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Review Article

Structural characteristics, bioavailability and cardioprotective potential of saponins

Q1 *Deepika Singh**, *Prabir Kumar Chaudhuri**

Medicinal Chemistry Division, Central Institute of Medicinal and Aromatic Plants (CIMAP-CSIR), Lucknow 226015, India

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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 *in 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, Ca^{2+} ion regulation, antiapoptotic, antiatherosclerosis, antihyperlipidemic, hypocholesterolemic, 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.

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

* *Corresponding authors.*
E-mail addresses: deepika.sh25@yahoo.com (D. Singh), pkchaudhuri_2000@rediffmail.com (P.K. Chaudhuri).

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(resveratrol, genistein, catechin, apigenin, ellagic acid, and aspirin), organosulphur (sulforaphane), cardiac glycosides (oleandrin), terpenoids (arjunolic acid and gymnemic acid), steroids (diosgenin), omega-3 fatty acids, and pigments (lycopene and carotenoids) have been studied for their cardioprotective potential.[4,8–12]

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.[13] 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).[14–18] 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 cardiotonic 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.[16,19] Saponins are distributed in plants, fungi, and marine organisms such as starfish and sea cucumbers.[17,20] The commercial importance of saponins came into existence in 1960 by the synthesis of sex hormone progesterone as a first oral contraceptive from diosgenin (derived from saponin named dioscin).[21] Ginseng has been emerged as one of the most explored natural product for cardioprotection due to its active constituent saponins.[22,23] Several saponin-enriched medicinal plants such as *Allium* species, *Terminalia arjuna*, *Clematis* species, *Glycyrrhiza glabra*, *Ilex cornuta*, *Crataegus oxyacantha*, and *Astragalus membranaceus* have been well studied for their cardioprotective potential.[24–26] Natural products e.g. digoxin, ouabain, digitoxin, acetyldigitoxin, rostafuroxin, deslanoside, atorvastatin (from fungal metabolite mevastatin), vorapaxar (himbacine analogue from *Galbulimima baccata*), cardiac glycoside, and pyridoxal-5-phosphate (a vitamin B6 derivative) have been found as lead candidates in cardioprotection.[27] Phytosterols such as diosgenin and its derivatives are well renowned cardioprotective agents that lower serum cholesterol in the intestinal tract by inhibiting cholesterol absorption.[2] 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.[15,16,18,28,29]

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.[30,31] The cardioprotective role of steroidal saponins from *Allium chinensis* attenuates the increased malondialdehyde (MDA) formation and nitric oxide (NO) release compared to nimodipine, a clinically approved calcium channel blocker against oxidative injury.[32] Saponins of *Allium* species, *I. cornuta* and *Dioscorea* or yam plants have been best studied against hydrogen peroxide (H_2O_2)-mediated oxidative injuries by generating highly reactive hydroxyl radicals.[33–35] 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.[24,36–42]

Clematichinenoside, a triterpenoid saponin from the roots of *Clematis chinensis* exhibited cardioprotective effects in ischemia/reperfusion injury via antioxidant effect by restoring the balance between inducible NO synthase and endothelial NO synthase.[43,44] 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% ($p < 0.05$, $p < 0.05$ 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.[44] A triterpenoid saponin, sasanquasaponin 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.[31] Another saponin from Chinese herb *A. membranaceus* named astragaloside IV (3-*O*-β-D-xylopyranosyl-6-*O*-β-D-glucopyranosyl-cycloastragenol) has been reported for anti-ischemic properties.[45] Astragaloside IV induces the activity of SOD and NO along with increase in coronary flow by reducing the infarct size (*in vivo*).[46]

Steroidal saponin ophiopogonin D from the tubers of *Ophiopogon japonicus* have been used to treat inflammation

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