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Original Research Article

Sonneratia alba Fruit Extract's Potential to Reduce Atherogenic Index of Plasma and Prevent Atherogenesis in Aortic Arch of High-Fat Diet Induced Wistar Rats

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ABSTRACT

Treatments for atherosclerosis have advanced, however many still come with adverse effects and limitations. Using safe, effective, and affordable natural compounds—like those found in *Sonneratia alba* fruit—shows promise as a potential alternative therapy. *S. alba* is known for its strong antioxidant, antidiabetic, antibiotic, and anti-inflammatory properties. This study aims to explore how *S. alba* fruit extract affects atherosclerosis risk and atherogenesis in high-fat diet (HFD) induced rats. This study used 24 male Wistar rats, aged 8–10 weeks and weighing 170–190 g, divided into six groups: a normal group, a positive control group receiving HFD, a group receiving HFD plus atorvastatin (10 mg/day), and three groups receiving HFD and *S. alba* extract at doses of 200, 400, and 800 mg/kg/day. The HFD was given 20 g/day for 10 weeks, while atorvastatin and *S. alba* extract were administered orally throughout the same period. Lipid profiles, LDL/HDL ratio and atherogenic index of plasma (AIP) were measured at weeks 5 and 10. The aortic arches were collected, processed into histological hematoxylin-eosin slides. Alterations of aortic structure were examined under a microscope and scored. The results showed *S. alba* extract has strong antioxidant properties. Giving *S. alba* at a dose of 800 mg/kg/day significantly reduced LDL/HDL ratio and AIP at both weeks 5 and 10. Histopathological analysis supported these findings, showing that *S. alba* extract significantly inhibited atherogenesis at the same dose. In conclusion, *S. alba* fruit extract may lower atherosclerosis risk and prevent atherogenesis in aorta of HFD-induced rats.

Keywords: AIP, antioxidant, atherosclerosis, high-fat diet, LDL/HDL ratio, *Sonneratia alba*

Introduction

Ischemic heart disease (IHD) continues to be the leading cause of morbidity and mortality worldwide.[1] Many treatments are available for IHD, but they often raise healthcare costs, which can negatively affect the global economy.[2] The main cause of IHD is atherosclerosis, a complex condition exacerbated by multiple risk factors such as dyslipidemia, diabetes, hypertension, oxidative and inflammatory stress, smoking, aging, and genetic alterations.[1,2] Vascular endothelial injury, low-density lipoprotein (LDL) retention in the subendothelial region and oxidative modification of LDL underlie the pathogenesis of atherosclerosis.[3] Hyperlipidemia is a one of major risk factors for atherosclerosis. It leads to the accumulation of LDL in the subendothelial layer of medium and large arteries. Once trapped, LDL is modified by reactive oxygen species (ROS), forming oxidized LDL (oxLDL). Oxidized LDL (oxLDL) interacts with scavenger receptors like SR-A, CD36, LOX-1, and toll-like receptors (TLRs), triggering inflammatory responses.

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This leads to endothelial dysfunction, vascular smooth muscle cells proliferation and migration into the intimal layer, plaques formation (atheromas) with a necrotic core resulting from cellular apoptosis. If a plaque ruptures, it may result in thrombosis and vascular stenosis, which may potentially lead to death.[4] Assessing the risk of atherosclerosis is essential for its prevention. Measuring plasma lipid levels can help indicate this risk. The Atherogenic Index of Plasma (AIP) is recognized as a strong predictor of atherogenesis. Calculated as the logarithmic ratio of triglycerides (TG) to high-density lipoprotein (HDL), AIP indirectly reflects the amount of small dense LDL. The small dense LDL (sdLDL) has a higher atherogenic tendency than other LDL subfraction because its small size allows it to bind strongly to proteoglycans in the arterial intima. In addition, the sdLDL is easily oxidized, exhibit a low afinity to its receptor, has a slow clearance rate and prolonged retention duration.[5]

Many atherosclerosis treatments, including cholesterol ester transfer protein (CETP) inhibitors, antioxidants, and vitamins, have either been partially or completely ineffective, or too expensive for widespread use in populations at risk of IHD. Statins, on the other hand, are considered effective and generally well-tolerated for managing IHD. However, statin use can cause side effects, including muscle pain or weakness (myopathy), rhabdomyolysis, a slightly higher risk of diabetes, and an increased risk of hemorrhagic stroke and cataracts.[6] Therefore, there is ongoing interest in developing new strategies to prevent or treat IHD. Over the past decade, researchers have focused on phytochemicals—natural bioactive compounds that are potent, safe, and cost-effective—as promising options for IHD therapy.[7]

The mangrove *Sonneratia alba* is widely found in tropical and subtropical regions and has been reported in more than 23 countries across Africa, Asia, and Australia.[8] *S. alba* is known locally for its edible fruit. Traditionally, it has also been used as a medicinal plant to

treat muscle swelling and sprains, hemorrhage, and cure various skin disorders. *S. alba* is rich in various secondary metabolites, such as flavonoids, phenols, triterpenoids, saponins, tannins, carboxylic acids, and steroids which exhibit antioxidant, antidiabetic, cytotoxic, anti-plasmodial, and antibacterial properties.[9–11] Polysaccharides from *S. alba* leaves have demonstrated antidiabetic effects in vivo, reducing blood glucose levels by 66.9% after 12 hours treatment in hyperglycemia-induced mice.[12] Triterpenoids in *S. alba* have been shown to reduce cholesterol levels in cholesterol salt solutions.[13] In addition, tannins from *S. alba* can lower blood sugar levels in diabetic mice and have shown no toxic effects on shrimp larvae.[14]

In our previous study, we developed an early-phase atherogenesis animal model by giving a single intraperitoneal dose of vitamin D3 (700,000 IU) followed by a high-fat diet for 5 days. Administering *S. alba* fruit extract at 400 mg/kg/day in this model was able to inhibit foam cell formation, although it did not affect plasma lipid levels.[15] The short treatment period in our previous study likely affected the results. Therefore, in this study, Wistar rats were given a high-fat diet along with *S. alba* fruit extract at three different doses for 10 weeks to evaluate its potential in reducing atherosclerosis risk and preventing atherogenesis in the aortic arches of rats.

Materials and Methods

This study used a post-control only group design. All study procedures and protocols were approved by the Ethics Committee of the Faculty of Medicine, University of Andalas, Padang, Indonesia (ethical approval number 231/UN.16.2/KEP-FK/2024).

Sonneratia alba Fruit Extraction

Sonneratia alba fruits were collected from the mangrove ecosystems in the coastal area of Sungai Apit District, Siak Sri Indrapura Regency, Riau Province, Indonesia, on October 19, 2024. The plant was identified by a taxonomist at the Faculty of Mathematics and Natural Sciences, University of Riau, Pekanbaru, Indonesia, with voucher specimen number 583/UN19.5.1.1.3-4.1/TU.00.01/2025. Unripe fruits, measuring 2–3 cm in diameter, were sliced and dried in an oven at 45–50°C. The dried fruits were ground into a fine flour. The flour was then macerated in 96% ethanol for three days in a dark room at room temperature, and the process was repeated for another three days. The extract was concentrated using a rotary vacuum evaporator at 100 rpm and 50°C to obtain a condensed *S. alba* fruit extract, which was stored at 4°C until use.

Phytochemical screening

Qualitative phytochemical screening of *S. alba* fruit extract was carried out to confirm the presence of major secondary metabolites, including flavonoids, phenols, alkaloids, saponins, triterpenoids, and steroids, following established protocols.[16]

Total flavonoid content determination

The total flavonoid content was measured using the aluminum chloride colorimetric method. Approximately 10 mg of the extract was dissolved in methanol to a final concentration of 1000 ppm. Similarly, 10 mg of quercetin (analytical grade, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in methanol to prepare standard solutions at concentrations of 40, 60, 80, 100, 120, and 140 ppm. About 1.5 ml of ethanol was added to the dilution, followed by 0.1 ml of 10% $AlCl_3$ solution in water and 0.1 ml of 1 M sodium acetate solution in water. Next, 2.8 ml of water was added to the mixture, which was then incubated in the dark at room temperature for 30 minutes. The absorbance of the extract was measured at the maximum wavelength of Quercetin. All procedures were performed in triplicate. The total flavonoid content is expressed as milligrams of Quercetin equivalent per gram of extract.

Total phenol content determination

The total phenolic content was measured using the Folin–Ciocalteu's method. Approximately 10 mg of the extract was diluted in methanol to reach a final concentration of 1000 ppm. Then, 0.5 ml of this dilution was mixed with 2.5 ml of 7.5% Folin–Ciocalteu's phenol reagent (Sigma-Aldrich, St. Louis, MO, USA) and left at room temperature for 8 minutes. About 2 ml of 1% NaOH in water was added to the mixture, which was then incubated in the dark at room temperature for one hour. After incubation, the absorbance was measured at 730 nm using a UV-VIS PharmaSpec 1700 spectrophotometer (Shimadzu Corp., Kyoto, Japan). All procedures were performed in triplicate. The total phenolic content is expressed as milligrams of gallic acid equivalent per gram of extract (analytical grade, Sigma-Aldrich, St. Louis, MO, USA).

Determination of antioxidant capacity

The extract and ascorbic acid were diluted in methanol at different concentrations (200, 100, 50, 25, 12.5, 6.25, and 3.125 ppm for the extract; 100, 50, 25, 12.5, 6.25, 3.125, and 1.5625 ppm for ascorbic acid). Then, 100 µL of each sample was placed in a 96-well plate in triplicate, followed by the addition of 100 µL of 500 µM DPPH solution. The plate was incubated in the dark at 37°C for 30 minutes. After incubation, absorbance was measured at 517 nm. The percentages of inhibition were calculated by using the formula (1 – mean of sample absorbance/blank absorbance) x 100%. The IC_{50} was determined using linear regression of extract concentration versus percentage of inhibition.

Experimental Animal Design

The samples were obtained from the animal house of the Faculty of Pharmacy, University of Andalas, Padang, Indonesia. Sample size was determined using the Equation Resource (ER) method, with each of the six groups containing between 3 and 4 samples. A total of 24 male Wistar rats, aged 8–10 weeks and weighing 170–190 g, were included in this study. They were divided into six groups: a negative control (N) group receiving a standard chow, a positive control (P) group fed a high-fat diet, a statin group (A) receiving a high-fat diet and atorvastatin (10 mg/day), and three treatment groups (T1, T2, and T3) given a high-fat diet and *S. alba* fruit extract at doses of 200, 400, and 800 mg/kg body weight per day, respectively. The animals were acclimated for one week before the start of treatment. Each rat was housed in a separate cage at room temperature (24–26°C) with a 12-hour light/dark cycle, and food and water were provided ad libitum.

To induce atherogenesis, a high-fat diet (HFD) consisting of 0.2% cholic acid (Sigma Aldrich, St. Louis, USA), 5% goat fat, and 2% cholesterol from egg yolk, mixed with commercial chow (Vivo 512), was administered at 20 g per day for 10 weeks, with daily monitoring of feed consumption. The protective effect of *S. alba* fruit extract against HFD-induced atherogenesis was assessed by administering the extract to the treatment groups from the first day of HFD feeding. After 10 weeks of treatment, the rats were anesthetized with a ketamine (70 mg/kg)–xylazine (7 mg/kg) cocktail. Blood samples were then collected via supraorbital vein puncture and transferred into microtubes. The blood samples were left at room temperature for 30 minutes, then centrifuged at 3000 rpm for 15 minutes. The serum was collected, transferred to new microtubes, and stored at –80°C for further analysis. A thoracotomy was performed to isolate the aortic arch, which was then collected for subsequent histopathological examination.

Lipid Profiles Examination

Total cholesterol, triglycerides, HDL, and LDL were measured using an enzymatic photometric assay according to the manufacturer's instructions (DiaSys Diagnostic Systems, Holzheim, Germany). The LDL/HDL ratio was then calculated to assess the risk of atherosclerosis.

Atherogenic Index of Plasma Calculation

The Atherogenic Index of Plasma (AIP) was calculated as the logarithmic ratio of triglycerides to HDL in molar concentration. Calculations were performed using an online atherogenic risk calculator (AIP calculator (cas.cz)). AIP values were categorized as high-risk (>0.21), intermediate-risk (0.11–0.21), and low-risk (<0.11).

Histopathological Examination

The aortic arches were embedded in paraffin and subjected to hematoxylin-eosin staining. Histopathological changes were examined under a light microscope (Leica ICC50HD) across 10 fields at 400× magnification. The alterations were analyzed and semi-quantitatively scored as follows: 0 for no abnormal changes; 1 for widened elastic

fibers, few foam cells formation, or mild discontinuity of the endothelial lining; 2 for increased number of foam cells formation, proliferation and disorientation of vascular smooth muscle cells, fibrous collagen formation, or medial lipid accumulation; and 3 for the presence of ulcerated plaques or thrombi.

Statitiscal Analysis

Data analysis was performed using GraphPad Prism v.8.4.0 (GraphPad Software, Boston, MA, USA). Results are presented as mean ± standard error of the mean (SEM). Parametric data were analyzed using one-way ANOVA followed by Tukey's multiple comparison test, while non-parametric data were analyzed using the Kruskal–Wallis test followed by Dunn's post hoc test. A p-value <0.05 was considered statistically significant.

Results and Discussion

Phytochemical Screening, Total Flavonoid and Phenolic Content and Antioxidant Capacity

Qualitative phytochemical screening was conducted to identify the major secondary metabolites in *S. alba* fruit extract, collected from Sungai Apit District, Siak Sri Indrapura, Riau Province, Indonesia. The results showed that the extract contains flavonoids, phenols, and saponins (Table 1). Some previous studies found the presence of steroids, alkaloids and triterpenoids besides flavonoids, phenols and saponins in *S. alba* fruit.[17,18] Additionally, the dichloromethane extract of *S. alba* fruit was found to contain several triterpenoids and sterols, including oleanolic acid, ursolic acid, α-amyrin cinnamate, β-amyrin cinnamate, β-sitosterol, and stigmasterol.[19]

Table 1: Secondary metabolites identified in *S. alba* fruit ethanol extract

Secondary Metabolite	*S. alba* Fruit
Flavonoid	+
Phenol	+
Alkaloid	+
Saponin	-
Triterpenoid	-
Steroid	-

Note: (+) = present, (-) = absent

The diversity of phytochemical compounds in mangroves can be influenced by genetic, nutritional, and environmental factors, including geographical location, salinity, temperature, and pollution. Naturally, bioactive compounds such as flavonoids and phenolics help protect the plants from oxidative damage caused by harsh conditions, including high salinity, intense radiation, and other environmental stressors. Tannins in mangrove play a role in protecting the plants from the herbivores, pathogens and environmental stress.[20] Variations in the secondary metabolite content of *S. alba* in this study may be due to differences in its growth environment compared to other regions.

The total phenol and flavonoid content of *S. alba* fruit extract were measured, revealing 171.99 ± 1.54 mg GAE/g extract of total phenols and 14.49 ± 0.32 mg QE/g extract of total flavonoids. In comparison, a study by Deviarni *et al*. in West Kalimantan reported that unripe *S. alba* fruit contained 27.19 ± 1.19 mg GAE/g dry extract of phenols and 3.99 ± 1.06 mg QE/g dry extract of flavonoids, which are approximately 6.3 and 3.6 times lower than the values found in our study, respectively. Furthermore, their study found that unripe fruits contained higher amounts of total phenols and flavonoids compared to ripe fruits.[21] These differences in concentration may be influenced by genetic and environmental factors, as well as the type and processing of the samples. In our study, ethanol extraction was used, while the study in West Kalimantan employed dry extracts.

The antioxidant capacity was evaluated using the DPPH assay, which showed that the extract had an IC50 of 61.42 ppm. Although this is higher than the IC50 of ascorbic acid (14.42 ppm), the extract still demonstrated strong antioxidant activity. These findings are consistent with a study conducted in West Kalimantan.[21] However, these results contrast with a study from South Sulawesi, which reported that *S. alba* fruit from the coastal area of Nunuk Village, South Bolaang Mongondow District, North Sulawesi, Indonesia, had an IC50 of 296.54 µg/mL, indicating relatively weak antioxidant activity compared to our findings.[22]

The total phenol content of a plant is often associated with its antioxidant capacity. To date, over 8,000 active phenolic compounds have been identified, many of which can undergo polarity changes and biochemical modifications. Technical factors during sample processing can also affect the levels of secondary metabolites and antioxidant activity, including the choice of extraction solvent, temperature, type of specimen, as well as the processing method and storage duration.[23]

Total cholesterol, Triglyceride, LDL and HDL Plasma Levels

During the treatment period, each animal received 20 grams of feed per day, and daily feed consumption was monitored. As shown in Table 2, treatment with atorvastatin and *S. alba* fruit extract reduced the average daily intake of rats compared to the negative and positive control groups. This variation in daily intake was statistically significant ($p = 0.016$), with further analysis revealing a significant difference between the negative control and *S. alba* at a dose 200 mg/kg/day groups ($p = 0.0428$).

Table 2: The average daily food intake, body weight and the increase of bodyweight

Variable / Groups	Mean ± SEM	p-value
Average daily intake (g/day)		
- Negative control groups (N)	12.73 ± 0.33[a]	
- Positive control groups (P)	9.72 ± 0.70	
- HFD + atorvastatin 10 mg/day (A)	9.00 ± 0.44	0.0166*
- HFD + *S. alba* 200 mg/kgBW/day (S1)	8.15 ± 0.54[a]	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	8.20 ± 0.33	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	8.00 ± 0.20	
Initial body weight (grams)		
- Negative control groups (N)	174.80 ± 2.25	
- Positive control groups (P)	180.50 ± 5.24	

- HFD + atorvastatin 10 mg/day (A)	179.00 ± 3.67	0.8374
- HFD + *S. alba* 200 mg/kgBW/day (S1)	174.50 ± 2.53	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	176.30 ± 5.37	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	178.30 ± 2.32	
Body weight after 10 weeks treatment (grams)		
- Negative control groups (N)	257.00 ± 13.44	
- Positive control groups (P)	304.80 ± 15.53	
- HFD + atorvastatin 10 mg/day (A)	283.30 ± 22.67	0.1157
- HFD + *S. alba* 200 mg/kgBW/day (S1)	247.30 ± 21.97	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	254.30 ± 5.09	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	249.80 ± 5.06	
Increase of body weight (%)		
- Negative control groups (N)	47.22 ± 8.49	
- Positive control groups (P)	68.66 ± 5.68	
- HFD + atorvastatin 10 mg/day (A)	57.84 ± 10.54	0.2678
- HFD + *S. alba* 200 mg/kgBW/day (S1)	42.69 ± 14.03	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	46.12 ± 7.58	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	41.55 ± 1.41	

Note: * indicates p-value <0.05 or a significant difference among groups; [a] indicates group pair that revealed significant difference in Dunn test

The animals' weight gain was monitored weekly. At the start of the treatment, the mean body weight of each group ranged from 174.50 ± 2.53 g to 180.50 ± 5.24 g, with no significant differences observed (p = 0.8374). After 10 weeks of treatment, the positive control group fed a high-fat diet showed the highest average body weight of 304.80 ± 15.53 g, corresponding to a 68.66 ± 5.68% increase from baseline. Among the treatment groups, rats receiving *S. alba* at 200 mg/kg/day had the lowest average body weight (247.30 ± 21.97 g), while those given 800 mg/kg/day showed the smallest percentage increase in body weight (41.55 ± 1.41%). Statistical analysis indicated no significant differences in either body weight (p = 0.1157) or percentage weight gain (p = 0.2678) among the groups at the end of the treatment period (Table 2).

The strong antioxidant activity of the ethanol extract of *S. alba* fruit suggests its potential to reduce oxidative stress caused by a high-fat diet, both in vitro and in vivo. A study by Musa WJA et al. (2019) showed that terpenoid secondary metabolites extracted from *S. alba* leaves could lower cholesterol levels in vitro in a dose-dependent manner. *S. alba* leaf extract was able to reduce cholesterol levels by up to 77% in vitro at a concentration of 80 ppm.[13] Jariyah *et al* (2013) found the powder of *Sonneratia caseolaris* fruit decreased the total cholesterol, triglyceride and LDL cholesterol in rats given high-calorie and high-fat diet.[24]

In this study, Wistar rats (Rattus norvegicus) were used as animal models and fed a high-fat diet for 10 weeks to induce dyslipidemia and atherogenesis. The high-fat diet and *S. alba* fruit extract were administered concurrently to evaluate the protective effects of the extract against atherosclerosis. Lipid profiles, including total cholesterol, triglycerides (TG), LDL, and HDL levels, were assessed at the end 5th and 10th weeks of treatment. The results showed that all groups experienced a reduction in total cholesterol, TG, and LDL levels by the end of the 10th week compared to the 5th week. HDL levels showed more variability: the positive control, HFD + atorvastatin, and HFD + *S. alba* 200 mg/kg/day groups exhibited a slight increase in HDL by the 10th week, while the negative control and HFD + *S. alba* 400 and 800 mg/kg/day groups showed a decrease in HDL over the same period. Figure 1 presents the lipid profiles at the end of the 5th and 10th weeks of treatment.

At the 5th week of treatment, the positive control group showed the highest total cholesterol, TG, and LDL levels, while the highest HDL level was observed in the group treated with *S. alba* at 800 mg/kg/day. By the 10th week, the positive control group still had the highest total cholesterol, TG, and LDL levels, whereas the negative control group exhibited the highest HDL levels. Administration of *S. alba* fruit extract to rats on a high-fat diet was able to inhibit the rise in total cholesterol, TG, and LDL levels at both the 5th and 10th weeks, with greater inhibition observed at higher doses. Additionally, the extract appeared to increase HDL levels at both time points, also in a dose-dependent manner. At the 5th week, *S. alba* fruit extract was more effective than atorvastatin in preventing increases in total cholesterol, TG, and LDL levels in rats on a high-fat diet. By the 10th week, however, only the group receiving the highest dose of the extract (800 mg/kg/day) showed greater suppression of total cholesterol and LDL levels compared to the atorvastatin group. Statistical analysis showed significant differences in total cholesterol, TG, LDL, and HDL levels at both the 5th and 10th weeks, except for HDL levels at week 10 (Table 3).

The results of this study are consistent with Jariyah et al. (2013), who found that giving rats a high-calorie, high-fat diet *Sonneratia caseolaris* fruit flour helped reduce their total cholesterol, triglycerides (TG), and LDL levels.[24] Another study on the mangrove fruit *Bruguiera gymnorhiza*, known for its high flavonoid and phenol content, showed similar effects in rats fed a high-fat, high-sucrose diet.[25] Similarly, a study in Brazil found that polyphenol compounds extracted from the leaves of *Rhizophora mangle* L. helped reduce total cholesterol and LDL levels in obese mice.[26]

Lipid metabolism is known to be highly complex, and the risk of dyslipidemia can occur at any stage. When the small intestine absorbs excessive fats from a high-fat diet, LDL cholesterol levels tend to rise. Exogenous lipids combine with cholesterol and fatty acids produced by the liver, forming VLDL. This VLDL is then broken down into triglycerides (TG) by lipase and eventually converted into LDL. LDL binds to LDL receptors or scavenger receptors in peripheral tissues. At the same time, a reduction in HDL production by the liver lowers reverse cholesterol transport (RCT) back to the liver and limits the removal of excess cholesterol through the bile and intestinal lumen. This process involves ATP-binding cassette transporters G5 and G8 (ABCG5/G8), which help mediate trans-intestinal cholesterol efflux (TICE).[27]

Table 3: Total cholesterol, triglyceride, LDL and HDL plasma levels

Variable/Group	5 Weeks		10 Weeks	
	Mean ± SEM	**p-value**	**Mean ± SEM**	**p-value**
Total cholesterol (mg/dL)				
- Negative control groups (N)	92.63 ± 6.01[a]		83.18 ± 4.20[a]	
- Positive control groups (P)	193.70 ± 15.72[a]		190.20 ± 8.70[a]	
- HFD + atorvastatin 10 mg/day (A)	175.50 ± 34.85	0.0265*	104.70 ± 13.14	0.0068*
- HFD + *S. alba* 200 mg/kgBW/day (S1)	164.10 ± 21.05		126.00 ± 5.72	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	147.90 ± 15.86		120.70 ± 16.90	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	129.40 ± 13.97		95.50 ± 5.64	
Triglyceride (mg/dL)				
- Negative control groups (N)	89.13 ± 6.46[ab]		72.63 ± 1.43	
- Positive control groups (P)	255.30 ± 18.62[acde]		140.60 ± 11.47[a]	
- HFD + atorvastatin 10 mg/day (A)	187.00 ± 10.01[b]	<0.0001*	108.30 ± 14.02	0.0303*
- HFD + *S. alba* 200 mg/kgBW/day (S1)	143.20 ± 20.44[c]		111.20 ± 27.93	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	153.80 ± 19.88[d]		102.70 ± 17.67	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	118.70 ± 19.73[e]		65.10 ± 2.34[a]	
Low-density Lipoprotein (mg/dL)				
- Negative control groups (N)	571.8 ± 4.94[a]		46.43 ± 5.41[a]	
- Positive control groups (P)	198.70 ± 16.85[a]		155.40 ± 14.61[abc]	
- HFD + atorvastatin 10 mg/day (A)	167.80 ± 32.45	0.0106*	81.00 ± 16.35[b]	0.0005*
- HFD + *S. alba* 200 mg/kgBW/day (S1)	150.00 ± 22.61		101.20 ± 7.39	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	131.40 ± 21.04		94.68 ± 23.31	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	94.95 ± 15.60		59.38 ± 4.67[c]	
High-density Lipoprotein (mg/dL)				
- Negative control groups (N)	55.80 ± 2.49[b]		51.30 ± 3.02	
- Positive control groups (P)	46.03 ± 3.77[c]		46.90 ± 4.95	
- HFD + atorvastatin 10 mg/day (A)	45.05 ± 4.82[d]	0,0453*	45.35 ± 1.75	0.7509
- HFD + *S. alba* 200 mg/kgBW/day (S1)	42.75 ± 5.37[ab]		47.00 ± 3.62	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	47.20 ± 1.81		46.50 ± 4.18	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	58.15 ± 2.59[acd]		49.15 ± 1.30	

Note: *indicates p-value <0.05 or a significant difference among groups; [abcde] indicate group pairs that revealed significant difference in Tukey or Dunn test

The cholesterol-lowering effects of phenolic compounds may be due to their ability to reduce intestinal cholesterol absorption, inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) activity, and boost the activity of cholesterol-7α-hydroxylase (CYP7A1), an enzyme involved in converting cholesterol into bile acids. Additionally, phenolic compounds can prevent triglyceride buildup by increasing the expression of peroxisome proliferator-activated receptor alpha (PPARα), which promotes fatty acid oxidation and suppresses fatty acid synthesis. They also enhance the expression of liver X receptor alpha (LXRα), which regulates CYP7A1 and boosts apoA-I and ABCA1 levels, supporting HDL-mediated reverse cholesterol transport (RCT).[28–30]

LDL/HDL Ratio and Atherogenic Index of Plasma

Assessing the risk of atherosclerosis is crucial for its prevention. Atherogenesis is a complex process, and abnormalities in lipoprotein metabolism contribute to roughly half of the population's risk for cardiovascular disease. Relying solely on LDL cholesterol to evaluate coronary heart disease is considered insufficient, especially for individuals at intermediate risk. The LDL/HDL ratio serves as a key indicator of vascular risk, as about two-thirds of plasma cholesterol is carried in LDL. An increased LDL/HDL ratio signals a higher risk of cardiovascular problems.[31]

Another reliable predictor of cardiovascular disease risk is the atherogenic index of plasma (AIP). AIP is calculated as the logarithm of the ratio of triglycerides to HDL, measured in molar units, and reflects the balance between harmful (atherogenic) and protective lipoproteins.[32] AIP is positively associated with the rate of HDL esterification and inversely related to LDL levels. By combining triglycerides and HDL cholesterol in this ratio, AIP highlights the complex interactions of lipoprotein metabolism and can serve as a useful predictor of plasma atherogenicity. AIP values are typically classified into three categories of risk: low, moderate, and high.[33]

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In this study, treatment with *S. alba* fruit extract was found to lower the risk of atherogenesis, as shown by decreasing in both the LDL/HDL ratio and AIP. At weeks 5 and 10, the positive control group showed the highest LDL/HDL ratios, while the negative control group consistently had the lowest values (Table 4). Statistical analysis using one-way ANOVA revealed significant differences in LDL/HDL ratios among the groups at weeks 5 and 10, with p-values of 0.0008 and 0.0069, respectively. Further comparison using the Tukey test showed significant differences between the negative and positive control groups ($p = 0.0017$), negative control and atorvastatin groups ($p = 0.0207$), negative control and *S. alba* 200 mg/kg/day groups ($p = 0.0211$), and positive control and *S. alba* 800 mg/kg/day groups ($p = 0.0129$). By the 10th week, Tukey test analysis revealed significant differences between the negative and positive control groups ($p = 0.0066$) and between the positive control group and the highest dose of *S. alba* group ($p = 0.0191$), as illustrated in Figure 2.

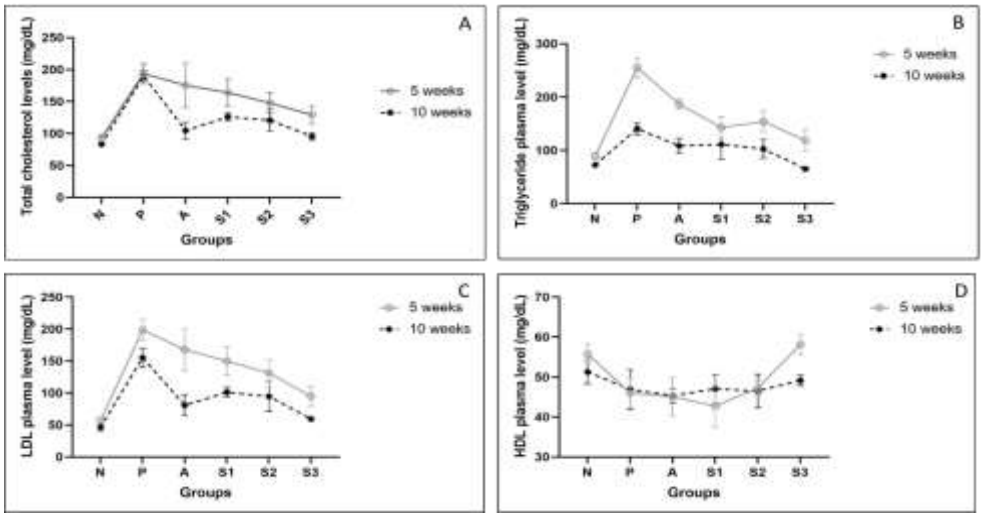

Figure 1: The total cholesterol, TG, LDL and HDL plasma levels at the 5th and the 10th week of treatment. N, P, A, S1, S2 and S3 refer to negative control group (N), positive control (P), treatment group with HFD + atorvastatin 10 mg/day (A), HFD + *S. alba* 200 mg/kg/day (S1), HFD + *S. alba* 400 mg/kg/day (S2) and HFD + *S. alba* 800 mg/kg/day (S3).

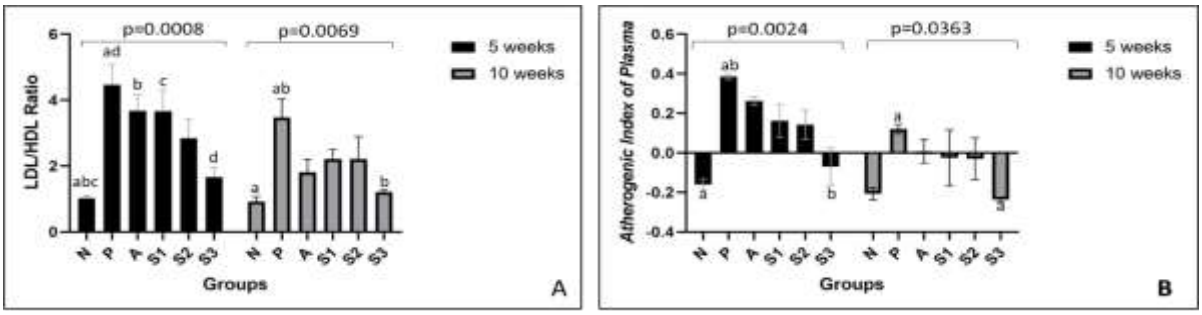

Figure 2: LDL/HDL ratio (A) and atherogenic index of plasma (B) at the 5th and the 10th week of treatment. [abcd] in the figure indicates the group pairs that showed significant differences either in Tukey or Dunn test analysis. N, P, A, S1, S2 and S3 refer to negative control group (N), positive control (P), treatment group with HFD + atorvastatin 10 mg/day (A), HFD + *S. alba* 200 mg/kg/day (S1), HFD + *S. alba* 400 mg/kg/day (S2) and HFD + *S. alba* 800 mg/kg/day (S3).

At week 5, the AIP indicated a high risk of atherosclerosis in the positive control and atorvastatin groups, a moderate risk in the *S. alba* 200 and 400 mg/kg/day groups, and a low risk in the negative control and *S. alba* 800 mg/kg/day groups. By week 10, the AIP showed a moderate risk in one group, while the other five groups were classified as low risk (Table 3). Statistical analysis revealed significant differences among the groups, with Kruskal-Wallis test at week 5 ($p = 0.0024$) and one-way ANOVA at week 10 ($p = 0.0363$). Further multiple comparison analysis revealed significant differences in AIP at week 5 between the normal and positive control groups ($p = 0.0221$) and between the positive control and *S. alba* 800 mg/kg/day groups ($p = 0.0223$). At week 10, a significant difference was observed between the positive control and *S. alba* 800 mg/kg/day groups ($p = 0.0434$), as shown in Figure 2.

Histopathological Changing in Aortic Arches of Wistar Rats

To verify atherogenesis caused by a high-fat diet and to evaluate the protective effect of *S. alba* fruit extract, a histopathological examination of the aortic arch was performed on Wistar rats. The results indicated that feeding rats a high-fat diet for 10 weeks triggered atherogenesis in the aortic arches. This was confirmed by several markers, including dilated elastic fibers, disrupted vascular endothelial cells, and the presence of foam cells in varying amounts within the subendothelial and medial layers of the aortic arches. Additionally, proliferation and disorganization of vascular smooth muscle cells, accumulation of intra- and extracellular lipids, and the formation of atheroma plaques were observed.

Table 4: LDL/HDL ratio and Atherogenic Index of Plasma (AIP)

Variable/Group	5 Weeks		10 Weeks	
	Mean ± SEM	p-value	Mean ± SEM	p-value
LDL/HDL ratio				
- Negative control groups (N)	1.02 ± 0.07^{abc}		0.92 ± 0.15^{a}	
- Positive control groups (P)	4.46 ± 0.63^{ad}		3.47 ± 0.56^{ab}	
- HFD + atorvastatin 10 mg/day (A)	3.67 ± 0.49^{b}	0.0008*	1.81 ± 0.39	0.0069*
- HFD + *S. alba* 200 mg/kgBW/day (S1)	3.67 ± 0.64^{c}		2.21 ± 0.29	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	2.84 ± 0.57		2.21 ± 0.69	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	1.66 ± 0.30^{d}		1.20 ± 0.07^{b}	
Atherogenic Index of Plasma (AIP)				
- Negative control groups (N)	-0.16 ± 0.03^{a}		-0.21 ± 0.03	
- Positive control groups (P)	0.38 ± 0.01^{ab}		0.12 ± 0.02^{a}	
- HFD + atorvastatin 10 mg/day (A)	0.26 ± 0.02	0.0024*	0.01 ± 0.06	0.0363*
- HFD + *S. alba* 200 mg/kgBW/day (S1)	0.16 ± 0.08		-0.02 ± 0.14	
- HFD + *S. alba* 400 mg/kgBW/day (S2)	0.14 ± 0.07		-0.03 ± 0.11	
- HFD + *S. alba* 800 mg/kgBW/day (S3)	-0.07 ± 0.09^{b}		-0.24 ± 0.01^{a}	

Notes: *: p-value <0.05 indicates a significant difference among groups; ^{abcd} indicates group pairs that revealed significant difference in Tukey or Dunn test

No signs of ulceration or plaque rupture were detected in this study (Figures 3 and 4). A semi-quantitative analysis of the aortic wall was carried out using a scoring system from 0 to 3. A score of 0 indicates normal tissue, 1 represents the early stage of atherogenesis, 2 reflects the proliferation stage and formation of atheromatous plaques, and 3 signifies complications such as plaque ulceration and thrombus formation. As shown in Table 5 and Figure 5, both atorvastatin and *S. alba* fruit extract inhibited atherogenesis, with the scores showing a statistically significant difference ($p = 0.0457$). Further analysis revealed that *S. alba* extract at a dose of 800 mg/kg/day significantly reduced atherogenesis compared to the high-fat diet group ($p = 0.0399$), with a similar effect observed in the atorvastatin-treated group ($p = 0.0475$).

Changes in the microscopic structure of blood vessels in atherosclerosis begin with the retention of LDL in the subendothelial space. The trapped LDL then undergoes oxidative and enzymatic modifications, forming oxidized LDL (oxLDL).[34] Oxidized LDL (ox-LDL) is then recognized and taken up by macrophages through scavenger receptors such as SR-A (CD204), CD36, LOX-1, and TLR2/4/6. This uptake leads to the accumulation of esterified cholesterol within macrophages, driven by the self-amplifying activity of these receptors. The buildup of intracellular cholesterol causes macrophages to transform into foam cells, a key hallmark of the early stage of atherogenesis.[35]

The oxidation of LDL trapped in the subendothelial space can trigger the endothelium to produce adhesion molecules, which in turn attract pro-inflammatory cells to the subendothelial layer.[3] Afterward, oxLDL triggers NADPH oxidase (Nox) through scavenger receptors, causing endothelial nitric oxide synthase (eNOS) to become uncoupled. This leads to increased production of reactive oxygen species (ROS) in the mitochondria and reduces the availability of nitric oxide (NO) in the endothelium.[36] When eNOS becomes uncoupled, it can boost the production of hypoxia-inducible factor 1 (HIF-1) and endothelin-1 (ET-1). High levels of ET-1 binding to ETB receptors prompt endothelial cells to produce adhesion molecules like intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesin molecule-1 (VCAM-1), while also activating both endothelial cells and macrophages to release monocyte chemo-attractant-1 (MCP-1). At the same time, ET-1 interacting with ETA receptors encourages vascular smooth muscle cells to multiply.[36, 37]

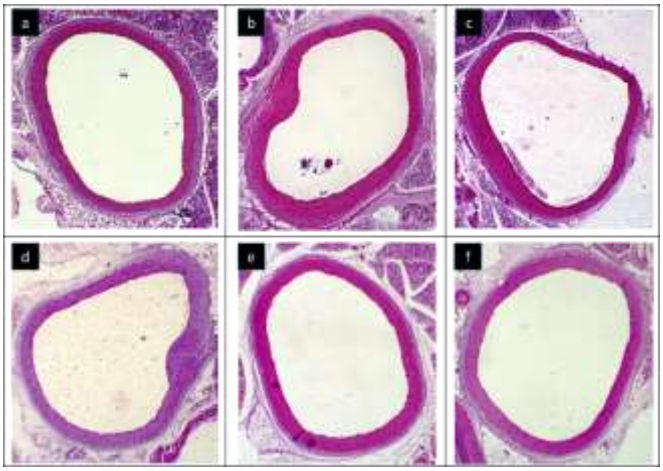

Figure 3: The histopathological appearance of rats' aortic arches with hematoxylin-eosin staining in 40x magnification. The mark a, b, c, d, e and f refer to negative control group (N), positive control (P), treatment group with HFD + atorvastatin 10 mg/day (A), HFD + *S. alba* 200 mg/kg/day (S1), HFD + *S. alba* 400 mg/kg/day (S2) and HFD + *S. alba* 800 mg/kg/day (S3), respectively. This image shows a very clear thickening of the aortic wall observed in groups P, A and S1, and the thickening in the P and S1 groups showed a tendency for atheroma plaque formation

The reactive oxygen species (ROS) generated can trigger the nuclear factor kappa B (NFκB) signaling pathway in endothelial cells, causing them to release a range of inflammatory molecules, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, matrix metalloproteinases (MMPs), and adhesion molecules like MCP-1, ICAM-1, VCAM-1, and E-selectin. This cascade gradually leads to progressive damage and dysfunction of the endothelium.[39,36] In addition, ROS raises calcium levels inside the cells, which increases their demand for ATP and puts stress on the mitochondria, potentially leading to cell death through apoptosis.[40]

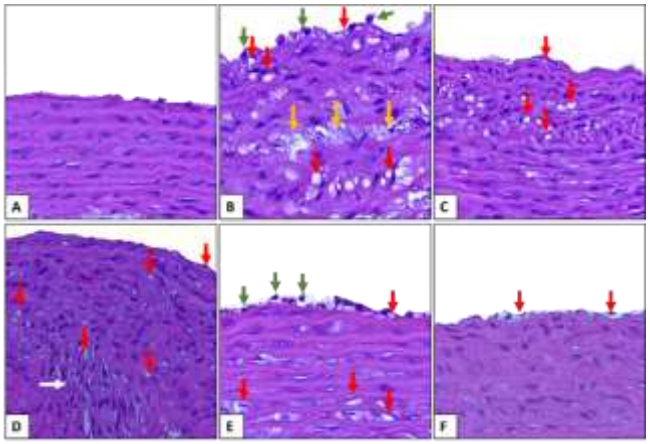

Figure 4: Histopathological image of the aortic arch at 400x magnification. A) negative control group (N); B) positive control administered HFD (P); C) HFD + atorvastatin 10 mg/day (A); D) HFD + *S. alba* 200 mg/kg/day (S1); E) HFD + *S. alba* 400 mg/kg/day (S2); F) HFD + *S. alba* 800 mg/kg/day (S3). The red arrows denote foam cells in the subendothelial layer and medial layer of aorta, the yellow arrows denote extracellular lipid accumulation, the green arrows indicate inflammatory cells, and the white arrows indicate disorientation of vascular smooth muscle cells. In the image B, C and E, endothelial discontinuities are observed.

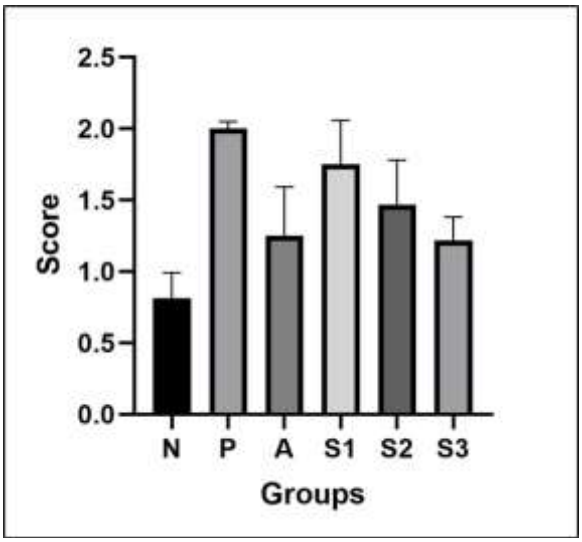

Figure 5: Histopathological atherogenic scores. The markers of [abcd] indicate the group pairs that showed a significant different in multiple comparison statistical analysis. N, P, A, S1, S2 and S3 refer to negative control group (N), positive control (P), treatment group with HFD + atorvastatin 10 mg/day (A), HFD + *S. alba* 200 mg/kg/day (S1), HFD + *S. alba* 400 mg/kg/day (S2) and HFD + *S. alba* 800 mg/kg/day (S3).

When macrophages and endothelial cells are activated by oxLDL, they release growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and IL-1β. This causes vascular smooth muscle cells to switch from their contractile form to macrophage-like cells with phagocytic abilities, while also triggering multiple pro-inflammatory responses.[41] When oxLDL activates LOX-1 via angiotensin-II and tumor growth factor-β1 (TGF-β1), it promotes fibroblast growth and the production of fibro-collagenous extracellular matrix. This helps preserve the contractile phenotype of vascular smooth muscle cells and prevents their phenotypic changes.[42] However, MMPs—especially MMP-9 produced by activated endothelial cells and macrophages—break down the extracellular matrix, change the behavior of vascular smooth muscle cells, and encourage these cells to multiply and move into the intimal layer, contributing to the formation of atherosclerotic plaque.[43]

Table 5: Atherogenesis histopathology scores

	Groups	Mean ± SEM	p-value
-	Negative control groups (N)	0.81 ± 0.180[ad]	0.0457*
-	Positive control groups (P)	2.00 ± 0.051[abc]	
-	HFD + atorvastatin 10 mg/day (A)	1.25 ± 0.342[b]	
-	HFD + *S. alba* 200 mg/kgBW/day (S1)	1.75 ± 0.312[d]	
-	HFD + *S. alba* 400 mg/kgBW/day (S2)	1.47 ± 0.312	
-	HFD + *S. alba* 800 mg/kgBW/day (S3)	1.22 ± 0.164[c]	

Notes: *: p-value <0.05 indicates a significant difference among groups; [abcd] indicates group pairs that revealed significant difference in Tukey test

Initially, the plaque grows away from the arterial lumen, but during the complication stage, it begins to encroach on it, reducing blood flow and increasing the risk of heart ischemia. Macrophages contribute to this process by inducing apoptosis in vascular smooth muscle cells through Fas activation and the release of pro-apoptotic factors like TNF-α and nitric oxide. They also hinder collagen production and promote degradation of the extracellular matrix via MMP-2 and MMP-9, which can ultimately lead to the rupture of the atherosclerotic plaque.[44]
The molecular mechanisms of phytochemicals, including phenolic compounds, have been extensively studied to reveal their many beneficial effects against atherosclerosis. Some compounds, in addition to their hypolipidemia effect as previously mentioned, have been shown to inhibit LDL oxidation, prevent ROS production by suppressing the catalytic subunit NADPH oxidase (p67phox, p47phox and p22phox) and upregulate the expression of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px) and heme oxygenase-1 (HO-1).[45] Furthermore, phenolic compounds stimulate the expression of nuclear erythroid-2 related factor 2 (Nrf2) in endothelial and vascular smooth muscle cells. This, in turn, boosts aldose reductase—a key enzyme that helps reduce oxidative stress—through the PI3K/Akt and p38MAPK/JNK signaling pathways.[27]

Conclusion

In conclusion, the ethanol extract of *S. alba* fruit appears to lower the risk of atherosclerosis, as shown by a decreased LDL/HDL ratio and a lower atherogenic index of plasma. Histopathological analysis of the rats' aortic arches supported these findings, demonstrating that the extract effectively inhibits atherogenesis, reflected by a significant reduction in the atherogenesis score. The extract showed a significant inhibitory effect at a dose of 800 mg/kg/day. These findings suggest that *S. alba* fruit has potential as a natural compound for preventing atherosclerosis. Further studies are needed to uncover the specific molecular pathways involved and to identify the most effective compounds in *S. alba* for inhibiting atherogenesis.

Conflict of Interest

The authors declare no conflicts of interest.

Authors' Declaration

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

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