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Cardioprotetic Effect of Diosgenin: Progress and Challenge

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Abstract

Introduction: Cardiovascular diseases are an important public health problem because they are the main causes of mortality in the world, especially in developing countries. Despite existing drug therapies, such diseases have particularities that hinder their control. For this reason many studies seek to identify new molecules, especially natural substances, with therapeutic potential to control cardiovascular diseases. Diosgenin is a steroidal saponin that has many biological activities and promotes cardiovascular action. ***Objective:*** Identify the cardiovascular effect of diosgenin and to describe the mechanisms of action involved in this activity. Methodology: An integrative review of the literature was carried out with articles that dealt with the topic researched in the last 10 years from 2009 to 2019, available in the PubMed, Web of Science, Scopus and BIREME/BVS databases, using advanced search with the descriptors "Diosgenin" "Cardiovascular System", "Heart" and "Diseases", interspersed with the "and" or "or" boolean operators. ***Results:*** After initial selections and readings of some articles in their entirety, 14 studies integrated the present review. Diosgenin showed important cardioprotective activity in studies with animal models that mimic the multiple cardiac pathologies in humans, which allow it to be considered with great future pharmacological potential. The mechanisms of action of this substance are related to antioxidant, antithrombotic, antiapoptotic and antiproliferative capacity. ***Conclusion:*** Diosgenin has a beneficial cardiovascular effect when used in multiple models of animal experimentation with cardiac alterations. This fact makes this substance an important and promising molecule for future research, such as clinical trials in humans with cardiovascular changes similar to those presented by animals.

Keywords: Diosgenin; Cardiovascular System; Heart.

INTRODUCTION

Cardiovascular disorders are a major public health problem due to their high prevalence and lethality in the world population [1]. Of cardiovascular diseases, ischemic heart disease is the leading cause of death in developed and developing countries, followed by cerebrovascular disease. Such disorders present as main risk factors systemic arterial hypertension and lifestyle, especially eating habits and physical inactivity [2].

Many studies indicate the beneficial effect of the use of natural substances in the protection of the cardiovascular system in the most varied pathological models of animal experimentation, which mimic the cardiovascular diseases that affect humans [3]. Among the substances are saponins, which are steroid glycosides with hydrophilic and lipophilic chemical characteristics in their structure, found in a large number of plant species, such as yam (Dioscorea dodecaneura), barbasco (Dioscorea composita), among others [4-6].

Diosgenin, a phytoestrogenic saponin, has multiple described biological activities, mainly by activating the estrogen receptor. Many studies demonstrate the activity of this substance in the cardiovascular system, showing the mechanisms of action triggered by this substance in experimental treatment protocols. Being therefore important to gather and characterize them is of fundamental importance for the knowledge of the scientific community [1, 4].

The aim of this study was to analyze in the literature the cardioprotective effect induced by diosgenin describing the multiple mechanisms of action triggered by diosgenin, which make it a pharmacological potential for the treatment of diseases affecting the heart.

METHOD

The study is an integrative, qualitative and descriptive review, in the Pubmed, Web of Science, Scopus and Bireme /VHL databases, to identify the

productions on the cardiac protective effect of diosgenin and the mechanisms of action involved. It was carried out from January 2018 to April 2019. Six steps were followed until the presentation of this review, namely: problem establishment, sample selection, definition of information to be examined, interpretation of results, presentation / discussion. Results and presentation of the review [7].

Articles were selected with restriction of year of publication, articles published in the last 10 years (2009-2019) were selected, using the following descriptors: “Diosgenin”, “Cardiovascular system”, “Heart”, with the combination of Boolean operators "And" or "or". The following selection criteria were also used for the inclusion of the studies: papers in the category of scientific articles, written in Portuguese or foreign (English or Spanish), which addressed the theme of this research and with access to the content / full text. Review articles, monographs, dissertations, theses, books and event annals were excluded. The selection began with the identification of duplicate works in the databases, followed by reading the title and abstract and then reading the full paper. A total of 14 studies were considered after selection and subsequently, regarding the researched theme. The study selection and analysis process is detailed in Figure 1.

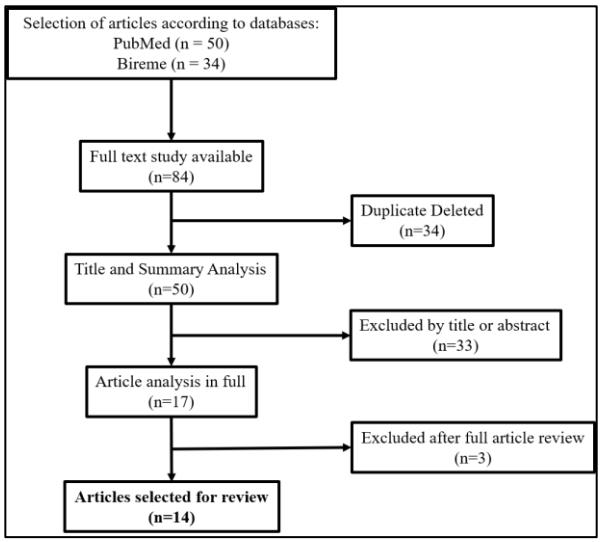

Fig-1: Illustrative flowchart of selection of scientific studies

RESULTS

Most of the articles analyzed were executed in China and published in the year 2018 in English language. The studies were developed in animal experimentation models. Cardiac pathologies were induced by diet, or by the use of some substance, such as isoproterenol or doxorubicin. In addition, other studies have used H9C2 myocardial cells. All aimed to evaluate the effect of diosgenin as a treatment intervention for pathologies, demonstrating the mechanisms of action involved in the protection of the heart. Studies have systematically presented a cardioprotective effect of this saponin in the most varied models of cardiac disorders (Table 1).

DISCUSSION

Natural substances with biological properties for the treatment of multiple pathologies that affect the human body become strong alternatives for the development of medicines. Substances extracted from nature that act on the cardiovascular system in a beneficial way are widely studied in the search for pharmacological potentials to reduce the occurrence of severe cardiac events [8, 9].

To identify the potential effect of natural products on the cardiovascular system, many experimental approaches are developed, including animal experimentation models or the use of isolated myocardial cells. There are several animal models that mimic the pathologies presented in humans and explain the mechanisms of action triggered by natural substances for the biological effect on the heart [10, 11].

The model of cardiac hypertrophy and remodeling induction using angiotensin II is well established and used in the literature. The changes commonly reported in animal hearts or isolated heart cells are increased cardiomyocyte size and increased expression of genes involved in hypertrophy, such as collagen fibers. Akt-1 protein when activated induces cardiac cell growth and increases protein synthesis [10].

Treatment of animals with diosgenin enabled restoration of cardiac function in models of angiotensin II-induced hypertrophy by Akt-1 inhibition and negative modulation of transcription of genes involved in cardiac hypertrophy [12, 13].

Other animal or cellular models are developed to study the influence of bedding on the cardiovascular system. The atherogenic diet promotes structural alterations in the arteries, which are observed in arterial diseases, especially coronary artery disease. These changes are related to the increase of low density lipoprotein concentration and reduction of high density lipoprotein, which triggers the production of inflammatory mediators by endothelial cells, causing damage to the intimate tunic of the arteries, resulting in a reduction of perfusion and imbalance in redox status of organs and tissues [14].

Studies show that atherosclerotic disease triggered by atherogenic diet is related to endothelial injury induced by increased formation of reactive species and induction of inflammation, the mechanisms involved are related to increased production of the following inflammatory mediators: TNFα and NFkβ via COX2 activation. Animals with atherosclerotic disease treated with diosgenin showed a reduction in the production of inflammatory mediators (TNFα and NFkβ) and also a decrease in the formation of reactive

species. This fact is related to the increased synthesis of essential proteins in cellular metabolism and support activities in hearts [1, 15].

Ischemia and reperfusion injury mimics the effect of acute infarction on cardiac tissue. With the reduction of heart perfusion and subsequent reperfusion, multiple changes occur, such as: exacerbation of oxidative stress, increased occurrence of cardiac arrhythmias, necrosis and death of cardiomyocytes. It has been well reported in the literature that infarction injury triggers mitochondrial potassium (Mito-KATP) channel blockade, reduced nitric oxide production, activation of mediators that trigger cellular apoptosis and also dysregulation of the superoxide dismutase enzyme (SOD) [16,18].

Analysis of the heart or myocardial cells isolated from animals treated with diosgenin submitted to ischemia and reperfusion injury showed that this substance promoted the restoration of contractile and electrical myocardial walls. In evaluating inflammatory markers, there was a reduction in TNFα release, interleukin 1-β and NFkβ inhibition, as well as a decrease in cardiac injury markers: CK-MB and LDH, activation of the SOD enzyme, and reduction of cell necrosis area by by inhibiting apoptosis. These effects are explained by the substance's ability to activate NO production, the mito-KATP channels, reduce oxidative stress and inhibit the release of cytochrome C, an important apoptosis inducer [19, 20].

Cell redox status in cardiomyocytes is widely studied because it is involved in multiple alteration processes triggered by many substances, such as the animal model of isoproterenol-induced heart failure and also cardiotoxicity by the doxorubicin antineoplastic. Both isoproterenol and dororrubicin trigger changes in the contractile component of the heart by interfering with the overlap of reactive species production due to the natural antioxidant defense, especially that established by the action of antioxidant enzymes. Thus, the treatment of animals with diosgenin triggered restoration of cardiac function in the presence of isoproterenol or dororrubicin, mainly due to the reduction of oxidative stress stimulated by cardiotoxics. Diosgenin was able to restore disorganized cell structure by isoproterenol, reduce lipid peroxidation, and increase the activity of antioxidant enzymes: dismutase superoxide, catalase and glutathione peroxidase, decrease apoptosis via caspase 3 inhibitions, restore Nrf2 and Srit2 protein expression [5, 21-23].

Diosgenin also induces a beneficial effect on thrombotic mechanisms in the heart, as it is capable of reducing platelet aggregation, prolonging prothrombin and partial thromboplastin time, preventing thrombus formation in the coronary arteries that supply the heart [24, 25].

Tabela-1: Studies that show the diosgenin cardioprotective activity and the mechanisms of action involved in this effect from 2009 to 2019

Author/Year	Country of origin	Main methods / models of cardiac pathologies	Main mechanisms of cardioprotective action of diosgenin
Chen *et al*. 2018 [15]	China	Using C57 / BL mice with angiotensin II-induced cardiac hypertrophy and treated with diosgenin (80 mg / kg / day) for 3 weeks, the effect of the substance on the extracellular matrix was investigated.	Diosgenin prevented the hypertrophic effect of animal hearts by reducing stimulation of collagen fibers and connective tissue growth factor. The substance also reduces cardiac remodeling via inhibition of MAPK and Akt.
Yang *et al*. 2018 [1]	China	Use of adult pigs with coronary artery disease induced from atherogenic diet and oral treatment with diosgenin, 80 mg / kg, for 4 weeks, the interference of the substance on cell injury markers and its relationship with oxidative stress was studied.	Treatment with diosgenin was able to reduce markers of cell damage and reestablish the architecture of the commonly impaired coronary artery in CAD, correlating with the reduction of oxidative stress and inflammation via Sirt1 / Nrf2 and MAPK p38.
Zhao *et al*. 2018 [23]	China	H9C2 cells, mice and rats with doxorubicin-induced cardiotoxicity were used. The treatment occurred with 20; 40 or 80 mg / kg diosgenin for seven days. The effect of the substance on doxorubicin-induced cardiac lesions was investigated.	Treatment with diosgenin was able to restore doxorubicin-triggered lesions to both cells and heart of animals. The mechanisms of action that explain this effect are: reduction of oxidative stress and restoration of Nrf2 and Srit2 protein expression.
Binesh *et al*. 2018 [19]	India	Rats submitted to atherogenic diet and treated with 80 mg diosgenin orally for 3 weeks were used. The effect of the substance on the progression of atherosclerotic disease and the mechanisms of action involved were evaluated.	Diosgenin triggered reduced progression of atherosclerotic disease in the heart and endothelial cells via decreased inflammation markers TNFα, NFkβ and COX2.
Wang *et al*. 2018 [20]	China	Ischemia and reperfusion injury in rats was promoted after pretreatment for 4 weeks with diosgenin 50 and 100 mg / kg. The action of the substance on the parameters of contractility and cardiac inflammation was studied.	Pretreatment with diosgenin restored cardiac contractility and reduced the heart infarction area, acting primarily on inflammation markers such as suppressing TNFα expression, interleukin 1-β, and NFkβ inhibition.

Zhou *et al*. 2017 [14]	China	Use of cardiac fibroblasts from rats that were preincubated with diosgenin and stimulated with angiotensin II which triggers remodeling of these cells.	Diosgenin was able to inhibit angiotensin II - induced extracellular matrix remodeling by suppressing the TGF - β1 / Smad3 signaling pathway.
Feng *et al*. 2017 [21]	China	Using Sprague – Dawley rats with isoproterenol-infarcted (ISO) hearts and treated with oral doses of 20, 40 or 80 mg / kg diosgenin for 3 days, the effect of the substance on ISO-triggered lesions was evaluated. in cardiomocytes, as well as cellular redox status by measuring the activity of antioxidant enzymes.	Diosgenin was able to reestablish patches that make up the cellular structure of hearts in animals subjected to ISO, such as cell size, normalization of transverse striations and restructuring of adjacent myofibrils. These results can be explained by the effect of the substance on oxidative stress, diosgenin triggered increased activity of SOD, CAT and GPx, reducing lipid peroxidation, which was evidenced by the reduction of malondialdehyde concentration.
Chen *et al*. 2015 [5]	China	Use of doxorubicin-exposed mice (Balb / c) treated with diosgenin 130 mg / kg for 4 weeks. The effect of the substance on cardiac function was assessed by measuring markers of tissue injury, apoptosis and oxidative stress.	Treatment with diosgenin restored cardiac function and heart weight, normalized cardiotoxicity markers (LDH, CK-MB and lactate dehydrogenase). The preservation effects of cardiac tissue were also significant in the activity of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) and also in anti-apoptotic function - by inhibiting caspase-3. These results are associated with protein kinase A (PKA) activation.
Badalzedeh , *et al*. 2014 [27]	Azerbaijan	Wistar rats had their hearts removed and mounted on a Langendorff retrograde perfusion system via the aorta. Diosgenin was administered acutely and the cardioprotective mechanisms against ischemia and reperfusion injury were evaluated.	Acute diosgenin administration promoted the normalization of cardiac injury markers (CK-MB and LDH), as well as restored the contraction force of the left ventricle. These results are explained by the activation of the mitoKATP channels in cardiomyocytes triggered by diosgenin.
Badalzadeh *et al*. 2014 [26]	Azerbaijan	Ischemia and reperfusion was performed in Wistar rat hearts using the Langendorff type system and diosgenin was administered to the preparations acutely. The participation of this substance on the occurrence of cardiac arrhythmias and on the concentration of markers of myocardial injury was investigated.	Diosgenin prevented the occurrence of severe cardiac arrhythmias such as ventricular fibrillation and ventricular tachycardia, as well as a reduction in the number of premature ventricular beats. On markers of cardiac tissue injury, the substance reduces the concentration of lactate dehydrogenase (LDH). And inhibition of potassium channels mitoKATP and nitric oxide production reverses the effect of diosgenin, indicating their participation in the effect of the substance on arrhythmias and reperfusion injury.
Ebrahimi *et al*. 2014 [25]	-	With the use of Wistar rats and retrograde perfused hearts in a Langendorff type system, ischemia and reperfusion was promoted. Acute diosgenin activity was investigated in markers of myocardial lesions and inflammation.	Treatment of hearts with diosgenin triggered improvement in cardiac function, ie restoration of left ventricular contraction force and reduction of LDH. In the markers of inflammation, there was a reduction in TNFα, IL-1β and IL-6. These results were significantly attenuated with the inhibition of mitoKATP channels, indicating the participation of these channels in the effect of diosgenin.
Qin *et al*. 2013 [18]	-	Using ischemia-reperfusion-induced H9C2 cardiac cells, the participation of diosgenin on reactive oxygen species, apoptosis and cell injury markers was investigated.	Diosgenin reduces the production of reactive oxygen species in cardiac cells, rebalances cellular function, decreases the release of lesion markers (LDH) and inhibits the activation of apoptosis pathways. These mechanisms are explained by the substance's potential to activate the SOD enzyme, reduce malondialdehyde (MDA) concentration, and reduce mitochondrial cytochrome c (Cyt-c) release to the cytoplasm, thereby inhibiting the activation of apoptosis.
Gong *et al*. 2011 [24]	China	Using Sprague – Dawley rats, the antithrombotic effect of oral diosgenin was evaluated. The effect of the substance on platelet aggregation and clot dissolution was measured.	Diosgenin inhibited platelet aggregation and thrombosis. It prolonged the partial thromboplastin time, prothrombin time and venous thrombosis in the animals. Thus it has beneficial antithrombotic effect on the cardiovascular system.
Jayachandran, *et al*. 2009 [22]	-	Heart failure was induced with isoproterenol in Wistar rats and the participation of diosgenin (80 mg / kg - for 35 days orally) on reactive oxygen species, myocardial injury masters, was evaluated.	Diosgenin rebalances redox status in heart cells, evidenced by reduced lipid peroxidation, as well as reduced release of CK-MB, a known marker of cardiac injury. Diosgenin also restores hydroelectrolytic balance by positively influencing the channels located in the cardiomyocyte membrane.

CONCLUSION

Diosgenin has been shown to have a beneficial effect on the treatment of cardiovascular disease in animal or cellular experimental models. Using specific mechanisms of action, the natural substance fights changes in the cardiovascular system, triggered by atherogenic diet, adrenergic hyperstimulation; imbalance in redox status in cardiomyocytes caused by doxorubicin and also reduces the cellular damage triggered by the ischemia and reperfusion process.

This fact makes this molecule a potential for pharmacology in the future. Notably, more studies are needed, especially randomized human trials in order to observe the reproduction of data obtained in animal models.

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