WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 5, 755-768. Review Article ISSN 2277– 7105

REVIEW ON HERBAL DRUG USED FOR CARDIOVASCULAR DISEASES AND REDUCE THE HEART RATE

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Article Received on
14 March 2022,

Revised on 03 April 2022,
Accepted on 24 April 2022

DOI: 10.20959/wjpr20225-23925

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ABSTRACT

Since the dawn of civilization, herbs have been utilized as medical therapies, and several derivatives (such as aspirin and digitalis) have become mainstays of human pharmacology. In patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia, herbal therapies have been used. Many herbal therapies in use today, however, have not been well evaluated by scientists, and some of them have the potential to induce serious adverse consequences and substantial drug-drug interactions. Given the significant prevalence of herbal usage in the United States today, practitioners should inquire about such health practices for cardiac illness and be informed about the potential benefits and risks. To understand the pharmacological activity of the numerous herbal treatments being utilized to treat cardiovascular problems, more research is required.

KEYWORDS: Herbal drug, Cardiovascular diseases, Heart rate.

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] 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 arrhythmias can be classified into two categories, abnormal impulse generation, abnormal impulse propagation or a combination of both.[2]

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. The newest classification divided AADs into 8 classes. Class 0 such as ivabradine block HCN channelmediated 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 Kþ channel blockers and openers that are divided into 3a, 3b and, 3c subclasses. Class 4 such as verapamil, diltiazem, and bepridil are Ca2þ 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[3]

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.

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.[4]

Plants and their ingredients with antiarhythmic properties

***Crocus sativus* (saffron)**

Crocus sativus is a perennial stemless herb belonging to the Iridaceae family. Its cardioprotective effect against isoproterenolinduced cardiac injury 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.[5]

***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. 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. In another study on rat ventricular myocytes, application of 6- gingerol, the main bioactive constituent of Ginger, decreased ICa-L of normal and ischemic cells as well as their contractility in a dosedependent manner.[6]

***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 mg/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.[7]

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. As well, some of the alkaloids of Sophora flavescens such as oxymatrine, matrine, and sophocarpine have indicated an antiarrhythmic property.[8]

***Melissa officinalis* (lemon balm)**

Melissa officinalis is a perennial herb from the Lamiaceae family. Melissa officinalis has both cardioprotecive and suppressing effects on ventricular arrhythmias induced by ischemia and reperfusion of the rat hearts. 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. 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.[9]

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. 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 ICa-L, ICa-T, Ca2þ-activated K þ -current, and INa are mechanisms that have been suggested for the anti-arrhythmic action of Tetrandrine.[10]

***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. 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.[11]

***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 ICa-L, reduction of IKr, as well as prolongation of both the APD and the activation time constant of If.[12]

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. [13]

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 INa, ICa-L, and Ito by depressing the INa, ICa-L and amplifying the Ito.[14]

***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 Ito and ICa-L currents were recovered compared with the untreated diabetic ones.[15]

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.[16]

Dracocephalum moldavica

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 A.[17]

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 component 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.[18]

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 (Vmax) in a dose-dependent manner as well as repressed early and delayed afterdepolarizations. Again, barbaloin dose-dependently blocked ICa-L and in Langendorff mounted hearts significantly inhibited aconitine-induced ventricular arrhythmias. It is reported that Aloe vera may increase the chance of hypokalemia and causing digitalis toxicity and arrhythmia.[19]

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.[20]

***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.[21]

***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 ischemiareperfusion 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.[22]

***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 6 A. Beik et al. / Journal of Traditional and Complementary Application of hydro-alcoholic extract of grape seed in rat isolated hearts pointed out an antiarrhythmic effect. Infusion of the extract (1 mg/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.[23]

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.[24]

Evodia rutaecarpa

Evodia rutaecarpa that is now classified in the genus Tetradium as Tetradium ruticarpum 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 Kþ current (delayed rectifier, Ik) and the Na-dependent inward current (INa) at a low concentration of dehydroevodiamine as well as was due to the moderate inhibition of the L-type Ca2þ current (ICa-L) at high its concentrations.[25]

***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. The

cardioprotective effects of licorice are ascribed more to a bioactive derivative named glycyrrhetinic acid. According to the results of a study, glycyrrhetinic acid dose-dependently blocked both rapidly activating (IKr) and slowly activating (IKs) components of delayed rectifier potassium current (IK) 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.[26]

***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 dosedependent 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.[27]

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.[28]

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 components with antiarrhythmic activities and their interaction with current cardiac drugs, 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.[29]

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 hydromethanolic extract at doses of 25 and 50 mg/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.[30]

***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.[31]

Ligusticum wallichii

Ligusticum wallichii is a medicinal herb from the Umbelliferaceae 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.[32]

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 Vmax 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 INa and Ito currents.[33]

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.[34]

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.[35]

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.[36]

CONCLUSION

Given the significant prevalence of herbal medicine use in the United States, health practitioners should remember to ask about such practises when conducting clinical histories and stay informed about the therapies' benefits and drawbacks. To understand the pharmacological activities of the various cardiopotent herbal medications and to promote future pharmaceutical development of therapeutically useful herbal pharmaceuticals, more research is required.

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