

Cardiotoxicity Effects of Herbal Medicine, A Review Article

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Abstract

With the development of human's modern society more and more people tend to use complementary and alternative medicine (CAM). Toxicological studies indicated that many herbal medicines have direct toxic effects on the circulatory system or cardiovascular system and cause harmful effects on the body. Cardiotoxicity or heart damage is a serious issue defined as heart electrophysiology dysfunction, affecting the cardiac structure, and muscle damage that arises from the drug or chemical poisoning agents, that may lead to heart failure. The aim of this review article is to provide various information about the potential adverse effects of herbal medicine on the cardiovascular system and introduce herbs that induced cardiac toxicity. To provide this review, all reported cases of cardiac toxicity induced by herbal medicines and natural products were collected through research articles and documents, and the most relevant articles, and books in various authentic search engines including Scopus, PubMed, SID (scientific information database), Science Direct and Google Scholar, from 1984 to April 2022 were searched, and selected herbs with therapeutic properties which induce toxic effects on the cardiovascular system are introduced. In this review, scientific data regarding cardiotoxicity showed that 16 herbs from 11 families may increase cardiac toxicity. Therefore, it's important to use herbal medicines and natural products under the guidance of medical professionals.

Keywords: Cardiotoxicity; heart damage; herbal medicine; toxicity; adverse effects.

INTRODUCTION

Throughout history, using of herbal medicines has been playing an increasingly important role to treat various health challenges (Chaachouay et al. 2022; Liu et al. 2022). Based on research, 80% of people all over the world, use complementary and alternative medicine (CAM) and traditional medicine to treat different diseases (Zhang et al. 2015; Ardalan and Rafieian-Kopaei 2013). Furthermore, several studies demonstrated that about 20,000 herbal medicines are available in different markets all around the world (Bent 2008), and a significant number of people rely on medicinal plants and use herbal remedies along with routine medication to treat various diseases, which increased the risk of herb–drug interactions (Brantley et al. 2014; De Smet 2007; Gavanji and Larki 2017). Researchers have reported that inappropriate use of natural products can induce various damages including kidney injury (Yang et al. 2018), nervous system injury (Wattanathorn et al. 2008), liver injury (Lin et al. 2019), skin injury (Ernst 2000) and heart damages (Sheth et al. 2015). Toxicological studies indicated that many herbal medicines have direct toxic effects on the circulatory system or cardiovascular system and cause harmful effects on the body (Fatima and Nayeem 2016; Valli and Giardina 2002). Cardiotoxicity or heart damage is a

serious issue defined as heart electrophysiology dysfunction, affecting the cardiac structure and muscle damage that arises from the drug or chemical poisoning agents, that may lead to heart failure (Sishi et al. 2013; Chung et al. 2018). Nowadays there is a growing concern over the cardiovascular adverse effects of herbal supplements and natural products and heart toxicity due to herbal medicines has recently become a source of interest (Ernst 2003). Several types of research demonstrated that several factors including inappropriate use of herbal remedies, using of herbal medicines for a long time, high-dose therapy and herb-herb or herb-drug interaction (Cupp 1999; Sun et al. 2021) may induce adverse reactions and side effects on the cardiovascular system, including arrhythmias, sympathomimetic activity, and hypertension and cause the irreversible damages which can lead to death.

Many people with a lack of knowledge, take herbal medicines based on their false beliefs and information to treat various diseases and increase the rate of heart adverse effects (Alonso-Castro et al. 2021). Several studies have shown that various herbal medicines can interact with cardiac medications and increase the risk of bleeding or inactivate the antiplatelet drugs. Also, inappropriate use of herbal medicine can cause problems cardiac cycle and pumping of blood throughout the body and may lead to various health problems. There has been

an overwhelming weight of obsession on monitoring the cardiac patients who use herbal medicine and natural supplement without prescriptions, while they are taking heart medications, and scientific research studies indicated that many common medications including anticoagulants like aspirin (acetylsalicylic acid) (Abebe 2002), warfarin (coumadin) (Leite et al. 2016), and phenprocoumon (falithrom, marcoumar) (Fasinu et al. 2012), also antiplatelet medications (prasugrel and clopidogrel) which have been used for cardiovascular diseases can interact with specific herbs (Ma et al. 2018) and should be used under professional supervision. It is very important to increase the knowledge of different societies about the potential health risks of self-medication and change our attitudes toward the inappropriate use of herbal medicines to reduce the risk of cardiotoxicity (Alghadir et al. 2022; Eichhorn et al. 2011; Consolini, and Ragone 2010). This review article provides various information about the potential adverse effects of herbal medicine on the cardiovascular system, and introduces herbs that induced cardiac toxicity.

METHODS

To provide this review, all reported cases of cardiac toxicity induced by herbal medicines and natural products were collected through research articles and documents, and the most relevant articles, and books in various authentic search engines including Scopus, PubMed, SID (scientific information database), Science Direct and Google Scholar, from 1984 to April 2022 were searched. The search was organized with several combinations of search strategies with different keywords including cardiotoxicity, heart damage, herbal medicine, toxicity, and adverse effects. In this review article, the selected herbs with therapeutic properties which induce toxic effects on the cardiovascular system were introduced.

Cardiotoxic plants

Ranunculaceae

Ranunculaceae family which is called buttercup or crowfoot includes over 2,200 flowering plants, and has been widely used in traditional medicine (TM) for cancer treatment (Christenhusz and Byng 2016; Hao et al. 2017). Researchers have reported that three species of ranunculaceae family including *Aconitum napellus*, *Aconitum kusnezoffii* and *Aconitum carmichaeli* showed the cardiotoxicity effects and people should be cautious to use these plants (Table 1). *A. kusnezoffii* is a plant which has been traditionally used in the clinical practice as an antimicrobial and pain killer (Su et al. 2021). Based on a research study, 15 patients who consumed *A. kusnezoffii* for treatment of rheumatism and respiratory tract infection, encountered tachyarrhythmias, and ventricular tachycardia and fibrillation (Tai et al. 1992).

Another species of this family is *A. napellus* which is used for muscle pain in folklore medicine (Shoaib et al. 2020). A case report study has reported, that ingestion of *A. napellus* roots induced cardiotoxicity and a 54-year-old Chinese man underwent ventricular tachycardia or arrhythmia and cardiac arrest (Bonanno et al. 2020). The other member of Ranunculaceae family is *A. carmichaeli* which shows wound healing and anti-inflammatory properties (Xia et al. 2019). According to a study, a 60-year-old man who consumed *A. carmichaeli* to treat his headache encountered aconitine poisoning which lead to myocardial necrosis (Lin et al. 2011). Zong and coworkers in 2019 demonstrated that *A. carmichaeli* contains diterpenoid alkaloids which have cardiotoxic potential (Zong et al. 2019). Another research study stated that aconitum plants have toxic effects on the cardiovascular system and two alkaloids including Aconitine (AC) and mesaconitine (MA) play a crucial role in cardiotoxicity and create some serious problems (Liu et al. 2019).

Dioscoreaceae

Dioscorea bulbifera is a medicinal plant of Dioscoreaceae or yam family which has been traditionally used to treat wounds, rectal carcinoma, sore throat, and stomach or gastric cancer (Chaniad et al., 2020). The result of a research study showed that extracting the rhizome of *D. bulbifera*, induced cardiotoxicity by pirarubicin accumulation which lead to necrosis, and muscle fiber damage, also indicated that cardiotoxicity effects of *D. bulbifera* is dose-dependent (Sun et al. 2021). Another study indicated that *D. bulbifera* can interact with doxorubicin (DOX) in cancer treatment and cause DOX accumulation which leads to cardiovascular injury including necrosis and breakage in cardiac muscle fibers (Qu et al. 2019).

Ginkgoaceae

Ginkgo biloba also called *ginkgo*, belonging to the family Ginkgoaceae, has been widely used in traditional medicine(TM) for the treatment of various diseases including asthma, cognitive problems, circulatory disorders, and vertigo (Brondino et al. 2013). Based on research, *G. biloba* has mild adverse effects and can cause heart palpitations (Nguyen and Alzahrani 2022). A study by Bent and coworkers in 2005 showed that many people consume ginkgo to decrease platelet aggregation but according to various research ginkgo may interact with warfarin and increase the risk of bleeding (Bent et al. 2005). However, a randomized controlled trials study, demonstrated that ginkgo may not interact with warfarin (Engelsen et al. 2002; Köhler et al. 2004). Also, another study stated that concurrent use of ginkgo and warfarin will increase bleeding adverse effects and patients should be cautious to use of herbs and drugs simultaneously (Stoddard et al. 2004).

Table 1. Cardiotoxicity effects of herbal medicine.

No	Plant name	Family	Potential therapeutic application (Traditional medicine)	Type of adverse effect	References
1	<i>Atropa belladonna</i>	Solanaceae	Treat of asthma, cough, and hay fever	Flushed and tachycardic	(Chadwick et al. 2015)
2	<i>Aconitum napellus</i>	Ranunculaceae	Treat of high fever	Aconitum napellus	(Bonanno et al. 2020)
3	<i>Aconitum kusnezoffii</i>	Ranunculaceae	Treat of sore throat, gout and rheumatism	Tachyarrhythmias, ventricular tachycardia and fibrillation	(Tai et al. 1992)
4	<i>Aconitum carmichaeli</i>	Ranunculaceae	Pain relief	Cardiotoxicity	(Tai et al. 1992)
5	<i>Datura stramonium</i>	Solanaceae	Treat of wounds, inflammation and rheumatism	Tachycardia	(Khoshnam et al. 2022; Arefi et al. 2016)
6	<i>Dioscorea bulbifera</i>	Dioscoreaceae	Treat of syphilis, ulcers, cough, leprosy and diabetes	Accumulation of THP in heart tissue	(Sun et al. 2021; Qu et al. 2019)
7	<i>Digitalis purpurea</i>	Plantaginaceae	Treat of asthma, epilepsy and tuberculosis	Heart Failure	(Gerakaris et al. 2022)
8	<i>Ephedra distachya</i>	Ephedraceae	Weight loss and obesity	Side effects on the cardiovascular system and cerebrovascular effects	(González-Juárez et al. 2020; Andraws et al. 2005)
9	<i>Ephedra sinica</i>	Ephedraceae	Treat of asthma, bronchitis, and hay fever	Serious cardiovascular adverse effects	(Ekor 2014; Nyska et al. 2005; Dunnick et al. 2007)
10	<i>Ginkgo biloba</i>	Ginkgoaceae	Treat of cognitive disorders and dementia	Increasing the bleeding tendency, heart palpitations	(Nguyen and Alzahrani 2022; Stoddard et al. 2004; Bent et al. 2005)
11	<i>Glycyrrhiza glabra</i>	Fabaceae	Treat of respiratory disorders, hyperdipsia and fever	Cardiac arrhythmias, pulmonary edema	(Deutch et al. 2019)
12	<i>Hypericum perforatum</i>	Hypericaceae	Treat of anxiety and depression	Arrhythmia, hypertension	(Rubini et al. 2019; Guru et al. 2021)
13	<i>Juniperus oxycedrus</i>	Cupressaceae	Anti-inflammatory and antimicrobial effects	Tachycardia	(Achour et al. 2011)
14	<i>Mandragora officinarum</i>	Solanaceae	Treat of asthma and hay fever	Serious supraventricular tachycardia	(Tsiligianni et al. 2009)
15	<i>Nerium oleander</i>	Apocynaceae	Treat of cancer, painful menstrual periods	Arrhythmia	(Guru et al. 2021)
16	<i>Piper methysticum</i>	Piperaceae	Treat of fever and respiratory disorders	Cardiovascular abnormalities, arrhythmia	(Toohey et al. 2013)

Solanaceae

Atropa belladonna, *Mandragora officinarum*, and *Datura stramonium* are three species of Solanaceae family, which contain various alkaloids with different negative effects on the body. *Atropa belladonna* is listed as a poisonous plant and called deadly nightshade. *A. belladonna* is traditionally used to treat bradycardia (slow heart rate) (Shah et al. 2019). But according to a study, demonstrated that the consumption of *A. Belladonna* in a 49-year-old woman can lead to anticholinergic toxic syndrome and heart rhythm disturbances (Demirhan et al. 2013). Also, the results of a study showed that ingestion of *A. belladonna* may cause abnormal heart rate (tachycardia) and other problems (Chadwick et al. 2015). *M. officinarum* is another member of Solanaceae family (Al-Maharik et al. 2022), which contains several phytochemicals including withanolides, tropane alkaloids (scopolamine and

hyoscyamine), and coumarins (Schlesinger et al. 2019; Hanus et al. 2005). The root of this plant has been used in traditional medicine (TM) for the treatment of various diseases (Monadi et al. 2021). A case study research indicated that two patients who consumed *M. officinarum* admitted to hospital with supraventricular tachycardia (SVT) (Tsiligianni et al. 2009). Another important species of Solanaceae family is *D. stramonium* which has been traditionally used to treat many diseases including fever, ulcers, wounds, toothache, rheumatism, and bronchitis (Sharma et al. 2021). a research study indicated that Alkaloids of *D. stramonium* can increased heart beat in mice (Benouadah et al. 2016), furthermore, researchers have reported that the flower, leave and seed *D. stramonium* can induce the tachycardia (Arefi et al. 2016; Amini et al. 2012; Disel et al. 2015).

Ephedraceae

Ephedra distachya is commonly known as sea-grape belongs to the family Ephedraceae (González-Juárez et al. 2020), which has a long history in folk medicine to treat bronchitis, asthma, low blood and colds (Ghavami and Soleimanejad, 2020). A study showed that ephedra alkaloids of *E. distachya* have negative effects on the cardiovascular system and adverse cerebrovascular effects (Andraws et al. 2005). Another important species of Ephedraceae family is *Ephedra sinica*, which is traditionally used to treat cold, asthma, and lung diseases (Mei et al. 2021). Dunnick and coworkers in 2007 demonstrated that a combination of *E. sinica* with caffeine can induce cardiotoxicity (Dunnick et al. 2007). Also, another research study stated that using ephedrine and caffeine affects the cardiovascular system and causes cardiotoxicity (Howden et al. 2005; Nyska et al. 2005).

Plantaginaceae

Digitalis purpurea is a species of Plantaginaceae family, which has been traditionally used for the treatment of respiratory problems and heart failure (HF) (Gerakaris et al. 2022; Aswal et al. 2019; Smith et al. 1984). So many people used *D. purpurea* to enhance their general health and well-being, but a study by Gerakaris indicated that people without heart failure should not consume digoxin, and patients can take herbal medicinal products (HMPs) with a doctor's supervision (Gerakaris et al. 2022; Lei et al. 2018).

Fabaceae

Glycyrrhiza glabra belonging to the family Fabaceae is an important medicinal plant that has been widely used for healing respiratory disorders, gastroesophageal reflux disease, fever, liver diseases, hyperdipsia, rheumatism, tuberculosis, sexual debility, and infectious diseases (Wahab et al. 2021; Gavanji 2022). A study demonstrated that using of licorice (*G. glabra*) candies can induce arrhythmias (Böcker and Breithardt 1991), also another research by Konik and coworkers in 2012 indicated that licorice can induce the coronary artery spasm (Konik et al. 2012). Licorice intake may have harmful effects on the cardiovascular system including cardiac arrhythmias and pulmonary edema, therefore it is essential to be cautious in using licorice (Deutch et al. 2019).

Hypericaceae

Hypericum perforatum, a species of Hypericaceae family, with various therapeutic potential, has been traditionally used to treat infectious diseases, anxiety, and burns, also several studies demonstrated that *H. perforatum* has anti-cancer activities (Gavanji 2022; Klemow et al. 2011). Various types of research indicated that using *H. perforatum* may cause adverse events, and induce cardiotoxicity and herb-drug

interactions. Researchers have reported that using *H. perforatum*, may also lead to Arrhythmia, and hypertension (Cohen and Ernst 2010; Ernst 1999).

Cupressaceae

Juniperus oxycedrus is a member of Cupressaceae family, which is traditionally used for the treatment of respiratory problems and different infectious diseases (Tavares and Seca 2018; Karaman et al. 2003). A number of studies reported that extract of *J. oxycedrus*, has toxic effects on the body and may cause fever, tachypnea, and tachycardia (Koruk et al. 2005; Achour et al. 2011).

Apocynaceae

One of the important ornamental and landscaping herbs is *Nerium oleander* or nerium, which belongs to the family Apocynaceae, and is widely cultivated in different areas. This plant has been traditionally used to treat eczema, ophthalmia, gastrointestinal disturbances, and ringworm infections (Akhtar et al. 2014). Several types of research demonstrated that ingesting *N. oleander* cause different side effects including abnormal heart rhythm (bradycardia) and nervous system disorders (Rubini et al. 2019). Another study showed that oleander poisoning can lead to arrhythmia and other negative effects (Guru et al. 2021).

Piperaceae

Piper methysticum, commonly known as Kava, belonging to the family Piperaceae, has been used for the treatment of various diseases including anxiety, restlessness, and psychological disorders (Ernst 2007; Boon and Wong 2003). Based on a study taking *P. methysticum* and psychotropic medications can increase the risk of herb-drug interaction and will be life-threatening, also it has negative effects on the heart which lead to cardiovascular abnormalities, and arrhythmia (Toohey et al. 2013).

CONCLUSIONS

Since the dawn of humanity, people have tried to seek new medications to treat various diseases. An issue of concern turning into an obsession for people all over the world is self-medication with herbal medicine which causes several harmful effects. In this review, all reported herbal medicines which induce cardiotoxicity were collected and introduced. The results of this review suggest that herbal medicine should be taken with the guidance of medical professionals.

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