Review Article

A Review on Cardioprotective mechanism of Chemical Constituents of Medicinal Plants

Abstract:

Plants are the major source of human living. Since the beginning of the era, plants have been used for medicinal purposes. There is dire to explore the mechanism of chemical constituents in plants and particularly saponins, cardiac glycosides, and flavonoids due to their mechanism to save damaged cells in cardiac muscle. Databases like Google Scholar, Medline, PubMed, and the Directory of Open Access Journals were searched to find the articles describing the cardioprotective mechanism of medicinal plants. Saponin, flavonoids, glycoside, steroid, alkaloids, tannin, phenol, phlorotannin, terpenoids, and anthraquinone are chemical constituents in plants that enhance cardioprotection activity and decreases cardiac abnormalities. The current review article provides data on the use of medicinal plants, specifically against cardiac diseases, as well as an investigation of molecules/phytoconstituents as plant secondary metabolites for their cardioprotective potential.

Keywords: Cardioprotective, Medicinal Plants, Oxidative Stress, Saponins, Cardiac Glycosides

1. Introduction:

Traditional medicines are knowledge, skills, and continuous practice which depends on theories, beliefs of different cultures in various countries used to maintain good health, prevention, diagnosis of both physical and mental health [1]. The use of medicinal plants is being followed for ages because therapeutic effects can be examined and evaluation of toxic doses can be done to maintain the quality of formulation [2]. Medicinal plants are a major resource base for the traditional medicine & herbal industry [3]. Plants have different components like alkaloids, glycosides, flavonoids, polyphenols, etc, and each of them has different actions in preventing, curing, or healing diseases.

Recently, WHO Estimated that 80% of the world population is using traditional medicine. India is known as the "Emporium of Medicinal plants" due to the availability of several thousand medicinal plants in the different bioclimatic zones. India is one of the richest countries in the world in terms of biodiversity and documented systems of medicine like Ayurveda, Unani, Siddha & Homoeopathy (AYUSH System of Medicine) [4]. Pharmacopeias all over the world contain at least 25% of herbal drugs or drugs derived from plants. According to WHO, 21000 plant species are being used as medicines. Usage of medicinal plants is increasing in both developed and developing nations, as they are non-narcotic, have fewer adverse effects, are low-cost, and are the only source of treatment in poor countries. The best advantage of herbal medicine is age and sex of a person are not considered in the treatment. Medicinal plants are widely used because they are easily available at a low cost and have fewer side effects.

Bioactive agents derived from natural sources have gained critical importance in modern medicine, lowering the risk of cardiac ailments by scavenging free radical formation [5]. Herbal medicines play an important role in the health of a large proportion of the world's population and have been recognized as a component of various tribes' cultural heritage. Polyphenols protect the heart by inhibiting oxidation. The majority of pharmaceutically significant drugs are derived from plants. Plant derivatives as drugs play an important role in animal and human healthcare systems all over the world [6,7]. Plants are an important source of traditional medicines that are used to treat a variety of ailments.

Chronic diseases like cancer, heart diseases can decrease effects on people by consumption of fruits and vegetables which are in bioactive compounds. Based on research so far, it is evident that phytochemicals have beneficial health effects. It is important to study the compounds from natural sources with effects against Myocardial Infarction and also prevents ischemic reperfusion injury, helps to reduce the damage caused by hypoxia and ischemia condition, reduces infarcts size [8]. Cardioprotective plants contain a variety of bioactive compounds, such as diosgenin, isoflavones, sulforaphane, carbonized, catechin, and quercetin, which have been shown to improve cardioprotection and thus reduce the risk of cardiac abnormalities [9].

Coronary artery disease (CAD) is a leading disease worldwide. The most common CAD is Myocardial infarction. Nearly 15-20% of the mortality rate is reported each year. The incidence of MI in the USA is about 525 billion people based on American heart association data and according to the national survey of UK, people suffered from MI was reported as 915 billion [10] Heart attacks, also known as myocardial infarctions (MI), and

their complications are the leading causes of death worldwide. Herbal antioxidants are increasingly being used as protective agents against a variety of cardiovascular abnormalities [11].

Approximately every 40 seconds, an American will have a myocardial infarction. The average age of MI occurrence is 66 years for men and 72 years for women [12]. In contrast to developed countries, developing countries like Sri Lanka, India, South Africa also reported a high incidence of MI mostly in younger individuals aged between 45 to 65 years.

MI is an occlusion in the artery which blocks the oxygenated blood supply to the heart and depletes the oxygen to the heart muscle which leads to oxidative stress and increased production of free radicals and causes cell death [13]. After the onset of Myocardial ischemia, cell death is not immediate it can be identified by imaging. The ischemic zone increases the demand for oxygen and nutrients which increases pressure and risk of cell death [14]. Earlier WHO defined MI from symptoms like ECG abnormalities, and enzymes. But Due to the development of specific serological biomarkers like glutamine-oxaloacetic transaminase (GOT), lactate dehydrogenase (LDH), creatine kinase (CK), MB fraction of CK, i.e., CKMB activity and CKMB, etc, can be detected in the case of myocardial necrosis and improved technology helps the accuracy of detecting MI with precise imaging [15].

Myocardial is a heart muscle and Infarction is a condition occurred due to increased oxygen demand or no oxygen supply to the heart. Myocardial infarction is divided into 2 types. type 1 MI is caused because plaque rupture and type 2 is caused due to reduction of

oxygen supply. Two conditions are having different treatments and their pathogenesis is also poles apart. During ischemia or hypoxia condition in the heart leads to a decrease in ATP production, which further increases cytosolic calcium and mitochondrial calcium [16].

The present article provides knowledge on the mechanism of different plant components and how they act in repairing MI tissue damage. World health organization has started a traditional medicine strategy that mainly encourages the use of traditional medicine as they play a vital role in people's health and traditional medicines are low cost and effective when compared to other treatments [17].

2. Pathology of Myocardial Infarction:

During myocardial infarction, hypoxia condition due to decreased oxygen in blood i.e., ischemia which results in the reduction of ATP production, ion pump function unbalance because of which increase in Na^+ and Ca^{2+}, which further increases cytosolic calcium and accumulation of calcium in mitochondria [18]. Mitochondria is the powerhouse of the cell and plays a vital in the pathogenesis of myocardial infarction as they are 40-50% of cardiomyocyte cytoplasmic volume and important in cardiac balance since energy supply for cardiomyocytes is mostly derived from mitochondrial oxidative phosphorylation as they are a special target for cellular damage. Besides this, activation of phospholipids, protease, increases in loss of cell membrane phospholipids which further deteriorates the function of cell membrane and death of cytosol skeleton. Due to damage to the cell membrane leakage of the cell occurs and leads to cell death (fig. 1). Activation of

free radicals leads to upregulation of a superoxide-generating enzyme as a result, production of Reactive Oxygen Species (ROS) starts [19-21].

Molecular and cellular mechanism during ischemic reperfusion injury is complex and damage occur in diverse pathways. Mitochondria are the major source for the production of ROS and major target for damage caused by ROS. Mitochondrial damage in cardiomyocytes leads to decreased energy production and loss of myocyte contractility and cell death [22]. During ischemic reperfusion, ROS induces cell dysfunction and death by activating metalloproteinases and mitochondrial permeability transition pore (MPTP) which leads to cell swelling and death. ROS interacts with NO and increases in production of NO-producing enzyme which further damages cell by reaction of NO with superoxide and leads to cytotoxicity [23-26].

3. Ischemic reperfusion injury:

Ischemia causes an increase in intracellular sodium, hydrogen, and calcium ions, resulting in tissue acidosis. Reperfusion, in turn, causes rapid changes in ion flux, which leads to increased cytotoxicity [27,28]. Sodium-dependent pH regulatory mechanisms, such as the Na^+-H^+ exchanger and the Na^+-HCO3 transporter, are activated, resulting in intracellular sodium accumulation. Increases in sarcoplasmic reticular $Ca2^+$ are caused by high sodium concentrations via the Na^+-$Ca2^+$ exchange [29] and 8 $Ca2^+$ overloads are exacerbated by increased $Ca2^+$ entry via sarcolemmal L-type $Ca2^+$ channels [30,31] and decreased import of cytosolic $Ca2^+$ into the sarcoplasmic reticulum by the SERCA $Ca2^+$ATPase [32,33]. As a result, ATP depletion, ultrastructural mitochondrial damage, and

myocardial stunning occur. Cardiac myocytes consume large quantities of energy. Normally, the generation of ATP occurs by the oxidative process to form water. Four electrons are required for oxygen to form water one at each step. The generation of free radicals causes cell damage and the release of toxins into the blood. Cell membrane damage also leads to the leak of cytosol enzymes due breakdown of cell membrane phospholipids. Subsequent inflammation occurs due to activated neutrophils which utilize oxygen and release a lot of oxygen-free radicals [34-36].

4. Cardioprotective Mechanism of Medicinal Plants:

Medicinal Plants have therapeutic effects which include inhibiting, regulating the expression of various proteins such as contractile, and regulating the calcium levels, and improvement in the functioning of mitochondria. Medicinal plants have evidence of decreasing the damage in heart muscles, and cardiomyocytes by regulating the K-ATP channel (fig.2) and avoiding damage through oxidative stress and apoptosis. Inflammation inhibition, oxidative stress and apoptosis, endothelial nitric oxide synthase-nitric oxide (NOS-NO) signaling pathway activation, angiogenesis induction, and endothelial permeability suppression have all been shown to be beneficial effects of medicinal plants/herbal products [37]. Types of chemical constituents present in plants are Saponin, flavonoids, glycoside, steroid, alkaloids, tannin, phenol, phlorotannin, terpenoids, and anthraquinone

5. Saponins and Cardioprotection:

Saponins contain amphiphilic compounds with high molecular weight and have triterpenoid and steroid as lipophilic moiety and sugars act as hydrophilic moiety [38-40].

Saponins have a rigid skeleton with at least four hydrocarbon rings with attached one or two sugar groups. Traditionally, they are subdivided into triterpenoid and steroid glycosides. Steroidal saponins contain 27 carbon atoms forming the core structures like spirosatan and furostan [41]. Saponins are 11 main classes: dammaranes, tirucallanes, lupanes, hopanes, oleananes, taraxasteranes, ursanes, cycloartanes, lanostanes, cucurbitanes, and steroids. The oleanane skeleton is the most common [42,43].

Pharmacological effects of saponins include stimulation of immune responses and also can inhibit cell proliferation, counteract angiogenesis, and stimulate apoptosis (44,45). Besides that, Saponins also exhibit effects like antioxidant, anti-hypoxic, anoxia/reoxygenation, $Ca2^{+}$ ion regulation or calcium antagonist, cardiocyte apoptosis, vasodilatory effect, and angiogenesis [46].

Ginseng has been the most popular and common product, known for its cardioprotection; which contains saponins as an active constituent [47,48]. Overall, structural similarities with cardioactive phytosterols, as well as intriguing pharmacological effects such as hemolytic or permeabilization of the cell membrane, antilipemic, serum cholesterol-lowering, and anticoagulant activity, prompted researchers to investigate the role of saponins in cardioprotection [49,50].

Saponins cause erythrocytes to expand, rupture, and release hemoglobin. Saponin's ability to cause erythrocyte death or hemolysis may limit the therapeutic use of the substances. Saponins have been proposed for the treatment of a variety of diseases, including diabetes, obesity, and osteoporosis.

Increased Reactive oxygen species (ROS) causes intracellular oxidative, which is the major reason for CVDs. ROS toxicity during reperfusion causes myocardial

ischemia/reperfusion (I/R) injury through xanthine decomposition in mitochondria, an increase in cellular accumulation of lipid peroxides, depletion of endogenous antioxidants, and $Ca2^{+}$ ion overloading [51]. A triterpenoid saponin exhibits cardioprotective effects in ischemic reperfusion injury by restoring the balance between inducible NO synthase and endothelial NO synthase [52].

The cardioprotective activity of *Allium Chinensis* is more when compared to a clinically approved calcium channel blocker nimodipine; which increases the malondialdehyde (MDA) formation and nitric oxide (NO) [53]. Other examples of Saponins viz., glycyrrhizic acid, asperosaponin VI, elatoside C, tribulosin, platycodin D, astragaloside IV, protodioscin, and trillin will enhance the superoxide dismutase (SOD), which work at cellular defense against ROS induced cardiac damage [54-57].

Saponins exhibit hypocholesterolaemic activity which involves forming insoluble complexes with cholesterol, affecting micelle formation, interfering with bile acid metabolism, inhibiting lipase activity, and regulating cholesterol homeostasis [58,59]. This activity has been demonstrated in both animal and human trials. The best example of saponins currently being used as cardiac drugs is Digoxin which is procured from the medicinal plant *Digitalis purpurea* and saikosaponin from *Bupleurumfalcatum* which is used as an herbal supplement. Saponins rich Food sources like *Saponaria*, soya, chickpea, *Yucca*, alfalfa, fenugreek, *Quillaja*, *Gypsophila*, and garlic resulted in reductions in cholesterol concentrations [60].

Total saponins and degradation products of total saponins of Panacis Majoris Rhizoma protect the cardiomyocytes from injury induced by MIR, and also decreases the

injury caused by oxidative stress, while maintaining the levels of LDH, CK-MB. But no significant change in infarct size is observed [61]. Other effects are shown in (Fig.3)[62].

6. Cardiac Glycosides and Cardioprotection:

Cardiac glycosides contain a steroidal framework in their core structure and their moiety is responsible for the activity. This steroid structure contains an unsaturated lactone ring which characterizes the subgroup of glycosides [63]. Usually, cardiac glycosides are identified as secondary metabolites in plants and most of them belong to angiosperms. Recently cardiac glycosides are being identified from animal origin also [64]. Cardiac glycosides contain two classes of compounds cardenolides and bufadienolides, both differ by the structure of Aglycone [65]. Plants produce both cardenolides and bufadienolides.

According to the pathology of cell injury, Na-K-ATPase (sodium-potassium) pump is located in the cell membrane that transports K ions in the cell and Na ions out the cell. This pump maintains the balance between the cytoplasm and extracellular fluid by using ATP [66]. Cardiac glycosides inhibit these pumps on Cardiac myocytes and prevent Na and calcium exist. Higher levels of cytoplasmic calcium improve the calcium intake into the sarcoplasmic reticulum which enhances contractility of myocytes, together with the ion build up in cell increases cardiac output by accelerating the force of contraction but the intensity is unpredictable [67,68].

Convallaria Majalis is a Highly poisonous plant that exhibits cardioprotective effects due to the presence of 38 types of cardiac glycosides and active constituents of convallarin. This is more preferred than digitalis as it is safer. Convallaria majalis is used in

the treatment of Arrhythmia and tachycardia [69]. Digoxin and digitoxin are the two most widely used digitalis inotropes which belong to the family of Scrophulariaceae [70]. The suffix "genin" refers to aglycone, without sugar, and digitoxin refers to digitoxigenin which contains aglycone and 3 sugar moieties. Aglycone portion in Cardiac glycosides is important for potential effect.

Normal, Na^{+}-K^{+} pumps in the cardiac myocytes infuse potassium ions inside and diffuse sodium ions out of the cell. Cardiac Glycosides inhibit the Na^{+}- K^{+} pump, which stops sodium exit leads to an increase in intracellular sodium. In the same way, the Na^{+}-Ca^{+} pump allows calcium ions out of the cell and sodium ions inside the cell and further raises intracellular sodium levels, which inhibit this pump; thus, calcium ions are not extruded and begin to build up inside the cell. Increased cytoplasmic calcium concentrations increase calcium uptake into the sarcoplasmic reticulum (SR) via the $Ca2^{+}$-ATPase transporter [71]. For faster and stronger contraction, increased calcium in the sarcoplasmic reticulum releases calcium on stimulation.

Usually, Na-K-ATPase and cardiac glycoside binding are slow, which increases intracellular calcium gradually and further, delaying the action of cardiac glycosides [72]. Besides this, increased extracellular potassium also decreases the binding of cardiac glycoside to Na-K-ATPase. Moreover, increases the toxicity of cardiac glycosides due to more presence in the body and also increases toxicity in presence of hypokalemia. When higher glycoside doses are administered, rhythm is lost and ventricular tachycardia develops, which is followed by fibrillation [73].

7. Flavonoids and Cardioprotection:

Flavonoids are aromatic keto compounds that can be found in a variety of natural edible products, including vegetables, fruits, legumes, and tea [74]. Because of their antioxidant, anti-inflammatory, antiviral, anticancer, and anti-aging properties, they have a high therapeutic value. Flavonoids have also been linked to liver protection, immune enhancement, and the prevention of cardiovascular disease [75]. flavonoids prevent mitochondrial injury, which induces apoptosis. Flavonoids are a class of polyphenol secondary metabolites. Flavonoids are classified as flavonols, flavones, isoflavones, flavanols, flavanonols, proanthocyanidins, anthocyanins, flavanones, and chalcones [76]. Flavonoids are antioxidants. Flavonoids reduced hydroxyl radical formation via the Haber–Weiss, and Fenton reactions. Flavonoids increased SOD activity in MIRI, indicating that they could inhibit free radical peroxidation and activate oxidase activity in tissues to protect the myocardium [77].

8. Conclusion:

The current review concluded that the therapeutic and prophylactic potential of plant phytoconstituents for the management of cardiovascular disorders has been investigated in several ways, though the exact molecular mechanisms remain unknown. Phytoconstituents appear to have cardioprotective properties by Decreasing various factors, inhibiting key enzymes, and scavenging oxygen-free radicals. Some known examples are Aspirin from Salix alba L. tree, digoxin from Digitalis purpurea is currently being used as formulated medicines. This review describes how phytochemicals like saponins, cardiac glycosides have diverse cardioprotective functions. Several plant-derived cardioprotective agents have been evaluated in clinical trials over the last few decades, with only a few

being successful. Due to limited access to research articles and our search strategy, we were unable to include all of the studies describing the cardioprotective effects of medicinal plants or herbal agents in this review. However, the evidence presented in this review strongly suggests that medicinal plants/herbal products are a source of emerging medicines for the prevention and treatment of cardiovascular diseases. Herbal medicines have potent therapeutic properties and can alleviate pathological conditions associated with CVDs. *In-vivo* and *in-vitro* cardioprotective activity of various medicinal plants viz., Colebrookea Oppositifolia, Sylimarin, Mangifera indica have been proved but, no clear clinical therapeutic benefits have been established. We conclude that better-designed studies and larger-sample-size clinical trials are required to investigate the role of various nutrients. Developing more effective and safe agents from natural herbs is thus a promising approach to preventing and treating cardiovascular abnormalities. Documentation of clinical study criteria, on the other hand, is critical for standardizing the evaluation of medicinal plants/herbal agents.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Significance:

The study highlights the efficacy of "Ayurved" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Fig 2: Cardioprotective mechanism of medicinal plants

Fig 3: Cardioprotective effect of Saponins

Figures:

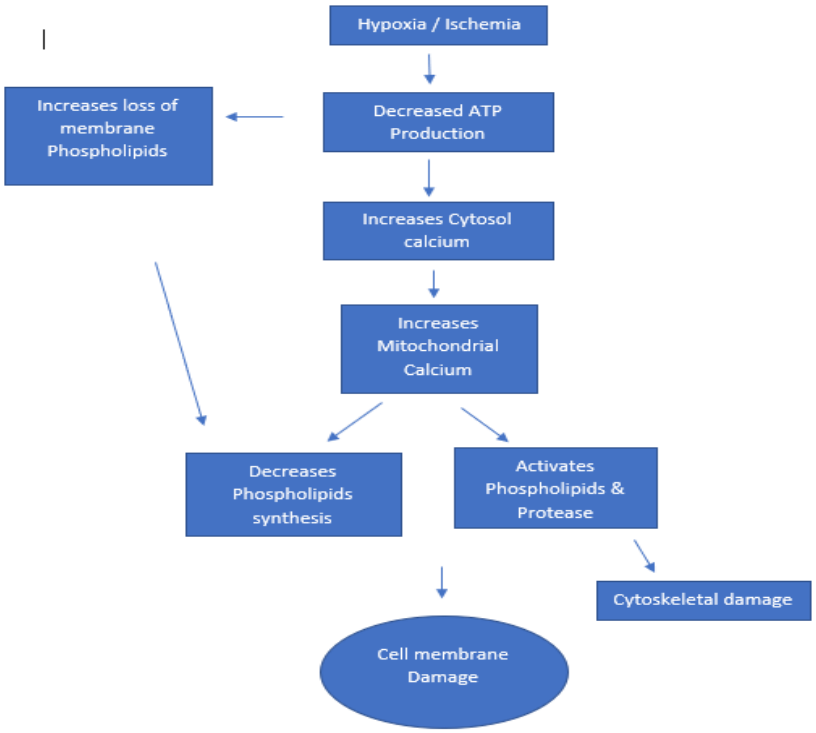

Fig 1:

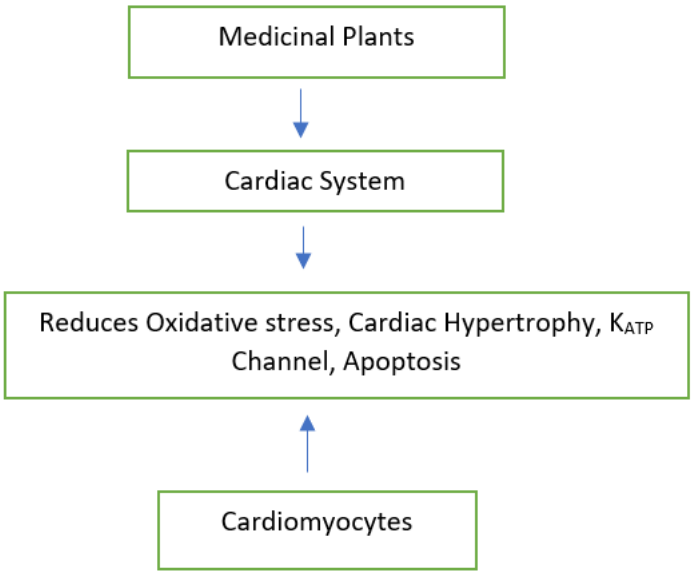

Fig 2:

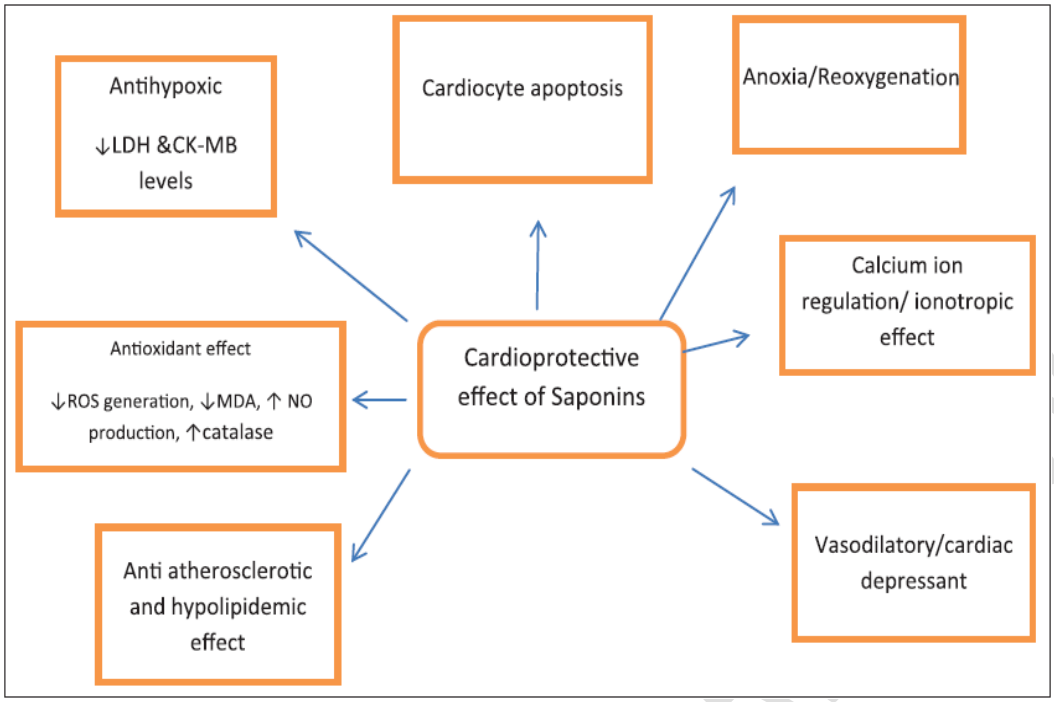

Fig 3: