treatments focus on suppressing enhanced automaticity, decrease in conduction velocity, delay in repolarization, and changing the effective refractory period to suppress re-entry. These effects are exerted by altering the activity of different channels in the heart. However, each of these mechanisms can have unfavorable effects on the heart. For example, slow conduction and delay in repolarization can lead to torsade de points, as do classes 1 and 3 of antiarrhythmic drugs. In addition, long-term use of classic antiarrhythmic drugs cause extracardiac complications as well as may produce drug resistance and decrease therapeutic efficacy.

The results of this study that partly have been summarized in Fig. 1 and Supplementary Table 1, indicate that some herbs are a rich source of antiarrhythmic agents and can repress different arrhythmias types in the various models of animal arrhythmias.

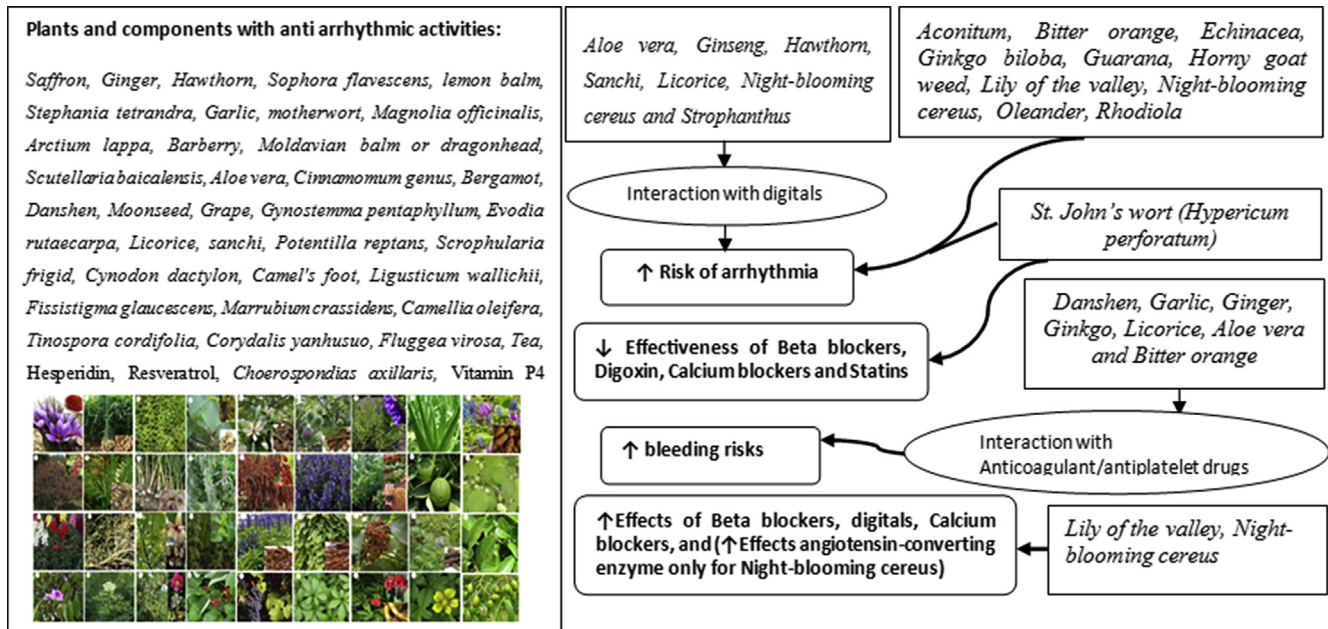


Fig. 1. Plants and components with antiarrhythmic activities and plants-cardiovascular drugs interactions.

Table 2

Possible antiarrhythmic mechanisms of some plants or herbal components.

Plant or herbal components	Antiarrhythmic effects	Probable Mechanisms	References
<i>Crocus sativus</i> (Saffron)	↓ Incidence and duration of VF ↓ Duration of VT and VT/VF	↓ ICa-L	[9,13]
<i>Crataegus</i>	↓ Severity of arrhythmia ↓ Number of PVC ↓ Duration of VF ↓ Occurrence of VF and VT, ↓ Mortality rate	↓ IK and IK1	[17–20]
Oxymatrine and Matrine	Delay in onset and ↓ Score and duration of ventricular arrhythmia	Shortening of APD, ↓ ICa-L, ↑ Ito, ↑ IK1	[25, 26]
Sophocarpine	↓ VF and tachyarrhythmia	↑ APD and ERP ↓ APA and IKr	[28]
Tetrandrine	↓ Arrhythmia score ↓ infarct size	↓ INa, ICa-L, ICa-T, and Ca ²⁺ -activated K ⁺ -current,	[34, 35]
Allicin	↓ RR interval, QTc interval, ↓ Score of arrhythmias and Delay in onset of arrhythmia	Shortening of APD ↓ ICa-L, ↑ IK1, ↓ Ito and ↓ Cav1.2 channel trafficking	[40–42]
<i>Leonurus cardiac</i> , Lavandulifolioside and Ferulic acid	↑ PR interval, cycle length, and activation recovery interval	↓ ICa.L and IKr,	[43, 44]
Arctigenin	↓ Incidence and duration of VF, VT and PVC ↓ arrhythmia score	Shortening of APD, Delay in activation of INa and ICa-L, ↑ Ito	[46, 47]
Berberine	↓ duration, and severity of arrhythmias ↓ Incidence and amplitude of DADs ↓ prolongation of QTc interval	↑ Ito and ICa-L, ↓ INa, ↓ IKs, ↓ hHCN currents, ↑ APD	[48, 49, 51, 53, 54]
Cinnamophilin	Stopping VT	↑ APD, ↓ Vmax, INa, ICa and Ito	[61]
Dauricine	↓ Number of PVC, VT and VF	↓ IKr, IKs and IK1 ↓ APD, EADs and ICa-L	[66–71]
Liriodenine	VT suppression	↑ APD, ↓ Vmax and RMP ↓ INa+ and Ito	[90]
Sasanquasaponin	↓ Incidence of VT, VF and salvos	↓ APD, and Hyperpolarization of cell	[92]

AF; Atrial fibrillation, AFL; Atrial flutter, AP; Action potential, APD; Action potential duration, AD; Early afterdepolarization, DAD; delayed afterdepolarization, ERP; Effective refractory period, HR; Heart rate, ICa-L; L-type calcium current, If; Funny current, IK1; Inwardly rectifying potassium current, IKr; Rapid delayed rectifier potassium current, IKs; Slow delayed rectifier potassium current, IKto; Transient outward potassium current, INa; Sodium current, ND; Not Determined, PAC; Premature atrial contraction, PVC; Premature ventricular contraction, QTc; corrected Q-T interval, RMP; Resting membrane potential, TDP; Torsade de points, Vmax; Maximal depolarization velocity, VF; Ventricular fibrillation, VT; Ventricular tachycardia.

Although the number of studies on some antiarrhythmic herbs or herbal compounds is few and molecular mechanisms in some of them have not been investigated, the available data show that targeting ionic channels is a common mechanism. Modulation of ionic currents such as I_{Na} , I_{Ca-L} , I_f and I_K (I_{Kr} , I_{Ks} , I_{K1} , I_{K0}) in different

phases of the action potential are among these mechanisms (Table 2). The agents like liriodenine from *Fissistigma glaucescens* inhibit I_{Na} and act similar to class 1 antiarrhythmic drugs. Some of them including glycyrrhetic acid from *Glycyrrhiza uralensis* and some species of *Crataegus* inhibit I_{K} and have an action similar to

class 3 antiarrhythmic drugs. Some others including *Crocus Sativus*, resveratrol, barbaloin from *Aloe vera*, oxymatrine from *Sophora flavescens*, and gingerol from *Zingiber officinale* inhibit I_{Ca} and behave like class 4 antiarrhythmic drugs. The others such as sophocarpine from *Sophora flavescens*, dehydroevodiamine from *Evodia rutaecarpa*, protopine from *Corydalis yanhusuo* and cinnamophilin from *Cinnamomum philippinense* inhibits I_{Ca} , I_{Na} and I_{K} currents, tetrandrine from *Stephania tetrandra* inhibits I_{Ca} and I_{Na} currents, arctigenin from *Arctium lappa* delays the activation of I_{Na} and I_{Ca-L} and increases the I_{to} currents, berberine from *Berberis vulgaris* blocks of I_{Na} , I_{K} s, and potentiates I_{Ca} currents, dauricine from *Menispermum dauricum* decreases the I_{Kr} , I_{K} s, I_{K1} and I_{Ca} currents and *Leonurus cardiaca* blocks $I_{Ca.L}$ and I_{kr} currents (Table 2). Alterations in ionic currents can lead to change in the amplitude and duration of action potential (depolarization or repolarization period or both), ERP, V_{max} , resting membrane potential, channel trafficking, or intracellular calcium concentration. Theoretically, it seems that an admissible antiarrhythmic drug in addition to low side-effects should prolong the action potential and increase ERP by an increase in the inactivation time of sodium channels. Despite the shortage of studies, some agents such as glycyrrhetic acid, dauricine, and sophocarpine prolonged APD and ERP, however, further studies are needed to confirm this claim and also examine probable side-effects. Besides, more studies should be undertaken on other herbs and compounds mentioned in this paper to different aspects such as their side-effects and efficacies are investigated. In addition, the management of drug interactions is very important especially when cardiovascular medications with a narrow therapeutic index, such as digoxin, are co-administered with some herbal agents that can boost or diminish their pharmacological effects.

The information presented herein signifies the capability of some herbs and herbal compounds to suppress arrhythmias or interact with prescribed cardiovascular drugs (Fig. 1). The majority of the studies have been done on animals, animal preparations or human heart myocytes. Few clinical trials such as the antiarrhythmic and inotropic effects of berberine⁵⁰ and antiarrhythmic effect of baicalin⁵⁸ in patients have been reported. More animal studies and clinical studies with adequate sample sizes are essential to examine their pharmacodynamics, pharmacokinetics, and safeties.

Declaration of competing interest

The authors declare that there are no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jtcme.2020.03.002>.

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