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Review Article

CARDIOTOXICITY AND USE OF HERBAL DRUGS- A REVIEW

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ABSTRACT

Cardiotoxicity is the occurrence of heart electrophysiology dysfunction and/or muscle damage. Acute myocardial infarction (MI), the most important consequence of cardiotoxicity, is the necrosis of a region of myocardium caused by an interruption in the supply of blood to the heart usually as a result of occlusion of a coronary artery. Evidence suggests that oxidative stress resulting from increased production of reactive oxygen species (ROS) may play a important role in the pathogenesis of myocardial infarction. There is evidence that antioxidants can protect against free radical defense, which is responsible for reperfusion-induced damage and thereby inhibit myocardial damage and arrhythmias during acute myocardial infarction. Various studies showed that the natural antioxidants have very less toxicity and proved to be safer and effective and they scavenge the free radicals and avoid excess ROS formation in the body thereby helping in mitigating cardiac diseases and several other disorders. Many herbal medicines have been reported to contain large amount of antioxidants. Many herbal drugs have observable beneficial actions on the heart serving as cardiotonics. Where in, digoxin (Lanoxinin) is even clinically prescribed for the treatment of congestive cardiac failure. Though herbal drug industry is growing at an astounding rate all over the world, their efficacy and safety is always questioned. There are only "evidence-based" medicine and "as-yet unproven" medicine, regardless of origin, conventionality or approach. Some of the herbal drugs which are good antioxidants, besides their use for cardiac insufficiency and other cardiac disorders are in turn responsible for causing potential cardiotoxic adverse effects. Thus, herbal products not regulated as medicines cannot be seen as alternative therapies unless they are shown to be equally effective as accepted agents.

Key words: Cardiotoxicity, Myocardial infarction, Oxidative stress, Antioxidants, Herbal drugs

INTRODUCTION

Cardiotoxicity is the occurrence of heart electrophysiology dysfunction and/or muscle damage. Heart becomes weaker and is not as efficient in pumping and therefore circulating blood. Cardiotoxicity may be caused by chemotherapy treatment, complications from anorexia nervosa, adverse effects of heavy metals intake, or incorrect administration of drugs [1].

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Cardiotoxicity is also described as the harmful effect on the heart mediated by various toxins (drugs). The National Cancer Institute defines cardiotoxicity in very general terms as “toxicity that affects the heart”. This definition includes a direct effect of the drug on the heart but also an indirect effect due to enhancement of hemodynamic flow alterations or due to thrombotic events [1].

Cardiotoxicity renders the heart unable to efficiently pump blood throughout the body. Symptoms of this effect include shortness of breath, fatigue, and anemia. These signal that the heart is having difficulty in maintaining its essential functions. If at risk of cardiotoxicity,

symptoms include chronic coughing, swelling of the ankles and feet, and weight gain. These signal that the heart is not beating correctly and therefore failing. Cardiac events may include mild blood pressure changes, thrombosis, electrocardiographic changes, arrhythmias, myocarditis, pericarditis, myocardial infarction, cardiomyopathy, cardiac failure (left ventricular failure) and congestive heart failure [2]. These may occur during or shortly after treatment, within days or weeks after treatment, or may not be apparent until months and sometimes years after completion of chemotherapy.

Oxidative stress resulting from increased production of free radicals plays a major role in cardiovascular disease (CVD) such as myocardial infarction, ischemic heart disease, atherosclerosis, congestive heart failure, cardio myopathy and arrhythmias. Damage to the myocardial cells arises due to the generation of free radicals and reactive oxygen species (ROS) [3]. Experimental and clinical studies have shown that there is increased generation of ROS such as superoxide anion and hydroxyl radicals in heart failure which are involved in the formation of lipid peroxides, damage of cell membrane and destruction of anti-oxidative defense system. Therapeutic intervention via suppression of free radical generation and/or enhancement of endogenous antioxidant enzymes may limit the infarct size and attenuate myocardial dysfunction [4].

MYOCARDIAL INFARCTION (MI)

Acute myocardial infarction (MI) is the most important consequence of cardiotoxicity. It is the acute condition of myocardial necrosis that occurs as a result of imbalance between coronary blood supply and myocardial demand [6]. Myocardial infarction commonly known as heart attack is a disease that occurs when the blood supply to a part of heart is interrupted, causing death of heart tissue. It means necrosis of a region of myocardium caused by an interruption in the supply of blood to the heart usually as a result of occlusion of a coronary artery also called as cardiac infarction [3]. Many patients may die within the first few hours of the onset, while the remainder suffers from effects of impaired cardiac function [6].

Reasons and risk factors

MI can also be caused due to several reasons such as:

- Congenital anomalies of the coronary arteries.
- Reactive oxygen species (ROS) can cause infarct like lesion in heart tissue.
- Embolism: Coronary emboli of varying nature from different sources e.g. vegetation of bacterial endocarditic, atheromatous plaques from major coronary artery, diminished coronary blood supply due to paroxysmal tachycardia. It increases the work load of the myocardium and shortens the diastole.
- Severe anemia, carbon dioxide poisoning etc. which reduce oxygen carrying capacity of blood and may lead to diminished oxygen supply to the myocardium.
- Atherosclerosis: Coronary atheroma is produced as a result of lipid deposition within the intimal coat of the coronary arteries. This leads to the narrowing of their lumen and then the diminution of the blood supply to the myocardium.
- Thrombus: The formation of thrombus in the coronary arteries may lead to the complete occlusion with resultant infarction or massive necrosis of the corresponding part of the myocardium.
- Vasospasm: It has been possible to document vasospasm of one of the major coronary arterial trunk in patients with no significant atherosclerotic coronary narrowing which may cause angina or myocardial infarction [6]

Six primary risk factors have been identified for the development of MI: hyperlipidemia, diabetes mellitus, hypertension, tobacco use, male gender and family history of atherosclerotic arterial disease. The presence of any risk factor is associated with doubling the relative risk of developing atherosclerotic coronary artery disease [7].

Types of Infarcts

- According to the anatomical region of the left ventricle involved, they are called anterior, posterior (inferior), lateral, septal and circumferential and their combinations like anterolateral, posterolateral (inferolateral) and anteroseptal.
- According to the degree of thickness of the ventricular wall involved, infarcts are of two types:
  - Full-thickness or transmural: When they involve the entire thickness of the ventricular wall.
  - Subendocardial or laminar: When they occupy the inner subendocardial half of the myocardium.
- According to the age of infarcts, they are of two types:
  - Newly formed infarcts, called acute, recent or fresh.
  - Advanced infarcts, called old, healed or organized [8].

Location of infarcts

Infarcts are most frequently located in the left ventricle. Right ventricle is less susceptible to infarction due to its thin wall, having less metabolic requirements and is thus adequately nourished by the besian vessels. Atrial infarcts, whenever present are more often in the right atrium, usually accompanying the infarct of the left ventricle. The oxygenated blood in the left atrial chamber relatively supplies left atrium. The region of infarction depends upon the area of obstructed blood supply by one or more of the three coronary arterial trunks.

Accordingly, there are three regions of myocardial infarction [8].

- Stenosis of left anterior descending coronary artery is the most common (40-50 %). The region of infarction is the anterior part of the left ventricle including the apex and the anterior 2/3rd of the interventricular septum.
- Stenosis of the right coronary artery is the next most frequent (30-40 %). It involves the posterior part of the left ventricle and the posterior 1/3rd of the interventricular septum.
- Stenosis of the left circumflex coronary artery is seen less frequently (15-20 %). Its area of involvement is the lateral wall of the left ventricle.

Diagnosis

The diagnosis of acute MI is made on the observation of 3 types of features [8]

- Clinical Features:
  Typically, acute MI has sudden onset. The following features usually characterize a case of acute MI:
- Pain: Usually sudden, severe, crushing and prolonged, substernal or precordial in location, unrelieved by rest or nitroglycerin, often radiating to one or both the arms, neck and back.
- Indigestion: Pain is often accompanied by epigastric or substernal discomfort interpreted as ‘heart burn’ with nausea and vomiting.
- Apprehension: The patient is often terrified, restless and apprehensive due to great fear of death.
- Shock: Systolic blood pressure is below 80 mmHg, lethargy, cold clammy limbs, peripheral cyanosis, weak pulse, tachycardia or bradycardias are often present.
- Oliguria: Urine flow is usually less than 20 ml per hour.
- Low-grade fever: Mild rise in temperature occurs within 24 h and lasts up to one week, accompanied by leucocytosis and elevated ESR.
- Acute pulmonary oedema: Some cases develop severe pulmonary congestion due to left ventricular failure and develop suffocation, dyspnea and bubbling respiration.
- ECG changes:
  - ST segment elevation,
  - T wave inversion and
  - Appearance of wide deep Q waves.
- Serum enzyme determination:
  Serum cardiac markers are useful for confirming the diagnosis of MI when patients present without ST segment elevation, when the diagnosis may be unclear and when physicians must

distinguish patients with unstable angina from those with a non- ST segment elevation (non-Q-wave) MI. They are also useful for confirming the diagnosis of MI for patients with ST-segment elevation. These biomarkers (called cardiac markers or serum cardiac markers) include creatinine kinase (CK) MB isoforms, AST, LDH and myoglobin [6, 8].

- Creatinine phosphokinase and CK-MB:

CK has three isoforms:

i. CK-MM derived from skeletal muscle;
ii. CK-BB derived from brain and lungs; and
iii. CK-MB derived from cardiac muscles and from extracardiac tissue

Thus total CK estimation lacks specificity while elevation of CK-MB isoenzyme is considerably specific for myocardial damage. CK-MB has further two isoforms: CK-MB2 is the myocardial form while CK-MB1 is an extracardiac form. A ratio of CK-MB2: CK-MB1 above 1.5 is highly sensitive for the diagnosis of acute myocardial infarction after 4-6h of onset of MI. CK-MB disappears from blood by 48h.

- Lactate dehydrogenase (LDH):

Total LDH estimation also lacks specificity since these enzymes are present in various tissues besides myocardium such as in skeletal muscle, kidneys, liver, lungs and blood cells. However, like CK, LDH too has two isoforms of which LDH1 is myocardial specific. Estimation of ratio of LDH1: LDH2 above 1 is reasonably helpful in making a diagnosis. LDH levels begin to rise after 24 hours, reach peak in 3-6 days and return to normal in 14 days.

- Aspartate aminotransferase (AST):

It increases 3-8 h after the onset of the attack and returns to normal in 3-6 days. The highest values are found on an average, some 24 h after the onset. The duration and extent of the increase is related to the size of the infarct.

- Alanine aminotransferase (ALT):

It increases 4-8 h after the onset of the attack and returns to normal in 3-5 days. The highest values are found on an average, some 24 h after the onset. The duration and extent of the increase is related to the size of the infarct.

- New cardiac marker enzyme (Troponin-I)

The diagnosis of myocardial infarction has conventionally relied on the presence of chest pain or typical ST segment and T wave abnormalities on the 12 lead electrocardiogram (ECG) and a rise in the serum concentrations of cardiac muscle enzymes. Whereas most patients with ST segment elevation also invariably have high serum cardiac muscle enzyme values, indicating myocardial damage, a considerable proportion of patients with less specific ST segment changes may not have increased cardiac muscle enzymes, and in the past have been diagnosed as having either stable angina or non-cardiac chest pain. Cardiac troponin T (cTnT) and troponin I (cTnI) are cardiac regulatory proteins that control the calcium mediated interaction between actin and myosin. The cardiac forms of these regulatory proteins are coded by specific genes and theoretically have the potential of being unique to the myocardium. Indeed, cTnI has not been identified outside the myocardium.

The measurement of serum cTnI and cTnT is superior in terms of sensitivity and specificity to cardiac muscle enzyme measurements in the identification of cardiac muscle damage. Raised cardiac troponin concentrations are now accepted as the standard biochemical marker for the diagnosis of myocardial infarction.

Complications

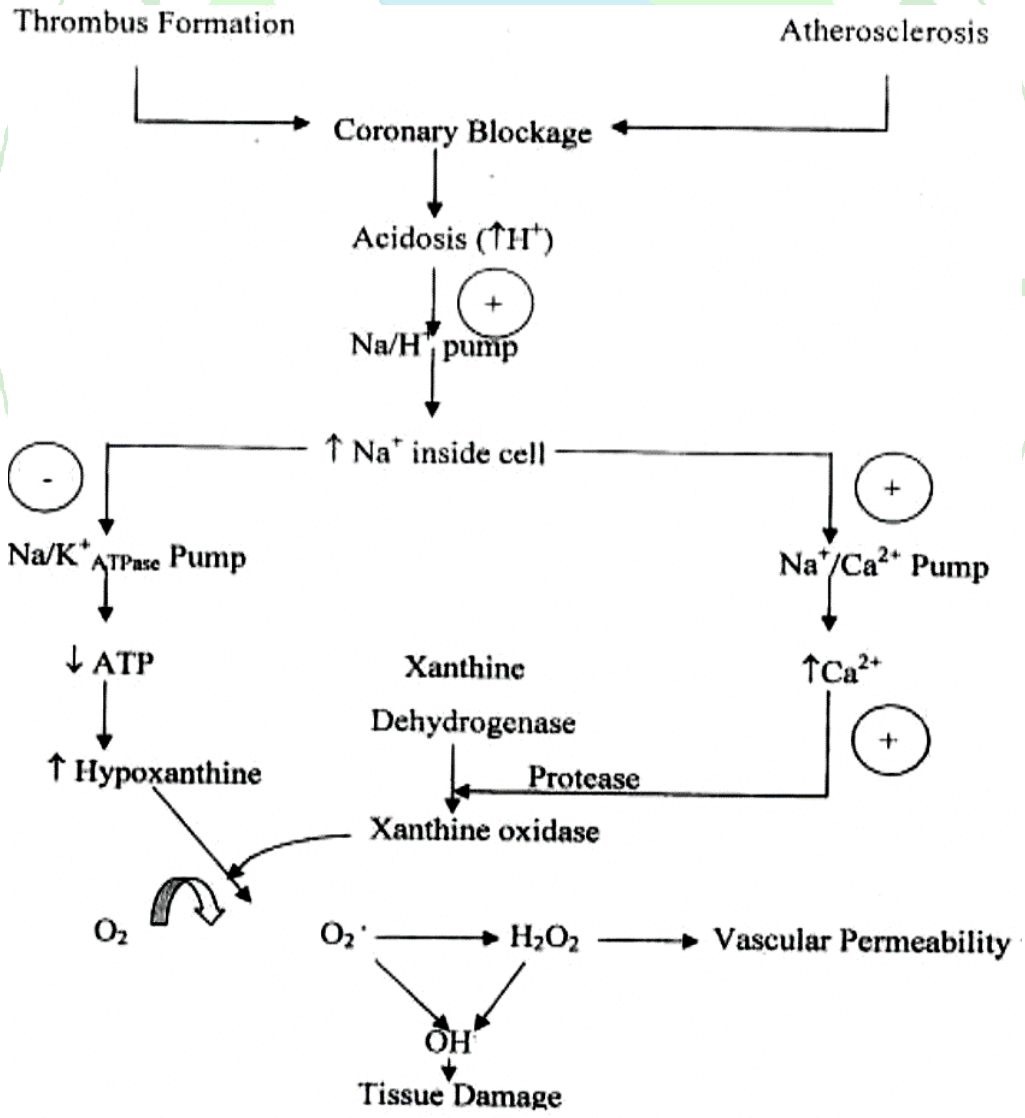
Following an attack of acute MI, only 10-20% cases do not develop major complications and recover. The remainder 80-90% cases develop one or more major complications, some of which are fatal. The immediate mortality for acute MI (sudden cardiac death) is about 25%. The important complications which may develop acute MI are as follows:

- Arrhythmias
- Congestive heart failure
- Cardiogenic shock

- Mural thrombosis and thromboembolism
- Rupture of heart
- Cardiac aneurysm
- Pericarditis
- Post MI syndrome: About 3-4% of patient who suffer from acute MI develop post MI syndrome or Dressler's syndrome subsequently. It usually occurs 1-6 weeks after the attack of MI. It is characterized by pneumonitis. The symptoms are usually mild and disappear in few weeks. The exact pathogenesis of this syndrome is not known. It may be due to autoimmune reaction as evidence by circulating anti-heart antibodies in the serum of these patients. But these antibodies are also present in patient with MI who does not develop this syndrome.

Mechanisms

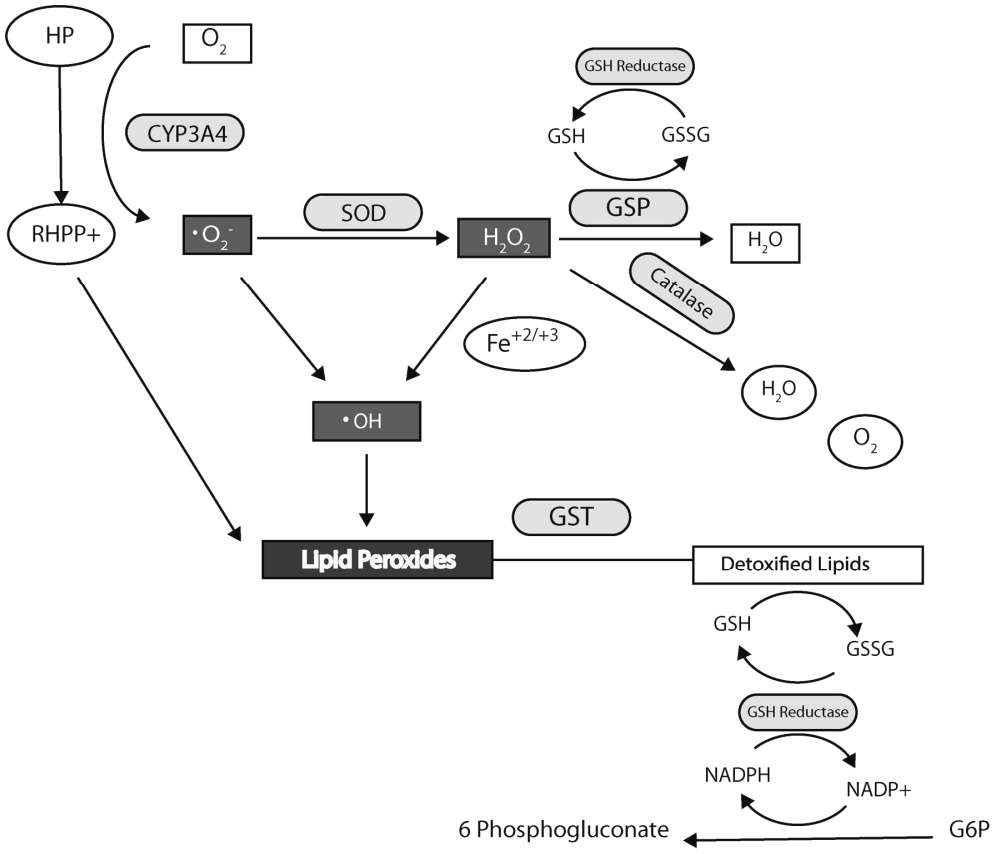
The underlined pathophysiological mechanisms of ischemic reperfusion (IR) have not been fully elicited. It has been suggested that an over production of oxygen derived free radicals and intracellular calcium overload or redistribution [9] during the first minute of reflow might be involved. However oxygen-derived free radicals and hyper contraction due to calcium overload are not the only candidates responsible for reperfusion injury. Other important factors in the pathogenesis of reperfusion include platelet and neutrophil injury, renin-angiotensin system and the complement activation.



Mechanisms involved in MI [10]

OXYGEN DERIVED FREE RADICALS & OXIDATIVE STRESS

A free radical may be defined as any atom or molecule that can exists independently with one or more unpaired electrons in its outer orbital. Because of the existence of unpaired electron, the atom or molecule is relatively unstable and in general it is highly reactive [9].



Major oxygen species pathways and antioxidant defense [11]

In heart, oxygen free radicals may be generated by many mechanisms, such as mitochondrial respiration, activated neutrophil and in some species by xanthine oxidase activity [12].

A small percentage of electron leaks away from the stream of the mitochondrial respiration chain, leading to univalent reduction of molecular oxygen, which generates superoxide anion $(\bullet O_2)^-$ In human cells superoxide is quickly transformed into hydrogen peroxide (H_2O_2). This reaction is greatly accelerated by superoxide dismutase (SOD), a widely distributed enzyme. H_2O_2 is a potent oxidant and in sufficient concentration, will kill any cell. The further reduction of H_2O_2 labializes the inter-oxygen bond resulting is cleavage to produce OH^- and •OH. The later one, hydroxyl radical, is a highly reactive radical species. Free transition metal ions (Fe, Cu) often act as electron donor necessary for generation of hydroxyl radical from H_2O_2 [13].

Evidence suggests that reactive oxygen species (ROS) may play important role in the pathogenesis of myocardial infarction. ROS are capable of reacting with unsaturated lipids and of initiating the self-perpetuating chain reactions of lipid peroxidation in the membranes. Free radicals can also cause oxidation of sulfhydryl groups in proteins and strand scission in nucleic acids is also possible. Myocardial antioxidants inhibit or delay the oxidative damage to sub cellular

proteins, carbohydrates, lipids and DNA. There is evidence that antioxidants can protect against free radical defense, which is responsible for reperfusion-induced damage and lipid peroxidation, and may thereby inhibit thrombosis, myocardial damage and arrhythmias during acute myocardial infarction (AMI). Antioxidant status is a critical tool for assessing redox status. The antioxidant status or related antioxidants may play an important role in protecting the organism from free-radicals-mediated damage. The role that such compounds play in AMI development is important, since their presence may decrease the damage resulting from blood ROS during reperfusion [14].

Table: Some of the major endogenous antioxidants and their sites of action in cardiomyocytes

Name	Site	Action
Superoxide dismutase (SOD) CuZn-SOD, Mn-SOD	– Cytoplasm, cell surface and mitochondria	Catalyzes $O_2^{\cdot-}$ dismutation to H_2O_2 $2O_2^{\cdot-} + 2H^+ \rightarrow H_2O_2 + O_2$
Catalase	Peroxisomes and mitochondrial membrane	$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$
Glutathione peroxidase	Cytoplasm	$2GSH + H_2O_2 \rightarrow GSSG + 2\ H_2O$
Glutathione	Intracellular	Cellular reductant
Coenzyme Q10 (ubiquinone)	Cell membrane	Redox active electron carrier
Vitamin E (α-tocopherol)	Cytoplasm and plasma	Break lipid peroxidation chain and LDL reaction
β-Carotene (provitamin A)	Plasma	Inhibits oxidation of LDL
vitamin C (ascorbic acid)	Cytoplasm and plasma	Directly as an antioxidant or as a cofactor for vitamin E

Some of the major endogenous antioxidants and their sites of action in cardiomyocytes [15]

Many herbal medicines have been reported to contain large amount of antioxidants. These antioxidants play a vital role in delaying, intercepting or preventing oxidative reactions, by scavenging reactive metabolites and converting them to less reactive molecules or by enhancing the resistance of sensitive biological target to ROS attack. The existence of flavonoids in the plant is likely to be responsible for the free radical scavenging effects. Flavonoids are phenolic compounds and plant phenolics are a major group of compounds that act as primary antioxidants or free radical scavengers.

HERBAL DRUGS IN CARDIOTOXICITY – SAFETY ISSUES

Herbal medicine is still the mainstay of about 75–80% of the world population, for primary health care because of better cultural acceptability, better compatibility with human body and lesser side effects. Today, herbal remedies are back into prominence because the efficacy of conventional medicines such as antibiotics, which once had near universal effectiveness against serious infections, is on the wane. In Ayurveda (traditional Indian medicine) about 2,000 plant species are considered to have medicinal value, while the Chinese Pharmacopoeia lists over 5,700

traditional medicines, most of which are of plant origin [16].

Natural products and their derivatives represent more than 50% of all the drugs in clinical use in world today [17]. Herbal products symbolize safety in contrast to the synthetics that are regarded as unsafe to human and environment. The chemical constituents present in them are a part of the physiological functions of living flora and hence they are believed to have better compatibility with the human body [18]. The drugs are derived either from the whole plant or from different organs, like leaves, stem, bark, root, flower, seed, etc. Some drugs are prepared from excretory plant product such as gum, resins and latex.

Even the Allopathic system of medicine has adopted a number of plant-derived drugs, which form an important segment of the modern pharmacopoeia. Some important chemical intermediates needed for manufacturing the modern drugs are also obtained from plants (Eg. diosgenin, solasodine, β-ionone). Not only, that plant-derived drug offers a stable market worldwide, but also plants continue to be an important source for new drugs [19].

Although modern drugs are effective in the symptomatic control of cardiovascular disease, their use is often associated with a number of undesirable effects [20]. Various ayurvedic formulations have been found to be clinically useful remedy in a number of disorders with advantages like better acceptance by the patient and less cost [21, 22]. However, the claimed pharmacological activities of many of these formulations have not been proven nor refuted by controlled studies. Present study on the safety of herbal cardiotonic formulations is an important consideration, since cardiovascular remedies are usually taken for long periods of time.

Many herbal drugs have observable beneficial actions on the heart serving as cardiotonics. Although generally safe they can interact with some pharmaceutical drugs [23]. E.g., *Aconitum ferox, Solanum indicum, Piper nigrum and Piper longum, Diospyros melanoxylon, Craetagus spp., Tilia spp., Terminalia arjuna, Leonurus cardiaca.*

Some of the herbal drugs which are good antioxidants, besides used for cardiac insufficiency and other cardiac disorders are in turn responsible for causing potential cardiotoxic adverse effects. Some of them are *Aconitum carmichaeli, Aconitum kusnezoffii, Digitalis lanata, Urginea maritima* and other Digitalis glycosides, *Glycyrrhiza glabra, Convallaria majalis, Ephedra sinica* [24]. Where in, digoxin (Lanoxinin) isolated from *Digitalis purpurea* Linn. is clinically prescribed for the treatment of congestive cardiac failure [25].

CONCLUSION

Various studies showed that the natural antioxidants have very less toxicity and proved to be safer and effective. The natural antioxidants scavenge the free radicals and avoid excess ROS formation in the body thereby helping in mitigating cardiac diseases and several other disorders [26]. Hence, search for herbal medicine to improve cardiac health possessing qualities of a natural antioxidant has greatly been increased in the recent scenario [27]. Though herbal drug industry is growing at an astounding rate all over the world, their efficacy and safety is always questioned. Although herbal medicines promise alternative and effective treatment for chronic disorders, no sufficient data is available on the quality certification with regard to their authentication, standardization, composition, stability and safety. Also, there may be variation even within the same herbal remedy in terms of the amount and strength of active ingredients depending on how and where the plants are grown, when they are harvested, how they are stored, what parts of them are used in the preparation etc. In addition, contaminants and adulterants are also held responsible for the varying amounts of active ingredients [28].

As medicinal agents, herbal products should be considered separate from other non-medicinal forms of "alternative" or "complementary" therapies (e.g., relaxation techniques, massage, chiropractic, hypnosis).

There are only "evidence-based" medicine and "as-yet unproven" medicine, regardless of origin, conventionality or approach. [29] Thus, herbal products not regulated as medicines cannot be seen as alternative therapies unless they are shown to be equally effective as accepted agents [30]. Adverse events associated with dietary supplements, medical foods, and infant formulas can be reviewed from the FDA database on the Internet (http://vm.cfsan.fda.gov/~dms/aems.html). It remains the responsibility of pharmacists, physicians, and other health care providers to gather and report information on adverse effects of drugs, including herbals.

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