Medical Sains : Jurnal Ilmiah Kefarmasian
Vol. 9 No. 2, April - June 2024
https:/ojs.stfmuhammadiyahcirebon.ac.id/index.php/iojs

REVIEW: ACTIVITY OF DIOSGENIN COMPOUND AS ATHEROSCLEROSIS THERAPY

Rusi Rismawanti[1*], Siti Saidah[1]
[1]*Fakultas Farmasi, Universitas Bhakti Kencana*
Universitas Bhakti Kencana, Bandung 40614, Indonesia
**Email Corresponding: rusirisma19@gmail.com*

Submitted: January 30, 2024 ***Revised: May 26, 2024*** ***Accepted: June 9, 2024***

ABSTRACT

Atherosclerosis is a disease that causes inhibition of the stability of the cardiovascular system in the body. Cardiovascular disease remains at the top of the list of diseases that cause death. Therefore, cardiovascular disease therapy, including atherosclerosis, still needs to be developed to reduce the mortality rate associated with this disease. Several studies have shown that diosgenin compounds can be used as a therapy for atherosclerosis. The purpose of this study was to determine whether diosgenin compounds and their derivatives can be used for atherosclerosis therapy with various mechanisms of action related to the development of atherosclerosis. This article review was conducted using the article search method on Google Scholar, Pubmed, and Science Direct with various keywords. The results obtained are diosgenin and several diosgenin-derived compounds that can be used as therapies for atherosclerosis with several responses obtained from experiments using rats.

Keywords: diosgenin; atherosclerosis; diosgenin derivatives

INTRODUCTION

Coronary heart disease (CHD) is caused by plaque build-up in the coronary arteries that supplies oxygen to the heart muscle. It is one of the most common cardiovascular diseases worldwide. According to global statistics, there are 9.4 million deaths each year caused by cardiovascular disease, and 45% of these deaths are caused by coronary heart disease. It is estimated that this number will increase to 23.3 million by 2030. According to the Sample Registration System survey, the coronary disease mortality rate was 12.9% of all deaths. The prevalence of coronary heart disease based on physician diagnosis in 2013 Basic Health Research (Rikesdas) was 0.5%, while based on physician diagnosis or symptoms, it was 1.5%. The Rikesdas results showed that coronary heart disease is the seventh highest non-communicable disease (NCD) in Indonesia (Ghani *et al*., 2016).

One of the UN's 2030 development goals is to reduce premature deaths from noncommunicable diseases by one third. Cardiovascular diseases, including coronary heart disease and stroke, are among the most common non-communicable diseases in the world and were responsible for 17-18 million deaths in 2017. To help reduce the global burden of cardiovascular disease, the WHO and its member states are committed to providing counseling and drug treatment to at least 50% of eligible people (aged >40 years and at high risk of cardiovascular disease) by 2025 (Kaptoge *et al*., 2019).

Cardiovascular disease, which is the number one disease in America, causes death because of risk factors such as elevated blood lipid levels, diabetes, and high blood pressure (Stewart *et al*., n.d.). .). Elevated levels of lipids in the blood can cause calcification in large arteries, formation of fibrous elements, and accumulation of lipids in blood vessels. In the early stages of the disease, the abundance of pathogens causes damage to the intima, which further increases the infiltration of inflammatory cells and lipids, and accelerates the

formation of foam cells. In later stages, a classification process occurs that forms plaques and tissue damage, leading to the formation of thrombosis, which then leads to ischemic injury syndromes in vital organs such as myocardial infarction, angina instability, stroke, and other complications (D. Wang & Wang, 2022).

Lowering blood lipids, controlling blood pressure, dilating blood vessels, and preventing platelet aggregation to prevent thrombotic complications are treatment methods that can be used for atherosclerosis (Parama *et al*., 2020). In addition, the role of anti-inflammatory treatments and inflammatory cytokine inhibitors is now well recognized. Prevention of atherosclerosis development through anti-inflammatory and immunologic regulation is considered to treat various risk factors associated with atherosclerosis (Zhu *et al*., 2018).

A growing understanding of the pathogenesis of atherosclerosis has led to more approaches for the development of new therapies. Identifying the pathogenesis of atherosclerosis is important for the development of atherosclerosis therapies with various aspects that can be tailored to the needs of each patient (Björkegren & Lusis, 2022). For this reason, effective therapy and prevention of this disease are very important because many of the drugs available for atherosclerosis still use statin class lipid-lowering drugs, which are one of the first choices compared to phytopharmaceutical drugs (C. Wang *et al*., 2018) . In addition to statins, antiplatelet drug therapy, such as aspirin, is the first-line drug used in the secondary prevention of atherosclerosis, which has been associated with several adverse reactions such as gastrointestinal bleeding, ulcers, and increased drug resistance (Cai *et al*., 2016). Thus, the development of safer and less toxic drugs is urgently required as an alternative treatment for atherosclerosis.

Several studies have shown that diosgenin compounds can be used as a therapy for atherosclerosis. Diosgenin is a triterpenoid steroidal sapogenin compound that exhibits several pharmacological activities, including anti-inflammatory, anti-infective, anti-cancer, anti-aging, anti-thrombosis, and anti-neurotic properties. In vitro and in vivo studies have demonstrated the potential role of diosgenin in the prevention of this disease (Parama *et al*., 2020).

In this article, we summarize the effects of diosgenin and its derivatives on the mechanism of action of disease pathogenesis to provide a new picture for the development of atherosclerosis drugs.

RESEARCH METHOD

This qualitative study focuses on proving non-numerical hypotheses and is descriptive. A search of international and national published scientific journals in the last 10 years from 2013-2023 with keywords: Diosgenin, Atherosclerosis, Mechanism of Diosgenin, Diosgenin and Atheroschlerosis through electronic databases such as Pubmed, ScienceDirect and Google Scholar.

Literature selection was based on the ability to answer questions related to the research objectives, namely, to determine the role of diosgenin as a therapy for atherosclerosis and its mechanism of action on the body. The journal or article criteria were filtered based on the publication period of the last 10 years, English (international), Indonesian (national), title, literature, abstract, and appropriate keywords. Articles were screened and re-selected by reading the entire text.

The number of articles used for the literature review was 18 articles with articles published at least in 2013. A total of 35 articles were obtained from all databases used. The articles included in this final stage selection process are 6 articles that are considered relevant to the research topic and will be reviewed completely and thoroughly further.

RESULTS AND DISCUSSION

The A study evaluating the effectiveness of diosgenin against cardiovascular disease showed that the drug causes overexpression of the ATP-binding transporter by suppressing the function of microRNA (miR)-19b in THP-1 macrophages (Lv *et al*., 2015). In addition,

diosgenin modulates the core intracellular translocation domain (NICD) pathway, **Figure 1**. There was an increase in the mRNA expression of notch1, Jagged1, and Hes1 in experimental atherogenic diet induced rats compared to diosgenin treated rats and control rats. Notch pathway proteins Notch1, DLL1, NICD, Hes1, and Hey1 were upregulated in the induced group of rats compared to the treated and control rats (Binesh, Devaraj, & Devaraj, 2018). The study presented that In cultured monocytes, Notch1 signaling induces M1 macrophage differentiation and promotes inflammation by increasing the production of IL-6, MCP-1, and TNF-α. Inhibition of Notch activity using the Notch Inhibitor DAPT can reduce macrophage migration and suppress ICAM-1 expression in macrophages, leading to a decrease in macrophage infiltration in atherosclerotic plaques (Sega *et al*., 2019).

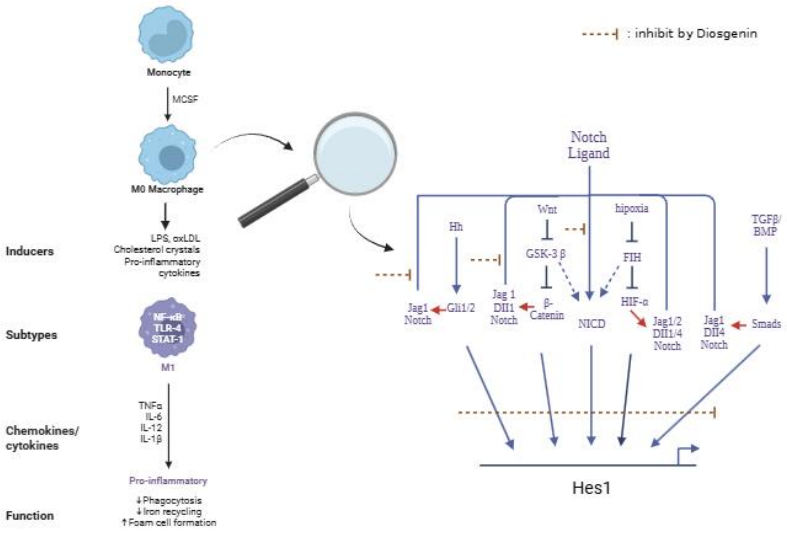

Figure 1. Mechanism of diosgenin inhibiting notch signaling pathway in macrophage.

Another study evaluated the potency of diosgenin in male Wistar rats fed an atherogenic diet (AD). The atherogenic diet increased the levels of COX-2, TNF-α, and NF-kB in the heart, liver, and brain of rats, and diosgenin played a role in reducing the levels of COX-2, TNF-α, and NF-kB, thereby inhibiting the development of atherosclerosis (Binesh, Devaraj, & Halagowder, 2018). Another study revealed that in addition to downregulating NF-kB expression, diosgenin increases macrophage polarization to act as an anti-atherosclerosis agent (Binesh *et al*., 2020). Diosgenin analogs, namely dioscin **Figure 2**, were evaluated to reduce plasma lipid levels, TNF-α, IL-1β, and IL-6 besides that dioscin also inhibits lectin oxidized LDL (oxLDL), (LOX)-1 receptor and NF-kB expression in vitro (P. Wang *et al*., 2017).

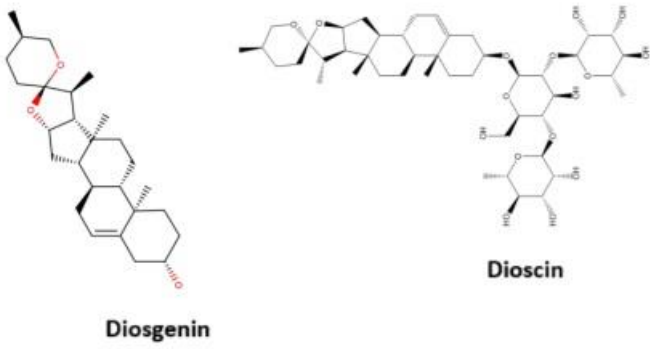

Figure 2. Chemical Structure of Diosgenin and Dioscin**.**

Dioscin has lipid-lowering (Sun *et al*., 2021), anti-tumor (Tong *et al*., 2014), hepatoprotective effects (Zhang *et al*., 2015), and has anti-inflammatory properties (H. Wang *et al*., 2020). Atherosclerosis is also widely recognized as an inflammatory disease characterized by increased adhesion of monocytes to endothelial cells (ECs) during atherogenesis. Therefore, the prevention of atherosclerosis can inhibit monocyte adhesion to endothelial cells. TNF-α is a pro-inflammatory factor secreted by monocytes and vascular endothelial cells, and is found in atherosclerotic lesions. In this study, dioscin inhibited monocytes to HUVEC (Human Umbilical Vein Endothelial Cells) through TNF-α by reducing the production of Inter Cellular Adhesion Molecule – 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and Endothelial Lipase (EL), and blocking the NF-kB signaling pathway, **Figure 3** (Wu *et al*., 2015). ICAM-1 (CD54) is a membrane-bound and soluble glycoprotein that appears or is expressed during inflammation, especially in the endothelium where expression can remain elevated for long periods of time (Ramos et al., 2014), VCAM (CD106) is expressed on the luminal and lateral sides of endothelial cells under inflammatory conditions, mediating rolling and adhesion of leukocyte subsets (Schlesinger & Bendas, 2015).

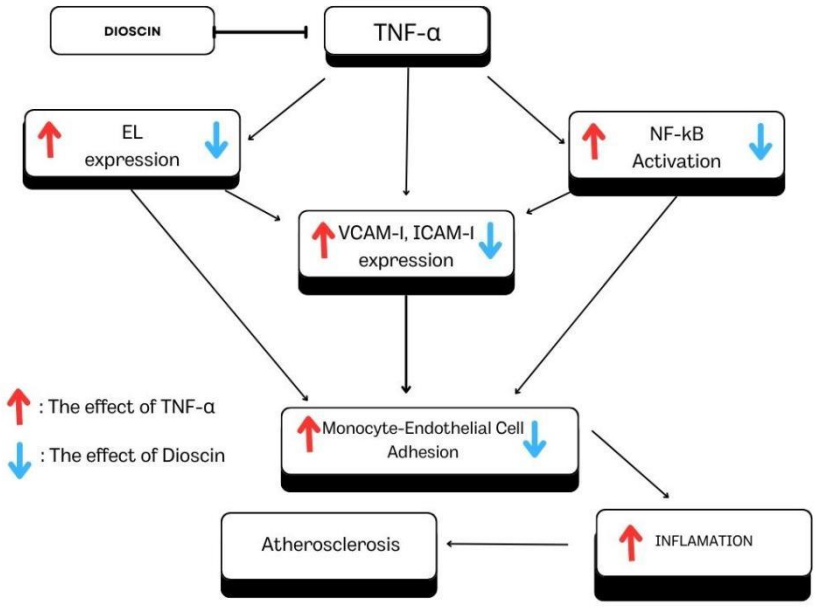

Figure 3. The mechanism of dioscin as anti-atherosclerosis by inhibiting TNF- α (Wu *et al*., 2015).

Table I. Results of Article Review

Reference	Title	Journal Publication	Mechanisme of Action
(Lv *et al*., 2015)	Diosgenin inhibits atherosclerosis via suppressing the MiR-19b-induced downregulation of ATP-binding cassette transporter A1.	*Molecular Medicine Reports*	Suppressing the function of microRNA (miR)-19b in THP-1 macrophages.
(P. Wang *et al*., 2017)	Inhibitory effects of Dioscin on atherosclerosis and foam cell formation in hyperlipidemia rats.	*Spinger - Inflammopharmacology Journal*	Reduces lipid, TNF-α, IL-1β, and IL-6 levels. Inhibits LDL, (LOX)-1, and NF-kB.
(Binesh, Devaraj, & Devaraj, 2018)	Inhibition of nuclear translocation of notch intracellular domain (NICD) by diosgenin prevented atherosclerotic disease progression	*Life Sciences Journal*	Modulates the level of the core pathway of intracellular translocation (Notch Intracellular Domain/NICD).
(Binesh, Devaraj, & Halagowder, 2018)	Atherogenic diet induced lipid accumulation induced NFκB level in heart, liver and brain of Wistar rat and diosgenin as an anti-inflammatory agent.	*Biochimmie Journal*	Decreases levels of COX-2, TNF-α, and NF-kB.
(Binesh *et al*., 2020)	Expression of chemokines in macrophage polarization and downregulation of NFκB in aorta allow macrophage polarization by diosgenin in atherosclerosis	*Journal of Biochemical and Molecular Toxicology*	Increases macrophage polarization so that it can act as an anti-atherosclerosis agent.
(Zhou *et al*., 2017)	Diosgenin inhibits II-induced extracellular matrix remodelin in cardiac fibroblasts through regulating the TGF-β1/Smad3 signaling pathway	*Journal of Molecular Medicine Reports*	Inhibits cell ploriferation in cardiac fibroblasts.

This study was conducted on male Wistar rats using several methods. First induction using an Atherogenic Diet The results were observed with a decrease in total cholesterol levels, triglycerides, LDL levels and VDL levels. The aortic histology method shows significant histopathological changes in the aorta with the formation or development of plaques in the aorta. There are changes in mRNA and protein expression of Notch pathway molecules in the aorta (Lv *et al*., 2015). The study used the same animals, Wistar rats, with several treatments. First, an atherogenic diet was provided to determine the increase in LDL and HDL levels.

Hyperglycemic mice showed focal discontinuity of the tunic intima endothelium, marked increase in thickness with focal hyalinization of the tunic media associated with large numbers of foam cells. Aortas of mice fed an atherogenic diet showed subintimal pooling of macrophages and foam cells, separation of tunic media with pooling of blood cells, and atheromatous plaque formation when compared to mice treated with diosgenin

(Binesh, Devaraj, & Devaraj, 2018). An atherogenic diet in the blood induces leukocytes to adhere to adhesion molecules on the endothelial surface and migrate to the subintimal compartment in response to chemokine gradients. This induces the differentiation of macrophages into foam cells in the subintima by engulfing LDL particles to form necrotic nuclei (Sanuja & Fernando, 2021) . Experiments using mice fed an atherogenic diet caused cellular disruption of the heart. Increased LDL and VDL are known to induce inflammation, which has been analyzed by the expression of the inflammatory mediators TNF-α, IL-6, and NFkBp65, which were found to be upregulated in the induced group (Binesh, Devaraj, & Halagowder, 2018).

The study was conducted using Wistar rats, which were divided into several groups and research methods. One of the methods used in this research is the THP1-cell. Oxidized LDL (OxyLDL) is used to induce inflammatory processes in THP-1 cells. THP-1 cells release mediators, such as COX-2 and NFkB, during inflammation. The reduction in COX-2 and NFkB levels is analyzed when conducting experiments using the THP-1 cell method (Binesh *et al*., 2020)

Atherosclerosis is a chronic disease of the blood vessels, where cholesterol and low-density lipoprotein accumulate in the inner wall of the blood vessels and form plaques. The wall becomes thicker and loses its elasticity, which eventually narrows, making it difficult for blood to flow to the organs (Björkegren & Lusis, 2022). The development of atherosclerosis is not only based on lifestyle therapy; cardiovascular disease risk factors also support the development of atherosclerosis. These risk factors can inhibit the activity of the enzyme nitric oxide synthesis (eNOS) on NF-kβ, induce NF-kβ, reduce NO and promote the development of atherosclerosis. The endothelial cell layer, commonly referred to as the endothelium, is located between circulating blood and tissues in the body and plays an important role in homeostatic regulation (Jebari-Benslaiman *et al*., 2022). Endothelial cells play a role in producing vasodilator prostaglandin hormones, NO, and endothelial-dependent hyper-polarizing factor (EDH) as well as endothelial-derived contracting factor (Godo & Shimokawa, 2017).

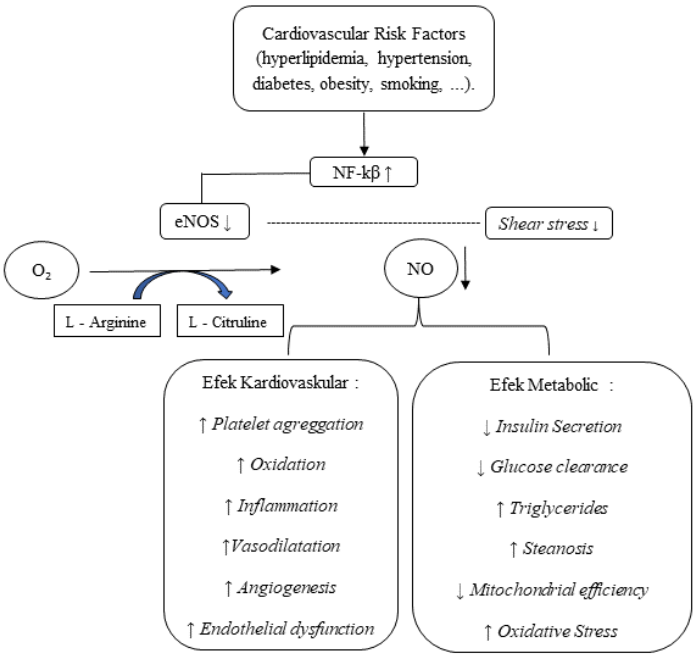

Figure 4. Mechanisms by which cardiovascular risk factors influence the development of atherosclerosis; eNOS catalyzes the production of NO from L-arginine. NO plays an important role in metabolism as an inhibitor of atherosclerosis progression by improving

vasorelaxation, angiogenesis, endothelial function, insulin secretion, glucose clearance and mitochondrial efficiency. (Jebari-Benslaiman *et al*., 2022).

All changes in the blood circulation are sensed by the endothelium, which then mediates signal transduction to other layers of the vascular wall. Such changes include stress mechanisms as well as changes in the concentration of metabolic factors that can influence the development of atherosclerotic disease (Godo & Shimokawa, 2017) .

In addition, in atherosclerotic disease, incoming LDL particles carrying cholesterol are retained in the arterial wall, causing retention. This retention leads to local inflammation with an influx of monocytes that differentiate into macrophages, accumulate intracellular cholesterol, and produce inflammatory mediators. Most of these T cells recognize LDL as an anti-gene and belong to the T helper type 1 (TH1) subtype, which produces pro-inflammatory mediators such as interferon-γ (IFNγ) and tumor necrosis factor (TNF) 11,12. Inflammatory mediators produced in the arterial wall include IL-6, which can trigger the activation of the acute phase response in the liver, leading to the release of C-reactive protein (CRP) into systemic circulation (Gisterå & Hansson, 2017). Several therapies can be provided by regulating the production of each of the factors that lead to the development of atherosclerotic disease.

CONCLUSION

In general, diosgenin and its derivatives have potential therapeutic effects against atherosclerotic disease. They improve endothelial dysfunction by regulating vascular tension, oxidative stress, leukocyte adhesion, platelet aggregation, and thrombosis. They can also inhibit ploriferation, migration and calcification, improve lipid metabolism by inhibiting foam cell formation, regulate hyperlipidemia, inhibit cholesterol absorption and promote biliary cholesterol excretion.

REFERENCES

Binesh, A., Devaraj, S. N., & Devaraj, H. (2018). Inhibition of nuclear translocation of notch intracellular domain (NICD) by diosgenin prevented atherosclerotic disease progression. *Biochimie*, *148*, 63–71. https://doi.org/10.1016/j.biochi.2018.02.011

Binesh, A., Devaraj, S. N., & Devaraj, H. (2020). Expression of chemokines in macrophage polarization and downregulation of NFκB in aorta allow macrophage polarization by diosgenin in atherosclerosis. *Journal of Biochemical and Molecular Toxicology*, *34*(2). https://doi.org/10.1002/jbt.22422

Binesh, A., Devaraj, S. N., & Halagowder, D. (2018). Atherogenic diet induced lipid accumulation induced NFκB level in heart, liver and brain of Wistar rat and diosgenin as an anti-inflammatory agent. *Life Sciences*, *196*, 28–37. https://doi.org/10.1016/j.lfs.2018.01.012

Björkegren, J. L. M., & Lusis, A. J. (2022). Atherosclerosis: Recent developments. In *Cell* (Vol. 185, Issue 10, pp. 1630–1645). Elsevier B.V. https://doi.org/10.1016/j.cell.2022.04.004

Cai, G., Zhou, W., Lu, Y., Chen, P., Lu, Z., & Fu, Y. (2016). Aspirin resistance and other aspirin-related concerns. In *Neurological Sciences* (Vol. 37, Issue 2, pp. 181–189). Springer-Verlag Italia s.r.l. https://doi.org/10.1007/s10072-015-2412-x

Ghani, L., Susilawati, M. D., & Novriani, H. (2016). Faktor Risiko Dominan Penyakit Jantung Koroner di Indonesia. *Buletin Penelitian Kesehatan*, *44*(3). https://doi.org/10.22435/bpk.v44i3.5436.153-164

Gisterå, A., & Hansson, G. K. (2017). The immunology of atherosclerosis. In *Nature Reviews Nephrology* (Vol. 13, Issue 6, pp. 368–380). Nature Publishing Group. https://doi.org/10.1038/nrneph.2017.51

Godo, S., & Shimokawa, H. (2017). Endothelial Functions. In *Arteriosclerosis, Thrombosis, and Vascular Biology* (Vol. 37, Issue 9, pp. e108–e114). Lippincott Williams and Wilkins. https://doi.org/10.1161/ATVBAHA.117.309813

Jebari-Benslaiman, S., Galicia-García, U., Larrea-Sebal, A., Olaetxea, J. R., Alloza, I., Vandenbroeck, K., Benito-Vicente, A., & Martín, C. (2022). Pathophysiology of Atherosclerosis. In *International Journal of Molecular Sciences* (Vol. 23, Issue 6). MDPI. https://doi.org/10.3390/ijms23063346

Kaptoge, S., Pennells, L., De Bacquer, D., Cooney, M. T., Kavousi, M., Stevens, G., Riley, L. M., Savin, S., Khan, T., Altay, S., Amouyel, P., Assmann, G., Bell, S., Ben-Shlomo, Y., Berkman, L., Beulens, J. W., Björkelund, C., Blaha, M., Blazer, D. G., … Di Angelantonio, E. (2019). World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *The Lancet Global Health*, *7*(10), e1332–e1345. https://doi.org/10.1016/S2214-109X(19)30318-3

Lv, Y. cheng, Yang, J., Yao, F., Xie, W., Tang, Y. yan, Ouyang, X. ping, He, P. ping, Tan, Y. lin, Li, L., Zhang, M., Liu, D., Cayabyab, F. S., Zheng, X. L., & Tang, C. ke. (2015). Diosgenin inhibits atherosclerosis via suppressing the MiR-19b-induced downregulation of ATP-binding cassette transporter A1. *Atherosclerosis*, *240*(1), 80–89. https://doi.org/10.1016/j.atherosclerosis.2015.02.044

Parama, D., Boruah, M., Yachna, K., Rana, V., Banik, K., Harsha, C., Thakur, K. K., Dutta, U., Arya, A., Mao, X., Ahn, K. S., & Kunnumakkara, A. B. (2020). Diosgenin, a steroidal saponin, and its analogs: Effective therapies against different chronic diseases. In *Life Sciences* (Vol. 260). Elsevier Inc. https://doi.org/10.1016/j.lfs.2020.118182

Ramos, T. N., Bullard, D. C., & Barnum, S. R. (2014). ICAM-1: Isoforms and Phenotypes. *The Journal of Immunology*, *192*(10), 4469–4474. https://doi.org/10.4049/jimmunol.1400135

Sanuja, W., & Fernando, L. (n.d.). Molecular Mediators of Macrophage Foam Cell Formation and Atherosclerosis and their Pharmacological Modification.

Schlesinger, M., & Bendas, G. (2015). Vascular cell adhesion molecule-1 (VCAM-1) - An increasing insight into its role in tumorigenicity and metastasis. In *International Journal of Cancer* (Vol. 136, Issue 11, pp. 2504–2514). Wiley-Liss Inc. https://doi.org/10.1002/ijc.28927

Sega, F. V. D., Fortini, F., Aquila, G., Campo, G., Vaccarezza, M., & Rizzo, P. (2019). Notch signaling regulates immune responses in atherosclerosis. In *Frontiers in Immunology* (Vol. 10, Issue MAY). Frontiers Media S.A. https://doi.org/10.3389/fimmu.2019.01130

Stewart, J., Mccallin, T., Martinez, J., Chacko, S., & Yusuf, S. (n.d.). Hyperlipidemia Practice Gaps. http://pedsinreview.aappublications.org/

Sun, F., Yang, X., Ma, C., Zhang, S., Yu, L., Lu, H., Yin, G., Liang, P., Feng, Y., & Zhang, F. (2021). The effects of diosgenin on hypolipidemia and its underlying mechanism: A review. In *Diabetes, Metabolic Syndrome and Obesity* (Vol. 14, pp. 4015–4030). Dove Medical Press Ltd. https://doi.org/10.2147/DMSO.S326054

Tong, Q., Qing, Y., Wu, Y., Hu, X., Jiang, L., & Wu, X. (2014). Dioscin inhibits colon tumor growth and tumor angiogenesis through regulating VEGFR2 and AKT/MAPK signaling pathways. *Toxicology and Applied Pharmacology*, *281*(2), 166–173. https://doi.org/10.1016/j.taap.2014.07.026

Wang, C., Niimi, M., Watanabe, T., Wang, Y., Liang, J., & Fan, J. (2018). Treatment of atherosclerosis by traditional Chinese medicine: Questions and quandaries. In *Atherosclerosis* (Vol. 277, pp. 136–144). Elsevier Ireland Ltd. https://doi.org/10.1016/j.atherosclerosis.2018.08.039

Wang, D., & Wang, X. (2022). Diosgenin and Its Analogs: Potential Protective Agents Against Atherosclerosis. In *Drug Design, Development and Therapy* (Vol. 16, pp. 2305–2323). Dove Medical Press Ltd. https://doi.org/10.2147/DDDT.S368836

Wang, H., Zhwu, H., & Yang, X. (2020). Dioscin exhibits anti-inflammatory effects in IL-1β-stimulated human osteoarthritis chondrocytes by activating LXRα. *Immunopharmacology and Immunotoxicology*, *42*(4), 340–345. https://doi.org/10.1080/08923973.2020.1775248

Wang, P., He, L. ya, Shen, G. dong, Li, R. lin, & Yang, J. li. (2017). Inhibitory effects of Dioscin on atherosclerosis and foam cell formation in hyperlipidemia rats. *Inflammopharmacology*, *25*(6), 633–642. https://doi.org/10.1007/s10787-017-0341-4

Wu, S., Xu, H., Peng, J., Wang, C., Jin, Y., Liu, K., Sun, H., & Qin, J. (2015). Potent anti-inflammatory effect of dioscin mediated by suppression of TNF-α-induced VCAM-1, ICAM-1 and EL expression via the NF-κB pathway. *Biochimie*, *110*, 62–72. https://doi.org/10.1016/j.biochi.2014.12.022

Zhang, X., Han, X., Yin, L., Xu, L., Qi, Y., Xu, Y., Sun, H., Lin, Y., Liu, K., & Peng, J. (2015). Potent effects of dioscin against liver fibrosis. *Scientific Reports*, *5*. https://doi.org/10.1038/srep09713

Zhou, H. T., Yu, X. F., & Zhou, G. M. (2017). Diosgenin inhibits angiotensin II-induced extracellular matrix remodeling in cardiac fbroblasts through regulating the TGF-β1/Smad3 signaling pathway. *Molecular Medicine Reports*, *15*(5), 2823–2828. https://doi.org/10.3892/mmr.2017.6280

Zhu, Y., Xian, X., Wang, Z., Bi, Y., Chen, Q., Han, X., Tang, D., & Chen, R. (2018). Research progress on the relationship between atherosclerosis and inflammation. In *Biomolecules* (Vol. 8, Issue 3). MDPI AG. https://doi.org/10.3390/biom8030080