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Review Article

Pharmacological Potential of *Andrographis paniculata* (Burm. f.) Nees in Preventing Atherosclerosis: A Review

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ABSTRACT

Andrographis paniculata (Burm. f) Nees (AP) is a medicinal plant often found in Southeast Asian countries such as Indonesia, Malaysia, the Philippines, and China. AP has been used traditionally for increasing appetite, curing dysentery, fever, tuberculosis infection, cough, and runny nose. The aim of this article was to explore the potential of AP and its pharmacological effects in the prevention of atherosclerosis. Scientific data were gathered from articles published in the last 10 years in PubMed, Science Direct, Scopus, Web of Science, and Google. The inclusion criteria comprised journal articles describing the effects of AP, their equivalents, and derivatives on metabolic syndrome dyslipidemia, atherosclerosis, and other disorders. According to the findings of the literature research, AP contains diterpene lactones like andrographolide (Andro). The major active compounds in this plant are the Andro and analogues. These compounds are responsible for AP's pharmacological effects, one of which is anti-dyslipidemia. It is known that there is a positive correlation between anti-dyslipidemia and anti-atherosclerosis activity. Andro and its derivatives have a wide range of pharmacological actions, including anti-dyslipidemia and antioxidant activity, as well as other pharmacological properties such as anti-inflammatory activity. The review is supported by research from *in vitro*, *in vivo*, to clinical trials in humans. As a result of these properties, AP has a strong potential to prevent atherosclerosis.

***Keywords*:** *Andrographis paniculata*, Andrographolide, Atherosclerosis, Pharmacological.

Introduction

Andrographis paniculata (Burm. f) Nees (AP) is beneficial in treating several diseases. In India, Taiwan, and China, AP is often used for treating liver disorders, intestinal complaints by children, fever, and upper respiratory tract infections. In addition, people of China also seemingly use AP to cure pain, inflammation, and tract infections.[1] In Indonesia, as in previous countries, AP are widely used as medicine by the population due to their pharmacological effects in a variety of health conditions. AP possesses several active compounds; nearly 20 types of diterpenoid groups (such as andrographolide [Andro], deoxy-andrographolide, 19ß-D-glucoside, and neo-andrographolide) and flavonoids. Terpenes compounds are obtained through extraction using solvents such as ethanol, methanol, ethyl acetate, or water. Among all those beneficial compounds, Andro seems to be one of the most studied and impactful compounds. Andro is a lactone-diterpene compound, mostly found in AP plants, which causes a very bitter taste. It can be extracted in every part of the AP plant, but the leaves have been proven to give the highest Andro content. Due to its various innate phytochemical compounds, the AP plant has many pharmacological activities, including antioxidants,[2] antidiabetic,[3-5] anti-dyslipidemia,[3-5] anti-atherosclerosis,[6,7] anticancer,[8] anti-inflammatory,[9] immunomodulator,[10] and anti-infection.[11,12] Dyslipidemia or plasma lipid abnormality is one of the most noticeable metabolic syndrome diseases throughout the world. It plays a significant role in the pathogenesis of atherosclerosis in blood vessel walls, which causes coronary heart disease (CHD) and stroke.[13,14] The atherosclerosis process is promoted by fatty streak formation by low-density lipoprotein-cholesterol (LDL-C) trapping, endothelial cells and leukocytes activation, and foam cells formation. This is followed by atheroma formation, then, finally, is the establishment of atherosclerotic plaques.[15] Various efforts have been made to prevent the prognosis of dyslipidemia from becoming atherosclerosis. However, one of the most recognized and sustainable efforts in treating the current disease is by empowering traditional medicine. The well-known causes of atherosclerosis pathogenesis are oxidative stress, inflammation, and dyslipidemia conditions. AP is known to have these three biological activities. It is broadly known as a versatile traditional medicinal plant that has anti-dyslipidemia, antioxidant, and anti-inflammatory properties. Also, AP has been used as a traditional bitter drink that empirically has a natural potential to prevent many health disorders. Therefore, it is necessary to further explore the potential of a bitter drink and its pharmacological benefits. The aim of the present study was to explore the potential of AP in the prevention of atherosclerosis.

Methods

Scientific data were gathered from new articles published in the last 10 years. PubMed, Science Direct, Scopus, Web of Science, and Google were the databases used. Journal articles describing the effects of AP, their equivalents, and derivatives on metabolic syndrome dyslipidemia, atherosclerosis, and other disorders were examined. Also, published data which included *in vitro*, *in vivo*, and clinical trials were considered. Scientific data other than metabolic syndrome and the reports that did not include AP enrichment were not included in this study. All publications matching the keywords were analyzed with the following objectives in mind: (1) to identify medicinal plants that affect atherosclerosis prevention; (2) to

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understand the molecular mechanism by which this herb prevents atherosclerosis.

Results and Discussion

Many researchers are currently interested in AP plants because AP is associated with a wide range of pharmacological qualities, it has become one of the most sought-after plants, particularly for its pharmacological efficacy. One of these is anti-dyslipidemia. Therefore, many researchers have been studying this plant for its potential as an anti-dyslipidemia agent.

AP herb contains many compounds which include flavonoids and diterpene. Andro ($C_{20}H_{30}O_5$) is one of the most terpene compounds found in this plant.[37,38] It is contained in ethanol, methanol, ethyl acetate extracts, and water extracts from AP herb.[39] Other compounds that are also widely contained in bitter herbs are deoxy-andrographolide, neo-andrographolide, 14-deoxy-11,12-didehydro-andrographolide, and iso-andrographolide.[39,46] Atherosclerosis occurs due to an increase in LDL levels in the blood, stimulating LDL oxidation (ox-LDL). Ox-LDL causes monocytes to be able to migrate into endothelial cells in the intima tunica. In the intima, monocytes undergo differentiation and bind to macrophages. Ox-LDL contained in the intima tunica is trapped in the macrophages.[40] Eventually, many ox-LDLs are caught in the macrophages, which become foam cells.[41] Fibroblasts Growth Factor (FGF) and Platelet-Derived Growth Factor (PDGF) are secreted by endothelial cells and foam cells.[42] Smooth muscle cells migrate into the foam cells over time, causing arterial constriction (Figure 1). AP has several pharmacological activities such as anti-dyslipidemia, antioxidant, and anti-inflammatory properties that support its ability to prevent atherosclerosis.

The effect is caused by chemical components found in AP, as well as Andro and its derivatives. *In vitro*, *in vivo*, and clinical trials in patients are all used to investigate AP activity. This combination of AP action causes it to have the ability to prevent atherosclerosis or cardiovascular disorders. In both *in vivo* and human clinical trials, AP can enhance lipid profiles by lowering total cholesterol, triglycerides, LDL, and boosting HDL blood levels.[16,20,21,23,29,30,34]. This ability is caused by AP inhibition of the HMG-CoA reductase enzyme. Hence, the production of cholesterol in the blood is inhibited. In addition, AP can activate the enzyme LCAT (lecithin cholesterol acyltransferase), causing an increase in HDL synthesis in the blood.[23] AP-containing Andro can prevent vascular damage in atherosclerosis by acting as an antioxidant. By boosting the expression of SOD and GPx as well as lowering malondialdehyde levels, Andro can prevent oxidation.[46] Andro can also reduce the production of macrophage foam cells by preventing the synthesis of ox-LDL. Foam cells that do not form will be able to prevent advanced atherosclerosis from developing.[13]

Andro prevents the NF-B transcription factor from binding to the target gene promoter by reducing cysteine 62 in p50, the transcription factor's major subunit. As a result, reducing NF-B activation will inhibit inflammation (Figure 2). Specific p50 inhibitors, such as Andro, can be useful for stopping and healing thrombotic artery disease, including neointimal hyperplasia of restenotic arteries. AP can activate Akt through the PI3K-dependent pathway, causing suppression of apoptotic HUVECs (human umbilical vein endothelial cells). The activation of the PI3/Akt apoptotic pathway from HUVESCs can inhibit growth hormones.[39] Furthermore, AP is significantly able to inhibit thrombin-induced platelet aggregation by inhibiting the ERK1/2 pathway.[7] As a result, AP can operate as an anti-atherosclerosis agent by decreasing HUVEC apoptosis by raising PI3K-Akt activity and inhibiting thrombin-induced platelet aggregation by inhibiting the ERK1/2 pathway.[44]

Table 1: Study of *Andrographis paniculata* in preventing atherosclerosis

Reference	Results	Conclusion
16	Hyperlipidemia rats are induced by fat-rich feed for four weeks. Rats were given water extract of AP can decrease blood lipid levels (TC, TG, LDL) and increase blood HDL levels	The water extract of AP 100 and 200 mg/kg BW have anti-dyslipidemia potency
17	In VSMCs (vascular smooth muscle cell) rats, it was seen that Andro can suppress LPS/IFN induced nitric oxide synthase. Andro can increase the formation of ceramide. In addition, Andro also increased PP2A activity in experimental animals and inhibited neointimal formation in a mouse carotid injury model	PP2A (protein phosphatase 2A) activation by Andro caused dephosphorylation of p65 Ser536, resulting in NF-kB inactivation and subsequent inducible nitric-oxide synthase down-regulation in rat VSMCs
18	Andro was proven to give a potent activity in inhibiting platelet aggregation	Andro can manage antiplatelet activity, e.g. activating the e-NO/cyclic GMP pathway, causing the inhibition of the PI3 kinase/Aktp38 MAPK (mitogen-activated protein kinase) and PLCγ2–PKC cascades, resulting in inhibition of platelet aggregation
19	Andro was able to decrease ICAM-1 (Intercellular Adhesion Molecule-1) expression through TNF-α (Tumor necrosis factor alpha) inhibition and attenuation of NF-κB in cells	Andro may be a potential cardiovascular protective agent
20	Rats induced hyperlipidemia and hyperglycemia use a fat-rich diet and fructose. Purified AP extract able to reduce blood glucose, TG and LDL levels in hyperlipidemia rats	A purified extract of AP has been able to reduce levels of LDL and TG from rats while it has not been able to reduce levels of TC in rat blood
21	Andro derivatives can reduce blood lipid levels and antioxidants (reducing ox-LDL) in mice induced by Triton	Andro derivatives have potential as anti-atherosclerosis
22	ceramide-p47phox signalling pathway in Andro induced ROS mediated cell apoptosis	Andro is feasible to be used as a therapeutic agent in cardiovascular disorders, especially those are involving VSMC proliferation and atherogenesis
23	Leaf extract of AP (50 mg/kg) can reduce blood lipid levels (total cholesterol, HDL, VLDL, LDL). The rats were induced to experience hyperlipidemia using Triton WR-1339 and fat-rich feed for 30 days	Andro compounds are also capable of activating lipolytic enzymes, thereby increasing the excretion of bile acids in faeces and increasing the activity of the enzyme Lecithin Cholesterol Acyl Transferase (LCAT)
24	Andro can regulate SREBP (sterol regulatory element-binding	Andro has the potential to prevent or treat obesity and insulin

	proteins), which can help overcome obesity and insulin resistance. SREPB is a regulatory factor that regulates the biosynthesis of cholesterol, fatty acids and triglycerides	resistance
25	Regarding statical analysis, Andro by 20-100 µM of concentration inhibited PDGF ((Platelet-derived growth factor) generated a significant cell proliferation. This may caused by the (extracellular signal-regulated kinase ½) expression reduction and blocking the PCNA (Proliferating cell nuclear antigen) expression. Andro also decreasing LPS-induced iNOS (inducible Nitric Oxide Synthase) and COX2 (cyclooxygenase-2) expression	Andro seems to be a promising agent in treating vascular diseases caused by VSMCs proliferation and CECs dysfunction
26	TC, TG and LDL levels seem to be diminished by administration of Andro ($P < 0.05$). On the other hand, the HDL level seems to be increased in the in-vivo study. Furthermore, the treated groups of animals showed alleviation of the interleukins (IL-1β and IL-6) and C-reactive protein (CRP) as compared to the atherogenic group	The current anti-atherogenic activity of Andro may be caused by the reduction of the interleukins and CRP. In addition, this also can be promoted by CRP and also decreased within the plaques of atherogenic in tested animals
27	The recent study resulted in that Andro was proven for having anti-atherogenic properties in testing animals. This is caused by the alleviation of TNF, ICAM-1, VCAM-1 (vascular cell adhesion molecule 1), and MCP-1 (Monocyte chemoattractant protein 1) activities. In addition, Andro also owns antioxidant activity in which it is able to elevate SOD (Superoxide dismutase), CAT GPx (glutathione peroxidase) and GSH (glutathione) serum levels	The anti-atherogenic properties of Andro are produced by its antihyperlipidemic, antioxidant and anti-inflammatory activities
28	AP ethanolic extract 1.2 mg/kg take effect on IL-17 and the ratio of Treg/Th17 cells in atherosclerosis rats. AP ethanolic extract 1.2 mg/kg could incresing expression of IL-17 significantly compared to the negative control	AP ethanolic extract can reduce chronic inflammation of atherosclerosis rats. It is support reduce the risk of atherosclerosis in the blood vessels of atherosclerosis rats
29	Hypertriglyceridemia patients given high doses of AP extract have the same ability as gemfibrozil 300 mg/day, reducing triglyceride levels in the blood	High-dose AP extract has the same ability as gemfibrozil 300 mg/day in reducing blood triglyceride levels in hypertriglyceridemia patient
30	Andro compound 18 mg/kg BW in AP herbs can reduce blood lipid levels (TC, TG, LDL) and can reduce levels of ox-LDL in rats induced atherogenic feed (5% yolk, 10% lard), 1% calcium and 20,000 IU vitamin D3 for 90 days	Andro compound 18 mg/kg BW has potential as an anti-atherosclerosis agent because it can act as a hypolipidemic and antioxidant agent
31	The release and expression of TNF-α, IL-6, and IL-1β was inhibited by Andro. This ability showing anti-inflammatory effect	Inhibition of activation NFk-B/MAPK signalling pathway and induction of proinflammatory cytokines is one of mechanism anti-inflammatory of Andro
13	Andro can reduce levels of ox-LDL in the blood. Inhibition of uptake CD36-mediated oxLDL (Oxidized Low-Density Lipoprotein) and induction of excretion of ABCG1-dependent cholesterol as a mechanism of inhibition of foam cell formation	Andro could be a potential candidate to prevent atherosclerosis
32	Andro-loaded PEG-PPS (copolymer of poly (ethylene glycol) and poly) micelle can reduce oxidation and inflammatory stress so that it becomes one of the innovative strategies in overcoming atherosclerosis[32]	Oxidative stress and expression of inflammatory factors such as IL-6 and MCP-1 are critical factors in developing atherosclerosis in rat aorta. Andro can inhibit IL-6 and MCP-1[32]
33	Rats that were given Vit D3 700,000 UI / kg on the first day and 2% cholesterol, 5% goat fat, 0.2% cholic acid and standard diet up to 100% for two days were able to initiate the formation of foam cells as the initial occurrence of atherosclerosis. Andro administration can inhibit the formation of these foam cells	Giving Andro 40 mg/kg BW in atherosclerosis-induced mice prevented the formation of cell foam compared to negative groups
34	Daily administration of Andro at 1.5 mg/kg rat body weight with atherogenic food prevented atherosclerosis development	The docking simulation showed that Andro interacted well with NF-kB, ICAM-1, VCAM-1, TNFα, IFN-γ and Cyt MAP kinase P32 proteins responsible for the anti-atherosclerotic effect. In addition, Andro inhibited the ox-LDL formation and interacted well with the atherosclerosis-protein receptor targets
35	Andro analog could lower hepatic lipid peroxides	Andro analog may ameliorate steatohepatitis and liver injury in atherosclerosis rats by increasing antioxidant and anti-inflammatory activities
36	It was stated that Anro able to lowering the TC, TG, and LDL-	The study proven that Andro was able to decreasing cardiac

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C level, while HDL-C levels increased. Andro seemed to reduce the TNF-α, MCP-1, hs-CRP and IL-1β levels by changing the macrophage phenotype, and weakened the endothelial dysfunction. These may gained by the elevation of the serum levels of ET-1 and TAX2 and allevation the levels of NO and PGI2 in rats

apoptosis event and also able to detaining the PPARα and NF-κB proteins activation

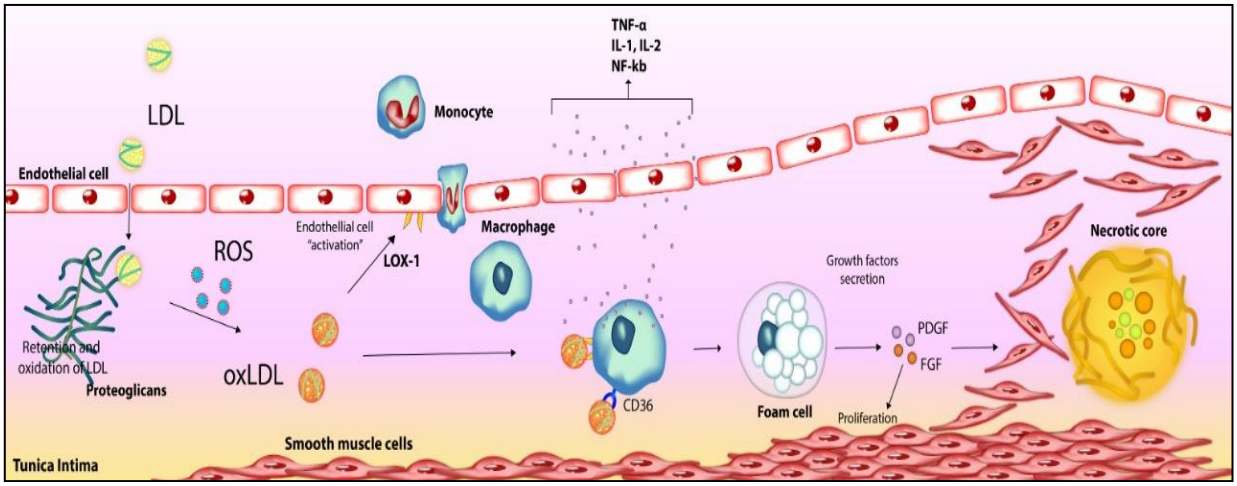

Figure 1: Atherosclerosis progression in tunica intima (simulation) (Adapted from Leiva[43])

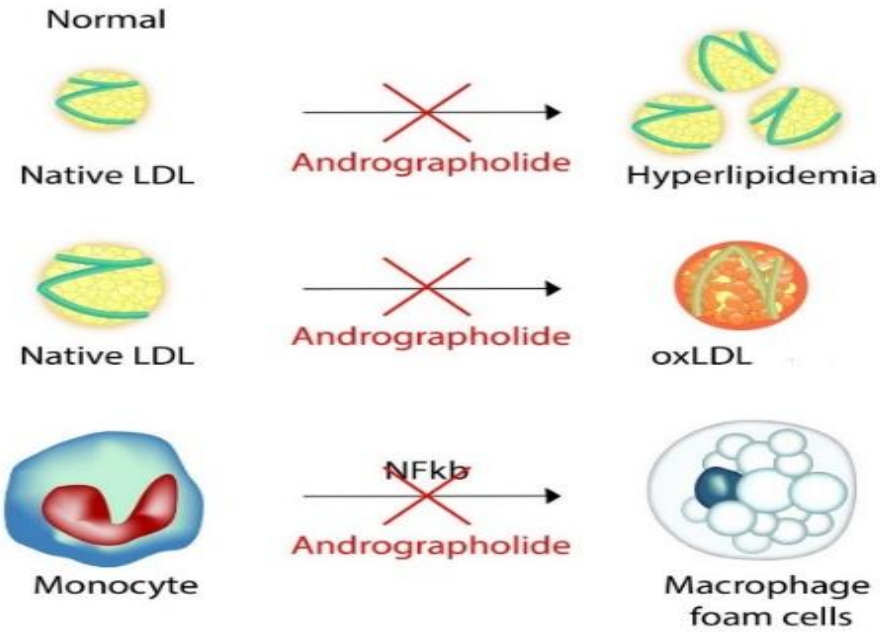

Figure 2: Action target of Andro to prevent atherosclerosis (Adapted from Leiva[43])

Conclusion

AP has been shown to have anti-atherosclerosis and heart-protective properties. As an antioxidant and anti-inflammatory, AP also displayed promising properties in lowering blood cholesterol levels. Furthermore, AP could prevent atherosclerosis by lowering blood LDL levels, inhibiting LDL oxidation, and reducing NF-B expression.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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