Review Article

Structural characteristics, bioavailability and cardioprotective potential of saponins

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ARTICLE INFO

Article history:
Received 19 August 2017
Received in revised form
8 December 2017
Accepted 15 January 2018
Available online 3 February 2018

Keywords:
Bioavailability
Cardioprotective activity
Saponins
Structure activity relationship

ABSTRACT

Cardiovascular diseases are the leading cause of death, accounting about 31% deaths globally in 2012. The major risk factors causing cardiovascular diseases are coronary atherosclerosis, hyperlipidemia, myocardial infarction, and stroke. The dominating cause of cardiovascular diseases is accredited to our modern lifestyle and diet. Medicinal plants have been used for the prevention and treatment of cardiovascular diseases from centuries. The built chirality and chemical space of natural products have been playing an important role in providing leads and templates for pharmacophore synthesis. This review highlights one of the important naturally occurring class saponins and their role in cardioprotection along with structural characteristics and pharmacological effects such as antioxidant, Ca²⁺ ion regulation, antiapoptotic, antiatherosclerosis, anti-hyperlipidemic, hypcholesterolemic, angiogenic, vasodilatory, and hypotensive. The characteristic cholesterol lowering, hemolytic, and anticoagulant properties of the saponins prompted us to select as one of the natural products class for cardioprotection. This review covers the most updated information on saponins related to their cardioprotective effects, mechanism of action, bioavailability, and structure activity relationship.

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide and according to World Health Organization about 17.5 million people died from CVDs in the year 2012.¹ Hyperlipidemia and hypercholesterolemia are the two major risks for CVDs along with atherosclerosis, coronary heart disease, coronary artery disease, coronary calcium, stroke, myocardial infarction, peripheral arterial disease, and arrhythmias.²,³ Medicinal plants have been a rich source of lead molecules for the treatment of CVDs including atherosclerosis, angina pectoris, congestive heart failure, systolic hypertension, cerebral insufficiency, and arrhythmia.⁴-⁶ Reserpine drugs, the first effective treatment for hypertension and digitoxin for congestive heart failure were derived from the plants Rauwolfia serpentina (snakeroot) and Digitalis species, respectively.⁷ Natural products of different classes such as flavonoids/phenolics

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https://doi.org/10.1016/j.imr.2018.01.003

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(resveratrol, genistein, catechin, apigenin, ellagic acid, and aspirin), organosulphur (sulforaphane), cardiac glycosides (oleandrins), terpenoids (arjunolic acid and gymnemic acid), steroids (diosgenin), omega-3 fatty acids, and pigments (lycopene and carotenoids) have been studied for their cardioprotective potential.

Although medicinal plants have been extensively studied for the treatment of CVDs from centuries, only a few natural products derived drugs are available so far. In a recent update on natural products as a source of new drugs stated that about 13 cardiotonic drugs has been approved for CVDs in duration of year 1981–2014 out of which 3 were semisynthetic modified natural product derivatives, 2 total synthetic drugs, 3 natural product mimics synthetic drugs and 5 total synthetic drugs having natural product derived pharmacophore. This study showed the gap of the research findings of plant based cardioprotective molecules as well as alluring our attention towards medicinal plants in search of new cardioprotective molecules.

In last two decades, saponins have been extensively researched and reviewed by different research groups for their isolation, structural elucidation, distribution, biosynthesis, classification, commercial and pharmacological importance in the form of pure compound as well as saponin enriched crude extract (total saponin). The present review summarizes pharmacological importance of plant-based saponins in cardiovascular disorders along with their mechanism of action and structure activity relationship (SAR) studies. Also, the physicochemical properties of saponins and cardiotoxic drugs have been evaluated through in silico method to understand their bioavailability and pharmacokinetics.

### 2. Saponins and cardioprotection

Saponins are high molecular weight amphiphilic compounds having triterpenoid and/or steroid aglycon as lipophilic moiety and sugars (usually glucose, rhamnose, glucuronic acid, arabinose, and xylose) as hydrophilic moiety. Saponins are distributed in plants, fungi, and marine organisms such as starfish and sea cucumbers. The commercial importance of saponins came into existence in 1960 by the synthesis of sex hormone progesterone as a first oral contraceptive drug from diosgenin (derived from saponin named dioscin). Ginseng has been emerged as one of the most explored natural product for cardioprotection due to its active constituent saponins. Several saponin-enriched medicinal plants such as Allium species, Terminalia arjuna, Clematis species, Glycyrrhiza glabra, Ilex cornuta, Crataegus oxyacantha, and Astra galus membranaceus have been well studied for their cardioprotective potential. Natural products e.g. digoxin, ouabain, digitoxin, acetyldigitoxin, rostafuroxin, deslanoside, atorvastatin (from fungal metabolite mevatatin), vorapaxar (hibmamine analogue from Galbulimima baccata), cardiac glycoside, and pyridoxal-5-phosphate (a vitamin B6 derivative) have been found as lead candidates in cardioprotection. Phytosterols such as diosgenin and its derivatives are well renowned cardioprotective agents that lower serum cholesterol in the intestinal tract by inhibiting cholesterol absorption. Overall, the structural similarities with cardioactive phytosterols along with interesting pharmacological effects such as hemolytic or permeabilization of cell membrane, antilipemic, serum cholesterol lowering and anticoagulant prompted to explore the importance of saponins in cardioprotection.

### 3. Cardioprotective activity of saponins

Different pharmacological effects including antioxidant, anti-hypoxic, anoxia/reoxygenation, Ca\(^{2+}\) ion regulation or calcium antagonist, cardiocyte apoptosis, vasodilatory effect, angiogenesis, inotropic and others have been compiled to explore the cardioprotective potential of saponins.

#### 3.1. Antioxidant activity

The intracellular oxidative damage caused by the increased production of reactive oxygen species (ROS) is considered as a major cause of CVDs. The ROS toxicity at the time of reperfusion causes myocardial ischemia/reperfusion (I/R) injury by xanthine decomposition in mitochondria, increase in cellular accumulation of lipid peroxides, depletion of endogenous antioxidants and overloading of Ca\(^{2+}\) ions. The cardioprotective role of steroidal saponins from Allium chinesis attenuates the increased malondialdehyde (MDA) formation and nitric oxide (NO) release compared to nimodipine, a clinically approved calcium channel blocker against oxidative injury. Saponins of Allium species, I. cornuta and Dioscorea or yam plants have been best studied against hydrogen peroxide (H\(_2\)O\(_2\))-mediated oxidative injuries by generating highly reactive hydroxyl radicals. Saponins, for example, glycyrrhizic acid, asperosaponin VI, elatoside C, tribulosin, platycodin D, astragaloside IV, protodioscin, and trillin are known to increase the activity of several antioxidant enzymes like super oxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px), which work at cellular defense against ROS induced cardiac damage.

Clematichinenoside, a triterpenoid saponin from the roots of Clematis chinesis exhibited cardioprotective effects in ischemia/reperfusion injury via antioxidant effect by restoring the balance between inducible NO synthase and endothelial NO synthase. The pre-administration of clematichinenoside (8 mg/kg, 16 mg/kg, 32 mg/kg) significantly reduces the infarct size to 32 ± 6%, 29 ± 7% and 26 ± 4% (p < 0.05 and p < 0.01 vs. model group), respectively compared to standard tanshinone IIA (16 mg/kg, 24 ± 4%, p < 0.01). Clematichinenoside attenuates infarct size, decreases low-density lipoprotein (LDL), creatine kinase and MDA level, increases SOD activity as well as improves hemodynamic indexes.

A triterpenoid saponin, sasangusaponin from Chinese traditional herb Camellia oleifera Abel. induces cardioprotection against ischemia-reperfusion (I/R) injury possibly via activation of bradykinin–NO pathway followed by the suppression of ROS release. Another saponin from Chinese herb A. membranaceus named astragaloside IV (3-O-β-D-xylpyranosyl-6-O-β-D-glucopyranosyl-cycloastragenol) has been reported for anti-ischemic properties. Astragaloside IV induces the activity of SOD and NO along with increase in coronary flow by reducing the infarct size (in vivo).

Steroidal saponin ophiopogonin D from the tubers of Ophiopogon japonicus have been used to treat inflammation.
and cardiovascular disorders also exhibited antioxidant effect against H$_2$O$_2$ injured human umbilical vein endothelial cells (HUVEC). Ophiopogonin D restores the cellular total antioxidative capacity, inhibits release of inflammatory cytokines and enzymatic activities (catalase, HO-1 and caspase) possibly via ERK pathway. Pretreatment of ophiopogonin D reduces the doxorubicin-induced excessive autophagy due to the reduction of ROS generation and thus protects the heart against doxorubicin-induced damage. These results suggest ophiopogonin D can be useful in the combination therapy with anticancer drugs causing cardiotoxicity.

Elatoside C from Aralia elata inhibited mitochondrial ROS overproduction and maintained [Ca$^{2+}$]$_i$ homeostasis in cardiac I/R injury through the activation of reperfusion injury salvage kinase (Akt and ERK1/2) and survivor activating factor enhancement JAK2/STAT3 pathways. The improved myocardial performance of elatoside C suggests its application during cardiac surgery and ischemic heart diseases. The pretreatment of another saponin, anacanthopanax senticoside B (200 μg/mL and 400 μg/mL) from Acananthopanax senticosus protects cardiomyocytes against H$_2$O$_2$ induced oxidative damage by increasing the activity of catalase, GSH-Px, SOD, levels of reduced glutathione and increase in cell viability. The saponins of I. cornuta exhibited protective effects against H$_2$O$_2$-mediated myocardial cell injury whereas did not show DPPH free radical scavenging activity (<30% at 200μM). The antioxidant activity results suggested that the protective effects of saponins were not directly associated with their free radical scavenging effect and warrant to investigate further.

3.2. Antihypoxia activity and anoxia/reoxygenation (A/R)

The reduced oxygen supply mainly causes ischemic injuries. A steroidal saponin named fistulosaponin A from Welsh onion (Allium fistulosum) seeds exhibited cardioprotective effects against hypoxia-induced HUVEC injury with a cell viability of 59.5 ± 3.0%, 76.3 ± 3.3%, 80.1 ± 3.6%, 82.7 ± 4.1% and 86.3 ± 4.6% using Diao-xin-xue-kang (an extract of the roots of Dioscorea victimina Prain et Burkill) as positive control with cell viability of 65.8 ± 3.3%, 69.6 ± 2.7%, 75.8 ± 1.8%, 79.9 ± 2.9% and 81.0 ± 3.4% at 0.5μM, 1.0μM, 5μM, 10μM and 50μM. In Tibet, Cleimatis tangutica is used for invigorating blood circulation, prevention, and treatment of cardiac diseases in clinical practices. Triterpenoid saponins of C. tangutica possess cardioprotective effects by decreasing the serum levels of lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB) against hypoxia-induced cell damage. As the serum levels of CK-MB and LDH are indicators of myocardial injury. C. tangutica saponins like lematangosides, cauloside D and asperosaponin VI at 0.05mM concentration showed anti-myocardial ischemic effects against LDH and CK-MB release with ED$_{50}$ values ranging from 75.77μM to 127.22μM in A/R-induced cell damage. In another study, C. tangutica saponins exhibited anti-ischemic activities with ED$_{50}$ values in the range of 75.77-127.22μM using diltiazem hydrochloride as positive control (ED$_{50}$ = 21.04 ± 0.84μM, LDH and ED$_{50}$ = 15.17 ± 0.35μM CK-MB) against LDH and CK-MB release.

3.3. Ca$^{2+}$ ion regulation/calcium antagonist activity

Calcium ion (Ca$^{2+}$) is an important second messenger that regulates various cellular processes like NO-synthase activation on increasing the cytosolic Ca$^{2+}$ levels in endothelial cells. Also, the cardiac I/R or hypoxia damage are associated with the Ca$^{2+}$ overloading. Saponins from A. macrostemon B bulbs named macrostemonoside B, macrostemonoside M, macrostemonoside N and (25R)-26-O-β-D-glucopyranosyl-22-hydroxy-furost-3β,26β-diol-3-O-β-D-glucopyranosyl(1-2)-β-D-galactopyranoside increased the Ca$^{2+}$ ion mobilization higher than potassium chloride and also increased the function of cardiac muscles in isolated cardiomyocytes of Guinea pig. Macrostemonoside E was found as a promising compound in the treatment of heart failure. Another furostanol saponin, methyl protodioscin from D. colletii var. hypoglauca upregulated the sodium and calcium pump and maintains the low calcium in cardiomyocytes. Also a saponin monomer named DT-13 [(25R,S)-ruscogenin 1-O-[β-D-glucopyranosyl (1→2)]β-D-xylopyranosyl (1→3)-β-D-fructopyranoside] from dwarf lily turf tubers (O. japonicus) possess potent cardiac protective effects both in normal and hypoxia condition in adult rat ventricular myocytes. DT-13 at 0.001μM/L, 0.01μM/L, 0.1μM/L, 1.0μM/L and 5.0μM/L inhibited the current density of L-type calcium current (I$_{Ca,L}$) by 14.59 ± 3.18% (n = 5, p < 0.05), 27.01 ± 5.12% (n = 5, p < 0.05), 36.82 ± 6.97% (n = 5, p < 0.05), 62.76 ± 8.17% (n = 5, p < 0.001) and 77.13 ± 7.15%, respectively. The cardioprotective effect of DT-13 might be the direct inhibition of L type Ca$^{2+}$ currents via voltage-gated calcium channels.

3.4. Cardiocyte apoptosis

Apoptosis is observed as one of the cause of heart failure in response to several pathological effects like ischemia, I/R, hypoxia, calcium excess, oxidative stress, gene induction and doxorubicin toxicity. Cardiotoxicity caused by anticancer drug, for example, doxorubicin is due to the oxidative damage of cellular components and formation of free radicals. Pretreatment of gymnemic acid phospholipid complex prevented the doxorubicin-induced cardiotoxicity in rats, improves the heart to body weight ratio, decreases serum Ca$^{2+}$, LDH, myocardial caspase-3, thiobarbituric acid reactive substances (TBARS) levels, as well as increases Na$^+/K^+$ ATPase and antioxidant enzyme levels. Further, the intracellular DNA laddering prevention suggests the anti-apoptotic effect of gymnemic acid phospholipid ester. Cardiocyte apoptosis is attributed to the functional deterioration of ischemia/hypoxia cardiomyopathies. A triterpenoid saponin, hecogenin-3-O-[β-D-glucopyranosyl (1→4)]-β-D-galactopyranoside from Tribulus terrestris attenuated apoptosis in NaCN digested rat ventricular cardiomyocytes. Hecogenin glycoside decreases the intracellular free Ca$^{2+}$ ion concentration, increases Bcl-2 protein levels and activated translocation of protein kinase (PKCδ)-mediated cellular signaling transduction pathways. Dioscin, a natural steroidal saponin of Dioscorea species has been traditionally used in China to prevent coronary diseases. Moreover, dioscin also
prevented ischemia/perfusion induced injury in H9c2 cells via mitochondrial apoptotic pathway by reducing oxidative stress. Additionally the cardioprotective potential of dioscin was also supported by its antithrombotic effects by improving anticoagulation activity and inhibiting platelet aggregation.

3.5. Anti-atherosclerosis and hypolipidemic activity

Atherosclerosis is a chronic inflammatory disorder usually initiated by the adhesion of monocytes to the vascular endothelium. Saponins like reinoside C, ginsenoside Rb1, Rg1, Re, and R1 are reported to inhibit monocyte-endothelial cell adhesion. Reinoside C from the roots of Chinese herb Polygala falx shows promising hypolipidemic effect due to the protective effects on oxidative lesions induced by oxidized low-density lipoprotein (OxLDL), inhibiting cholesteryl ester accumulation in macrophages as well as decreasing \([Ca^{2+}]\), and smooth muscle cells proliferation. Reinoside C inhibited OxLDL-induced \([Ca^{2+}]\), elevation in smooth muscle cells by 35.1% compared to calcium antagonist verapamil (41.3% at 10 \(^{-6}\) mol/l) and suggests that reinoside C can partially abolish the OxLDL action by inhibiting the calcium influx into macrophages. Further, reinoside C inhibited the adhesion of monocytes to endothelial cells via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase/ROS/nuclear factor-kappa B (NF-\(\kappa\)B) pathway.

Natural products including dietary fibers, herbal formulations/extracts, plant sterols and yeast extracts have been used as anti-hyperlipidemic agent. The steroidal constituents such as dioscin, diosgenin, protodioscin, and trillin from the rhizomes of Dioscorea nipponica showed anti-hyperlipidemic activity by improving the levels of lipid peroxidation and SOD activity mediated through anti-lipase mechanism. The anti-hyperlipidemic potential of D. nipponica emerges it as a food supplement against several cardiovascular disorders in future.

3.6. Vasodilatory activity

Luna-Vazquez et al (2013) have reviewed 270 plant derived metabolites as vasodilator along with their possible mechanism of action. Authors further concluded that the activation of NO/cGMP pathway and/or blocking of voltage-dependent calcium channels is the major vasodilatory mechanism of action for different classes of compounds including saponins. Bacoside A3 and bacopaside II belong to class jujubogenin and pseudojujubogenin, respectively isolated from Ayurvedic medicinal plant Bacopa monnieri possess blood pressure reducing effect by releasing NO from endothelium and influences smooth muscle \(Ca^{2+}\) ion homeostasis.

Ginsenosides Rb1 and Re from P. ginseng were reported to possess cardiac depressive response at ventricular myocyte level through NO-mediated vasodilation. The cardiac depressive activity of ginsenosides has clinical applications in the treatment of cardiovascular disorders like hypertension and heart failure.

3.7. Inotropic activity

Saponins are known to interact with cholesterol and generate sub-skimming condition that can modify the electrical and mechanical properties of cardiac muscles. Enomoto et al (1986) studied the positive inotropic effect of saponins of Panax species and concluded that modification of calcium channel might be involved in this effect. Saponins with positive inotropic effect were showed haemolysis in rabbit erythrocytes. A cardioactive steroidal saponin containing rare neogotegenin as aglycon named cistocardin from Ayurvedic medicinal plant Tribulus cistoides (thistle of the hot country) exhibited strong positive inotropic effect at \(10^{-6}\)M to \(10^{-5}\)M concentration in papillary muscles of Guinea pigs.

3.8. Angiogenic activity

Angiogenesis is the formation of new vessels from existing one and has importance in the diseases with insufficient blood vessels formation such as peripheral and coronary ischemia and infarction, chronic wounds failure and ulcers. Panaxtrol (PTS), a designed extract of P. notoginseng enriched with three major bioactive saponins notoginsenosides R1 (11%), gensenoside Rg1 (50%) and gensenoside Re (6%) is reported to possess pro-angiogenic effect and thereby used to treat ischemic stroke in China. A study in middle cerebral artery occlusion (MACO) rat model showed in vivo efficacy of PTS against cerebral ischemic injury by enhancing cerebral blood flow, angiogenesis, and modulating cytokines vascular endothelial growth factor and angiopoietin-1 expression. The protective effect of PTS is mediated through the activation of Shh signaling pathway mechanism. In addition, the ginsenosides (R1, Rg1 and Re) were individually evaluated in different models and emerged as promising pro-angiogenic agents. The results suggest PTS and its active saponins can be used in therapeutic angiogenesis such as ischemic stroke.

3.9. Other pharmacological activities

The cardioprotective potential of saponins have been evaluated for several other pharmacological effects including fibrinolytic activity of endothelial cells, antiplatelet and/or antithrombotic, endothelial protectant, contractile effect, bradycardiac effect, cardiac depressant and cyclic AMP phosphodiesterase inhibitory activity. Saponin \(\beta\)-Ascim from Aesculus hippocastanum seeds showed improved endothelium dysfunction and contractile effect in oxidative stressed rat aortic rings that can be useful in the treatment of venous insufficiency and limiting side effects, respectively.

Ginsenoside Ro, an oleane saponin of P. ginseng inhibits \(\alpha_{1B}/\beta_{3}\)-mediated fibrinogen binding mediated by cyclic adenosine monophosphate (cAMP)-dependent phosphorylation of vasodilator-stimulated phosphoprotein (Ser\(^{157}\)) and might be responsible to prevent the platelet aggregation-mediated thrombotic diseases. Interestingly, the cardiac tissue regeneration effect has also been studied for few saponins e. g. ginsenoside Rg1 and Rb1, tanshinone IIa, astragalloside IV, salvianolic acid B, and cardigenin (Nigahichigoside F1). The cardiac regeneration activity of saponins
can be used as a tool for the effective treatment of injured hearts and other body organs.77

4. Bioavailability of saponins

The high molecular weight and poor membrane permeability of saponins make them low bioavailable, and hence restricting saponins as a drug candidate. The poor bioavailability of saponins might be a reason for lesser studies on its pharmacological mechanism of action. During the last decade, total saponins and isolated pure saponins of the plants have been evaluated for their pharmacokinetic studies. Saponins like clematichinasenose AR, astragaloside IV, methylprotodioscin and ginsenosides have been studied for their pharmacokinetics and metabolites identification. The oral bioavailability of ginsenosides Rα3, Rb1, and Rd was found as 0.1–0.2%, whereas ginsenosides Re, Rg1, and notoginsenside R1 of 0.2–0.6%.78

Because of the poor bioavailability and permeability of saponins, the calculated important physicochemical parameters of saponins and natural products derived cardiotoxic drugs were compared to understand the intestinal absorption and bioavailability of saponins through in silico approach. The key physicochemical properties including predicted lipophilicity (log P), topological polar surface area (TPSA), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and number of rotatable bonds (nRotB) responsible for bioavailability were calculated and given in Table 1 for 14 selected cardioprotective saponins and 6 Food and Drug Administration (FDA) approved natural product derived cardiotoxic drugs.79 It is evident from in silico analysis that the deviation from key drug-like physicochemical properties is the primary reason for poor bioavailability of the saponins, such as high molecular weight (>500 Da); large number of rotatable bond, nRotB (>10) responsible for molecular flexibility; high HBA (>10); high HBD (>5); large TPSA (>140 Å²) and low lipophilicity (Log P) that associated with poor membrane permeability. In silico assessment of aqueous solubility (log S) suggested that most of the saponins could be defined as moderately to good soluble (Fig. 1). Log S value of saponins ranges from −5.97 to −3.44, which were significantly greater than the predicted apparent membrane permeability (Papp Caco-2 cell). However, the solubility was shown to decrease for saponins with fewer sugar moieties attached in the similar aglycon skeleton and similar observations have been reported on ginsenosides.80 The Log S values of similar skeleton of timosaponin B II and timosaponin A-III is −4.46 and −5.24, respectively which corresponds to their number of sugar count 3 and 2. On the other hand, most of the saponins have poor membrane permeability (Papp Caco-2 cell), while cardiotoxic drugs have membrane permeability ranging from 0.197 × 10⁻⁶ cm/s to 8.610 × 10⁻⁶ cm/s suggesting the good membrane permeability and hence better bioavailability of the cardiotoxic drugs compared to saponins. As shown in Fig. 1, almost all saponins have unfavorable physicochemical traits and violating the drug likeness rules, which could be influenced by the increasing number of sugar moieties. Also, cardiotoxic drugs are not following all thresholds of key physicochemical properties for drug likeness. While on comparison of saponins with cardiotoxic drugs, >90% cardiotoxic drugs follow the optimal property ranges for nRotB (responsible for molecular flexibility), HBD, and lipophilicity (Log P). Saponins have shown very high molecular weight ranging from 741 Da to 1808 Da, high HBD count from 7 to 24, and high TPSA from 197 Å² to 669 Å². Further, on reducing the number of sugar moieties in saponins could decrease the hydrogen-bonding capacity (HBA and HBD), molecular mass as well as TPSA but also reduces their solubility (Fig. 1).

5. Structure activity relationships (SAR)

Saponins have been well studied for their cardioprotective potential along with their mechanism of action, while very few reports are available on discussing their SAR. Saponins are
Fig. 1 – Relationship between the sugar substitution in cardioprotective saponins, drugs and their physicochemical properties that responsible for bioavailability.
Fig. 2 – Structures of saponins for structure activity relationship (SAR).

glycosides of triterpenoids or steroids and glycosidation makes saponins more complex and poor bioavailable. In few available reports, aglycon was found as better cardioprotective agents than their respective glycoside. The importance of esterification of sugar moiety in saponin has discussed here with given parent and their respective ester derivatives in Fig. 2.

Wang et al (2010) have discussed the structure function relationship of 20(S)-protopanaxadiol along with its two synthetic epimeric analogues (20S,24S)-epoxydammarane-3β,12β,25-triol and (20S,24R)-epoxydammarane-3β,12β,25-triol, and found that the configuration at C-24 position of furan ring was responsible for the cardioprotective effect of protopanaxadiol saponins against isoproterenol induced myocardial injury as shown in Fig. 2. Further, the 20(S)-protopanaxadiol (C24-25 alkene) and its 24(R)-epoxy epimeric derivatives were found to be active against myocardial ischemic injury by enhancing the antioxidant activity of heart tissues, whereas 24S-epoxy derivative was inactive due to the configuration of C-24 of furan ring. These SAR suggest the importance of stereochemistry of the saponins in cardioprotection. Another two separate studies on the glucuronooyranosyl methyl ester derivatives of ursane triterpenoid saponins of I. cornuta were found to have better cardioprotective effects than their parent non-methylated saponins against H2O2 induced cardiomyocyte injury along with increased cell viability at 25μM. These results suggest that the esterification on glucuronic
acid moiety at C-3 position of ursane saponins improve the cardioprotective effect of methylated saponins, as shown in Fig 2. Sugar linkage position and residue numbers also played cardioprotective role e.g., anti-atherosclerotic activity of different ginsenosides, as mentioned in Table 1, ginsenoside Re having 2 sugar units showing better physicochemical properties versus ginsenoside Rg3 with 3 sugar moieties.22,80 Another study by Zhang and coworkers on six bisdesmosidic triterpenoid saponins was found that the presence of a free hydroxyl group at C-3 position in bisdesmosidic saponin (kalopanaxsaponin G) plays an important role in cardioprotection.43 Whereas other bisdesmosidic saponins with reduced-cardioprotective activity despite having similar aglycon and sugar chain at C-28 further suggest that the chemical class and sequence of oligosaccharide chain at C-3 position played an important role in cardioprotection.

Recently, Quynh Vo et al have evaluated the SAR on the hemolytic potential of triterpenoid saponins and sapogenins, and suggest that not only the complexity of sugar moieties but also the types and stereochemical configurations of functional groups at different positions as well as the skeleton types (oleanane, ursane, and dammarane) are important structural features affecting the hemolytic potential. They found that the oleanane-type sapogenins had stronger hemolytic effects than those of the ursane and dammarane types as well as the presence of polar regions on sapogenins significantly enhanced hemolysis.82 Overall, the available SAR studies on saponins concluded that functionalization at aglycon as well as in sugar linkage position, derivatization of sugar moiety, and sugar residue number played an important role in the cardioprotection. However, investigation of the biological activity of natural saponins along with their semi-synthetic analogues in different bioassay models is required in depth understanding of the importance of functionalities, stereochemistry, number of sugar moieties, and their linkage position of saponins in cardioprotection.

6. Conclusions and future prospect

Present review summarizes the importance of naturally occurring saponins, their role in cardioprotection, bioavailability, and SAR. The cardioprotective effects of plant based saponins can be a good source of nutraceutical in life style diseases. The saponin enriched diets such as alfalfa, onion, garlic, soybean, and ginseng have been found to inhibit the intestinal absorption of cholesterol with reduction of serum cholesterol. Saponins such as astragaloside IV, gynemic acid, and ophiopogonin D are effective in protecting heart from cardio toxicity induced by anticancer drugs such as doxorubicin. Glycyrrhizin and ginsenosides from edible herbs can be used as a health supplement in routine intake for cardiac protection. DT-13, dioscin, astragaloside IV, glycyrrhizin, ophiopogonin D and trillin possess strong cardioprotective activity and need to be explored further in clinical applications. The ginsenosides Rg1, Re, Rb, Rc, and Rg3 have vasorelaxant activity by inhibiting Ca2+ influx via receptor-operated Ca2+ channels in vascular smooth muscle cells, and ginsenoside Rg3 emerges as the most potent vasodilatory agent to open the Ca2+ activated K+ channel. The in silico analyses have shown that most of the saponins have poor membrane permeability and unfavorable physicochemical properties, whereas cardiotoxic drugs have shown the optimal membrane permeability and hence better bioavailability of the cardiotoxic drugs compared to saponins.

In past few decades, several natural products derived cardioprotective agents have been evaluated in clinical trials and unfortunately very few are successful so far. Therefore, there is a need to further exploration of natural products in search of new cardioprotective agents in view of life style changes and global emergence of chronic diseases like cancer and diabetes. Besides having good pharmaceutical and nutraceutical value in lowering of serum cholesterol, there is no FDA approved saponin based drug available in the market so far. Although total saponins (in crude form) have been well explored for cardiac protection, very few reports on cardioprotection of pure saponin warrant further study. The search for pharmacologically active saponins will be useful in the development of dietary supplements as well as potential therapeutic agents against hyperlipidemia and drug induced cardiovascular disorders. Moreover, the potent antioxidant and cholesterol lowering effects of saponins across the literatures, further attract its attention as a preventive medicine for cardiovascular disorders.

Conflict of interest

The authors have no conflict of interest to declare for this publication.

Acknowledgement

The authors are thankful to the Director, CIMAP-CSIR, Lucknow, India.

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