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The Effect of Gum Arabic on Cholesterol Synthesis and Serum Lipids in Atherogenic Rats

Abeerz Al-Otaibi*

Department of Biochemistry, King Saud University,Riyadh, Saudi Arabia

***Corresponding author:** Abeer Al-Otaibi, Department of Biochemistry, King Saud University, Riyadh, Saudi Arabia, Tel: 551933703; E-mail: Abeerotb12@gmail.com

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Abstract

The current study was aimed to evaluate the effect of Gum Arabic (GA) as soluble dietary fiber on Normal Control (NC) and Atherogenic induced rats (AT). Male wistar rats with body weights (180 g-200 g) were divided into six groups each consisting of 8 rats: NC, NC treated with 3.75% GA, NC treated with 10% GA, AT group, AT group treated with 3.75% GA and last group AT rats treated with 10% GA. All NC and AT groups were kept on their specific diets for 2 weeks before oral treatment with GA which continued for six weeks. Body weights, food and water intake were recorded daily. Serum concentrations of TC, LDL, VLDL and TG were decreased significantly for all treated groups except NC treated with 3.75% GA that showed no significant difference in TC and LDL ($P \leq 0.001$). Serum HDL levels were increased significantly for all studied groups, also serum glucose concentrations decreased significantly with increasing dosage of GA in all treated groups ($P \leq 0.001$). Phospholipids showed no significant difference between all groups. HMGR was significantly diminished in AT group treated with 3.75% and 10% GA as it dropped from 5.94 ± 0.272 units/mg to 1.67 ± 0.151 unit/mg and 2.54 unit/mg ± 0.086 unit/mg respectively ($P \leq 0.001$). On the other hand, no significant changes were observed in the enzyme activity of NC treated with GA 2.206 ± 0.085 unit/mg and 2.42 ± 0.005 unit/mg, respectively. Histopathology observations revealed that GA has no toxic effect on normal control treated groups, as their structures looked normal. As well, GA has tissue protective property through supporting healing of livers and preventing the inflammation and necrosis as that obviously appeared in AT

Keywords: Gum arabic; *Acacia senegal*; Atherogenic; Hypercholesterolemia; Total cholesterol; Low density lipoprotein

Introduction

Cardio Vascular Diseases (CVDs) are the leading causes of death in the world and responsible for over 17.3 million deaths every year. Atherosclerosis is a chronic disease characterized by narrowing and inflammation of arteries due to deposition of plaques of fatty materials inside arterial walls. The risk factors for atherosclerosis are dyslipidemia (abnormal lipid levels in the blood), hypertension, diabetes and smoking. For managing atherosclerosis and dyslipidemia, numbers of pharmacological agents are available in the pharmacies; but these drugs were reported to induce adverse effects. As it has been reported long-term use of statins lead to the development of autoimmune diseases and type 2 diabetes mellitus [1-4].

GA (E-Number 414) is dried, an edible, gummy exudate from the branches and stems of *A. senegal* and *A. seyal* that is plentiful in soluble non-viscous fiber. GA has been used in food industries as an emulsifier, stabilizer and thickening agent (e.g. used in soft drinks, marshmallows and gummy candies), also in the pharmaceutical and cosmetics industries. For this, alternative agents with wide tolerance and lower toxicity are necessary and continue to be discovered for future therapeutics. Alternative medicine is commonly used in developing countries up to 80%. And to see the valuable of GA we must mention a study done about the effects of the perinatal exposure of Gum Arabic (GA) on the growth, which showed a sharp decrease in glucose concentration in blood through the ablactating (at postnatal day 15) where GA was obtainable to pups during the milk of the mother, as the hypoglycemic effect lowered through the post-weaning period but was still obvious at postnatal day 30 where the pups had reduced glucose concentrations in blood. Interestingly, cardiovascular diseases can be improved at different steps in their development with using herbal nutritional supplementation without any side effects. Rajasthani people who consume a specific kind of long-established food known as “Pachkutta” in their nutrition; which one of the main components is *Acacia senegal* (L.) Willd, they report almost nonentity incidence of cardiovascular diseases. GA is very crucial as its rich in flavonoids, polyphenols, tannins, alkaloids and saponins. Primarily GA is indigestible to both animals nor humans because it is not broken down in the small intestine, but fermented in the large bowel to produce propionic acid. The current investigation was carried out to study the effect of Gum Arabic on serum lipid profile and liver hydroxy-methyl-glutaryl CoA reductase activity in atherogenic induced rats (Figure 1) [5-9].

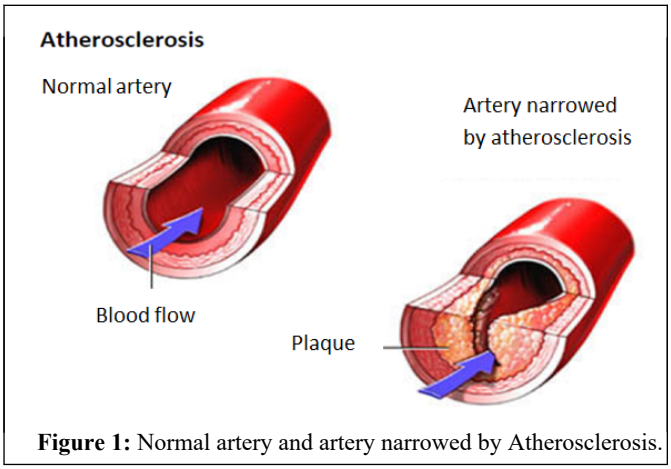

Figure 1: Normal artery and artery narrowed by Atherosclerosis.

Materials and Methods

Gum Arabic pellets were purchased from local herbal market with specific component, Riyadh, Saudi Arabia. Total cholesterol, triglyceride, HDL, Glucose kits were purchased from United Diagnostics Industry. Rat Anti-Phospholipid Antibody (APA) Enzyme linked immunosorbent assay kit was obtained from, HMG-CoA reductase assay kit with was purchased from, Atherogenic diet was obtained from ICN. Chemicals for tissue processing that include, 10% neutral buffered formalin, xylenes, paraffin wax, hematoxylin, eosin, grades of alcohol reagent and Canada balsam were obtained from (leica biosystems, Germany). All other chemicals used were analytical grade [10-13].

Experimental design and dosages

48 male wistar rats (180 g-200 g) assigned to 6 groups each group composed eight rats. The rats were housed in individual stainless-steel cages with free access to water in a room maintained at 24°C with a 12:12 hour in light-dark cycle. Hyperlipidemia was induced by maintaining three groups on atherogenic diet (appendix: A) and three groups were kept on standard laboratory diet for 2 weeks, then followed by 6 weeks of treatment with GA. Group 1 (NC) includes normal control rats kept on standard laboratory diet. Group 2 (NC+ 3.75% GA) includes normal control rats kept on standard laboratory diet and treated orally with GA at a concentration of 3.75% in distilled water. Group 3 includes (NC+ 10% GA) includes normal control rats kept on standard laboratory diet and treated orally with GA at a concentration of 10% in distilled water. Group 4 (AT) includes atherogenic induced rats kept on atherogenic diet. Group 5 (AT + 3.75% GA) includes atherogenic rats kept on atherogenic diet and treated orally with GA at a concentration of 3.75% in distilled water. Group 6 (AT+ 10% GA) includes atherogenic rats kept on atherogenic diet and treated orally with GA at a concentration of 10% in distilled water. GA solution was administrated by gavage 2 ml per rat. By completion of 42 days, rats were received 3.15 g and 8.4 g of GA from 3.75% and 10% doses, respectively (Table 1) [14-17].

Blood aliquots were extracted in weekly basis, centrifuged at 4000 rpm for 10 min, then collected sera were stored in -2°C until tests done. At the end of treatment duration, rats' livers were removed quickly, washed thoroughly with ice-cold phosphate buffered saline pH 7.4 and weighed. A piece from each liver was fixed with 10% formalin solution at 4°C for histologic examination. The rest of livers were kept at -80°C for HMG CoA reductase assay. Serum concentrations of the following biochemical parameters: TC; HDL; LDL; VLDL; TG and glucose were determined by standard enzymatic spectrophotometric methods using kits (UDI, Dammam, Saudi Arabia). Serum phospholipid level was determined by ELISA Kit (mybiosourse, USA) after obtaining of phospholipid standard curve (Figures 2) [18-25].

Group	Type of group	Standard diet
Group 1	NC	Rats kept on standard laboratory diet.
Group 2	(NC+ 3.75% GA)	Treated orally with GA at a concentration of 3.75% in distilled water.
Group 3	(NC+ 10% GA)	Treated orally with GA at a concentration of 10% in distilled water.
Group 4	AT	Rats kept on atherogenic diet.
Group 5	(AT + 3.75% GA)	Treated orally with GA at a concentration of 3.75% in distilled water.
Group 6	(AT+ 10% GA)	Treated orally with GA at a concentration of 10% in distilled water.

Table 1: Representing group type and standard diet.

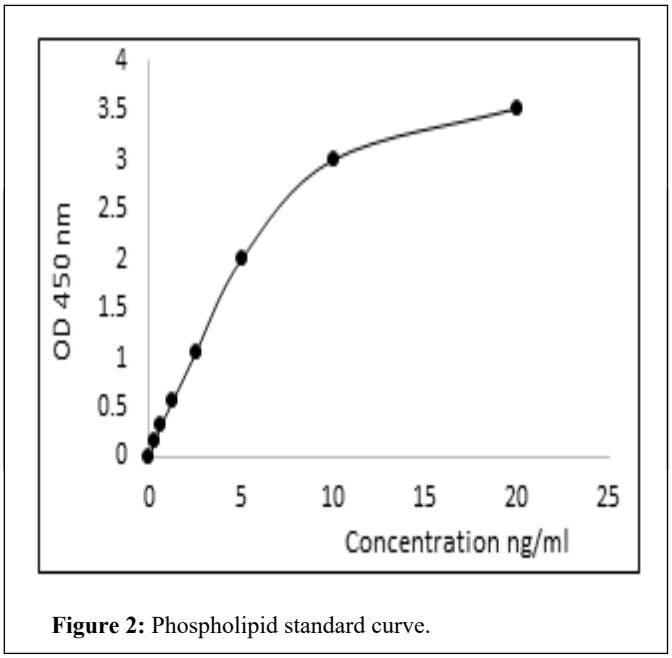

Figure 2: Phospholipid standard curve.

HMG-CoA Reductase assay in liver microsomal fractions was performed by using Sigma-Aldrich kit. Protein concentration was estimated by Folin-Lowry method using BSA as standard. Liver tissues were fixed, processed, embedded, sectioned, stained, and histological examination was observed under light microscope supplied with camera (Leica Biosystems) at 400-x magnification (Figure 3) [26-31].

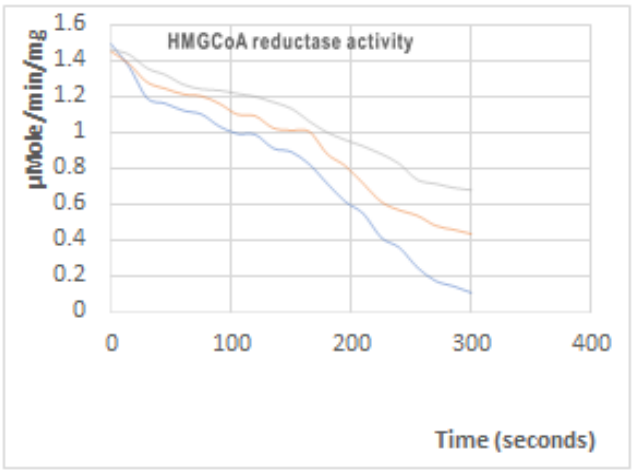

Figure 3: HMGCo-A reductase activity (µMole/min/mg) for NC and NC treated groups with GA and HMGCo-A reductase activity measured through decreasing of NADPH at 340 nm. **Note:** —— -NC —— -NC+3.75% GA —— -NC+10% GA.

Data analysis

Data were analyzed using statistical analysis software SPSS (Statistical Package for the Social Sciences) and the results were presented mean ± SEM. Analysis of Variance One Way (ANOVA) test was used for comparison between groups at the significance level of ($P \leq 0.05$) and ($P \leq 0.001$).

Results

Normal control group treated with 3.75% of Gum Arabic (GA) showed non-significant decrease in total cholesterol when compared with NC ($P<0.001$). On the other side LDL-C decreased significantly when compared with NC ($P \leq 0.001$) whereas normal control group treated with higher dose 10% of Gum Arabic showed a significant reduction of TC by 28% from 96.66 ± 2.8 mg/dl to 69.52 ± 2.85 mg/dl ($P \leq 0.001$). On the other hand, LDL concentration decreased significantly by 70% from 33.79 ± 3.12 to 9.94 ± 1.9 mg/dL, when compared 10% GA treated control group with the Normal Control (NC). Whilst for atherogenic groups the significance decreased by 33% and 51% of TC for atherogenic 3.75% and 10% GA treated groups, respectively ($P \leq 0.001$). The higher dose used at 10% of GA in NC, 3.75% and 10% treated atherogenic groups suggested that GA has hypo-cholesterolemic effect reflected in lowering serum TC. In addition, for atherogenic groups this study found a significant reduction in LDL concentration by 44% from 197.49 ± 8.5 mg/dL to 110.66 ± 7.9 mg/dL when treated atherogenic groups with 3.75% GA and higher reduction by 69% from 197.49 ± 8.5 mg/dL to 61.43 ± 3.25 mg/dL with increasing GA to 10% in atherogenic rats [32-39].

Moreover, this study showed TAG reduced significantly from 119.99 ± 2.7 mg/dL to 87.3 mg/dL and 69.45 mg/dL ± 2.21 mg/dL for normal control groups treated with 3.75% and 10% of Gum Arabic, respectively. In addition, for atherogenic groups there is significant decrease in TAG by both doses of GA and the last group showed more reduction by 44% (131.9 mg/dl ± 4.5 mg/dl) ($P \leq 0.001$). A significant increase of the protective factor HDL concentration from 38.87 mg/dl± 0.76 mg/dl to 42.6 mg/dl ± 0.81 mg/dl and 45.68 mg/dl ± 2.4 mg/dl in treated normal control groups with 3.75% and 10% GA, respectively, as compared with their matched NC group ($P>0.05$). In addition, there is a significance increase of HDL concentration by 22% (41.15 mg/dl ± 0.39 mg/dl) in treated atherogenic group with 3.75% GA, whereas elevated of HDL concentration by 32% (47.18 mg/dl ± 0.54 mg/dl) with 10% GA treatment ($P \leq 0.001$). VLDL decreased significantly with increasing dose of GA for both treated normal controls and atherogenic groups. In addition, normal control groups treated with 3.75% and 10% of Gum Arabic showed a decrease in VLDL from 23.99 ± 0.54 to 17.46 ± 0.46 ($P<0.05$) and 13.88 mg/dl ± 0.44 mg/dl ($P \leq 0.001$), respectively [40-43].

While VLDL concentrations in atherogenic groups have reduction by 26% (34.84 ± 0.75 mg/dl) after treated with 3.75% gum Arabic and 44% reduction to (26.38 ± 0.9) after dosing with 10% of GA ($P \leq 0.001$). GA has antihyperglycemic effect as glucose concentration dropped significantly from 101.83 ± 3.42 mg/dl to 73.8 ± 1.61 mg/dl and 61.34 ± 1.001 mg/dl in NC 3.75% and 10% GA treated groups, respectively. In addition, atherogenic treated groups showed a significant decrease when compared with AT group and the last atherogenic group treated with 10% GA had a reduction to 118.01 mg/dl ± 3.21 mg/dl that around glucose level in normal control 101.83 mg/dl ± 3.42 mg/dl. This study also, revealed that phospholipids showed no significance difference between all studied groups ($P \leq 0.001$).

Final body weight decreased significantly by 12.6% and 13.6%, for rats treated with 3.75% and 10% GA compared to NC group ($P \leq 0.001$). On the other hand, atherogenic groups treated by 3.75% GA was decreased significantly by 26% ($P \leq 0.001$) and atherogenic group treated with 10% GA was decreased final body weight significantly to 322.12 g ± 20 g ($P \leq 0.05$).

In addition, there was significant reduction of body weight gain from 126.75 g to 85.5 g and 82.14 g for NC treated groups compared to NC ($P \leq 0.001$). Moreover, there is significant decrease in weights for both atherogenic treated groups with 3.75% and 10% GA compared to atherogenic group but atherogenic group treated with 3.75% GA observed more reduction than the higher dose from 180 g to 83.3 g body weight ($P \leq 0.001$). Whereas last group showed a slight decrease of body weight to 131.37 g ($P \leq 0.001$).

Both treatments showed significant reduction of 8% and 24% in food intake in normal treated groups with 3.75% and 10% GA, respectively. While for both treated atherogenic groups by 3.7% and 10% GA showed the same significant reduction by 12% for each when compared to AT group ($P \leq 0.001$), this means that GA could reduce high fat food (composed of 25% cholesterol) intake irrespectively to amount of GA whether high or low. Besides that, water intake reduced significantly by comparing treated groups to their matched controls but there is no significant difference when compare the two atherogenic treated groups together [44-49].

Liver weights in 3.75% and 10% GA treated NC groups had no significant effect while there was significant decrease in AT 3.75% GA treated group to 8.53 g ± 0.43 g ($P \leq 0.001$). However, this study considered there is no effect of GA on liver organ weight as liver weights to the body weights ratio of rats (organ somatic index) showed no significance different between all studied groups ($P>0.001$).

There is no significant effect of GA on HMGR activities in normal controls treated groups. Atherogenic group had significant increase of HMGR activity 5.94 units/mg ± 0.272 units/mg as compared to all studied groups. While a significant decrease to 1.67 ± 0.151 unit/mg

and 2.54 unit/mg ± 0.086 unit/mg of HMGR activity in AT treated with 3.75% and 10% GA, respectively ($P \leq 0.001$) (Figures 4 and 5).

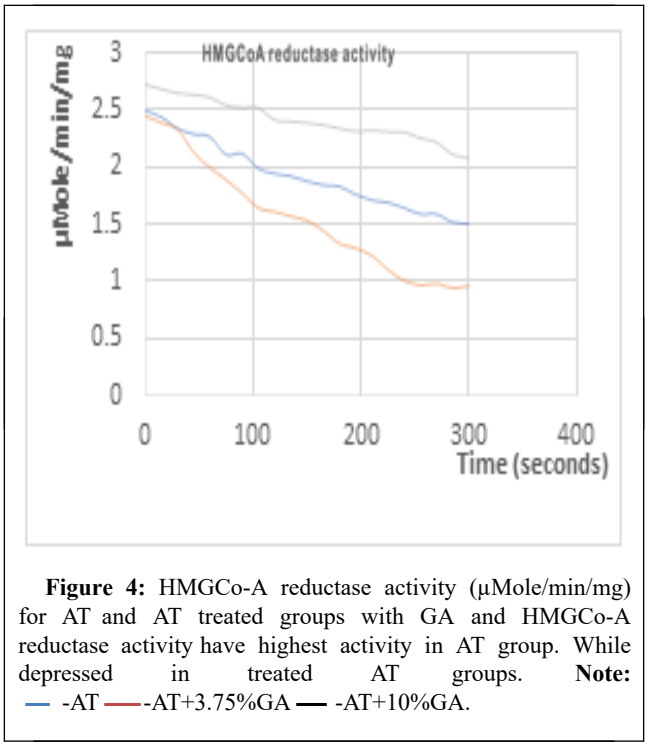

Figure 4: HMGCo-A reductase activity (µMole/min/mg) for AT and AT treated groups with GA and HMGCo-A reductase activity have highest activity in AT group. While depressed in treated AT groups. **Note:** — -AT —-AT+3.75%GA — -AT+10%GA.

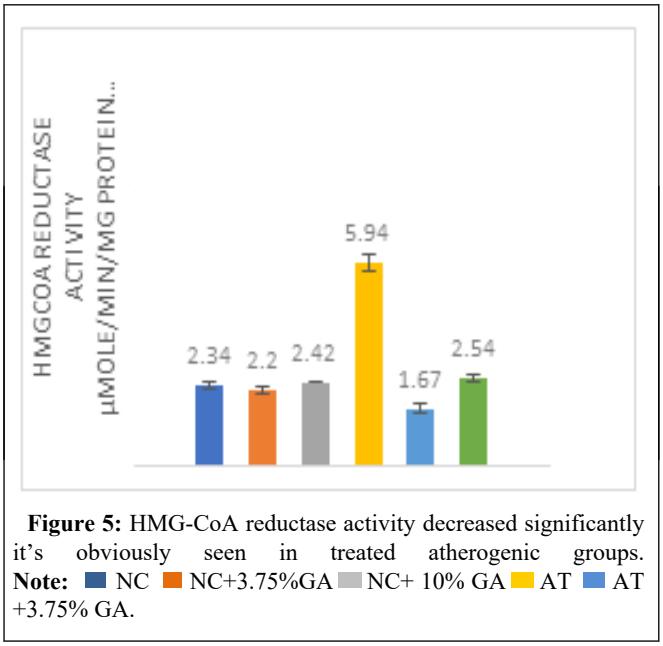

Figure 5: HMG-CoA reductase activity decreased significantly it's obviously seen in treated atherogenic groups. **Note:** NC NC+3.75%GA NC+ 10% GA AT AT +3.75% GA.

In the present study livers fixed with 10% neutral buffer formalin, stained with hematoxylin and Eosin, were observed under 400-x magnification. Livers photomicrograph (10% neutral buffer formalin fixed, stained with hematoxylin and Eosin (H and E), with 400-x magnification) (Figure 6).

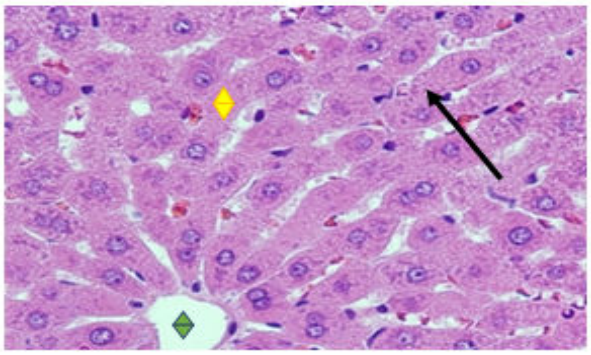

Figure 6: This micrograph represented control group without GA treatment.

As noticed here normal look hepatocyte (black arrow) and central vein (green triangle) also normal sinusoids (yellow triangle).

Normal control group without any GA treatments which present in undamaged liver cells with normal central vein and intact sinusoids. In addition, NC treated with 3.75% GA in howed normal portal traid (Figures 7 and 8).

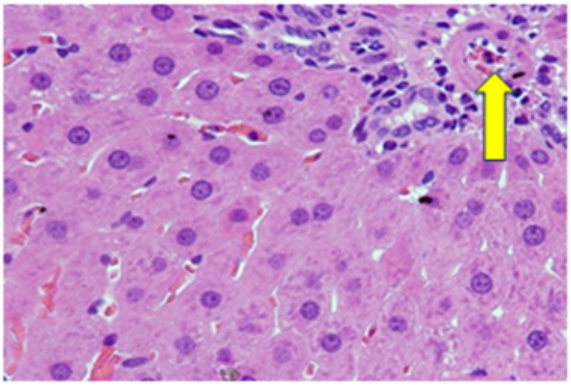

Figure 7: Photomicrograph represented control liver treated with 3.75% GA showing normal portal traid composed of (artery, vein, and bile duct) (yellow arrow).

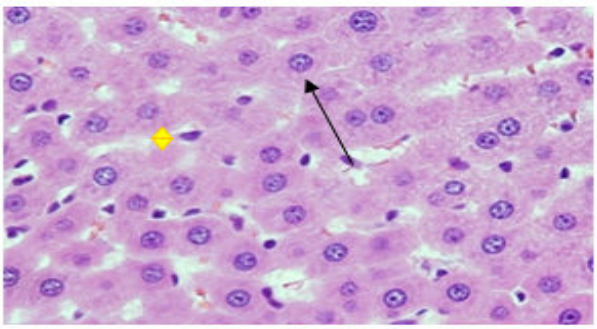

Figure 8: Control liver treated with 10% GA showed normal look hepatocyte (black arrow) with normal sinusoids (yellow triangle).

Moreover, NC treated with 10% GA showed normal liver architecture. GA had no harmful effect according to these observations on NC groups. While Microscopic image of a liver section from atherogenic group without any GA treatments activated cells as binucleated hepatocytes with enlargement liver cells called ballooning degeneration of hepatocytes (Figure 9).

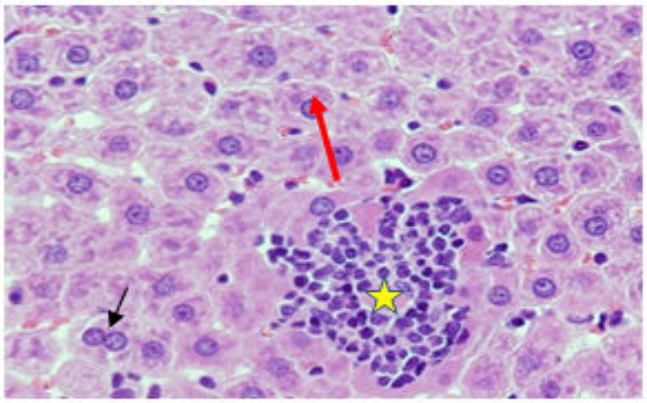

Figure 9: Microscopic imaging of a liver section from atherogenic group without any GA treatment, showing bi-nucleated hepatocytes (black arrow) (activated). Balloon degeneration of hepatocytes (enlarged liver cells (red arrow). Necrotic hepatocytes (yellow star) surrounded by inflammatory cells (lymphocyte and macrophages) also inflammation of hepatocyte lobules due to high fat diet injury.

In addition, inflammation of hepatocyte lobules appeared due to high fat diet injury and showed necrotic hepatocytes surrounded by inflammatory cells as lymphocyte and macrophages aggregated. However, in the other side for atherogenic group treated with 3.75% GA, liver trying to be retained to normal architecture and healing itself. This photomicrograph showed portal tract mononuclear cell infiltration that helps in clear away the destroyed fragments. Hepatocytes look like near normal without lobular inflammation nor necrosis, with mild enlargement of cytoplasm but there is no ballooning degeneration appeared as in atherogenic group (Figure 10).

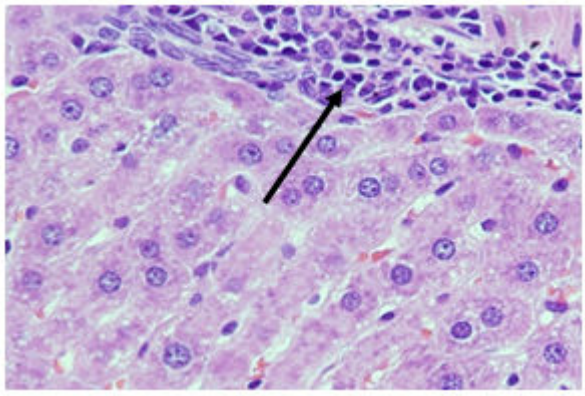

Figure 10: Microscopic imaging of a liver section from AT group

It is treated with 3.75% GA showing portal tract mononuclear cell infiltration, where white blood cells mainly lymphocytes and macrophages collect at the site of injury to help clear away the destroyed fragments (Black arrow). Hepatocytes look near normal without lobular inflammation nor necrosis, with mild enlargement of cytoplasm but no ballooning degeneration appear as in atherogenic group, here liver trying to heal itself and retained normal architecture.

Finally the last micrograph represents atherogenic group treated with 10% GA demonstrated marked vacuolar degeneration of hepatocyte and occasional numerous large fats in vacuoles within hepatocytes called macro-vesicular steatosis in which the lipids accumulate due to fatty acids accumulation caused by consumption of high fat diet but even there is no any inflammation appeared may be increase duration of experiment would showed better result with 10% GA (Figure 11).

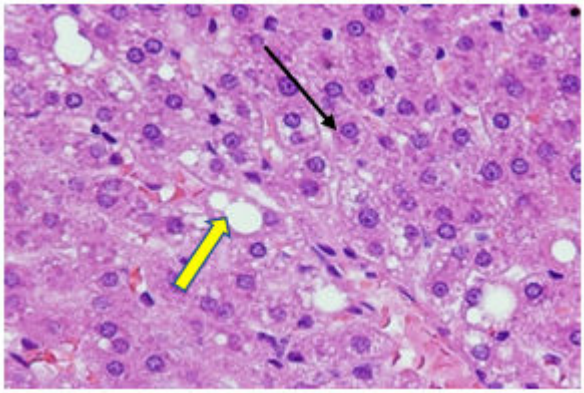

Figure 11: Microscopic figure represents atherogenic group treated with 10% GA demonstrating marked vacuolar degeneration of hepatocyte (black arrow) with occasional numerous large fats in vacuoles within hepatocytes (yellow arrow). There is no inflammation appeared.

Discussion

Since 1969, the Joint FAO/WHO expert committee on food additives evaluated Gum Arabic as acceptable daily intake for humans and Sudanese people in Western Sudan had been using it for long time without limitations. In support of our study, a case-control study done at Omdurman Hospital, Sudan, that monitored the effect of GA on serum lipids in patients with hyperlipidemia. Cases were treated with 20 mg atorvastatin tablet/day and 30 mg of GA while controls received atorvastatin only for month. This study showed a statistically significant reduction in T-cholesterol (7.8%), TG (2.9%) and LDL (8.1%) in GA treated group when compared to the control group without significant difference in the levels of HDL ($P \leq 0.001$). Another study on total of 192 unsexed broiler chicks (Cobb strain) were randomly assigned to four dietary treatments (0, 2.5, 5 and 7.5% Gum Arabic). Each treatment was composed of six replicates (8 birds/replicate). Feed and water were offered throughout the 42 days experimental period. Chicks fed with 5% and 7.5% of Gum Arabic groups showed the lowest level of cholesterol in serum ($P \leq 0.05$).

In contrast, consumption of GA at a dose of 15 g/day for 4 weeks by normal or hyper-cholesterolemic subjects showed different result.

This may be due to the role of viscosity degree of collective fibers effect, which must be explored in further studies. Since a medium viscosity water soluble dietary fiber (pectin, psyllium, locust bean gum and guar gum) mixture showed significant reduction on plasma lipids but an equal amount of a lower viscosity WSDF of Acacia gum (Gum Arabic), had no significant effect on plasma lipids. Treatments with WSDF did not produce significant changes in mean dietary intakes within or between treated groups. The variable lipid lowering effects of GA might be related to the dose used, the chemical constituents of GA that can vary with its source or may be due to genetic and personal differences. The presence of monovalent ions: Potassium and sodium in gum Arabic are responsible for increasing its viscosity. Divalent ions by contrast (Calcium and Magnesium) have a lesser effect on its viscosity [50-54].

The effects of Gum Arabica on lipid metabolism were at variance. As an old study reports that GA increased cholesterol synthesis in rats fed a cholesterol-diet, but without any effect on rats fed by diet free of cholesterol. Whereas other reports that when subjects receive Gum Arabic at 25 g/day and 30 g/day in the periods of 21 and 30 days there were reductions of total cholesterol in serum by 6% and 10.4%, respectively. The decrease was correlated to VLDL and LDL cholesterol only, without any effect on triglycerides and HDL.

Also, a study, on a collection of fibers from Gum Arabic and apples which were separately known to have potential hypocholesterolemic effects for duration of six weeks. Despite the levels of fiber supplement used during this study which was moderate when compared to the previous studies, there was a significant lowering effect on Total cholesterol by 10% and LDL by 14%, without significant changes in either HDL or TG concentrations. The authors ascribed the overstated outcome to the collective effects of these fibers [55-57].

On the other hand, consumption of Gum Arabic for one month at a dose of 15 g/day by hypercholesterolemic or normal subjects had no significant action on their plasma lipids. However, the outcomes were as paradoxical in rats, were some studies show increased and others show reduced level of lipid profile. On the other hand, another study has shown that feeding with GA did not affect plasma cholesterol concentrations, but plasma TG in treated groups were significantly lower than in controls. In a different study, rats were fed with Gum Arabic substituting cellulose in purified diets that supplemented with cholic acid and cholesterol, showed no significant effects of increasing concentrations of GA on the concentrations of either plasma or liver cholesterol when compared to levels found in rats that consumed control diet containing cellulose alone. However, Plasma TG concentrations were higher in rats fed GA, whereas liver triacylglycerols were lower.

Several mechanisms have been suggested for explaining the hypocholesterolemic property of Gum Arabic. As some of studies have proposed that the viscosity of fermentable dietary fibers participate basically to the lipid reducing effects in human and animals, whilst other suggests that this property doesn't relate to plasma lipids. Most obviously, the mechanism may be related to increased neutral sterol and fecal bile acid excretion or a modification of lipid absorption and digestion.

Moreover, it was suggested that Gum Arabic has well binding capacity to cations, especially to calcium (Ca^{+2}). In cecum the degradation of Gum Arabic occurred, for that the sequestered bile acids were liberated and during the fermentation process the acidic pH generated made them insoluble. In addition, calcium bounded is released and forms insoluble complexes with bile acids thereby increasing their excretion rate.

In this study the drop of glucose levels from 199.63 mg/dl ± 6.3 mg/dl in AT group to 118.01 mg/dl ± 3.21 mg/dl in AT treated with 10% GA which near the level in NC 101.83 mg/dl ± 3.4 mg/dl, means that GA effectively recovered glucose concentration to normalcy, which opposite the statin effect that develop type 2 diabetes mellitus as time progressed. This study support the suggestion by that reported GA has hypoglycemic effect through induce secretion of insulin from pancreatic β- cells. Also through slow the empty of stomach as in other study that resulted in reduction of glucose response after incorporation of guar gums in the meal for 6 healthy subjects. In agreement with our study report that evaluated the effects of Gum Arabic on glucose levels by using two models, white rice mush and mixed grain mush, as often consumed in many countries. Gum Arabic was incorporated into the two types of mush individually, showing significantly decreased blood glucose after oral administration of mush in mice ($P \leq 0.05$). Therefore, for the reduction of postprandial glycemic response, Gum Arabic may be a helpful ingredient, which could be added in porridge. Previously, experiments were done for follow up *in vitro* and in normal subjects to estimate, alternative viscous polysaccharides as agents for reducing post-prandial hyperglycemia. Mixtures of various types of gums (not including Gum Arabic) have been shown to block glucose movement *in vitro* and reduced post-prandial blood glucose in subjects when combined in drinkables having 50 g of glucose.

Also, Pareek studied 45 subjects with type 2 diabetes mellitus aged from 45 to 65 years, male or female, not on insulin therapy, not taking medication for other health conditions and their fasting blood glucose levels between (110 mg/dl-300 mg/dl). Subjects were divided randomly in three groups (I, II and III) consumed respectively: 2, 3 and 4 g of *Acacia nilotica* pods powder daily for month. This study suggested that the inclusion of pods powder in the diet of people with type 2 diabetes mellitus mainly 4 g/day dose will reduce the blood glucose, lipid profile (TC, TAG, LDL and VLDL) and blood pressure associated with diabetes and cardiovascular diseases. There is also a double -blind placebo-controlled trial conducted at Academy Charity Teaching Hospital in Sudan for 3 month which follow up 91 patients out of 100 after exclusion of individuals not suitable for certain criteria such as alcoholism, placebo group took 5 g of pectin and the second group kept on regular ingestion of GA 30 g/day. Gum Arabic (*Acacia senegal*) leads to metabolic changes that deserve attention as diet supplementation for improving nutritional value of type 2 diabetic patients with inexpensive and safe type of soluble dietary fiber by improving fasting plasma glucose, HbA1c, and lipid profiles. Also, this study mentions that as the patients were treated with metformin alone or combination of drugs; these medications have different pharmacological effects. Therefore, further studies based on the types of drugs must be considered in the future. Gum Arabic (*Acacia senegal*) leads to a range of metabolic changes that deserve attention as dietary supplementation for improving nutritional value of type 2 diabetic patients with cheap and safe type of soluble dietary fiber by improving fasting plasma glucose, HbA1c, and lipid profiles. Also, this study mentions that as the patients were treated with metformin only or in combined with drugs; these medications have different pharmacological effects. Therefore, further studies based on the types of drugs must be considered in the future. Phospholipids monitoring is important as many studies suggested that phospholipid oxidation products could integrate into lipid membranes of cells; they then can either cause local membrane disruption or act as ligands.

Moreover, strong evidence has been presented for the ability of oxidized phospholipids to form protein adducts. Probably the most well characterized are the levuglandins that are associated with atherosclerosis. The present study revealed that phospholipids showed no significance difference between all groups. As this study only occupied 42 days which may be not enough to cause changes on phospholipids concentrations but if the duration increased to be 12 weeks or more it may give alteration of phospholipids as the atherogenic state reaches later stages on which the bio-membranes have more disruption. Benefits of Gum Arabic have been extensively studied in animals. However, there is paucity of data also regarding its quantified use in humans. For example, a study determined the effects of regular Gum Arabic (*Acacia senegal* gum) ingestion on body mass index and body fat percentage among healthy adult females (30 gm/day) for 6 weeks. The study concluded that GA (Acacia gum) ingestion causes significant reduction in body fat percentage and BMI whereby the effect could be exploited in the treatment of obesity and hence preventing increase prevalence of CVDs.

GA is very rich in soluble dietary fiber. Several epidemiological studies suggest that a high intake of dietary fiber is associated with beneficial effects on fat metabolism]. Dietary fiber promotes satiation, alter glycemic index, affects gastric emptying, gut hormone secretion and thus helps to manage weight. GA promotes weight loss by two different mechanisms. It reduces appetite and thus food intake at the same time increases energy expenditure. In addition, a study has shown that GA inhibits intestinal glucose absorption *via* interaction with membrane abundance of SGLT1 in mice. Gum Arabic significantly blunted the increase in body weight, fasting plasma glucose and fasting insulin concentrations during high fat diet [58].

Liver weights on NC treated groups had no significant effect while there was significant decrease in AT 3.75% GA treated group to 8.53 g ± 0.43 g. But we considered there is no effect of GA on liver organ weight as liver weights to the body weights ratio of rats showed no significance different between all studied groups ($P>0.05$). This result opposed the outcome of studied the effects of *Acacia senegal* seed extract (500 mg/kg/day) treatment for 45 days on the alteration in liver weight of hypercholesterolemic diet fed atherosclerotic male rabbits as liver weight was brought to normalcy ($P \leq 0.05$). HMGR catalyzes the conversion of HMG-CoA to mevalonic acid, a necessary step in the biosynthesis of cholesterol, which is targeted for inhibition by GA as statin action. We measured HMGR activities of studied groups through measuring NADPH depletions at 340 nm. There is no significant effect of HMGR activities in Normal controls treated groups. Atherogenic group had significant increase of HMGR activity 5.94 units/mg ± 0.272 units/mg as compared to all groups. While a significant decrease to 1.67 ± 0.151 unit/mg and 2.54 ± 0.086 unit/mg of HMGR activity in AT treated with 3.75% and 10% GA, respectively. As there is no effect on HMGR activity in NC treated with 10% GA, lowering of TC in this group can be attributed to sequestering or binding of dietary fibers to bile acids, decreasing their active reabsorption in ileum, hence leading to their excretion in feces. As consequence, this resulted in increasing cholesterol diversion to bile acid synthesis in liver, which leads to promote increased numbers of LDL-R on the liver and reduced cholesterol concentration in plasma. On the other hand, lowering of TC in atherogenic 3.75% and 10% GA treated groups can be attributed to GA action to inhibit HMGR activities and hence lowering cholesterol synthesis.

The effects of GA supplementation treatment on liver protection have not been reported. But Note that Acacia fiber may help guard against liver damage according to study published in Pharmacology Research which found that treating mice with Acacia fiber prior to administering acetaminophen helped protect their livers from the drug's toxic effects. According to the authors, GA fiber may help combat liver damage by reducing oxidative stress. GA also has strong antioxidant properties, and is used to reduce the experimental nephrotoxicity against gentamicin and cisplatin and to ameliorate cardiotoxicity. Moreover, GA is reported to reduce oxidative and inflammation against adenine induced chronic renal failure in rats.

Long-term high-fat diet increases oxidative stress. The deleterious effects of oxidative stress come from either an increased amount of Reactive Oxygen Species (ROS) production, or a decrease of natural cell antioxidant capacity of an organism. However, the utilization of foods rich with antioxidant phytochemicals may reduce the deleterious effects caused by oxidative stress [59].

As previously proposed GA possess potent anti-oxidant activity and works as superoxide scavenger against cardiotoxicity induced by doxorubicin in mice. We suggested GA has anti inflammation effect, in accordance with who reported that officinal parts of *A. Senegal* such as seeds, bark, leaves, fruits and gum are rich in flavonoids, polyphenols, tannins, alkaloids and saponins. In addition preliminary studies indicated that flavonoids may affect inflammatory mechanisms *via* their ability to inhibit reactive oxygen or nitrogen compounds. Flavonoids have also been proposed to inhibit the pro-inflammatory activity of enzymes involved in free radical production, such as cyclooxygenase, lipoxygenase or inducible nitric oxide synthase and not causing an inflammation of liver treated tissues. Authors obviously noticed that restoration of tissue histology following 3.75% and 10% administration of GA might be an outcome of inhibitions in the activities of HMGCo-A reductase enzyme which catalyzes conversion of HMG CoA to mevalonate, a rate limiting step in the formation of endogenous cholesterol leading to the decrease in the intracellular status of cholesterol. It is speculated that *Acacia senegal* seed might lower LDL-cholesterol through inhibiting hepatic cholesterol biosynthesis and VLDL-cholesterol production which is the source of LDL-cholesterol production.

Conclusion

The findings of the present study reveal that *Acacia senegal* gum (Gum Arabic) ameliorated diet-induced atherosclerosis and could be considered as aid in the development of novel therapeutics as it can effectively decrease the enzyme HMG-CoA reductase activity in atherogenic rats ($P \leq 0.001$). Also, to get beneficial effect from GA, we recommend using it in continuous duration for month and more. GA has significant lowering effect on TC, LDL, VLDL and TAG with increasing HDL concentrations, leading to reduce development of atherosclerosis and hence prevent cardiovascular disease. In addition, GA decreases glucose concentration adversely the effect of long-term use of statins then prevents development of type 2 diabetes mellitus. GA especially at 3.75% dose worked as protective factor against liver injury and inflammation occurred from high fat diet, also 10% GA showed no inflammation and necrosis in liver.

We recommend that further studies could be done on smoking or diabetic human with high incidence to develop atherosclerosis and monitor their recovery to normalcy by incorporating GA to their diets. However, further studies on the isolated active components of GA are required, and some further studies about type of inhibition on HMGR which carried out by GA.

Conflict of Interest

Authors declare there is no conflict of interest.

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