MEDS Clinical Medicine (2021) 2: 10-14
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2021.020103
ISSN ISSN 2616-1907

Anti-Cardiovascular Effects of Diosgenin and Its Related Derivatives

Yingfeng Xue[1], Jiayan Lin[1], Hongbo Zhang[1], Fuyao Xiao[1], Weigang Li[1] and Nannan Huang[1*]

[1] Heilongjiang University of Chinese Medicine, Harbin 150040, China

**Corresponding Author*

Keywords: Diosgenin, Cardiovascular disease, Diosgenin derivatives, Pharmacological effects

Abstract: Research has found that diosgenin can play a pharmacological role in anti-thrombotic, anti-atherosclerotic, anti-inflammatory, anti-hyperlipidemic, anti-hypertensive, etc. The derivatives synthesized from diosgenin: diosgenin prodrugs, diosgenin amine derivatives, diosgenin acyl derivatives also show anti-thrombotic, anti-inflammatory, and enhanced pharmacological effects. Therefore, they can exert a wide range of inhibitory effects on cardiovascular diseases, which are a serious threat to human health. Based on this, this article discusses the anti-cardiovascular disease effects of diosgenin and the above derivatives, aiming to lay the foundation for the deeper research and application of diosgenin and its derivatives against cardiovascular diseases.

1.Introduction

Diosgenin is a natural steroidal saponin element (Figure 1), which is an important basic raw material for the production of steroid hormone drugs. It has a wide range of effects, such as anti-thrombotic, anti-atherosclerotic, anti-inflammatory, and anti-hyperlipidemic[1], and has applications across common cardiovascular diseases[2].

Yet, diosgenin is a fat-soluble compound, which is not easily absorbed in the organism, and its oral bioavailability is low[3]. In order to improve its bioavailability and application breadth, researchers have synthesized a variety of novel derivatives based on diosgenin. So this article takes the anti-cardiovascular disease of diosgenin as an entry point to study the anti-disease activity of diosgenin and its related derivatives, with the expectation of laying the theoretical foundation for the indepth development of diosgenin against cardiovascular diseases.

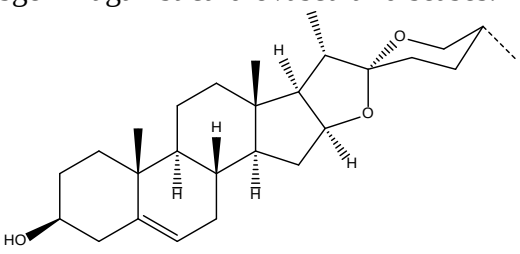

Fig.1 Chemical Structure Formula of Diosgenin

2. Effects of Diosgenin Against Cardiovascular Diseases

2.1 Anti-Thrombotic

Thrombi are composed of platelets, fibrin, and red blood cells[4] and form due to platelet aggregation, fibrin deposition, and abnormal clotting of clotting factors. Tian Y Q et al.[5] and Zhang Y[6] came to the same conclusion: diosgenin can regulate intravascular nitric oxide(NO) levels as a way to inhibit platelet aggregation and relaxation of the vascular wall. Besides, diosgenin can increasing the content of myeloperoxidase (MPO), which in turn reduces the permeability of the vessel wall and exerts an inhibitory effect on thrombus formation. Another study[7] showed that diosgenin inhibited thrombosis by prolonging bleeding and clotting times, preventing platelet aggregation. Ning K Y et al.[8] found that diosgenin can reduce the process and extent of thrombosis development ($P < 0.05$), so it can inhibit the formation of thrombus *in vitro*.

2.2 Anti-Atherosclerosis

Atherosclerosis is a progressive chronic inflammatory disease, its pathogenesis is mainly based on impaired lipid metabolism. For example, plaques form due to lipid accumulation, resulting in damage or necrosis of the tissues and organs due to insufficient blood supply[9]. Wu F C et al.[10] summarized that diosgenin can increase NO production, reduce endothelial cell apoptosis and thus improve endothelial cell function and prevent atherosclerosis formation. Studies have shown that diosgenin can inhibit the expression of miR-19b in macrophages, promote cholesterol efflux, and play an anti-atherosclerotic role in the development of atherosclerosis[11]. Another study showed that diosgenin was able to inhibit Notch signaling pathway, and its anti-atherosclerotic properties were more pronounced when the expression of a nuclear translocation of Notch intracellular domain was inhibited in aorta and differentiated macrophages[12].

2.3 Anti-Inflammatory

Inflammation plays an important role in the pathogenesis of cardiovascular disease, and the etiology of common cardiovascular diseases include it. Diosgenin can inhibit the production of inflammatory molecules and provide anti-inflammatory protection against myocardial ischemia reperfusion injury organisms by inhibiting the phosphorylation of nuclear factor-kappa B (NF-κB), regulating c-JUN N-terminal kinase (JNK) and the p38-MAPK signaling pathways[13]. In addition, diosgenin can lower the level of MPO after reperfusion, reduce the inflammatory response and improve cardiac function. Hadi E et al.[14] found that the levels of inflammatory mediators in myocardial ischemia reperfusion injured organisms and the amount of lactate dehydrogenase were significantly reduced after pretreatment with diosgenin, which could be anti-inflammatory and improve cardiac function and protect the damaged heart.

2.4 Anti-Hyperlipidemic

Hyperlipidemia is caused by abnormalities lipid metabolism. Ma H Y et al.[15] found that diosgenin was more effective in the prevention and treatment of hyperlipidemia compared to total saponin of *Yellow yam*. Experimental data showed that diosgenin inhibited the formation of exogenous cholesterol microcolloids under the action of bile up to 98.8%. Another study[16] illustrated that diosgenin significantly enhanced the activity of metabolic enzyme, accelerated lipid metabolism and alleviates symptoms of lipid metabolism disorders. Moreover, it was pointed out that diosgenin could reduce the absorption of cholesterol and increase its secretion, bringing about a

hypolipidemic effect, and the entire intensity of action was in a dose dependent manner.

2.5 Anti-Hypertension

Hypertension is one of the most common cardiovascular diseases, which can lead to systemic complications. Diosgenin maintained the normal expression of endothelial NOS (eNOS) in pulmonary hypertension (PH) and inhibited the overexpression of the harmful inducible NOS (iNOS). Maintaining NO homeostasis, exerted protective effects in the PH[17]. In another study, it was found that diosgenin significantly reduced the mean pulmonary artery pressure, increased the lumen area, improved pulmonary vascular remodeling and lowered pressure. Additionally, diosgenin significantly reduces perivascular inflammatory cell infiltration, inhibits the proliferation of vascular smooth muscle cells, and suppresses the inflammatory response of small pulmonary arteries. In summary, by exerting the above dual action, diosgenin can prevent other complications along with anti-hypertension[18].

3. Effects of Related Derivatives Against Cardiovascular Diseases

3.1 Precursors of Diosgenin

Although diosgenin has good anti-thrombotic effects without side effects, its application is severely limited by its extremely poor solubility and poor bioavailability. Wei Z L et al.[19] combined with polyethylene glycol to generate a novel prodrug nanomicelles, which was tested and found to be significantly more stable and could be rapidly released in acidic environment, and improved the blood concentration, half-life and bioavailability of diosgenin. In addition, this prodrug inhibited thrombosis remarkably more strongly than diosgenin, producing a significant reduction in both the length and weight of the thrombus.

3.2 Diosgenin Meta-Amine Derivatives

To improve the metabolic kinetic characteristics of diosgenin, Cai B R et al.[20] synthesized the primary amine-containing derivatives of diosgenin: DGP. Study of its effect on lipopolysaccharide (LPS)-stimulated microglia BV2 revealed that it could significantly inhibit NO synthesis and reduce pro-inflammatory factors such as IL-6, IL-1, TNF-α and reactive oxygen species by blocking the nuclear factor NF-κB signaling pathway and JNK phosphorylation, causing downregulation of iNOS and cyclooxygenase-2 activity production, which in turn exerts anti-inflammatory effects.

3.3 Diosgenin Meta-Acyl Derivatives

Acetylsalicylic acid, also known as aspirin, acts as a prophylactic and therapeutic agent for thrombosis. However, long-term use of aspirin may lead to gastric ulcers and gastric bleeding, as well as damage to the liver, kidneys and nervous system[21]. Zheng H J et al.[22] synthesized acetylsalicylic acid diosgenin and demonstrated that this derivative prolongs the clotting time, significantly reduces the degree of thrombosis development, and its anti-thrombotic effect is more significant and has fewer side effects. Fu X L et al.[23] reacted diosgenin with acetylsalicylic acid, ferulic acid etc. and tested their activity, which finally showed that 3β-disalicyl diosgeninogen and 3β-acetylsalicyl ferulic acid ester acyl diosgeninogen showed better anti-thrombotic activity. Both could inhibit thrombosis extremely significantly and had significantly higher activity than the parent diosgenin.

4. Discussion

As a natural chemical component with diverse pharmacological effects and few side effects, diosgenin has high clinical value and deserves to be fully developed, nevertheless, due to its small solubility and poor bioavailability, more research has been conducted to develop diosgenin derivatives based on its structure and pharmacological properties. The article combines the practical aspects and finds that anti-cardiovascular disease is not only one of the important aspects of the pharmacological effects of diosgenin, but also one of the most threatening and serious diseases to human health today. As such, this article discusses the anti-cardiovascular disease pharmacological effects of diosgenin and its related derivatives, intending to create theoretical support for researchers' advanced research as well as its more comprehensive development and application.

Acknowledgement

The article was funded by the Science and Technology Innovation Experimental Project of Heilongjiang University of Chinese Medicine. The project name is the process research of the synthesis of diosgenin compounds based on diosgenin of diosgenin salicylate, project number is 2020-12.

References

[1] He Y, Wang J S, Zhang P, et al. Research progress on pharmacological properties of diosgenin and its mechanism[J]. Chinese Traditional and Herbal Drugs, 2013, 44(19): 2759-2765.

[2] Ma M H, Wu X H, He Y, et al. Anti-inflammatory and Analgesic Effects of Saponins from D.zingiberensis C.H. Wright and Diosgenin Derivative on Mice[J]. Journal of Sichuan University(Medical Science Edition), 2011, 42(04): 494-497.

[3] Luo Z M, Hu Y G, Wang L H, et al. Study on the Synthesis and Bioactivity of Diosgenin Antitumor Derivatives[J]. Chinese Journal of Organic Chemistry, 2018, 38(04): 919-925.

[4] Ji S D. Thrombosis mechanism and pharmacological characteristics of anticoagulants[J]. Chinese Journal of Family Planning & Gynecotokology, 2021, 13(03): 25-28.

[5] Tian Y Q, Ding P, Kou J P, et al. Effect of Diosgenin on Stasis-Induced Venous Thrombosis in Mice[J]. Research and Practice on Chinese Medicines, 2007(01): 32-34.

[6] Zhang Y. Analysis of the mechanism of action of Diosgenin-based Chinese patent medicines in anti-thrombotic and their biological activity[J]. Journal of North Pharmacy, 2014, 11(04): 52.

[7] Gong G H, Qin Y, Huang W. Anti-thrombosis effect of diosgenin extract from Dioscorea zingiberensis C.H. Wright in vitro and in vivo[J]. Phytomedicine: international journal of phytotherapy and phytopharmacology, 2011, 18(6): 458-463.

[8] Ning K Y, Li Y K, Gao H L, et al. Effects of Methyl Protodioscin on In-Vivo and In-Vitro Thrombosis and Blood Viscosity in Rats[J]. Traditional Chinese Drug Research and Clinical Pharmacology, 2008(01): 3-5.

[9] Zhang J M, Jing Y S, Zhang D S. Pathogenesis and treatment of atherosclerosis[J]. Chinese Journal of Pharmacology and Toxicology, 2019, 33(06): 472.

[10] Wu F C, Jiang J G. Effects of diosgenin and its derivatives on atherosclerosis[J]. Food & function, 2019, 10(11): 7022-7036.

[11] Lv Y C, Yang J, Yao F, et al. Diosgenin inhibits atherosclerosis via suppressing the MiR-19b-induced downregulation of ATP-binding cassette transporter A1[J]. Atherosclerosis, 2015, 240(1): 80-89.

[12] Binesh A, Devaraj S N, Devaraj H. Inhibition of nuclear translocation of notch intracellular domain (NICD) by diosgenin prevented atherosclerotic disease progression[J]. Biochimie, 2018, 148: 63-71.

[13] Wang H W, Liu H J, Cao H, et al. Diosgenin Protects Rats from Myocardial Inflammatory Injury Induced by Ischemia-Reperfusion[J]. Medical science monitor: international medical journal of experimental and clinical research, 2018, 24: 246-253.

[14] Hadi E, Reza B, Mustafa M, et al. Diosgenin attenuates inflammatory response induced by myocardial reperfusion injury: role of mitochondrial ATP-sensitive potassium channels[J]. Journal of physiology and biochemistry, 2014, 70(2): 425-432.

[15] Ma H Y, Zhao Z T, Wang L J, et al. Comparative Study on Anti-Hypercholesterolemia Activity of Diosgenin and

Total Saponin of Dioscorea panthaica[J]. China Journal of Chinese Materia Medica, 2002(07): 51-54.

[16] Gong G H, Qin Y, Huang W, et al. Protective effects of diosgenin in the hyperlipidemic rat model and in human vascular endothelial cells against hydrogen peroxide-induced apoptosis[J]. Chemico-Biological Interactions, 2010, 184(3): 366-375.

[17] Ahmed L A, Obaid A A Z, Zaki H F, et al. Role of oxidative stress, inflammation, nitric oxide and transforming growth factor-beta in the protective effect of diosgenin in monocrotaline-induced pulmonary hypertension in rats[J]. European journal of pharmacology, 2014, 740: 379-387.

[18] Yan T. The study on effects of Diosgenin against pulmonary artery hypertension and NF-κB expression in rats[D]. Hunan Normal University, 2016.

[19] Wei Z L, Xin G, Wang H B, et al. The diosgenin prodrug nanoparticles with pH-responsive as a drug delivery system uniquely prevents thrombosis without increased bleeding risk[J]. Nanomedicine: nanotechnology, biology, and medicine, 2018, 14(3): 673-684.

[20] Cai B R, Seong K J, Bae S W, et al. A synthetic diosgenin primary amine derivative attenuates LPS-stimulated inflammation via inhibition of NF-κB and JNK MAPK signaling in microglial BV2 cells[J]. International Immunopharmacology, 2018, 61: 204-214.

[21] Zhang Y X, Gao H C, Zhang C R, et al. Advances in the Study of Structural Modification of Aspirin and Their Biological Activities[J]. Chinese Journal of Organic Chemistry, 2020, 40(02): 300-326.

[22] Zheng H J, Wei Z L, Xin G, et al. Preventive effect of a novel diosgenin derivative on arterial and venous thrombosis in vivo[J]. Bioorganic & medicinal chemistry letters, 2016, 26(14): 3364-3369.

[23] Fu X L, Han Y M, Zhang S J. Synthesis of diosgenin derivatives and their antithrombotic activity (II)[J]. Chinese Traditional and Herbal Drugs, 2011, 42(09): 1683-1688.