ISSN: 3032-3134 (ONLINE)

InaJBCS Indonesian Journal of Biomedicine and Clinical Sciences

Effect of *Hibiscus sabdariffa* Linn. on the development of atherosclerosis in diabetes mellitus: a rapid review

Fakhrul Gamal Putra[1*], Nurul Paramita[1,2], Dewi Irawati Soeria Santoso[1,2]

[1]Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia,
[2]Department of Medical Physiology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

https://doi.org/10.22146/inajbcs.v57i1.19981

Submitted: 2023-09-16
Accepted : 2025-01-03

ABSTRACT

Atherosclerosis is closely linked to disturbances in lipid metabolism and chronic inflammation. In diabetes mellitus (DM), hyperglycemia exacerbates atherosclerosis by inducing structural changes in blood vessel endothelium through chronic inflammation triggered by oxidized low-density lipoprotein (OxLDL) formation. Inflammation plays a major role in atherosclerosis pathogenesis, with OxLDL, nuclear factor kappa B (NFkB), intercellular adhesion molecule-1 s(ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) being crucial players in this process. Hibiscus (*Hibiscus sabdariffa* Linn.) a medicinal plant rich in polyphenols, is believed to have a role to prevent atherosclerosis development through its antioxidant activity, inhibiting vascular smooth muscle cell (VSMC) proliferation, and modulating inflammation pathways. This review explores the potential of hibiscus to prevent atherosclerosis development in DM, focusing on its phytochemical compounds and their impact on oxidative stress, hyperlipidemia, and inflammation pathways. The review highlights the importance of targeting VSMC proliferation, migration, and inflammatory responses mediated by ICAM-1 and VCAM-1 to attenuate atherosclerosis progression. Hibiscus shows promise as a natural treatment for atherosclerosis, but further research is still needed to fully understand its mechanisms and therapeutic potential.

ABSTRAK

Aterosklerosis berkaitan erat dengan gangguan metabolisme lipid dan inflamasi kronis. Pada diabetes mellitus (DM), hiperglikemia memperburuk aterosklerosis dengan menginduksi perubahan struktural pada endotelium pembuluh darah melalui inflamasi kronis yang dipicu oleh pembentukan *oxidized low-density lipoprotein* (OxLDL). Inflamasi memainkan peran penting dalam patogenesis aterosklerosis, dengan OxLDL, *nuclear factor kappa B* (NFkB), *intercellular adhesion molecule-1* (ICAM-1), dan *vascular cell adhesion molecule-1* (VCAM-1) menjadi mediator penting dalam proses ini. Rosella (*Hibiscus sabdariffa* Linn.) merupakan tanaman obat yang kaya polifenol dan dipercaya memiliki peran dalam mencegah perkembangan aterosklerosis melalui aktivitas antioksidan dalam menghambat proliferasi *vascular smooth muscle cell* (VSMC) dan mengatur jalur inflamasi. Tinjauan ini bertujuan membahas potensi rosella dalam mencegah perkembangan aterosklerosis pada DM, berfokus pada senyawa fitokimia dan dampaknya pada stres oksidatif, hiperlipidemia, dan jalur peradangan. Tinjauan ini menyimpulkan pentingnya menargetkan proses proliferasi serta migrasi VSMC, dan respons inflamasi yang dimediasi oleh ICAM-1 dan VCAM-1 untuk mengurangi perkembangan aterosklerosis. Rosella menunjukkan adanya potensi sebagai pengobatan alami pada penanganan aterosklerosis, namun, penelitian lebih lanjut masih diperlukan untuk sepenuhnya memahami mekanisme dan potensi terapeutiknya.

Keywords:
Hibiscus sabdariffa Linn;
atherosclerosis;
diabetes mellitus;
oxidative stress;
inflammation

*corresponding author: fakhrulgamalputra@gmail.com

INTRODUCTION

Hibiscus sabdariffa Linn., commonly known as roselle, is a member of the Malvaceae family and is characterized by its red calyces with five large sepals (FIGURE 1).[1] This plant is native to Africa and is cultivated in various countries, including Sudan, Eastern Taiwan, Burkina Faso, Senegal, Togo, Mali, and Côte d'Ivoire.[2] The calyx of *H. sabdariffa* Linn. has been found to contain various antioxidant constituents such as hibiscus anthocyanin, quercetin, L-ascorbic acid, and protocatechuic acid, which contribute to its potential health benefits.[3] The plant is known for its medicinal properties and is widely consumed in various forms such as tea, syrup, pudding, and cake, particularly in Indonesia.[4] Research has shown that *H. sabdariffa* Linn. possesses anti-inflammatory activities, and its essential oil has been found to regulate gene expression, cytokines, and nitric oxide in cell survival, indicating its potential therapeutic applications.[5] Additionally, studies have reported on the various constituents of different plant parts like flowers, leaves, stem, root, bark, and seeds of *H. sabdariffa* Linn., highlighting its rich phytochemical composition and pharmacological activities.[5]

FIGURE 1. *Hibiscus sabdariffa* Linn plant

The preventive effects of *H. sabdariffa* Linn. on the development of atherosclerosis through the inflammatory pathway have been a subject of interest in recent research. In addition to the therapeutic potential of *H. sabdariffa* Linn., recent research has also explored other plants for treating atherosclerosis in diabetes mellitus (DM) cases. Studies have investigated the potential benefits of *Abroma augustum* Linn.,[6] *Nelumbinis semen* (Lotus seeds),[7] *Azadirachta indica* (Neem), and *Bougainvillea spectabilis*.[8] These plants have shown promise in managing diabetes-related complications and atherosclerosis, highlighting a growing interest in natural substances as alternative therapies in this area.

The underlying mechanism behind the preventive effect is attributed to the antioxidant activity of *H. sabdariffa* Linn. extract, which has been found to inhibit the proliferation and migration of vascular smooth muscle cells (VSMC) induced by hyperglycemia, thus preventing the occurrence of atherosclerosis.[9,10] Studies have reported that *H. sabdariffa* Linn. calices extracts contain several polyphenols, including flavonoids such as cyanidin 3-rutinoside, delphinidin 3-sambubioside, cyanidin 3-sambubioside, cyaniding-3-glucoside, delphinidin 3-glucoside, and hibiscus acid, which contribute to its antioxidant properties.[11] Furthermore, research has shown that *H. sabdariffa* Linn. possesses anti-inflammatory activities, which may further contribute to its preventive effects on atherosclerosis through modulation of the inflammatory pathway.[1]

Moreover, the potential of *H. sabdariffa* Linn. in preventing atherosclerosis is supported by its traditional use in folk medicines for the treatment of hypertension, a risk factor for atherosclerosis.[12] Additionally, *H. sabdariffa* Linn. has been found to inhibit LDL oxidation and foam cell formation, which are key processes in the development of atherosclerosis, through the up-regulation of the LXRα/ABCA1 pathway.[10] Furthermore, the vasorelaxation mechanisms of bioactive compounds extracted from *H. sabdariffa* Linn. on rat thoracic aorta have been investigated, indicating its potential cardiovascular benefits.[13] These findings collectively suggest that *H. sabdariffa* Linn. may indeed have preventive effects on the development of atherosclerosis through multiple pathways, including antioxidant, anti-inflammatory, and vasoprotective mechanisms.

The formation of atherosclerotic plaques is closely related to lipid metabolism and inflammation disturbances. Diabetes mellitus is a chronic hyperglycemia condition that may leads to disturbances in lipid metabolism (FIGURE 2).[14,15] Modification of low-density lipoprotein (LDL) into oxidized LDL (OxLDL) can trigger inflammation in the endothelium of blood vessels and initiate atherosclerosis.[16,17] Inflammation is a major pathway in the pathogenesis of atherosclerosis, with OxLDL, nuclear factor kappa B (NFkB), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) playing crucial roles in this inflammatory process.[16,18] OxLDL is known to increase reactive oxygen species and activating the NF-kB transcription factor on the vascular cell walls.[19] Proinflammatory cytokines activate NF-kB through binding to receptors present on the surface of endothelial cells in blood vessels. This pathway can induce the expression of both E-selectin and immunoglobulin adhesion molecules, specifically ICAM-1 and VCAM-1.[19,20] The underlying mechanism behind this effect is due to the antioxidant activity of *H. sabdariffa* Linn. extract, which can prevent the occurrence of atherosclerosis through inhibition of VSMC proliferation and migration induced by hyperglycemia.[9,16,21] However, the exact mechanism of action of hibiscus in inhibiting the atherogenesis process in DM, especially via inflammatory pathways is not yet clearly understood.

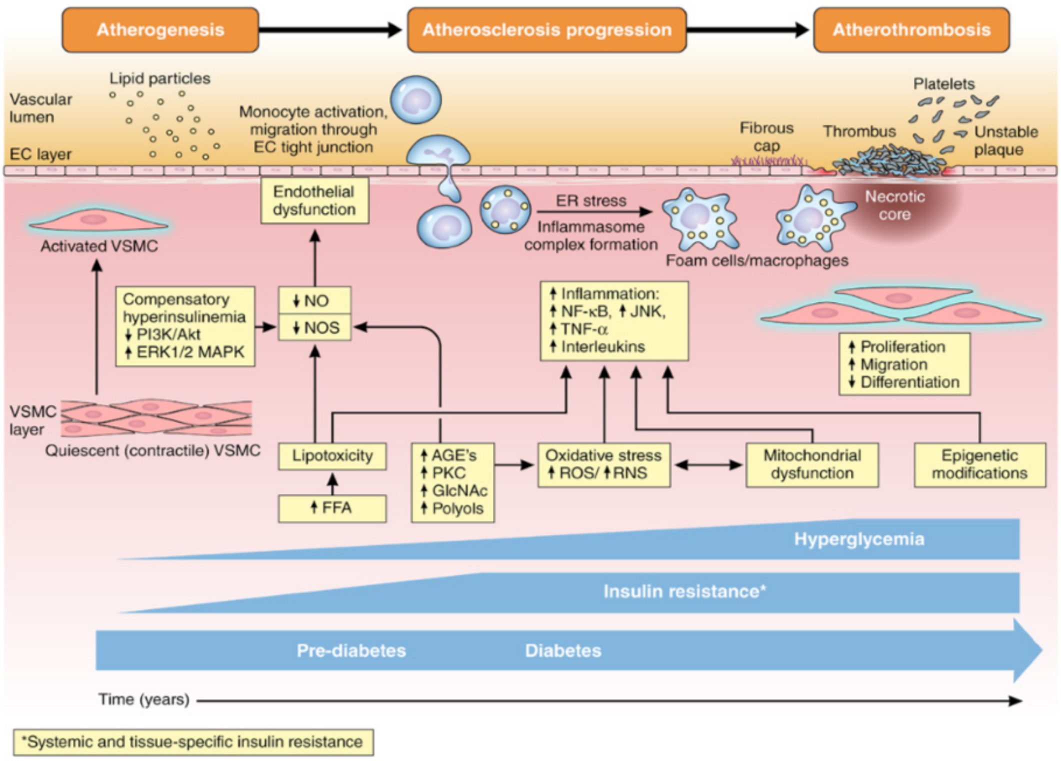

FIGURE 2. Atherosclerosis development in diabetes mellitus[15]

MATERIAL AND METHODS

Literatures were searched from Science Direct, Scopus, and PubMed databases. The keywords used were “Hibiscus sabdariffa Linn” OR “hibiscus” OR “roselle” AND “diabetes mellitus” OR “diabetes” AND “atherosclerosis”. The data were then identified, analyzed, and selected based on their relevance to the topic. The inclusion criteria for the journals included the pharmacological activity of hibiscus and the association with atherosclerosis progression in diabetes mellitus. Literature searching was limited to publication in English or Bahasa.

Following this initial search, a meticulous process of deduplication was undertaken, resulting in 1,639 unique records. Subsequently, a systematic screening process was applied, during which 1,463 records were excluded based on predefined criteria. The eligibility assessment involved a detailed examination of abstracts, leading to the inclusion of 176 articles for further consideration. From this subset, 28 articles were selected for a comprehensive review based on a full-text evaluation. During the full-text review, eight studies were deemed not relevant to the research question’s aim and objectives, resulting in their exclusion (FIGURE 3).

RESULTS

A total of 10 studies met the criteria for inclusion in the review, forming the basis for the comprehensive analysis presented in this study to describe the potential of *H. sabdariffa* Linn. to prevent atherosclerosis development in DM (TABLE 1).

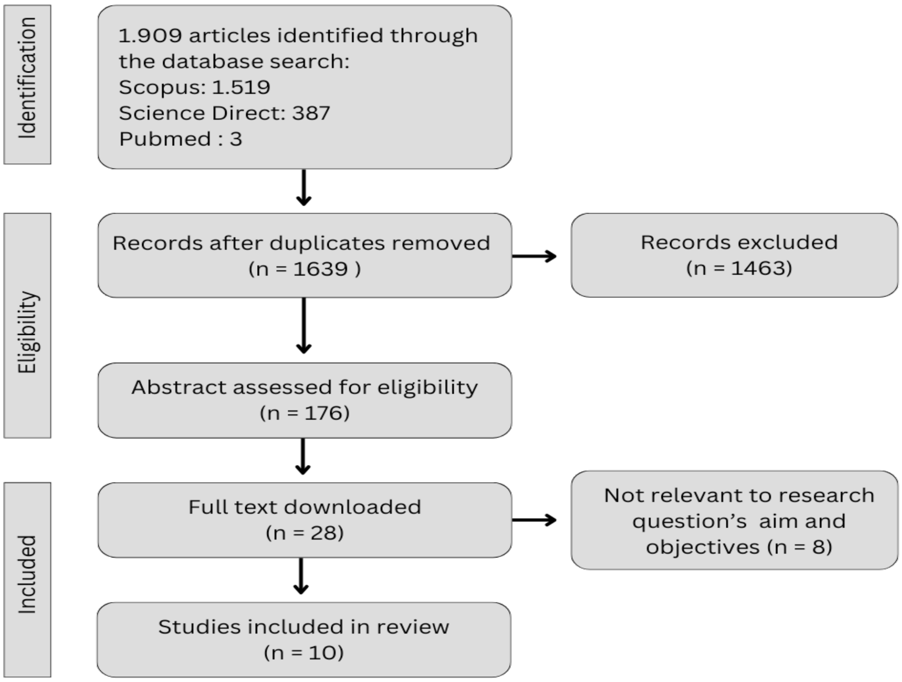

FIGURE 3. Flowchart of rapid review

TABLE 1. Summary of selected studies (n = 10)

Author	Extract type (dosage)	Types of study	Effect on atherosclerosis
Yusof *et al.*[22]	Dried calyces, polyphenol extract (100 mg/kg)	*In vivo* (rats)	Antioxidant and angioprotective
Tseng *et al.*[23]	Dried flowers, ethanol extract (0.1; 0.2; 0.5; and 1.0 mg/mL)	*In vitro* (rat hepatocytes)	Antioxidant
Eldeen *et al.*[24]	Dried calyces, aqueous extract (5, 10, and 20 mg/mL)	*In vivo* (rats) and *in vitro* (aortic tissue)	Antioxidant, angioprotective, anti-inflammation
Fernández-Arroyo, *et al.*[25]	Dried calyces, aqueous extract (10 g/l)	*In vitro* and *in vivo* (rats)	Anti-hyperlipidemia
Hirunpanich *et al.*[26]	Dried calyces, aqueous extract (250, 500, 1000 mg/kg)	*In vitro* and *in vivo* (rats)	Anti-hyperlipidemia
Chen *et al.*[27]	Dried flowers, aqueous extract (0.5-2 mg/mL)	*In vitro* (rats)	Anti-hyperlipidemia
Chen *et al.*[10]	Dried leaves, polyphenolic extract (2.5 g)	*In vivo* (macrophage-derived foam cells)	Anti-hyperlipidemia
Mardiah *et al.*[28]	Dried calyces, aqueous extract (72 and 288 mg/d)	*In vitro* (rats)	Anti-inflammation
Yang *et al.*[29]	Dried calyces, methanol extract (100, 200 mg/kg)	*In vitro* (rats) and *in vivo* (kidney)	Anti-inflammation
Chou *et al.*[30]	Dried leaves, methanol extract (2.5 g)	*In vivo* (VSMC)	Anti-inflammation

Phytochemical compounds of *H. sabdariffa* Linn.

The flower calyx of *H. sabdariffa* Linn. (hibiscus) exhibits therapeutic effects on various pharmacologically active compounds.[31] White and red hibiscus variants differ slightly in their active compound contents, with red varieties showing higher total phenolic, flavonoid, and anthocyanin levels than white varieties. White varieties are characterized by a greater ability to scavenge free radicals than red varieties.[32] Another study indicates that the purple calyces demonstrate stronger antioxidant activity and contain higher flavonoid content than the red ones.[33] However, most of the research has been conducted on the active compounds of red varieties. Various publications indicated that the flower calyx of hibiscus and other parts of the plant are rich in polyphenols (anthocyanins, flavonoids, phenolic acids, tannins), polysaccharides, pectin, non-phenolic organic acids, and carotenoids.[34-39] The most important organic acids in hibiscus include hibiscus acid, hydroxy citric acid, malic acid, ascorbic acid, oxalic acid, succinic acid, tartaric acid, arachidic acid, and citric acid.[34,36,40,41] The most important anthocyanins in hibiscus are delphinidin-3-sambubioside and cyanidin-3-sambubioside.[34,36,40]

Anti-oxidant and angioprotective properties

A study by Yusof *et al.*[22] using

polyphenol-rich extract of hibiscus on the aorta of diabetic rats induced by streptozotocin, reported that the treatment of polyphenol-rich extract of hibiscus not only reduced hyperglycemia but also improved dyslipidemia and restored blood pressure.[22] Malondialdehyde (MDA) and advanced oxidation protein product (AOPP) levels were found to be lowered in the evaluation of oxidative stress markers. Furthermore, as a key component of the cellular anti-oxidant defence system, the increased glutathione (GSH) level has also been evaluated.[22] MDA and AOPPs are biomarkers of oxidative stress and play crucial roles in the oxidative process. Their formation is closely linked to ROS activity, which contributes to lipid peroxidation and protein oxidation and contributes to the development of atherosclerosis in DM.[42-44] It was reported that the protocatechuic acid compound in hibiscus is responsible as an antioxidant to decrease the formation of MDA and AOPP. In addition to protocatechuic acid, it was also reported that anthocyanin pigments contained in hibiscus can terminate free radical reactions.[23,45]

Hibiscus is well known for its antioxidant properties by attenuating ROS overexpression.[34] Previous studies reported that various phytochemical compounds can inhibit the damaging effect of oxidative stress, such as organic acids (hibiscus acid), phenolic acids, anthocyanin, and flavonoids.[46] In the study using an aortic remodeling hypertension model, it was reported that hibiscus extract could protect the artery by inhibiting vascular smooth muscle cell proliferation through downregulation of Ang II/cyclophilin A/ERK1/2 signaling and ROS production. Furthermore, a strong positive correlation between cyclophilin A and VCAM-1 has also been reported, showing a protection effect of hibiscus to avoid atherosclerosis production in the vessels.[24]

Anti-hyperlipidemia properties

The main compounds of hibiscus, such as anthocyanins, flavonoids, and polyphenolic acids, can be resistant agents, restricting the onset of OxLDL. Fernández *et al.*[25] reported the effect of hibiscus extract on serum lipid concentration in a hyperlipidemic animal model and found that under a hypercaloric diet, the infusion of hibiscus was potentially reduced over 50% of serum triglyceride.[25] Similar study by Hirunpanich *et al.* also investigated the role of hibiscus in lowering hypercholesterolemic animal models and found that reducing not only serum cholesterol but also serum triglycerides and LDL.[26] Similar study showed that the inhibitory effect of hibiscus on OxLDL was also reported by Chen *et al.*[27]

An *in vitro* study by Chen *et al.* focused on the inhibitory effects of hibiscus flavonoid compound on the oxidation and lipid peroxidation of LDL revealed that flavonoid has the potential to reduce foam cell formation and intracellular lipid accumulation in macrophages exposed to OxLDL at non-cytotoxic concentrations.[27] The molecular data suggested that the beneficial effects of hibiscus in preventing atherosclerosis may be mediated through the liver-X receptor alpha (LXR**α**)/ATP-binding cassette transporter A1 (ABCA1) pathway. Hibiscus was found to upregulate this pathway, leading to enhanced cholesterol removal from macrophages. By promoting cholesterol efflux, hibiscus helps prevent the transformation of macrophages into foam cells, which play a crucial role in atherosclerotic lesion formation. Ultimately, the stimulation of cholesterol removal from macrophages delays the progression of atherosclerosis. Therefore, the presence of polyphenols, particularly flavonoids, in hibiscus makes it a promising candidate for combating hyperlipidemia and preventing atherosclerosis.[10]

Anti-inflammation properties

Previous studies on DM animal models reported that the inflammatory process triggered by DM can be suppressed using hibiscus extract.[28,29] A study by Mardiah *et al.* reported that an animal model of DM induced by streptozotocin showed a decreased pro-inflammatory mediator TNF-a in a dosage of 72mg and 288 mg per day of hibiscus extracts.[28] An *in vivo* and *in vitro* study observed the role of hibiscus in inhibiting TNF-a and reported that even at a lower dose of polyphenol extract of hibiscus can inhibit the migratory process of VSMC that lead to atherosclerosis progression through inducing ROS production.[47] The protection of the vessel by reducing cell adhesion molecule VCAM-1 via downregulating pro-inflammatory mediator TNF-a has also been reported.[24] Furthermore, the phenolic compounds of caffeic acid and ellagic acid has been reported to lower the inflammatory mediators, including IL-6, IL-1b, TNF-a, and MCP-1 in diabetics mice.[48] It was reported that a dose of 200 mg polyphenol extract of hibiscus could inhibit fat deposition and advanced glycation end-products (AGE) in the kidney, which may prevent the atherosclerosis progress.[29] The key components of phytochemical compound and mechanisms in preventing atherosclerosis in diabetes mellitus is summarized in TABLE 2 and FIGURE 4.

TABLE 2. Phytochemical compounds and mechanisms of *H. sabdariffa* Linn. in preventing atherosclerosis in DM

Compound	Biological activity	Mechanisms of actions
Anthocyanins (e.g., delphinidin-3-sambubioside, cyanidin-3-sambubioside)[49,50]	Antioxidant, anti-inflammatory, anti-hyperlipidemia	Inhibits LDL oxidation, reduces ROS, prevents foam cell formation
Quercetin[51]	Anti-inflammatory	Modulates NF-kB pathway, reduces cytokine production
Protocatechuic acid[52]	Antioxidant, anti-inflammatory	Lowers MDA and AOPP levels, decreases ROS
Hibiscus acid[53,54]	Angioprotective	Promotes vasodilation, reduces hypertension
Polyphenols (flavonoids, phenolic acids)[29,47,55]	Antioxidant, anti-inflammatory, anti-hyperlipidemia	Modulates lipid metabolism, reduces inflammation, inhibit the migratory process of VSMC, inhibit fat deposition and AGE
Organic acids (citric, malic, ascorbic)[56]	Antioxidant	Scavenges free radicals, supports antioxidant defense
Tannins, polysaccharides, pectin[34-39]	Anti-inflammatory, anti-hyperlipidemia	Inhibits VSMC proliferation, enhances lipid metabolism
Caffeic acid, ellagic acid[48]	Anti-inflammatory	Lowers IL-6, IL-1b, TNF-a, MCP-1 levels

DISCUSSION

In atherosclerosis, VSMC play a crucial role in the pathogenesis of the disease. These cells undergo phenotypic changes, transitioning from a quiescent and contractile state to a proliferative and migratory phenotype. This transformation is marked by increased production of extracellular matrix proteins, contributing to the formation of fibrous plaques within the arterial wall. The interaction between leukocytes and smooth muscle cells, mediated by ICAM-1 and VCAM-1, adds another layer of complexity to the inflammatory response in atherosclerosis. Moreover, emerging evidence suggests that these adhesion molecules actively participate in the progression and stability of atherosclerotic plaques.[57]

Inhibition of VSMC proliferation and migration induced by hyperglycemia involving connective tissue growth factor using hibiscus extract has been investigated previously.[21] It has been reported that hibiscus extract could protect vascular in hyperglycemia by inhibiting VSMC proliferation through downregulation of Ang II/cyclophilin A/ERK1/2 signalling. The ROS production has a strong positive correlation between cyclophilin A and VCAM-1. Therefore, a downregulation effect of hibiscus on the VSMC proliferation and migration mediators has the potential to avoid atherosclerosis formation. Furthermore, this study also reported that the proinflammatory factor (Ang II and TNF-a) activates NF-kB to mediate the production of VCAM-1.[24]

The adhesion process in the early stages of atherosclerosis begins with leukocytes rolling on the surface of the blood vessel endothelium due to interactions with selectins. This adhesion process is believed to occur through induction by leukocyte adhesion molecules on the endothelium, such as ICAM-1 and VCAM-1, as well as integrins on the surface of leukocytes.[58] In the early phase, mononuclear leukocytes, including monocytes and T cells, migrate towards the blood vessel wall and cross the endothelium. This process requires endothelial activation to express leukocyte adhesion molecules. The changes in the blood vessel endothelium lead to increased NFkB activity.[59] The high expression of VCAM-1 and ICAM-1 in the blood vessels promotes the proliferation of macrophages, leading to their accumulation in the plaque and increase plaque instability.[60] Therefore, inflammation is a primary pathway in the pathogenesis of atherosclerosis, with OxLDL, NF-kB, ICAM-1, and VCAM-1 being part of this inflammatory process. If the activities of all these proteins can be inhibited, then the inflammatory process can also be suppressed. According to the previous study by Sarbini *et al.*,[16] the extract of hibiscus exhibits a phytopharmaceutical effect to prevent atherosclerosis through this inflammatory pathway involving NF-kB, ICAM-1, and VCAM-1.[16]

A study by Kao et al. investigated the potential of hibiscus compounds, specifically anthocyanin, in preventing atherosclerosis. The study examined the effect of hibiscus on foam cell formation and the expression of scavenger receptor CD36 and its upstream transcription factor, PPARγ, in OxLDL-treated mouse macrophage J774A.1 cells. Hibiscus significantly reduced lipid accumulation in OxLDL-treated cells, indicating its potential to prevent foam cell formation. Moreover, hibiscus downregulated CD36 expression and reduced PPARγ protein levels in nuclear extracts, indicating its role in inhibiting macrophage uptake of OxLDL.[61] To elucidate the multifaceted mechanisms through which hibiscus components combat atherosclerosis in diabetes mellitus, a comprehensive illustration is presented FIGURE 4.

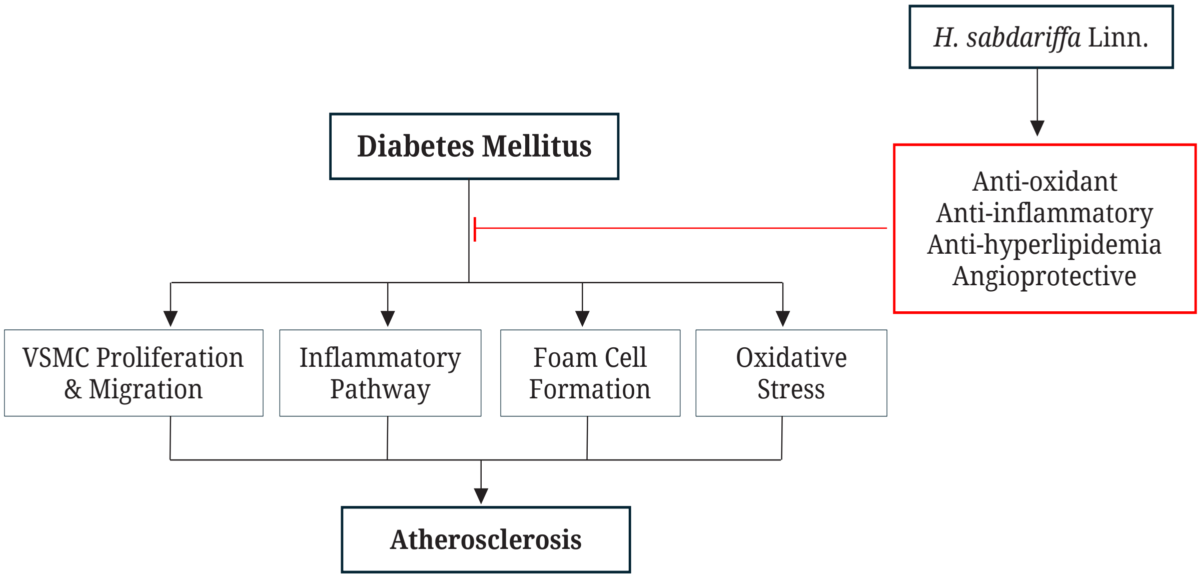

FIGURE 4. Mechanisms of *H. sabdariffa* Linn. in preventing atherosclerosis in DM

The study has several limitations. Firstly, it is subject to language bias as it exclusively considered publications in English or Bahasa, potentially excluding relevant studies in other languages. Secondly, there might be publication bias, given the reliance on specific databases, which may favor studies reporting positive outcomes. The search criteria, focusing on specific keywords, might have missed relevant studies using different terminology. The diverse study designs in TABLE 1, including *in vivo*, *in vitro*, and various animal models, make it challenging to draw consistent conclusions. Variability in hibiscus extract types and dosages among the selected studies hinders the establishment of standardized recommendations. Furthermore, the predominantly animal and *in vitro* focus limits direct applicability to clinical scenarios. The emphasis on red hibiscus varieties and the complex phytochemical composition pose challenges in generalizing findings. Mechanistic insights into hibiscus effects are insufficient, and the study lacks long-term data on the sustained impact of hibiscus on atherosclerosis in DM.

CONCLUSION

Hibiscus sabdariffa Linn. holds promise in combating diabetes-related atherosclerosis due to its rich phytochemical composition. Active compounds like polyphenols, anthocyanins, and flavonoids confer antioxidant, anti-hyperlipidemic, and anti-inflammatory properties. These components collectively address key factors in atherosclerosis development, reducing serum cholesterol, triglycerides, and LDL cholesterol, and modulating foam cell formation. *Hibiscus sabdariffa* Linn. also shows potent anti-inflammatory effects, suppressing pro-inflammatory mediators, and intervening in pathways that limit inflammatory cell recruitment. This scope review underscores its potential as a natural therapeutic agent against diabetes-related atherosclerosis, emphasizing its multifaceted approach in tackling oxidative stress, hyperlipidemia, and inflammation. Further research is needed to understand mechanisms, optimize dosages, and explore its translational potential as adjunct therapy for diabetes-related atherosclerosis.

ACKNOWLEDGMENT

No conflict of interest was declared.

REFERENCES

1. Shen C, Zhang T, Zhang W, Jiang J. Anti-Inflammatory Activities of Essential Oil Isolated From the Calyx of Hibiscus Sabdariffa L. Food Funct 2016; 7(10):4451-9. https://doi.org/10.1039/c6fo00795c
2. Alfred ADD, Djagouri K, Jean-Claude BO. Determination of Natural Radioactivity of the *Hibiscus Sabdariffa* Linn (Roselle) Used in Cote d'Ivoire (Ivory Coast). Advances in Materials Physics and Chemistry 2021; 11(3):59-66. https://doi.org/10.4236/ampc.2021.113006
3. Hirunpanich V, Utaipat A, Morales NP, Bunyapraphatsara N, Sato H, Herunsalee A, *et al.* Antioxidant effects of aqueous extracts from dried calyx of hibiscus sabdariffa LINN. (Roselle) in vitro using rat low-density lipoprotein (LDL). Biol Pharm Bull 2005; 28(3):481-4. https://doi.org/10.1248/bpb.28.481
4. Fithrotunnisa Q, Arsianti A, Kurniawan G, Qorina F, Tejaputri NA, Azizah NN. In Vitro Cytotoxicity of Hibiscus Sabdariffa Linn Extracts on A549 Lung Cancer Cell Line. Pharmacogn J 2020; 12(1):14-9. https://doi.org/10.5530/pj.2020.12.3
5. Bedi PS, Bekele M, Gure G. Phyto-Chemistry and Pharmacological Activities of Hibiscus Sabdariffa Linn.-a Review. International Research Journal of Pure and Applied Chemistry 2020; 21(23):41-54. https://doi.org/10.9734/irjpac/2020/v21i2330301
6. Shaha MDA, Biswas KK, Shaha RK. Alcoholic Green Fruits Extract of *Abroma Augustam* Linn. (Ulatkambal) Used for the Treatment of Diabetes. JECET 2021; 10(4):542-52. https://doi.org/10.24214/jecet.a.10.4.54252
7. Bhupathie D, Kumar MS, Rengasamy KRR. A comprehensive network pharmacology study of nelumbinis semen (Lotus Seeds) phytochemicals for atherosclerosis and Type 2 Diabetes Mellitus. Natural Resources for Human Health 2023; 3(4):469-76. https://doi.org/10.53365/nrfhh/175559
8. Bhat M, Kothiwale SK, Tirmale AR, Bhargava SY, Joshi BN. Antidiabetic Properties of Azardiracta Indica and Bougainvillea Spectabilis: In Vivo Studies in Murine Diabetes Model. Evid Based Complement Altern Med 2011; 2011:561625. https://doi.org/10.1093/ecam/nep033
9. Chen CC, Hsu JD, Wang SF, Chiang HC, Yang MY, Kao ES, *et al.* Hibiscus sabdariffa extract inhibits the development of atherosclerosis in cholesterol-fed rabbits. J Agric Food Chem 2003; 51(18):5472-7. https://doi.org/10.1021/jf030065w
10. Chen JH, Wang CJ, Wang CP, Sheu JY, Lin CL, Lin HH. Hibiscus sabdariffa leaf polyphenolic extract inhibits LDL oxidation and foam cell formation involving up-regulation of LXR**α**/ABCA1 pathway. Food Chem 2013; 141(1):397-406. https://doi.org/10.1016/j.foodchem.2013.03.026
11. Micucci M, Malaguti M, Toschi TG, Di Lecce G, Aldini R, Angeletti A, *et al.* Cardiac and Vascular Synergic Protective Effect Of Olea Europea L. Leaves And Hibiscus Sabdariffa L. Flower Extracts. Oxid Med Cell Longev 2015; 2015:318125. https://doi.org/10.1155/2015/318125
12. Hopkins AL, Lamm MG, Funk JL, Ritenbaugh C. Hibiscus sabdariffa L. in the treatment of hypertension and hyperlipidemia: a comprehensive review of animal and human studies. Fitoterapia 2013; 85:84-94. https://doi.org/10.1016/j.fitote.2013.01.003
13. Sarr M, Ngom S, Kane MO, Wale A, Diop D, Sarr B, *et al.* In vitro vasorelaxation mechanisms of

bioactive compounds extracted from hibiscus sabdariffa on rat thoracic aorta. Nutr Metab2009; 6:45. https://doi.org/10.1186/1743-7075-6-45

14. Eckel RH, Bornfeldt KE, Goldberg IJ. Cardiovascular disease in diabetes, beyond glucose. Cell Metab 2021; 33(8):1519-45. https://doi.org/10.1016/j.cmet.2021.07.001
15. Wang CCL, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus–mechanisms, management, and clinical considerations. Circulation 2016; 133(24):2459-502. https://doi.org/10.1161/CIRCULATIONAHA.116.022194
16. Sarbini D, Sargowo D, Rohman MS. Hibiscus Sabdariffa Linn) terhadap NF-**κβ**, TNF-**α** dan ICAM-1 pada Human Umbilical Vein Endothelial Cells (HUVECs) Cultured yang dipapar Low Density Lipoprotein (LDL) Teroksidasi. J Exp Life Sci 2011; 1(2):102-10. https://doi.org/10.21776/ub.jels.2011.001.02.07
17. Gonçalves I, Edsfeldt A, Ko NY, Grufman H, Berg K, Björkbacka H, *et al.* Evidence supporting a key role of Lp-PLA2-generated lysophosphatidylcholine in human atherosclerotic plaque inflammation. Arterioscler Thromb Vasc Biol 2012; 32(26);1505-12. https://doi.org/10.1161/ATVBAHA.112.249854
18. Pamukcu B, Lip GYH, Shantsila E. The nuclear factor--kappa B pathway in atherosclerosis: a potential therapeutic target for atherothrombotic vascular disease. Thromb Res 2011; 128(2):117-23. https://doi.org/10.1016/j.thromres.2011.03.025
19. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, *et al.* New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biol 2019; 20:247-60. https://doi.org/10.1016/j.redox.2018.09.025
20. de Winther MPJ, Kanters E, Kraal G, Hofker MH. Nuclear factor kappaB signaling in atherogenesis. Arterioscler Thromb Vasc Biol 2005; 25(5):904-14. https://doi.org/10.1161/01.Atv.0000160340.72641.87
21. Huang CN, Chan KC, Lin WT, Su SL, Wang CJ, Peng CH. Hibiscus sabdariffa inhibits vascular smooth muscle cell proliferation and migration induced by high glucose--a mechanism involves connective tissue growth factor signals. J Agric Food Chem 2009; 57(8):3073-9. https://doi.org/10.1021/jf803911n
22. Mohammed Yusof NL, Zainalabidin S, Mohd Fauzi N, Budin SB. Hibiscus sabdariffa (roselle) polyphenol-rich extract averts cardiac functional and structural abnormalities in type 1 diabetic rats. Appl Physiol Nutr Metab 2008; 43(12):1224-32. https://doi.org/10.1139/apnm-2018-0084
23. Tseng TH, Kao ES, Chu CY, Chou FP, Wu WHL, Wang CJ. Protective effects of dried flower extracts of Hibiscus sabdariffa L. against oxidative stress in rat primary hepatocytes. Food Chem Toxicol 1997; 35(12):1159-64. https://doi.org/10.1016/s0278-6915(97)85468-3
24. ShamsEldeen AM, Fawzy A, Ashour H, Abdel-Rahman M, Nasr HE, Mohammed LA, *et al.* Hibiscus attenuates renovascular hypertension-induced aortic remodeling dose dependently: the oxidative stress role and Ang II/cyclophilin A/ERK1/2 signaling. Front Physiol 2023; 14:1116705. https://doi.org/10.3389/fphys.2023.1116705
25. Arroyo SF, Medina IR, Beltran-Debon

R, Pasini F, Joven J, Micol V, *et al.* Quantification of the polyphenolic fraction and in vitro antioxidant and in vivo anti-hyperlipemic activities of Hibiscus sabdariffa aqueous extract. Food Res Int 2011; 44(5):1490-5. https://doi.org/10.1016/j.foodres.2011.03.040

26. Hirunpanich V, Utaipat A, Morales NP, Bunyapraphatsara N, Sato H, Hernsale A, *et al.* Hypocholesterolemic and antioxidant effects of aqueous extracts from the dried calyx of Hibiscus sabdariffa L. in hypercholesterolemic rats. J Ethnopharmacol 2006; 103(2):252-60. https://doi.org/10.1016/j.jep.2005.08.033
27. Chen CC, Chou FP, Ho YC, Lin WL, Wang CP, Kao ES, *et al.* Inhibitory effects of Hibiscus sabdariffa L extract on low-density lipoprotein oxidation and anti-hyperlipidemia in fructose-fed and cholesterol-fed rats. J Sci Food Agric 2004; 84(15):1989-96. https://doi.org/10.1002/jsfa.1872
28. Mardiah, Zakaria FR, Prangdimurti E, Damanik R. Anti-inflammatory of Purple Roselle Extract in Diabetic Rats Induced by Streptozotocin. Procedia Food Science 2015; 3:182-9. https://doi.org/10.1016/j.profoo.2015.01.020
29. Yang YS, Huang CN, Wang CJ, Lee YJ, Chen ML, Peng CH. Polyphenols of Hibiscus sabdariffa improved diabetic nephropathy via regulating the pathogenic markers and kidney functions of type 2 diabetic rats. J Funct Foods 2013; 5(2):810-9. https://doi.org/10.1016/j.jff.2013.01.027
30. Chou CC, Wang CP, Chen JH, Lin HH. Anti-Atherosclerotic Effect of Hibiscus Leaf Polyphenols against Tumor Necrosis Factor-alpha-Induced Abnormal Vascular Smooth Muscle Cell Migration and Proliferation. Antioxidants 2019; 8(12):620. https://doi.org/10.3390/antiox8120620
31. Salem MA, Zayed A, Beshay ME, Mesih MMA, Khayal RFB, Gerge FA, *et al.* Hibiscus sabdariffa L.: phytoconstituents, nutritive, and pharmacological applications. Adv Trad Med 2021; 22(23):1-11. https://doi.org/10.1007/s13596-020-00542-7
32. Tahir HE. Assessment of antioxidant properties, instrumental and sensory aroma profile of red and white Karkade/Roselle (Hibiscus sabdariffa L.). J Food Meas Charact 2017; 11(1):1559-68. https://doi.org/10.1007/s11694-017-9535-0
33. Nerdy N, El-Matury HJ, Barus BR, Ginting S, Zebua NF, Bakri TK. IOP Conference Series: Earth and Environmental Science Comparison of flavonoid content and antioxidant activity in calyces of two roselle varieties (Hibiscus sabdariffa L.) You may also like Appearance of Agronomic Characters and Genetic Parameters Estimation on M 3 Population of Roselle [Hibiscus sabdariffa Comparison of flavonoid content and antioxidant activity in calyces of two roselle varieties (Hibiscus sabdariffa L.). IOP Conference Series Earth and Environmental Science 2022; 956(012001).
34. Da-Costa-Rocha I, Bonnlaender B, Sievers H, Pischel I, Heinrich M. Hibiscus sabdariffa L.–A phytochemical and pharmacological review. Food Chem 2014; 165:424-43. https://doi.org/10.1016/j.foodchem.2014.05.002
35. Cid-Ortega S, Guerrero-Beltrán J. Roselle calyces (Hibiscus sabdariffa), an alternative to the food and beverages industries: a review. J Food Sci Technol 2015; 52(11):6859-69. https://doi.org/10.1007/s13197-015-1800-9
36. Bedi P, Bekele M, Gure G. Phyto-chemistry and pharmacological activities of Hibiscus sabdariffa Linn.-A review. Int. J Pure Appl Chem 2020; 21:41-54.

https://doi.org/10.9734/irjpac/2020/v21i2330301

37. Lin HH, Chen JH, Wang CJ. Chemopreventive properties and molecular mechanisms of the bioactive compounds in Hibiscus sabdariffa Linne. Curr Med Chem 2011; 18(8):1245-54. https://doi.org/10.2174/092986711795029663
38. Pérez-Torres I, Ruiz-Ramírez A, Baños G, El-Hafidi M. Hibiscus sabdariffa Linnaeus (Malvaceae), curcumin and resveratrol as alternative medicinal agents against metabolic syndrome. Cardiovasc Hematol Agents Med Chem 2013; 11(1):25-37. https://doi.org/10.2174/1871525711311010006
39. 39 Koala, M. *et al.* HPTLC Phytochemical Screening and Hydrophilic Antioxidant Activities of Apium graveolens L., Cleome gynandra L., and Hibiscus sabdariffa L. Used for Diabetes Management. *American Journal of Analytical Chemistry* 12, 15 (2021).
40. Riaz G, Chopra R. A review on phytochemistry and therapeutic uses of Hibiscus sabdariffa L. Biomed Pharmacother 2018; 102:575-86. https://doi.org/10.1016/j.biopha.2018.03.023
41. Guardiola S, Mach N. Therapeutic potential of Hibiscus sabdariffa: a review of the scientific evidence. Endocrinol Nutr 2014; 61(5):274-95. https://doi.org/10.1016/j.endonu.2013.10.012
42. Ruiz-Ojeda FJ, Olza J, Gil Á, Aguilera CM. in *Obesity* (eds Amelia Marti del Moral & Concepción María Aguilera García) 1-15 (Academic Press, 2018).
43. Bagyura Z, Takacs A, Kiss L, Dosa E, Vadas R, Nguyen TD, *et al.* Level of advanced oxidation protein products is associated with subclinical atherosclerosis. BMC Cardiovasc Disord 2022; 22(1):5. https://doi.org/10.1186/s12872-021-02451-2
44. Ito F, Sono Y, Ito T. Measurement and Clinical Significance of Lipid Peroxidation as a Biomarker of Oxidative Stress: Oxidative Stress in Diabetes, Atherosclerosis, and Chronic Inflammation. Antioxidants (Basel) 2019; 8(3):72. https://doi.org/10.3390/antiox8030072
45. Balkis Budin S, Othman F, Louis SR, Abu Bakar M, Radzi M, Osman K, *et al.* Effect of alpha lipoic acid on oxidative stress and vascular wall of diabetic rats. Rom J Morphol Embryol 2009; 50(1):23-30.
46. Morales-Luna E, Pérez-Ramírez IF, Salgado LM, Castaño-Tostado E, Gómez-Aldapa CA, Reynoso-Camacho R. The main beneficial effect of roselle (Hibiscus sabdariffa) on obesity is not only related to its anthocyanin content. J Sci Food Agric 2019; 99(2):596-605. https://doi.org/10.1002/jsfa.9220
47. Chou CC, Wang CP, Chen JH, Lin HH. Anti-atherosclerotic effect of Hibiscus leaf polyphenols against tumor necrosis factor-alpha-induced abnormal vascular smooth muscle cell migration and proliferation. Antioxidants 2019; 8(12):620. https://doi.org/10.3390/antiox8120620
48. Chao CY, Mong MC, Chan KC, Yin MC. Anti-glycative and anti-inflammatory effects of caffeic acid and ellagic acid in kidney of diabetic mice. Mol Nutr Food Res 2010; 54(3):388-95. https://doi.org/10.1002/mnfr.200900087
49. Basu A, Rhone M, Lyons TJ. Berries: Emerging Impact on Cardiovascular Health. Nutr Rev 2010; 68(3):168-77. https://doi.org/10.1111/j.1753-4887.2010.00273.x
50. Oliveira H, Correia P, Pereira AR, Araújo P, Mateus N, de Freitas V, *et al.* Exploring the Applications of the Photoprotective Properties of Anthocyanins in Biological Systems. Int J Mol Sci 2020; 21(20):7464. https://doi.org/10.3390/ijms21207464
51. Xue F, Nie X, Shi J, Liu Q, Wang Z, Li X,

et al. Quercetin Inhibits LPS-Induced Inflammation and Ox-LDL-Induced Lipid Deposition. Front Pharmacol 2017; 8:40. https://doi.org/10.3389/fphar.2017.00040

52. Lin CY, Huang CS, Huang CY, Yin MC. Anticoagulatory, antiinflammatory, and antioxidative effects of protocatechuic acid in diabetic mice. J Agric Food Chem 2009; 57(15):6661-7. https://doi.org/10.1021/jf9015202
53. Zheoat AM, Gray AI, Igoli JO, Ferro VA, Drummond RM. Hibiscus Acid From Hibiscus Sabdariffa (Malvaceae) has a vasorelaxant effect on the rat aorta. Fitoterapia 2019; 134:5-13. https://doi.org/10.1016/j.fitote.2019.01.012
54. Salem MA, Michel HE, Ezzat MI, Okba MM, El-Desoky AM, Mohamed SO, *et al.* Optimization of an Extraction Solvent for Angiotensin-Converting Enzyme Inhibitors From Hibiscus Sabdariffa L. Based on Its UPLC-MS/MS Metabolic Profiling. Molecules 2020; 25(10):2307. https://doi.org/10.3390/molecules25102307
55. Herranz-López M, Olivares-Vicente M, Encinar JA, Barrajón-Catalán E, Segura-Carretero A, Joven J, *et al.* Multi-targeted molecular effects of Hibiscus sabdariffa polyphenols: An opportunity for a global approach to obesity. Nutrients 2017; 9(8):907. https://doi.org/10.3390/nu9080907
56. Morales-Luna E, Pérez-Ramírez IF, Salgado LM, Castaño-Tostado E, Gómez-Aldapa CA, Reynoso-Camacho R. The Main Beneficial Effect of Roselle (Hibiscus Sabdariffa) on Obesity Is Not Only Related to Its Anthocyanin Content. J Sci Food Agric 2018; 99(2):596-605. https://doi.org/10.1002/jsfa.9220
57. Braun M, Pietsch P, Schrör K, Baumann G, Felix SB. Cellular adhesion molecules on vascular smooth muscle cells. Cardiovasc Res 1999; 41(2):395-401. https://doi.org/10.1016/S0008-6363(98)00302-2
58. Vlassara H, Fuh H, Donnelly T, Cybulsky M. Advanced glycation endproducts promote adhesion molecule (VCAM-1, ICAM-1) expression and atheroma formation in normal rabbits. Mol Med 1995; 1(4):447-56.
59. Boamponsem A, Boamponsem L. The role of inflammation in atherosclerosis. Adv Appl Sci Res 2011; 2:194-207.
60. Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X, *et al.* Research progress on the relationship between atherosclerosis and inflammation. Biomolecules 2018; 8(3):80. https://doi.org/10.3390/biom8030080
61. Kao ES, Tseng TH, Lee HJ, Chan KC, Wang CJ. Anthocyanin extracted from Hibiscus attenuate oxidized LDL-mediated foam cell formation involving regulation of CD36 gene. Chem Biol Interact 2009; 179:212-8. https://doi.org/10.1016/j.cbi.2009.01.009