Asian Journal of Research in Animal and Veterinary Sciences

8(3): 1-12, 2021; Article no.AJRAVS.68878

Dietary Gum Arabic Alleviates Carbon Tetrachloride Induced Liver Fibrosis in Wistar Rats

Mohammed Hamid[1*], Yassin Abdulrahim[1,2], Abdelnasir A[1,3], Khalid M. Mohammedsalih[1], Nagmeldin A. Omer[4], Juma Ahamed Abaker[1], Hassan M. A. Hejair[1],Tamour Elkhier[1], Tagwa Norain Mahmoud[1] and Hidaia B. Zolain[1]

[1]Faculty of Veterinary Sciences, University of Nyala, Sudan.
[2]College of Veterinary Medicine, Nanjing Agricultural University, Nanjing 210095, Jiangsu Province, China.
[3]Department of Pathology and Sample Management, Veterinary Laboratories Division, Animal Wealth Sector, AbuDhabi Agriculture and Food Safety Authority (ADAFSA), Abu Dhabi, UAE.
[4]College of Allied Medical Sciences, University of Nyala, Sudan.

Authors' contributions

This work was carried out in collaboration among all authors. Authors MH and YA designed the study. Authors MH, YA, JAA, HMAH performed the experiments. Authors MH and NAO analyzed the data. All authors were involved in writing. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Hager Tarek Hassan Ismail, Zagazig University, Egypt.
(2) Prof. Hazem Mohammed Ebraheem Shaheen, Damanhour University, Egypt.
(3) Dr. Nesrien Mohamed Hashem, Alexandria University, Egypt.
Reviewers:
(1) Junjie Zhang, Zhejiang Chinese Medical University, China.
(2) Barde Israel Joshua, National Veterinary Research Institute, Nigeria.
Complete Peer review History: http://www.sdiarticle4.com/review-history/68878

Original Research Article

Received 02 April 2021
Accepted 07 June 2021
Published 14 June 2021

ABSTRACT

Aims: This study was carried out to investigate the effect of Gum Arabic (GA) on liver fibrosis induced by carbon tetrachloride (CCl_4) in Wistar rats.
Methods: Rats were randomly divided into three groups (each group: n=8). Group 1 served as untreated control with just 2 ml/kg of olive oil. Group 2 administered only by intraperitoneal (I.P) injection of CCl_4 dissolved in olive oil at a dose of 2 ml/kg body weight twice a week for 7 week. Group 3 administered in additional to CCl_4 a basal diets containing GA (5%).

**Corresponding author: E-mail: mhamed448@gmail.com;*

Results: The outcomes of the current study exhibited that, CCl_4 elevated the serum levels of liver enzymes, malondialdehyde (MDA) and hydroxyproline. In addition, CCl_4 increase the expression of inflammatory cytokines TLR-4, TNF-α, IL-6, IL-β1and MCP-1or fibrotic markers cytokines; TGFβ1and α-SMA while decreasing the activity of T-AOC, SOD and GSH-Px . Administration of GA effectively attenuated these changes, in additional to promotion of antioxidants enzymes and reducing the collagen deposition and hepatocytes necrosis.
Conclusion: These results suggested that GA has antifibrotic properties and could be used as potential dietary agent against CCl_4-induced liver fibrosis in rats.

Keywords: Gum Arabic; carbon tetrachloride; liver, fibrosis; rats.

1. INTRODUCTION

Liver fibrosis, represent the major health problems that increase morbidity and mortality worldwide and signify the final pathways of almost all chronic hepatocellular injuries [1]. Liver fibrosis may result from excessive accumulation of fibrous connective tissue in the liver and nodule formation leading to loss of liver function, cirrhosis, hepato-cellular carcinoma, and liver failure [2,3]. Carbon tetrachloride (CCl_4) is a recognized toxicant agent used extensively to produce liver fibrosis and oxidative stress [4]. Fibrosis persuaded by CCl_4 is accompanying by the progression of lipid peroxidation, inflammation and the weakening of antioxidant status [5]. Unfortunately, to date no specific anti-fibrotic drugs are available. But in recent years, interventions by antioxidant agents represent an effective potential therapeutic strategy for the treatment and prevention of the liver diseases [4,5].

There are numerous of evidence indicating that natural products from edible and medicinal plants exhibited potent antioxidant activity that could act against hepatic toxicity caused by various toxicants [6,7]. One of those natural products is Gum Arabic (GA). GA is well-defined as an edible, dried gummy polysaccharide acquired from the Acacia trees (*Acacia. seyal & Acacia senegal*) and rich in non-viscous soluble fiber which is commonly utilized as a stabilizer and emulsifier in the food, cosmetic, and pharmaceutical industry [8,9]. GA has been used in North Africa and the Middle East in the folk medicine to decrease the occurrence of the acute and chronic renal failure [10,11]. It is also reported to be effective as an oral antioxidant substance to treats and prevents the skin and intestinal mucosa inflammation [12]. Additionally, many reports indicated that, GA mitigates gentamicin-induced nephrotoxicity and lipid peroxidation in the kidney tissue [9]. Furthermore, GA has anti-inflammatory, antidiarrheal, anti-obesity, antihypertensive, and antimicrobial effects [8,13,14]. Moreover, GA has also a potential role in the prevention of liver injury; it has been useful to alleviate the acetaminophen-intoxication by blocking liver macrophage function, reduction of hepatic oxidative stress, and nitric oxide scavenging. It has been confirmed to be used for the inhibition of high fat diet, CCl_4 or trichloroacetate intoxication [15-17].

To the best of our knowledge, there are no reports regarding the antifibrotic effect of GA against CCl_4 intoxication. Therefore, the current study was undertaken to investigate the dietary administration effect of GA on the progression of liver fibrosis induced by CCl_4 in rats based on histopathological alterations and fibrosis quantification, serum biochemical parameters, oxidative stress, anti-inflammatory and fibrogenesis genes expression.

2. MATERIALS AND METHODS

2.1 Chemicals

Carbon tetrachloride was acquired from Shoude Institute (Nanjing, China). Superoxide (SOD), malondialdehyde (MDA), glutathione peroxidase (GPx), total antioxidant capacity (T-AOC), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hydroxyproline assay kits were provided by Jiancheng Biotechnology (Nanjing, China). Antibodies against TLR-4and α-SMA were purchased from Abcam, (Cambridge, UK). Gum Arabic (SUPERGUM^{TM} EM 10) was obtained from San-Ei Gen FFI Inc, Japan.

2.2 Animals, Diet and Experimental Design

Twenty-four male Wistar rats of (190 – 230 g) body weight were obtained from the center for

laboratory animals, Yangzhou University (Yangzhou, China). The rats were kept at 25ºC±3 with 12 h dark / light cycles and provided with rat food and water ad libitum and acclimatized for one week before the experiment. The dose of GA was designated according to a previous report [18]. The animals were randomly assigned to three groups. The first group (n=8; Control) was given 2 mL/kg body weight of olive oil through I.P twice a week for 7 weeks, the second group (n=8; CCl_4) was given 2 mL/kg body weight of CCl_4 mixed with olive oil through I.P twice a week for 7 weeks, and the third group (n=8; CCl_4+ GA) was given 2 mL/kg body weight of CCl_4 mixed with olive oil through I.P twice a week and fed with GA 5.0% for 7 weeks. The rats were detected daily regarding food and water intake. The rats were slaughtered after the 7th week after fasting overnight. Blood and liver samples were collected from all groups; liver sections were immediately frozen in liquid nitrogen and stored at -80 °C until subsequent analyses.

2.3 Liver Function Indices Analysis

ALP, ALT and AST hepatic specific indices of serums were assessed using an automated chemistry analyzer. (BS-300, MindrayMedical International Limited). According to the instructions.

2.4 Evaluation of an Antioxidant Enzyme Activities and Lipid Peroxidation Levels

Liver tissue homogenates were used for estimating antioxidant enzymes activity T-AOC, SOD, and GSH-PX in addition to lipid peroxidation marker (MDA), according to the manufacturer's guidelines.

2.5 Hepatic Hydroxyproline Evaluation

The stages of hydroxyproline content were evaluated from wet liver tissues as μg/g following the guidelines of the commercial assay kit.

2.6 Histopathological Evaluation

Liver tissue sections were fixed in 10% formaldehyde solution, embedded in paraffin, and sectioned into 4μm thicknesses. The sections were stained by Hematoxylin and eosin and Sirius red using standard procedures to examine the grade of liver fibrosis by using a computerized image analysis system for 5 random fields on each slide. (Image-Pro Plus version 6.0; Media Cybernetics, Md., USA.) [19].

2.7 Immunohistochemical Estimation

Paraffin embedding sections of the liver were exposed to immunohistochemical estimation by blocking and incubating with mouse monoclonal antibody against TLR-4 (1:100).The sections were also pounded and incubated with a secondary antibody according to our previous publications [20].

2.8 mRNA Extraction and Real-time Quantitative RT-PCR

Frozen liver tissues were used to extract the total RNA by Trizol reagent (Invitrogen), following the instructions. Synthesis of cDNA was performed by using PrimeScript RT Master Mix Perfect Real Time (Takara Co., Otsu, Japan), and were amplified using SYBR Green (Takara Co., Otsu, Japan) as previously reported [19]. The Real-time quantitative RT-PCR was conducted on an ABI Prism 7300 Detection System (Applied Biosystems, USA). Primers for TLR-4, TNF-α, IL-6, IL-β1, MCP-1, TGFβ1, α-SMA and GAPDH were designed by online Primer-Blast of NCBI and showed in Table 1.

2.9 Statistical Analysis

Data were statistically analyzed by One-way analysis of variance (ANOVA) and Duncan test using SPSS 20 for Windows, followed by a least-significant difference (LSD) test for specific comparisons. The experimental data were expressed as mean ± S.E.M.; the P value of 0.05 or less was considered to be a significant difference between the groups.

3. RESULTS

3.1 Effects of GA on General Features of Rats

The differences in the final body weight, liver weight and index, food and water intake between control and treatment groups during the experimentation are given in Table 2. Group treated only by CCl_4 showed high decrease (P=0.007) in final body weight as compared with control group. The final body weight of GA + CCl_4 group was increased significantly (P<0.001) compared to the group treated only by CCl_4. Group treated only by CCl_4 showed high

increase (P<0.001) in the liver weight as compared with control group. The liver weight of GA + CCl_4 group was decreased (P<0.001) compared to the group treated only by CCl_4.The liver index of CCl_4 group was increased opposed to control group (P<0.001), while GA + CCl_4 group revealed significant reduce (P<0.001) in the liver index opposed to group treated by CCl_4 alone.

The food intake decreased significantly in the CCl_4 group compared with that of the control group (P=0.003). The group treated with GA + CCl_4 improved the levels of food intake compared to the CCl_4 group (P=0.031). Water intake significantly increased in the CCl_4 group compared to the control group (P<0.001). However, GA + CCl_4 supplementation significantly lowered the water intake levels compared with the CCl_4-treated group (p<0.001).

3.2 Evaluation of the Serum Enzymes

The effect of GA on serum levels of AST, ALT and ALP were shown in Fig. 1. The AST, ALT and ALP serum levels of rats treated only by CCl_4 prominently increased compared with the control group (P<0.001). The group treated with GA + CCl_4 showed reduced (P<0.001) biochemical levels of AST, ALT and ALP compared to the CCl_4 group.

3.3 Histopathological Evaluation

The liver histopathology forms of control and others treated rats was shown in (Fig. 2). The histopathological appearance of the control liver sections showed typical histological architecture (Fig. 2A). Group treated only by CCl_4 demonstrated massive necrosis with severe inflammation and inflammatory cells infiltration in addition to hepatocytes steatosis, and collagen accumulation (Fig. 2B). Whereas GA + CCl_4 groups showed obvious lessening in the hepatocytes damage and collagen accumulation when compared with group treated only by CCl_4 (Fig. 2C).

Table 1. Primer pairs used for Real-Time PCR

Gene	Primers: sequences (5' 3')	Accession
TNF-α	F: CTGTGCCTCAGCCTCTTCTC	NM_012675.3
	R: ACTGATGAGAGGGAGCCCAT	
IL-6	F: AGCGATGATGCACTGTCAGA	NM_012589.2
	R: GGAACTCCAGAAGACCAGAGC	
TGF-β_1	F: AGGGCTACCATGCCAACTTC	NM_021578.2
	R: CCACGTAGTAGACGATGGGC	
α-SMA	F: ACCATCGGGAATGAACGCTT	NM_031004.2
	R: CTGTCAGCAATGCCTGGGTA	
MCP-1	F: TGATCCCAATGAGTCGGCTG	NM_031530.1
	R: GGTGCTGAAGTCCTTAGGGT	
TLR-4	F: TCCACAAGAGCCGGAAAGTT	NM_019178.2
	R: TGAAGATGATGCCAGAGCGG	
IL-β1	F: AGGCTGACAGACCCCAAAAG	NM_031512.2
	R: CTCCACGGGCAAGACATAGG	
GAPDH	F: GCGAGATCCCGCTAACATCA	XM_017593963.1
	R: CTCGTGGTTCACACCCATCA	

Table 2. Effects of Gum Arabic (GA) and GA+CCl_4 on the food intake, water intake, body weight, liver weight and liver index (liver weight/ body weight x 100%) of rat*

	Control	CCl_4	CCl_4+GA
Initial body weight (g)	222.75 ±3	219.75 ±2.5	212.75 ±7.9
Final body weight (g)	281^{a}± 4.6	225^{c}± 3.4	272.5^{b} ± 6.5
Liver weight (g)	9.35^{b}± 0.46	13.31^{a}±0.23	10.15^{b}±0.29
Liver index (%)	3.33^{b}±0.22	5.95^{a}±0.04	3.71^{b}±0.21
Food intake(g/day)	21.5^{b}	14.7^{d}	17.2^{c}
Water intake(ml/day)	17.3^{d}	47.2^{a}	24.4^{b}

**Data are represented as mean ± SEM (n = 8). Different letters above the values within each test parameter indicate significant differences between groups (p < 0.05)*

To evaluate the impact of GA on CCl_4-induced hepatic fibrosis, hepatic sections were stained with Sirius red to notice the accumulation of collagens. CCl_4-treated rats developed substantial collagens deposition as indicated by intensive red staining (Fig. 2B) when compared with control group that showed absence of collagen fibers (Fig. 2A). However, treatment with GA + CCl_4 showed few areas containing collagen as compared with the group treated only by CCl_4 (Fig. 2C).

3.4 Effects of Gum Arabic on the Antioxidant Enzymes and Lipid Peroxidation

T-AOC, SOD, GSH-PX and MDA were assessed in the current study (Fig. 3a). There were a significant reduction in T-AOC, SOD and GSH-PX activities in the liver homogenates of rats treated only by CCl_4 as compared to the control animals (P = 0.006, P=0.003 and P<0.001, respectively). The supplementation of GA with CCl_4 produced a significant increase in T-AOC, SOD and GSH-PX activities when compared with CCl_4 animals (P = 0.028, P=0.044 and P=0.004, respectively). CCl_4 injection caused a significant increase in MDA opposed to control rats (P < 0.001). While treatment with GA plus CCl_4 resulted in a significant decrease in MDA opposed to rats treated only by CCl_4 (P = 0.009).

3.5 Hepatic hydroxyproline level

Liver hydroxyproline was approved to inspect the influence of GA on the grade of hepatic fibrosis induced by CCl_4 (Fig. 3b). The rats treated only by CCl_4 revealed a high content of hydroxyproline opposed to control rats (P = 0.012), which was decreased in GA + CCl_4 group (P = 0.046), demonstrating the antifibrotic effect of GA.

3.6 Effect of Gum Arabic on Hepatic Proinflammatory Cytokines

The mRNA expression levels of TLR-4, TNF-α, IL-6, IL-β1and MCP-1were markedly increased following CCl_4 treatment as compared with the control group (P < 0.001). GA + CCl_4 treatment significantly reduced (P = 0.001, P<0.001, P<0.001, P = 0.002 and P < 0.001 respectively) the expression of these above cytokines compared with the group treated only by CCl_4 (Fig. 4a). These finding were also confirmed by immunohistochemistry expression of TLR-4. A high expression of TLR-4 in the CCl_4-treated rats which was reduced in GA + CCl_4 group, indicating the anti-inflammatory influence of GA (Fig. 4b).

3.7 Effects of Gum Arabic on Hepatic Fibrotic Genes Expression

The mRNA expression levels of α-SMA and TGFβ1, in the hepatic tissues were significantly increased following exposure to CCl_4 alone as opposed to control rats (P < 0.001). GA + CCl_4 treatment obviously decreased (P = 0.006 and P < 0.001 respectively) the mRNA expression of α-SMA and TGFβ1compared with the CCl_4 only treated group (Fig. 5a). These findings were also confirmed by immunohistochemistry expression of α-SMA. A high expression of α-SMA in the CCl_4-treated rats which were reduced in the GA + CCl_4 group, indicating the antifibrotic influence of GA (Fig. 5b).

4. DISCUSSION

Liver fibrosis is a consequence of numerous chronic illnesses and associated with substantial and life-threatening complications, such as hepatocellular carcinoma, portal hypertension, liver failure and represents the most important cause of morbidity and mortality worldwide [2,21]. At present-day there is no accepted and effective treatment for liver fibrosis. Gum Arabic is effective an antioxidant and anti-inflammatory natural product, it has a possible role in the inhibition of liver damage [15,22] .

In this study administration of GA considerably mitigated the progression of hepatic fibrosis in rats intoxicated by CCl_4 injection. This is evident from the reduction in the severity of hepatocellular necrosis, lipid peroxidation, proinflammatory cytokines, collagen accumulation and the expression of α-SMA and TGFβ1in addition to the improvement of liver and antioxidant enzymes. CCl_4 is a well-known hepatotoxic element, which induces liver damage and fibrosis by the free radicals that react with cell membrane constituents, and disrupt cell membrane integrity,which result in the secretion of ALT, AST and ALP. Therefore, these enzymes are used as biochemical markers of liver damages [4,23]. In the current study, we noted that, GA could suggestively decline the activities of serum AST, ALT and ALP enzymes compared with the CCl_4 only treated group, which suggest that GA had protective effect on liver damages.

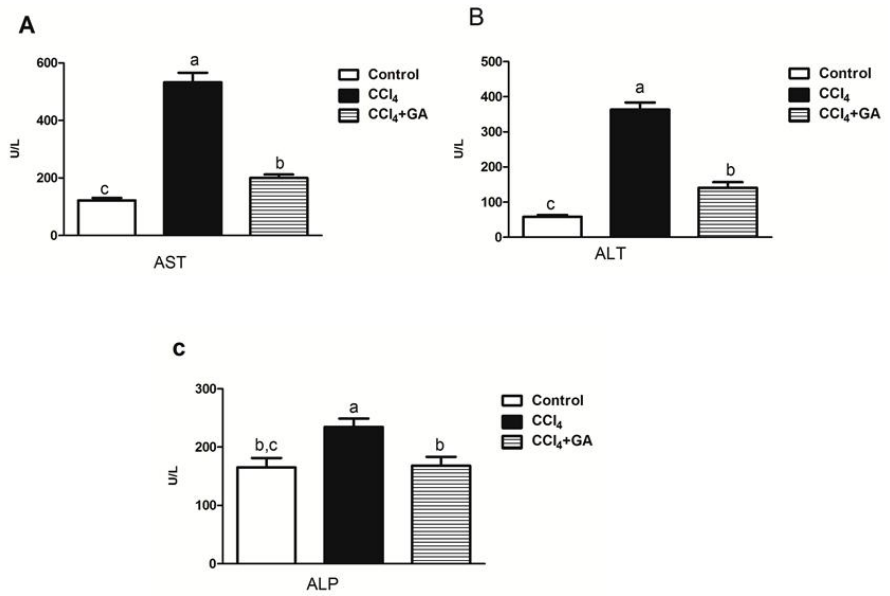

Fig. 1. Effects of GA on liver marker enzymes in the serum (A) Serum aspartate aminotransferase; (B) serum alanine aminotransferase; and (C) serum alkaline phosphatase. Data are represented as mean ±SEM (n=8). Columns with different letters differ significantly (*P* < 0.05)

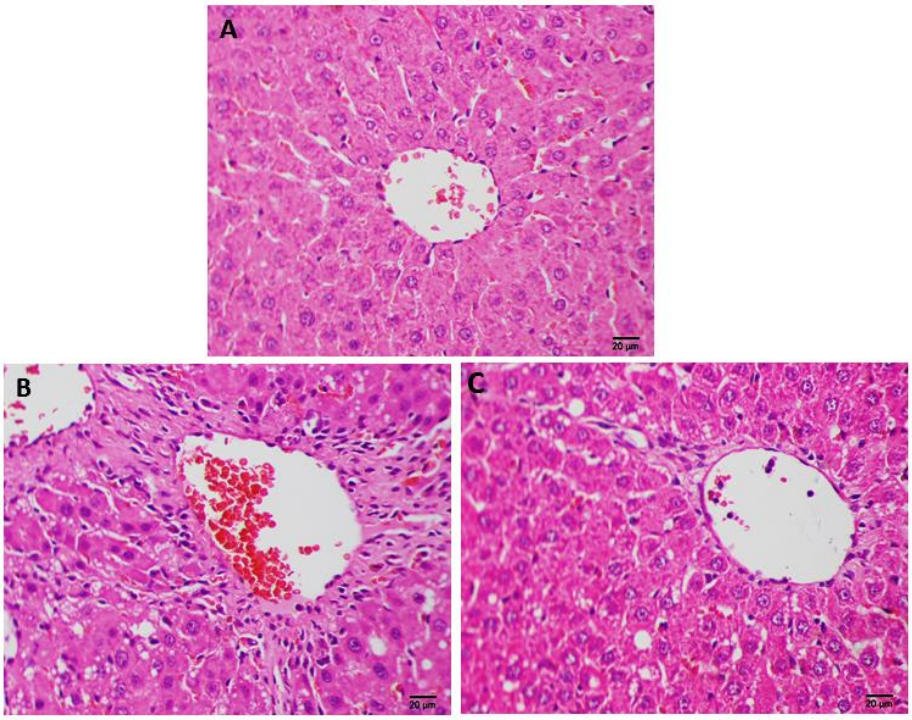

Fig. 2. Liver sections stained with H & E (scale bar = 20 µm). (A) Control group, (B) CCl_4 group, and (C) GA+ CCl_4 group

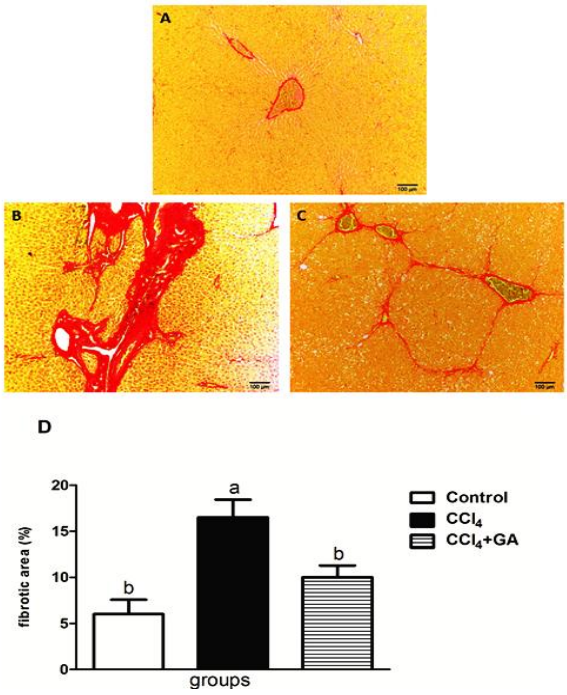

Fig. 3. Liver sections were stained with Sirius red (scale bar = 100 µm). (A) Control group, (B) CCl_4 group, and (C) CCl_4 + GA group. The Area ratio of stained collagen was quantified from 5 different fields of 8 liver sections and shown in (D). Values of each bar are means ± SEM (n = 8). Columns with different letters differ significantly (*P* < 0.05)

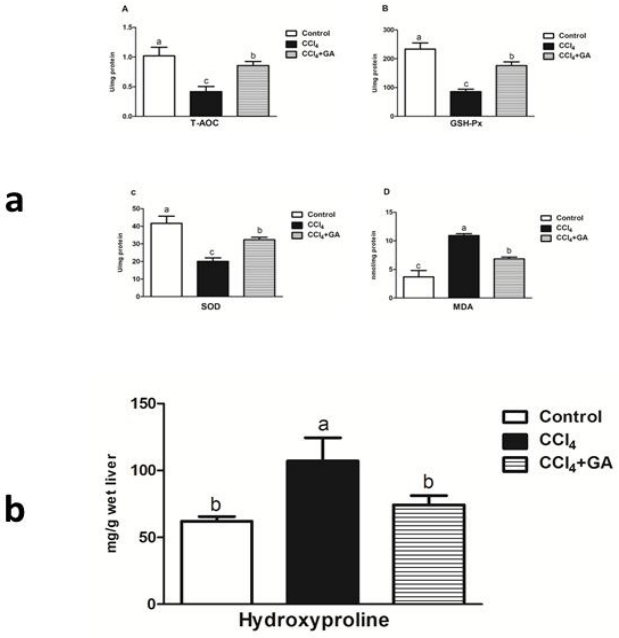

Fig. 4. (a) Effects of GA on hepatic oxidative stress parameters. (A) the levels of T-AOC; (B) the levels of GSH-Px; (C) the activities of SOD; and (D) the levels of MDA. Data are represented as mean ± SEM (n=8). Columns with different letters differ significantly (*P* < 0.05). (b) Effects of GA on hepatic hydroxyproline content. Data are represented as mean ± SEM (n= 8). Columns with different letters differ significantly (*P* < 0.05)

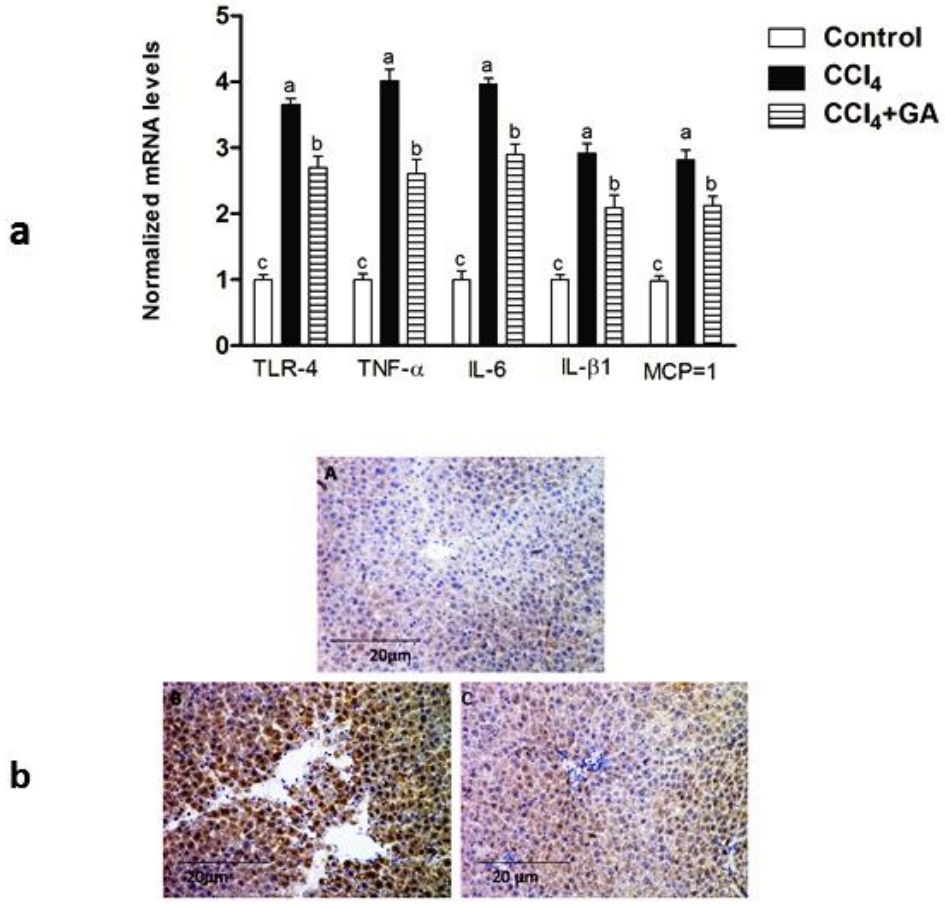

Fig. 5. (a) Effects of GA on the hepatic mRNA expression of some inflammatory factors; TLR-4, TNF-α, IL-6, IL-β1and MCP-1of different groups by Quantitative Real-Time PCR. GAPDH served as internal control. Data were presented as mean ± SEM (n=8). Columns with different letters differ significantly ($P < 0.05$). (b) The expression of TLR-4 by immunohistochemistry staining (scale bar = 20 μm). (A) Control group, (B) CCl_4 group, and (C) CCl_4+ GA group

Reactive oxygen species (ROS) induce weakening of cellular membrane integrity and hepatocyte necrosis by lipid peroxidation [4,24]. Malondialdehyde is the main lipid peroxidation yields, its raised levels could reveal the grades of lipid peroxidation damage in the liver tissue [25]. However, GSH-Px could particularly initiate the reductive action of GSH to prevent the stability of plasma membrane and functions [26]. While SOD is a scavenger of peroxide anion radicals, which could prevent the stimulation of lipid peroxidation by free radicals [27]. Our finding displayed that the amount of MDA in liver tissue augmented in the CCl_4 only treated group, and the activities of T-AOC, GSH-Px, and SOD, reduced correspondingly. Gum Arabic obviously reserved the rise of MDA level and enhanced the levels of the T-AOC, GSH-Px, and SOD. These outcomes showed that GA had protected effects against lipid peroxidation [22].

Increasing evidences display that inflammation is a significant constituent in the initiation and progression of hepatic fibrosis [28,29]. Chronic inflammation of the liver may be accompanied by increased expression of proinflammatory cytokines, including TNF-α, ILβ1, IL-6, TLR-4, and MCP-1 [29,30]. Activated hepatic stellate cells (HSCs) have a capability to produce fibrogenic and inflammatory cytokines leading to collagen accumulation and liver inflammation. Furthermore, numerous inflammatory cell interactions with Kupffer cells, endothelial cells, platelets, and hepatocytes mediated by IL-6, ILβ1 and TNF-α are implemented in the mechanism of fibrosis [2,31]. Our finding

exposed raised levels of the inflammatory mediators counting TNF-α, ILβ1, IL-6, TLR-4, and MCP-1 in CCl_4-intoxicated rats which could be associated with the free radicals overproduction that enhances elevated expression of proinflammatory cytokines. Increased levels of proinflammatory cytokines were also earlier informed in the hepatic fibrogenesis in rats [32-34]. In the present study, the inflammatory reaction in our data was considerably inhibited by administration of GA, which suggests the anti-inflammatory effects of GA as a protective tool for hepatic fibrosis in the CCl_4-intoxicated liver.

Inactivation of HSCs and the fibrotic markers such as TGF-β1 and α-SMA are considered as the main targets in the antifibrotic treatment [35,36]. Moreover, α-SMA and TGF-β1 are involved in the fibrogenesis through inflammation and free radicals production [37,38]. In the current study, hepatic fibrosis was indicated by the substantial great hepatic stages of hydroxyproline and by Sirius red staining that displayed elevated collagen accumulation in the CCl_4-intoxicated rats. Our data exposed also augmented levels and expression of TGF-β1 and α-SMA in CCl_4-intoxicated rats demonstrating liver fibrosis and HSCs activation as previously reported [39]. The present study confirmed that, GA could reduce CCl_4-induced liver fibrosis through decreasing collagen accumulation and expression of α-SMA and TGF-β1, confirming its role in the protecting fibrosis and HSCs activation.

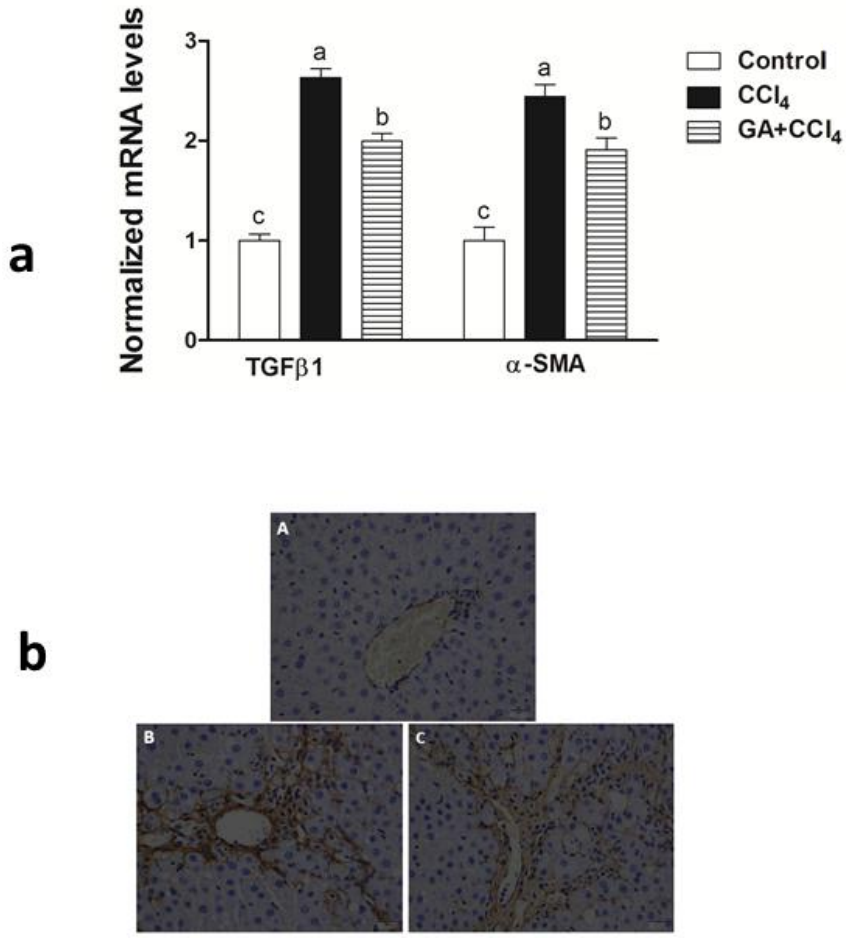

Fig. 6. (a) Effects of GA on the hepatic mRNA expression of some fibrotic markers; α-SMA and TGF-β1of different groups by Quantitative Real-Time PCR. GAPDH served as internal control. Data were presented as mean ± SEM (n=8). Columns with different letters differ significantly ($P < 0.05$). (b) The expression of α-SMA by immunohistochemistry staining (scale bar = 20 µm). (A) Control group, (B) CCl_4 group, and (C) CCl_4+ GA group

CONCLUSION

In conclusion, our results confirmed the role of GA as a potential dietary agent in the progression of liver fibrosis and the protection of hepatocytes via antioxidant, anti-inflammatory mechanisms, suppression of the fibrogenic marker cytokines α-SMA and TGF-β1 and inactivation of HSCs.

ETHICAL APPROVAL

The animals' experiment in this study was approved by the Animal Care Committee for laboratory animal experiments of Nanjing Agricultural University (Certification No.: SYXK (Su) 2011-0036). And with "Principles of Laboratory Animal Care and Use in Research" (State Council of China, 1988).

ACKNOWLEDGEMENTS

The authors are extremely thankful to Professor Kehe Huang and Mrs. Dandan Liu at Nanjing Agricultural University, China, for their provision to carry out this research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Iredale JP. Models of liver fibrosis: exploring the dynamic nature of inflammation and repair in a solid organ. The Journal of clinical investigation, 2007;117(3):539-548.
2. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology, 2008;134(6):1655-1669.
3. Newton BW. A Proteomic Study of Oxidative Stress in Alcoholic Liver Disease. Master's thesis, Texas A&M University.
   Available:https : / /hdl .handle .net /1969 .1 /ETD -TAMU -2008 -05 -12. 2008.
4. Deng G, Wang J, Zhang Q, HE H, WU F, Feng T, Zhou J, Zou K, Hattori M. Hepatoprotective effects of phloridzin on hepatic fibrosis induced by carbon tetrachloride against oxidative stress-triggered damage and fibrosis in rats. Biological and Pharmaceutical Bulletin. 2012;35(7):1118-1125.
5. Fu Y, Zheng S, Lin J, Ryerse J, Chen A. Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. Molecular pharmacology. 2008;73(2):399-409.
6. Othman MS, Nada A, Zaki HS, Moneim AEA. Effect of Physalis peruviana L. on cadmium-induced testicular toxicity in rats. Biological Trace Element Research. 2014;159(1-3):278-287.
7. Othman MS, Safwat G, Aboulkhair M, Moneim AEA. The potential effect of berberine in mercury-induced hepatorenal toxicity in albino rats. Food and Chemical Toxicology. 2014;69:175-181.
8. Ali BH, Ziada A, and Blunden G. Biological effects of gum arabic: a review of some recent research. Food and chemical Toxicology. 2009;47(1):1-8.
9. Said AM, Atwa SA, Khalifa OA. Ameliorating effect of gum arabic and lemongrass on chronic kidney disease induced experimentally in rats. Bulletin of the National Research Centre. 2019;43(1):47.
10. Becker GJ, Hewitson TD. Animal models of chronic kidney disease: useful but not perfect. Nephrology Dialysis Transplantation. 2013;28(10):2432-2438.
11. Al-Majed AA, Mostafa AM, AL-rikabi AC, AL-shabanah OA. Protective effects of oral arabic gum administration on gentamicin-induced nephrotoxicity in rats. Pharmacological Research. 2002;46(5):445-451.
12. Gamal el-din AM, Mostafa AM, AL-shabanah OA, AL-bekairi AM, Nagi MN. Protective effect of arabic gum against acetaminophen-induced hepatotoxicity in mice. Pharmacological research, 2003;48(6):631-635.
13. Elshama SS. The preventive role of Arabic gum in the treatment of toxicity. Open Access: Toxicology & Research. 2018;1:1-27.
14. Jaafar NS. Clinical effects of Arabic gum (Acacia): A mini review. Iraqi Journal of Pharmaceutical Sciences. 2019;28(2):9-16.
   (P-ISSN: 1683-3597, E-ISSN: 2521-3512).
15. Ayaz NO, Ramadan KS, Farid H. Protective role and antioxidant activity of arabic gum against trichloroacetate-induced toxicity in liver of male rats. Indian Journal of Animal Research. 2017; 51(2):303-309.

16. Pal R, Hooda MS, Bias CS, Singh J. Hepatoprotective activity of Acacia senegal pod against carbon tetrachloride-induced hepatotoxicity in rats. International Journal of Pharmaceutical Sciences, 2014. 26(1): p. 165.
17. Taha AR, Alokbi S, Mabrok H. Hepatoprotective Effect of Gum Arabic in Non-Alcoholic Fatty Liver and Potential Modulation of Intestinal Microbiota (FS07-07-19). Current Developments in Nutrition. 2019;3(Supplement_1):nzz040. FS07-07-19.
18. Doi Y, Ichihara T Hagiwara. A ninety-day oral toxicity study of a new type of processed gum arabic, from Acacia tree (Acacia senegal) exudates, in F344 rats. Food and Chemical Toxicology. 2006;44(4):560-566.
19. Hamid M, Liu D, Abdulrahim Y. Amelioration of CCl_4-induced liver injury in rats by selenizing Astragalus polysaccharides: role of proinflammatory cytokines, oxidative stress and hepatic stellate cells. Research in Veterinary Science. 2017;114:202-211.
20. Hamid M, Liu D, Abdulrahim Y. Inactivation of kupffer cells by selenizing astragalus polysaccharides prevents CCl 4-induced hepatocellular necrosis in the male Wistar rat. Biological Trace Element Research. 2017;179(2):226-236.
21. Bataller R, Brenner DA. Liver fibrosis. The Journal of clinical investigation. 2005;115(2):209-218.
22. Evans WC. Trease and evans' pharmacognosy E-book. Elsevier Health Sciences; 2009.
23. Schindhelm RK, Diamant M, Dekker JM. Alanine aminotransferase as a marker of non-alcoholic fatty liver disease in relation to type 2 diabetes mellitus and cardiovascular disease. Diabetes/metabolism Research and Reviews. 2006;22(6):437-443.
24. Parola M, Robino G. Oxidative stress-related molecules and liver fibrosis. Journal of Hepatology. 2001;35(2):297-306.
25. Kim J, Chehade J, Pinnas JL. Effect of select antioxidants on malondialdehyde modification of proteins. Nutrition. 2000;16(11-12):1079-1081.
26. Dolezych B, Szulinska E. Selenium modifies glutathione peroxidase activity and glutathione concentration in mice exposed to ozone-provoked oxidative stress. Journal of Trace Elements in Medicine and Biology. 2003;17(2):133-137.
27. Cassani P, Beconi MT, O'Flaherty C. Relationship between total superoxide dismutase activity with lipid peroxidation, dynamics and morphological parameters in canine semen. Animal Reproduction Science. 2005;86(1-2):163-173.
28. Pinzani M, Rombouts K. Liver fibrosis: from the bench to clinical targets. Digestive and Liver Disease. 2004;36(4):231-242.
29. Iredale J. Defining therapeutic targets for liver fibrosis: exploiting the biology of inflammation and repair. Pharmacological Research, 2008;58(2):129-136.
30. Ghatak S, Biswas A, Dhali GK. Oxidative stress and hepatic stellate cell activation are key events in arsenic induced liver fibrosis in mice. Toxicology and applied pharmacology, 2011;251(1):59-69.
31. Kisseleva T, Brenner DA. Hepatic stellate cells and the reversal of fibrosis. Journal of Gastroenterology and Hepatology. 2006;21:S84-S87.
32. Yu J, Hui AY, Chu ES. The anti-inflammatory effect of celecoxib does not prevent liver fibrosis in bile duct-ligated rats. Liver International, 2009;29(1):25-36.
33. Liang J, et al. The Effect of Antifibrotic Drug Halofugine on Th17 Cells in Concanavalin A-Induced Liver Fibrosis. Scandinavian Journal of Immunology. 2014;79(3):163-172.
34. Liang J, Zhang B, Shen RW. Preventive effect of halofuginone on concanavalin A-induced liver fibrosis. PLoS One. 2013;8(12):e82232.
35. Bataller R, Brenner DA. Hepatic stellate cells as a target for the treatment of liver fibrosis. in Seminars in liver disease. 2001. Copyright© 2001 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New.
36. Chen S, Chen Y, Zhang X. Targeted inhibition of platelet-derived growth factor receptor-β subunit in hepatic stellate cells ameliorates hepatic fibrosis in rats. Gene Therapy. 2008;15(21):1424-1435.
37. Dooley S, Ten Dijke P. TGF-β in progression of liver disease. Cell and Tissue Research. 2012;347(1):245-256.
38. Gressner A. Transdifferentiation of hepatic stellate cells (Ito cells) to myofibroblasts: a key event in hepatic fibrogenesis. Kidney International Supplement. 1996;(54).

39. Tsukamoto H. Cytokine regulation of hepatic stellate cells in liver fibrosis. Alcoholism: Clinical and Experimental Research. 1999;23(5):911-916.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/68878