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Gum arabic down-regulate PPAR-γ and SCD mRNA expression in mice

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ABSTRACT

Introduction: Gum arabic is a complex polysaccharide used in the food industry as a thickener and stabilizer. It reduced plasma cholesterol level in animals and humans, and it has prebiotic, anticarcinogenic and anti-oxidant effect with a protective role against hepatic and cardiac toxicities.

Aim: To study the impact of gum arabic on body weight, adipose tissue weight, lipid profiles and expression of some gene control lipid metabolism.

Material and methods: 20 female CD-1 mice at 5 weeks age were divided into two groups, one served as control and the second received 10% of gum arabic in drinking water for 6 weeks. Liver and visceral adipose tissue and serum were collected from all groups. Total cholesterol, triglyceride, HDL-c and LDL-c were assayed using kits, and the expression of lipid metabolic enzyme gene was detected by RT-PCR.

Results and discussion: The results showed that gum arabic significantly decreased body weight ($P < 0.05$) and visceral adipose tissue weight ($P < 0.01$). Gum arabic non-significantly ($P < 0.05$) reduces blood glucose and total cholesterol, and increased HDL-c. The expression of lipid metabolic enzyme gene showed that gum arabic significantly ($P < 0.05$) down-regulated PPAR-γ and SCD expression. However, gum arabic has no significant ($P < 0.05$) effect on HMGR, G6P, CYP17, Sreb, TNF-α, FAS, MGL, ATGL, HSL and ACC gene expression.

Conclusions: The results conclude that gum arabic can reduce body weight and visceral adipose tissue weight, and down-regulated PPAR-γ and SCD gene expression.

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1. Introduction

Gum arabic is an exudative polysaccharide from the African tree *Acacia senegal* and is used widely in the food industry as a thickener and stabilizer.[1,2] It contains high molecular weight (lipoprotein) and low molecular weight (heterogeneous gum polysaccharides) compounds.[3] The use of gum arabic dates back to the second millennium BC when the Egyptians used it as an adhesive and ink. Gum arabic was evaluated for acceptable daily intake levels by man by the Joint FAO/WHO Expert Committee on Food Additives since 1969[4]; however, Sudanese people in Western Sudan have been using it for a longer time without limitations. It is indigestible in both humans and animals, and is not degraded in the intestine but fermented in the colon to give short-chain fatty acids, leading to a large range of possible health benefits.[5] One of these benefits is its prebiotic effect.[6,7] It had been claimed that four week supplementation with gum arabic (10 g/day) led to significant increases in Bifidobacteria, Lactobacteria, and Bacteriodes in humans indicating a prebiotic effect.[7] Other effects include reduction in plasma cholesterol level in animals and humans,[8] anticarcinogenic effect[9] and anti-oxidant effect[10,11] with a protective role against hepatic and cardiac toxicities. Additionally, gum arabic alleviates effects of chronic renal failure in humans; however, further studies are needed for confirmation.[12,13]

Obesity is a well-known risk factor for coronary heart disease, stroke, diabetes and many other abnormalities, including cancer.[14,15] These complications depend not only on absolute amount of fat but also on its distribution. Absolute total body fat and adipose tissue distribution are known to be associated with cardio-metabolic risk in adult females.[16] Processes that determine fat deposition in adipose tissue include the rates of fat uptake, de novo fatty acid synthesis, triacylglycerol synthesis, lipid degradation and transport processes of fatty acids.[17] Several key factors are involved in lipid metabolism in adipose tissues. Lipogenic enzymes include acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and glucose-6-phosphate dehydrogenase (G-6-PDH), and changes in their activities can alter the rates of biosynthesis of fatty acids.[18,19] Furthermore, peroxisome proliferator-activated receptor γ (PPAR-γ) has recently been identified as a key enzyme regulating in lipid metabolism in adipose tissue by regulating targeting gene expression related to lipid metabolism, or by transporting fatty acids.[20] Gum arabic can serve to reduce obesity and therefore prevent associated complications in humans. The current therapeutic options to improve cardiovascular risk and slow progression of renal failure are quite limited. Therefore, our current results together with other authors confirm that gum arabic may be a beneficial dietary addition to this group of patients.

2. Material and methods

2.1. Experimental animals

Twenty female CD-1 mice at 5 weeks age were obtained from the Experimental Animal Center of Nanjing Medical University (Nanjing, China). The mice were housed under controlled lighting (12 h light, 12 h dark), temperature (21 °C–22 °C) and humidity at 65%–70%. The mice were allowed free access to a commercial pellet diet and drinking water throughout the experiment period. The experimental protocol involving mice was approved in accordance with the guide for the care and use of laboratory animals prepared by the Institutional Animal Care and Use Committee of Nanjing Agricultural University.

2.2. Experimental design

After an acclimatization period of a week, mice were randomly divided into two equal groups. The first group continued to receive the same diet without treatment until the end of the study (control group). The second group was given normal food and received 0.5% of gum arabic aqueous solution as drinking water for 7 days, and then 10% solution for further 6 weeks. During the treatment period, the mice were weighed weekly. After 6 weeks, the mice were killed. Serum samples and liver and visceral adipose tissue were collected and stored at −80 °C.

2.3. Biochemical measurements

Total cholesterol, triglyceride, high density lipoprotein – cholesterol (HDL-c) and low density lipoprotein – cholesterol (LDL-c) were assayed using kits purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

2.4. Lipid metabolic enzyme gene expression

Liver was ground in liquid N_2, and a portion of about 100 mg was used for RNA extraction using TRIzol total RNA kit (Invitrogen, Biotechnology Co, Ltd, Carlsbad, CA, USA) according to the manufacturer's instruction. Two approaches were taken to ensure that all the total RNA preparations are free of genomic DNA contamination. Firstly, total RNAs were treated with 10 U DNase I (RNase Free, D2215, Takara, Japan) for 30 min at 37 °C, and purified according to the manufacturer's protocol. Secondly, the primers for the reference gene (GAPDH) were designed to span an intron, so any genomic DNA contamination can be reported easily with an extra product in the melting curves for real-time PCR. Lipid metabolic enzyme gene expression was carried out by real-time PCR performed in Mx3000P (Stratagene, USA). Mock reverse transcription (RT) and No Template Controls (NTC) were included to monitor the possible contamination of genomic and environmental DNA at both RT and PCR steps. The pooled sample made by mixing equal quantity of RT products (cDNA) from all samples was used for optimizing the PCR condition and tailoring the standard curves for each target gene, and melting curves were performed to insure a single specific PCR product for each gene. The PCR products were sequenced to validate the identity of the amplicons. Primers specific for HMGR, PPAR-γ, CYP17, G6P1, G6P2, ATGL, HSL, ACC, FAS, SCD and MGL were synthesized by Geneary (Shanghai, China) (Table 1). A mouse GAPDH was used as a reference gene for normalization purposes. The method of $2^{-\Delta\Delta Ct}$ was used to analyze the real-time PCR data.[21] The mRNA abundances were presented

Table 1 – Primer sequences used for gene expression analysis by real-time PCR.

Target genes	Gene bank number	Size	Forward primer	Reverse primer
PPAR-γ	NM_001127330.1	110	5′-CACAATGCCATCAGGTTTGG-3′	5′-GCTCGCAGATCAGCAGACTCT-3′
ACC	NM_133360.2	250	5′-AGGCAGCTGAGGAAGTTGGCT-3′	5′-CGCTGCACAGAGCAGTCACG-3′
FASN	NM_007988.3	129	5′-GATATTGTCGCTCTGAGGCTGTTG-3′	5′-GGAATGTTACACCTTGCTCCTTGC-3′
SCD	NM_009127.4	75	5′-GGCCTGTACGGGATCATACTG-3′	5′-GGTCATGTAGTAGAAAATCCCGAAGA-3
HSL	NM_001039507.2	123	5′-CGCACGATGACACAGTCG-3′	5′-CTAGGCCAACTGTTGGGTG-3′
ATGL	NM_001163689.1	236	5′-CTGAACCAACCCAACCCT-3′	5′-GGTCATCAGGTCCTTTGGT-3′
MGL	NM_001166251.1	168	5′-ACAGACTTGTGCCCGTCAACT-3′	5′-CGAATGCGCGGTGCCGCGGA-3′
SREBP2	NM_011480.3	86	5′-GTGCGCTCTCGTTTTACTGAAGT-3′	5′-GTATAGAAGACGGCCTTCACCAA-3′
HMGCR	NM_008255.2	83	5′-TGACCTTTCTAGAGCGAGTGCAT-3′	5′-CACGAGCTATATTTTCCCTTACTTCA-3″
TNF-α	NM_013693.2	175	5′-CATCTTCTCAAAATTCGAGTGACAA-3′	5′-TGGGAGTAGACAAGGTACAACCC-3′
G6P	NM_008061.3		5′-AACGCCTTCTATGTCCTC-3′	5′-GCTGTAGTAGTCGGTGTCC-3′
GAPDH	NM_008084.2	141	5′-ACATGGTCTACATGTTCCAGTA-3′	5′-GGAGTCTACTGGTGTCTTCA-3′
CYP7α1			5′-GCTGAGAGCTTGAAGCACAAGA-3′	5′-TTGAGATGCCCAGAGGATCAC-3

as the fold change relative to the average level of the control group.

2.5. *Statistical analysis*

Data are expressed as the mean ± SEM and compared by one way analysis of variance (ANOVA) and Student's *t*-test, and $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA).

3. Results

3.1. *Body weight and organs weight*

Gum arabic significantly ($P < 0.05$) decreased body weight from week 4 compared to the control (Fig. 1A), but did not affect food intake (Fig. 1B). Gum arabic significantly reduced ($P < 0.01$) visceral adipose tissue compared to control group (Fig. 1C) but not liver weight (Fig. 1D).

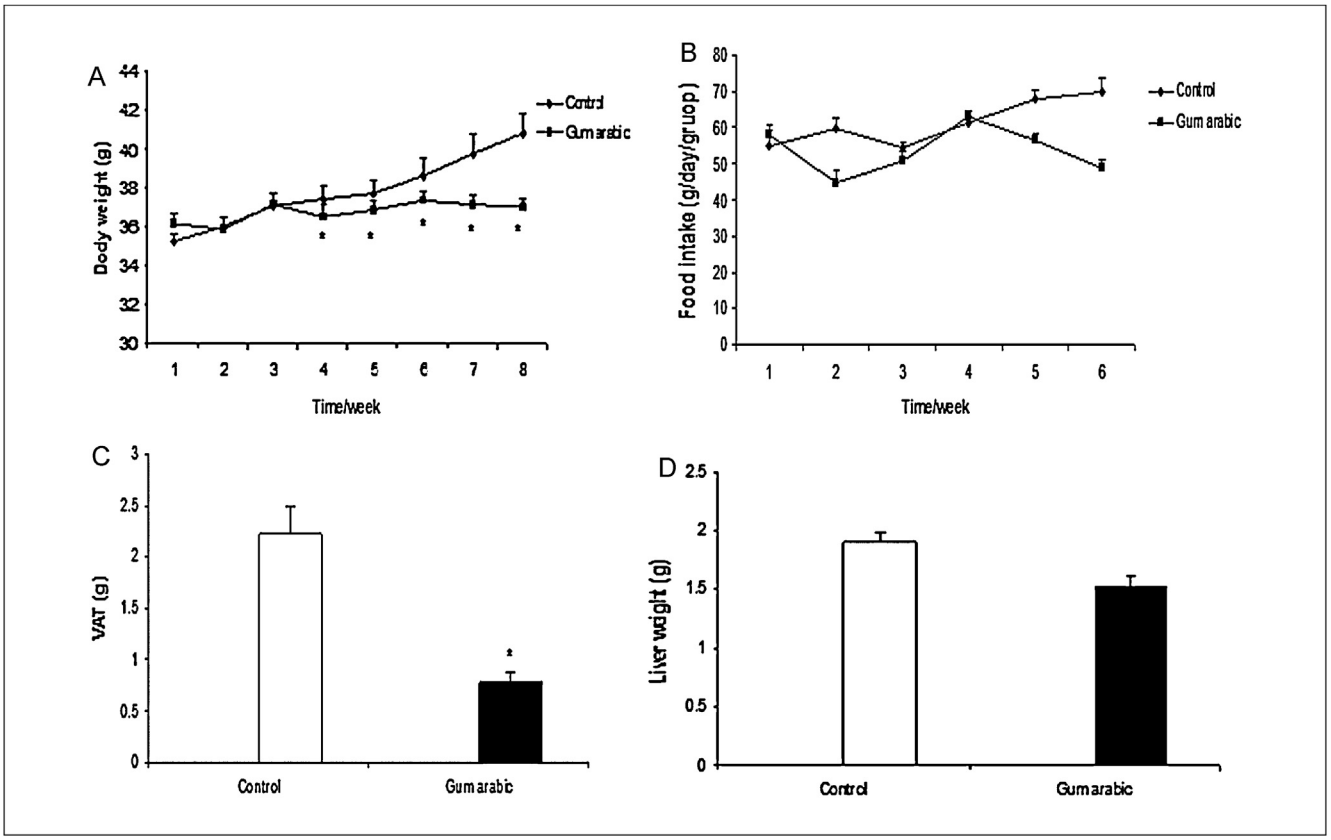

Fig. 1 – Effect of gum arabic on body weight, organ weight and food intake: body weight (A); food intake (B); visceral adipose tissue weight (C); liver weight (D).

Table 2 – Effect of gum arabic on lipid profiles.

Group ($n = 5$)	Blood glucose	Triglyceride	Total cholesterol	HDL-c	LDL-c
Control	7.04 ± 047a	1.4 ± 0.14a	2.0 ± 0.11a	1.2 ± 0.09a	0.2 ± 0.02a
Gum arabic	5.9 ± 0.44a	1.4 ± 0.11a	1.8 ± 0.13a	1.4 ± 0.09a	0.2 ± 0.01a

Blood glucose, total cholesterol, triglyceride, LDL-c (low density lipoprotein – cholesterol) and HDL-c (high density lipoprotein – cholesterol) were measured in mmol/L.

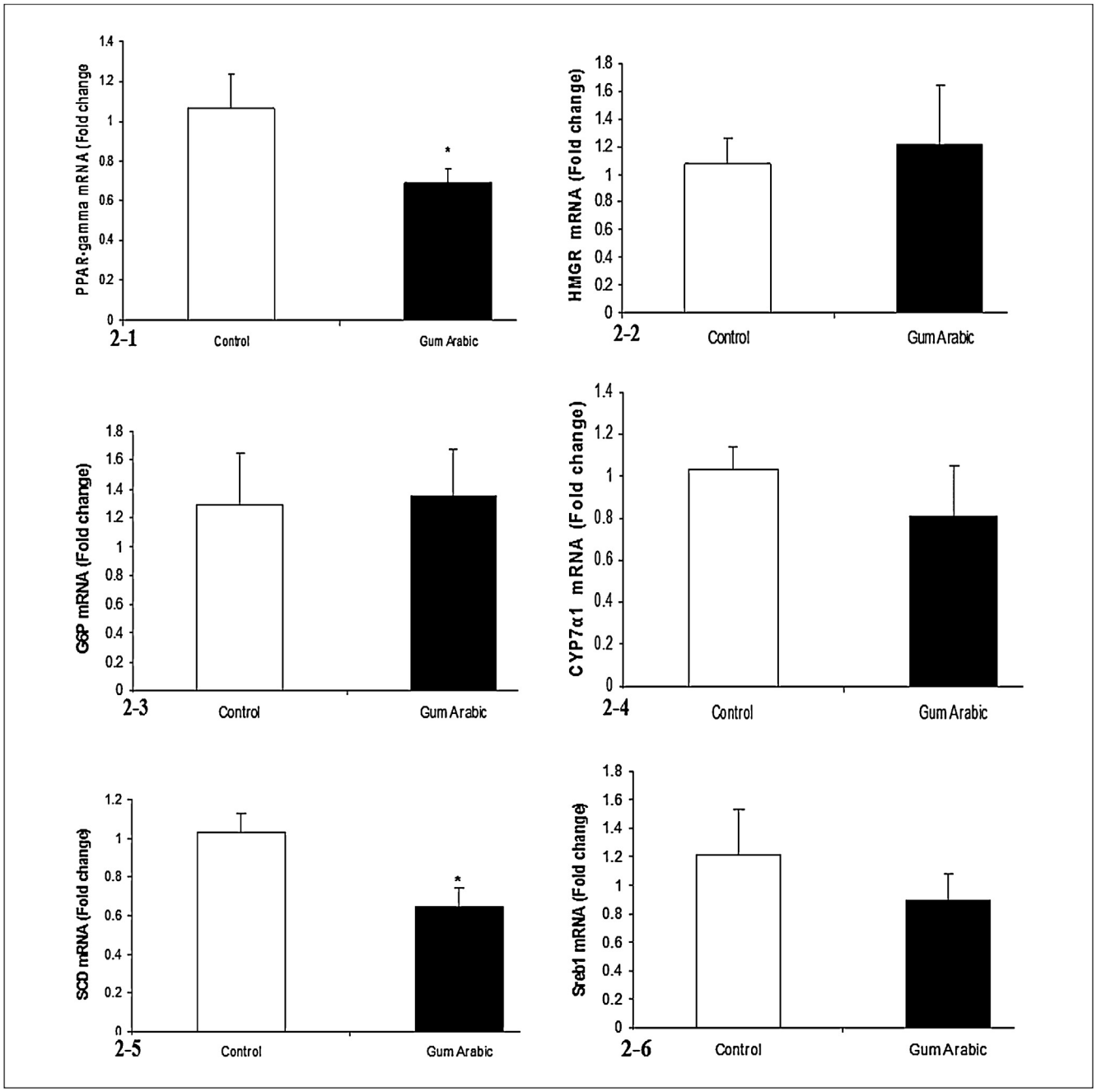

Fig. 2 – The effect of gum arabic on lipid metabolic enzyme gene expression. Mice were treated with 10% gum arabic, or untreated served as control: PPAR gamma (2-1); HMGR (2-2); G6P (2-3); CYP7α1 (2-4); SCD (2-5); Sreb 1 (2-6); TNF (2-7); FAS (2-8); MGL (2-9); ATGL (2-10); HSL (2-11); ACC (2-12).

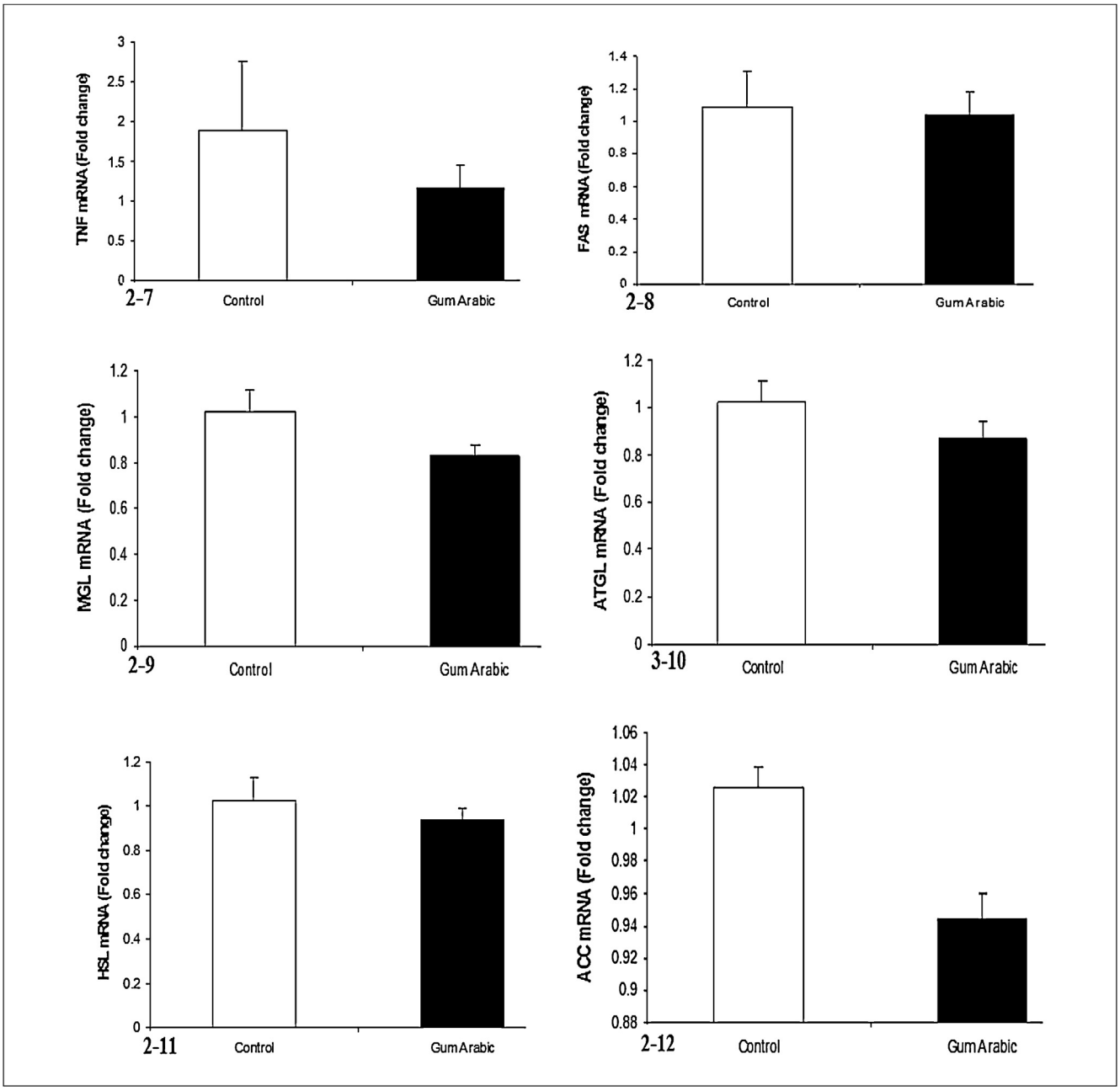

Fig. 2. (Continued).

3.2. *Serum lipid profile*

Gum arabic has no significant ($P < 0.05$) effect on blood glucose, serum triglyceride, total cholesterol, HDL-c and LDL-c. However, gum arabic non-significantly ($P < 0.05$) reduces blood glucose and total cholesterol, and increased HDL-c (Table 2).

3.3. *Lipid metabolic enzyme gene expressions*

Gum arabic significantly ($P < 0.05$) down-regulated PPAR-γ mRNA expression in the liver compared to control group (Fig. 2-1). However, the gum arabic did not affect HMGR (Fig. 2-2), G6P (Fig. 2-3), CYP17 and (Fig. 2-4) gene expression. Gum arabic significantly down-regulated ($P < 0.05$) SCD mRNA expression compared to control (Fig. 2-5) but not Sreb (Fig. 2-6) or TNF-α (Fig. 2-7). On the other hand, gum arabic did not affect FAS (Fig. 2-8), MGL (Fig. 2-9), ATGL (Fig. 2-10), HSL (Fig. 2-11) and ACC (Fig. 2-12) mRNA expression in liver.

4. Discussion

Understanding the molecular mechanisms that regulate lipid synthesis and deposition is of paramount importance, since obesity increases the risk of prevalent, life-threatening diseases such as diabetes and atherosclerosis. In the present study our results showed that gum arabic significantly ($P < 0.05$) decreased body weight, and significantly reduced

($P < 0.01$) visceral adipose tissue. Various mechanisms have been proposed to explain the hypocholesterolemic effect of gum arabic.[1,22,23] Some studies have suggested that the viscosity of fermentable dietary fibers contribute substantially to the lipid lowering effects in animals and humans,[22,24,25] whereas another suggests that this property does not relate to plasma lipids.[26]

The results showed that gum arabic non-significantly ($P < 0.05$) reduces blood glucose and total cholesterol, and increased HDL-c. Gum arabic increases cholesterol biosynthesis in rats that fed a cholesterol-containing diet, but had no effect in rats on a cholesterol-free diet.[27] Ross et al.[28] and Sharma[8] reported reductions of total serum cholesterol by 6% and 10.4%, respectively when subjects received 25 g/day and 30 g/day of gum arabic for 21 and 30 days. The decrease was confined to LDL and VLDL cholesterol only, with no effect on HDL and triglycerides. Other studies indicated that consumption of gum arabic at a dose of 15 g/day for 4 weeks by normal[29] or hypercholesterolemic subjects[30] had no significant effect on plasma lipids. Topping et al.[31] have shown that plasma cholesterol concentrations were unaffected by feeding gum arabic, but plasma triacylglycerols were significantly lower than in controls. In another study,[1] gum arabic was fed to rats replacing cellulose in purified diets supplemented with cholesterol and cholic acid. No significant effects of increasing concentrations of gum arabic were found on the concentrations of either plasma or liver cholesterol when compared to levels found in rats that consumed control diet containing cellulose alone. Plasma triacylglycerol concentrations were, however, higher in rats fed with gum arabic, whereas liver triacylglycerols were lower.[1]

The mechanism of hypocholesterolemic effect of gum arabic most clearly implicated is related to increase in fecal bile acid and neutral sterol excretion or a modification of lipid digestion and absorption.[22,32] Dietary fibers are believed to either bind or sequester bile acids, diminishing their active reabsorption in the ileum and leading to their excretion in the feces. This consequently results in promoting diversion of cholesterol to bile acid synthesis; in addition, to inducing bile acid excretion was found essential in the cholesterol lowering effect of soluble fibers, and this was connected with induction of key enzymes of cholesterol metabolism (i.e. HMG CoA reductase and cholesterol 7a-hydroxylase). In the present study we found that gum arabic significantly ($P < 0.05$) down-regulated PPAR-γ and SCD mRNA expression in the liver compared to control group. Adipose tissue plays an important role in energy balance and metabolism and is the major target for insulin-sensitizing PPAR-γ agonists. The PPAR-γ is a member of the ligand-activated nuclear receptor superfamily and is expressed at high levels in adipose tissue.[33] PPAR-γ regulates genes that modulate lipid utilization and storage, and lipoprotein metabolism and adipocyte differentiation and insulin action.[33] Thus, PPAR-γ is the master regulator of adipogenesis and is activated by the thiazolidinediones that are used clinically to stimulate the action of insulin in adipose tissue.[33] Peroxisome proliferator-activated receptor (PPAR) α and several PPARα-responsive genes were up-regulated in liver, thus increasing the capacity for uptake and oxidation of fatty acids. Stearoyl-CoA desaturase (SCD) is a crucial lipogenic enzyme necessary for the biosynthesis of monounsaturated fatty acids (MUFA). The major desaturation substrates are long-chain saturated acyl-CoAs such as palmitoyl (16:0)-CoA and stearoyl (18:0)-CoA, which are converted to palmitoleoyl (16:1)-CoA and oleoyl (18:1)-CoA, respectively.[34] An intriguing model proposes that obesity is attenuated by lowering the amount of hepatic and/or adipose stearoyl-CoA desaturase-1 (SCD1), the rate-limiting enzyme in biosynthesis of monounsaturated fatty acids, which are preferred for triglyceride assembly.[35]

5. Conclusions

The results conclude that gum arabic can reduce body weight and visceral adipose tissue weight, and down-regulated PPAR-γ and SCD gene expression.

Conflict of interest

The authors declare that they have no conflict of interests.

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REFERENCES

1. Annison GF, Trimble RP, Topping DL. Feeding Australian Acacia gums and gum arabic leads to non-starch polysaccharide accumulation in the cecum of rats. *J Nutr*. 1995;125(2):283–292.
2. Nasir O, Artunc F, Saeed A, et al. Effects of gum arabic (*Acacia senegal*) on water and electrolyte balance in healthy mice. *J Ren Nutr*. 2008;18:230–238.
3. Verbeken D, Dierckx S, Dewettinck K. Exudate gums: occurrence, production, and applications. *Appl Microbiol Biotechnol*. 2003;63:10–21.
4. FAO/WHO: 1969 evaluations of some pesticide residues in food. FAO/PL: 1969/M/17/1; WHO/Food Add./70.38;1970: 145–177. On INCHEM. http://www.inchem.org/pages/jmpr.html.
5. Phillips AO, Phillips GO. Biofunctional behavior and health benefits of a specific Gum Arabic. *Food Hydrocolloids*. 2011;25:165–169.
6. Phillips GO, Ogasawara T, Ushida K. The regulatory and scientific approach to defining Gum Arabic (*Acacia senegal* and *Acacia seyal*) as a dietary fibre. *Food Hydrocolloids*. 2008;22:24–35.
7. Calame W, Weseler AR, Viebke C, Flynn C, Siemensma AD. Gum Arabic establishes prebiotic functionality in healthy human volunteers in a dose-dependent manner. *Br J Nutr*. 2008;100:1269–1275.
8. Sharma RD. Hypocholesterolemic effect of gum acacia in men. *Nutr Res*. 1985;5:1321–1326.
9. Nasir O, Wang K, Foller M, et al. Downregulation of angiogenin transcript levels and inhibition of colonic carcinoma by Gum Arabic (*Acacia senegal*). *Nutr Cancer*. 2010;62:802–810.

10. Al-Majed AA, Mostafa AM, Al-Rikabi AC, Al-Shabanah OA. Protective effects of oral arabic gum administration on gentamicin-induced nephrotoxicity in rats. *Pharmacol Res*. 2002;46:445–451.
11. Ali BH, Al-Qarawi AA, Haroun EM, Mousa HM. The effect of treatment with Gum Arabic on gentamicin nephrotoxicity in rats: a preliminary study. *Renal Fail*. 2003;25:15–20.
12. Ali BH, Al-Salam S, Al-Husseni I, et al. Effects of Gum Arabic in rats with adenine-induced chronic renal failure. *Exp Biol Med (Maywood)*. 2010;235:373–382.
13. Glover DA, Ushida K, Phillips AO, Riley SG. Acacia (sen) SUPERGUM™ (Gum Arabic): an evaluation of potential health benefits in human subjects. *Food Hydrocolloids*. 2009;23:2410–2415.
14. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA*. 2004;291:2847–2850.
15. Lear SA, Toma M, Birmingham L, Frohlich JJ. Modification of the relationship between simple anthropometric indices and risk factors by ethnic background. *Metabolism*. 2003;52:1295–1301.
16. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med*. 1990;322:882–889.
17. Hirsch J, Han PW. Cellularity of rat adipose tissue: effects of growth, starvation, and obesity. *J Lipid Res*. 1969;10:77–82.
18. Smith S, Witkowski A, Joshi AK. Structural and functional organization of the animal fatty acid synthase. *Prog Lipid Res*. 2003;42:289–317.
19. Young JW, Shrago E, Lardy HA. Metabolic control of enzymes involved in lipogenesis and gluconeogenesis. *Biochemistry*. 1964;3:1687–1692.
20. Grindflek E, Sundvold H, Lien S, Rothschild MF. Rapid communication: physical and genetic mapping of the Peroxisome Proliferator Activated Receptor g (PPARg) gene to porcine chromosome 13. *J Anim Sci*. 2000;78:1391–1392.
21. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2 (−Delta Delta C(T)) method. *Methods*. 2001;25:402–408.
22. Moundras C, Behr SR, Demigné C, Mazur A, Remesy C. Fermentablepolysaccharides that enhance fecal bileacid excretion lower plasma cholesterol and apolipoprotein E-rich HDL in rats. *J Nutr*. 1994;124:2179–2188.
23. Tiss A, Carrière F, Verger R. Effects of gum arabic on lipase interfacial binding and activity. *Anal Biochem*. 2001;294:36–43.
24. Gallaher DD, Hassel CA, Lee KJ. Relationships between viscosity of hydroxypropyl methylcellulose and plasma cholesterol in hamsters. *J Nutr*. 1993;123:732–738.
25. Superko HR, Haskell WL, Sawrey-Kubicek L, Farquhar JW. Effects of solid and liquid guar gum on plasma cholesterol and triglyceride concentrations in moderate hypercholesterolemia. *Am J Cardiol*. 1988;62:51–55.
26. Evans AJ, Hood RL, Oakenfull DG, Sidhu GS. Relationship between structure and function of dietary fibre: a comparative study of the effects of three galactomannans on cholesterol metabolism in the rat. *Br J Nutr*. 1992;68:217–229.
27. Kelley JJ, Tsai A. Effect of pectin, gum arabic and agar on cholesterol absorption, synthesis, and turnover in rats. *J Nutr*. 1978;108:630–639.
28. Ross AH, Eastwood MA, Brydon WG, Anderson JR, Anderson DM. A study of the effects of dietary gum arabic in humans. *Am J Clin Nutr*. 1983;37:368–375.
29. Haskell WL, Spiller GA, Jensen CD, Ellis BK, Gates JE. Role of water soluble dietary fiber in the management of elevated plasma cholesterol in healthy subjects. *Am J Cardiol*. 1992;69:433–439.
30. Jensen CD, Spiller GA, Gates JE, Miller AF, Whittam JH. The effect of acacia gum and a water-soluble dietary fiber mixture on blood lipids in humans. *J Am Coll Nutr*. 1993;12:147–154.
31. Topping D, Illman RJ, Trimble RP. Volatile fatty acid concentrations in rats fed diets containing gum Arabic and cellulose separately and a mixture. *Nutr Rep Int*. 1985;32:809–814.
32. Eastwood MA. The physiological effect of dietary fiber: an update. *Annu Rev Nutr*. 1992;12:19–35.
33. Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. *Nat Med*. 2001;10:1–7.
34. Miyazaki M, Dobrzyn A, Elias PM, Ntambi JM. Stearoyl-CoA desaturase-2 gene expression is required for lipid synthesis during early skin and liver development. *Proc Natl Acad Sci U S A*. 2005;102:12501–12506.
35. Nichols LA, Jackson DE, Manthey JA, Shivendra D, Shukla SD, Holland LJ. Citrus flavonoids repress the mRNA for stearoyl-CoA desaturase, a key enzyme in lipid synthesis and obesity control, in rat primary hepatocytes. *Lipids Health Dis*. 2011;10:36.