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Inhibition of obesity through alterations of C/EBP- α gene expression by gum Arabic in mice with a high-fat feed diet

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ABSTRACT

Obesity is a metabolic disease associated with high morbidity and mortality worldwide. Previously we showed that Gum Arabic (GA) inhibited obesity in fed with diet-induced obesity. However, the mechanism underlying the mode of action is not fully elucidated. Here we aimed to identify the effects of GA on CCAAT-enhancer-binding protein- α (C/EBP- α) in mouse-fed diet-induced obesity. Thirty female CD-1 mice 90 days old were randomly divided into three groups (n=10). Mice were fed either a regular diet (control), a high-fat diet (HFD), or a high-fat diet containing 10% w/w GA (HFD+GA) for 15 weeks. Body weights, visceral adipose tissue (VAT), plasma lipid, blood glucose, plasma insulin, adiponectin, and leptin levels were measured. In addition, 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and C/EBP- α gene mRNA expressions were measured, and 11β-HSD1 as well. Supplementation of GA significantly ($P < 0.05$) decreased body weight gain and VAT associated with decreases in blood glucose, total cholesterol LDL, and increased HDL concentrations. Likewise, administration of GA significantly ($P < 0.05$) decreased plasma Corticosterone (CORT) and leptin concentrations, whereas increased adiponectin compared to the control and HFD groups. In addition, GA administration significantly ($P < 0.05$) reduced the abundance of both hepatic 11β-HSD1 and C/EBP- α gene mRNA expression compared to the control and HFD groups. Supplementation of GA significantly ($P < 0.05$) down-regulated hepatic 11β-HSD1 protein expression compared to control and HFD groups. These findings indicate that GA consumption may be useful to prevent obesity through suppression of C/EBP- α gene expression.

1. Introduction

The occurrence of obesity is growing and resumes to be the main public health issue worldwide (James, 2018). Obesity forms the basis of the metabolic syndrome associated with dyslipidemia (Vekic, Zeljkovic, Stefanovic, Jelic-Ivanovic, & Spasojevic-Kalimanovska, 2019), insulin resistance (Noakes, 2018), type 2 diabetes (Leitner et al., 2017), heart disease (Carbone et al., 2019), hypertension (Leggio et al., 2017) and nonalcoholic fatty liver disease (Polyzos, Kountouras, & Mantzoros, 2019). Abdominal obesity is the main manifestation of metabolic syndrome which considered a fatal outcome of visceral obesity (Paley & Johnson, 2018). To understand the consequence of abdominal obesity and its role in development of metabolic syndrome is fundamental to understand the link between the diseases associated with this condition (L. Hu et al., 2017). The visceral fat reduction is vital to decrease the risk of metabolic diseases in this context (Myers, Kokkinos, & Nyelin, 2019; Nishizawa & Shimomura, 2019; Pi-Sunyer, 2019). Thus, it is essential to establish strategies for preventing obesity.

Glucocorticoids (GCs) are well-known to play a key role in the regulation of various biological activities, such as stress responses (Aerts, 2018), inflammatory responses (Liberman et al., 2018), immune response (Bereshchenko, Bruscoli, & Riccardi, 2018), energy balance

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(Borba et al., 2017) and development of obesity (Woods et al., 2015). 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is the key GC metabolizing enzyme that regulates intracellular active GC's bioavailability through converting inactive GC to their active forms in vivo (Chapman, Holmes, & Seckl, 2013). The overexpression of 11β-HSD1 is fundamental in the development of metabolic syndrome (Li et al., 2017) and its related conditions including obesity (Stomby, Andrew, Walker, & Olsson, 2014), atherosclerosis (Hadoke, Kipari, Seckl, & Chapman, 2013), insulin resistance (Peng et al., 2016), type 2 diabetes millets (Shukla et al., 2019a) and nonalcoholic fatty liver disease (Candia et al., 2012). Downregulation of 11β-HSD1 contributes in resistant of metabolic syndrome (Harno et al., 2013). 11β-HSD1 inhibitors are found to improve lipid profile (G.-X. Hu et al., 2013), blood glucose (Shukla et al., 2019b) and improved adipose tissue functions (Rathinasabapathy et al., 2017). An adipose tissue selected inhibitor is also found to improve hepatic metabolism by decreasing phosphoenolpyruvate carboxykinase (Winnick et al., 2013) and increasing carnitine palmitoyltransferase I (Anagnostis et al., 2013) expression.

Leptin is an adipose tissue hormone that plays a vital role in body weight regulation (Xu & Xie, 2016) when produced and released from adipocytes into the bloodstream (D'Souza, Neumann, Glavas, & Kieffer, 2017). Leptin stimulates energy expenditure and inhibits food intake (Hussain & Khan, 2017). The central roles of leptin are regulation of body weight manifested by excessive obesity, which occurs both in mice and humans (Gruzdeva, Borodkina, Uchasova, Dyleva, & Barbarash, 2019). On the other hand, Adiponectin is the predominant peptide produced by adipocytes which play a fundamental role in obesity (Tumminia et al., 2019) and its related conditions such as type 2 diabetes (Y. Wang et al., 2018) and cardiovascular disease (Menzaghi & Trischitta, 2018). It's also secreted by other cell types (Barbe et al., 2019), such as cardiac myocytes (Woodward, Akoumianakis, & Antoniades, 2017), skeletal muscle (Krause, Milne, & Hawke, 2019) and endothelial cells (Sena, Pereira, Fernandes, Letra, & Seiça, 2017). Adiponectin influences are mediated via Adiponectin receptors (Karnati, Panigrahi, Li, Tweedie, & Greig, 2017). Adiponectin is well documented to increase insulin sensitivity in the liver and muscle (Ruan & Dong, 2016). It is ultimately regulates peripheral blood glucose (Yanai & Yoshida, 2019) and fatty acid metabolism (Stern, Rutkowski, & Scherer, 2016).

Dietary fibre (DF) is used to treat a wide variety spectrum of obesity associated conditions (Bozzetto et al., 2018). A diet containing high fat, in particular, Trans (TFAs) and saturated fatty acids (SFAs) plays a critical role in the development of metabolic syndrome (Sekar et al., 2017). In contrast, a diet containing polyunsaturated fatty acids offers protection against metabolic syndrome development (Khan & Jackson, 2018). Chronic feeding of saturated fatty acids increased hepatic 11β-HSD1 mRNA expression in rats (Vara Prasad, Jeya Kumar, Kumar, Qadri, & Vajreswari, 2010). Hepatic CCAAT-enhancer binding protein-α (C/EBP- α) is the main transcription factor required for 11β-HSD1 mRNA expression found to increase by supplementation of TFAs and SFAs in the rat. The consumption of medicinal plants such as tea is reported to reduce 11β-HSD1 activity (Hintzpeter, Stapelfeld, Loerz, Martin, & Maser, 2014). About five compounds isolated from tea showed slight inhibitory effects on both human and mouse 11β-HSD1 activity (G. C. Wang et al., 2016).

Gum arabic (GA) (Fig. 1), is an edible dried sticky exudate from the stems and branches of *Acacia seyal* and *Acacia senegal* (Hammad & Mohammed, 2018) that is rich in non-viscous soluble fiber with 240–580 kDa of molecular weight (Mariod, 2018; Slavin, 2013). It is composed of six carbohydrate moieties (galactopyranose, arabinopyranose, arabinofuranose, rhamnopyranose, glucuropyranosyl uronic acid and 4-O methyl glucuropyranosyl uronic acid) and also contains a small proportion of proteins. The main chain is composed of 1,3-linked βD-galactopyranosyl units. These 1,3-linked β-D-galactopyranosyl units are composed of side chains linked to the main chain by 1,6-linkages. Both the main and side chains contain units of the carbohydrates moieties presented before. The uronic acid moieties, mostly end-units, have been used widely in the food industry and pharmaceutical field medicine (B. H. Ali, Ziada, & Blunden, 2009). For decades, it has been used as an oral hygiene substance by several communities in North Africa and the Middle East (Al-Majed, Mostafa, Al-Rikabi, & Al-Shabanah, 2002; Badreldin H. Ali et al., 2013; Baien et al., 2020). The treatment of GA has been revealed to ameliorate some biochemical (Nemmar, Al-Salam, Beegam, Yuvaraju, & Ali, 2019), such as decreased total cholesterol (Mohamed, Gadour, & Adam, 2015), low-density lipoprotein (LDL), triglycerides (TG) (Kaddam, Fadl-Elmula, Eisawi, Abdelrazig, & Saeed, 2019), and blood glucose (Larson et al., 2021). Moreover, the administration of GA increased the quality of high-density lipoprotein (HDL) both in humans (Babiker, Elmusharaf, Keogh, & Saeed, 2018) and animal (Ahmed, Fedail, Musa, Musa, & Sifaldin, 2016). In addition, the treatment of GA has been reported to serve as a dietary fibre that and decrease body mass index (BMI) (Babiker et al., 2012), improves reduction of body fat deposition (Ushida, 2012), and serves as anti-obesity effects when supplemented with diet (Ahmed, Musa, Fedail, Sifaldin, & Musa, 2016). Previous studies have revealed that GA lowered caloric density and glucose absorption (Larson et al., 2021; Nasir et al., 2010). In our earlier report, we administrated the normal mice with 10% of GA in the form of drinking water. It decreased visceral adipose tissue, which was associated with the downregulation of hepatic 11β-HSD1 mRNA expression (Ahmed, Musa, Fedail, Sifaldin, & Musa, 2015). However, the mechanism of action through which GA decreased hepatic 11β-HSD1 mRNA expression remains unclear. In the present study, we used mice to test our hypotheses that GA may decrease 11β-HSD1 through hepatic C/EBP- α and the changes in C/EBP- α may be associated with plasma CORT concentrations.

2. Materials and methods

2.1. Experimental design and animal treatment

Thirty female CD-1 mice of 90 days old were purchased from the Sudanese National Research Center, Khartoum, Sudan and housed at the Department of Toxicology, Faculty of Veterinary Medicine, and the University of Khartoum in plastic cages (each containing 5 mice) in room kept at 25°C with a 12-h light and dark cycle. The mice were provided *ad libitum* access of a commercial diet and drinking water for at least 7 days of adaptation and throughout the experiment. After the adaptation period, mice were allocated into three groups. The control group (Control, n = 10) was fed a standard mouse diet, the high-fat diet group (HFD, n =10) was fed high-fat diet, and the high-fat diet group was supplemented with 10% of Gum Arabic (GA) groups (HFD+GA, n = 10). GA was purchased from Khartoum Local Market, Sudan. The food was obtained from Jiangsu Province Cooperative Medical and Biological Engineering Co. Ltd (Shown in Table 1). The body weights were recorded during the experimental period. After 15 weeks, the blood samples were collected from the mice's orbital fossa in EDTA containing tubes. The plasma samples were separated via centrifugation for 15 min at 4 °C and stored at -80 °C until biochemical measurements. The mice were killed using a rapid decapitation protocol. Visceral adipose tissue (VAT) and liver samples were then dissected and weighed after being washed in cold phosphate buffer saline (pH 7.4). The liver and VAT tissue was stored at −80 °C until further investigations. The experimental procedures were done based on the Animal Ethics of the University of Khartoum.

2.2. Blood lipid profile and glucose

Blood glucose, plasma total cholesterol, triglycerides (TG), low density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL) were measured using commercially assay kits (Nanjing Jiancheng Bioengineering Company, Nanjing, China), according to the manufacturers' instructions.

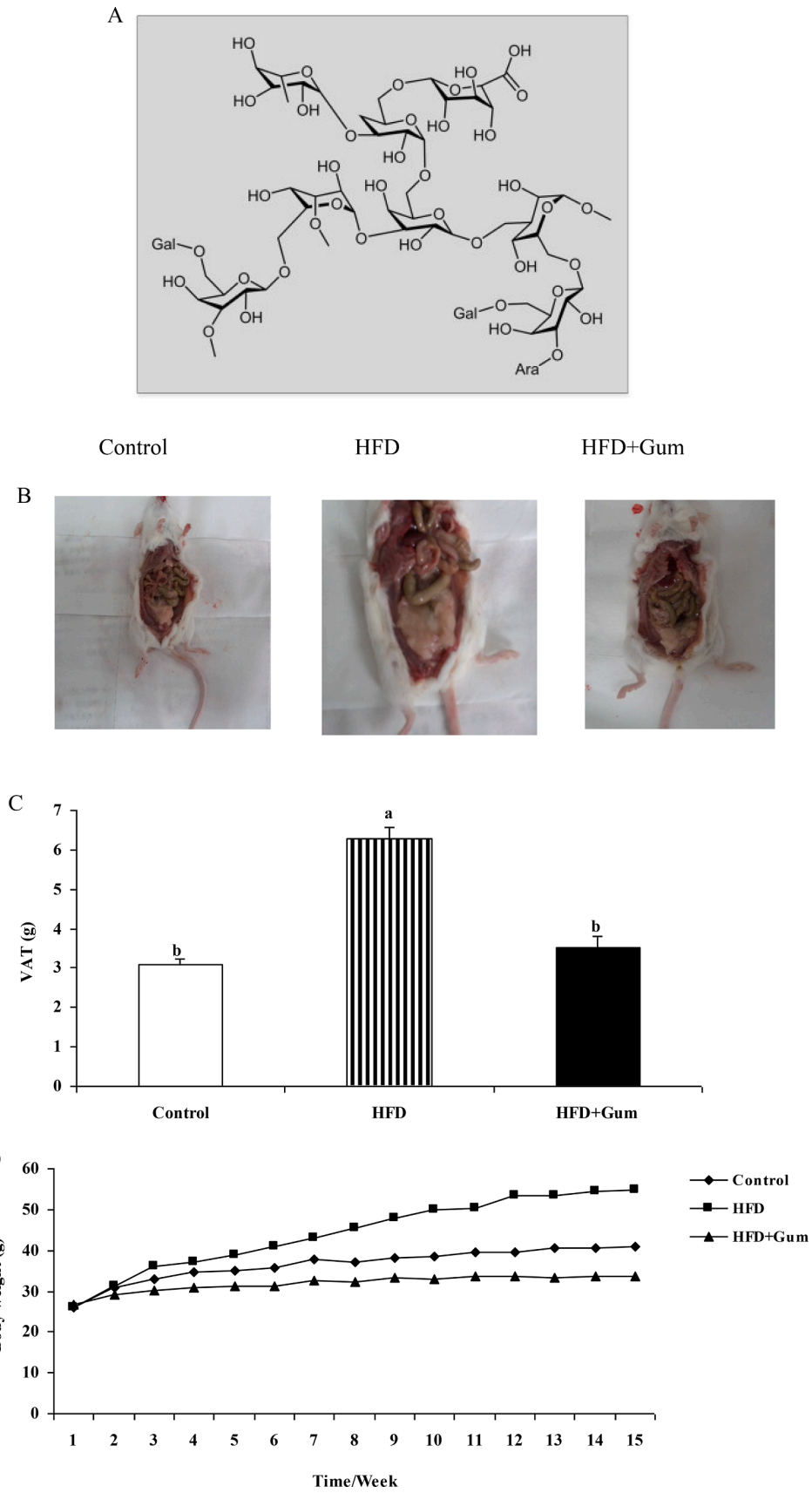

Fig. 1. Chemical structure of Gum Arabic (A), the effect of GA treatments on visceral adipose tissue (B and C) and body weight (D). The values are the means ± SEM, n=10/group.

Table 1
Composition of experimental diets

Nutrient	High-fat	High-fat with Gum
Casein	25.8	25.8
L-Cystine	0.4	0.4
Cornstarch		
Maltodextrin	16.2	10.2
Sucrose	8.9	6.4
Cellulose	6.5	5.5
Soybean oil	3.2	3.2
Lard	31.17	31.17
Mineral mix1	1.3	1.3
Dicalcium phosphate	1.7	1.7
Calcium carbonate	0.7	0.7
Potassium citrate 1H20	2.1	2.1
Vitamin mix1	1.3	1.3
Choline bitartrate	0.3	0.3
Gum arabic		10
Total	100.0	100.5

2.3. Plasma CORT and insulin measurements

Plasma CORT concentration was determined using an enzyme immunoassay. CORT in 5 μl plasma and 195 μl water was extracted with 4 ml dichloromethane, re-dissolved in phosphate buffer, and triplicate in the enzyme immunoassay. The dilution of the CORT antibody (Chemicon, Temecula, CA, USA; cross-reactivity: 11-dehydrocorticosterone 0.35%, progesterone 0.004%, 18-OH-DOC 0.01%, cortisol 0.12%, 18-OHB 0.02% and aldosterone 0.06%) was 1:8000. Horseradish peroxidase (1:400,000) linked to CORT served as the enzyme label and ABTS [2,2_-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid)] as the substrate. The concentration of CORT in plasma samples was calculated by using a standard curve run in duplicate on each plate. Plasma pools from mice with two different CORT concentrations were included as internal controls on each plate. If the concentration was below the detection threshold, the determination was repeated with 10 μl plasma. If the concentration was still below the detection threshold, the value of the lowest detectable concentration (1ngml-1) was assigned. Intraassay variation ranged from 4.5 to 10.8% and inter-assay variation from 9.6 to 17.6%, depending on the concentration of the internal control and the year of determination.

Plasma insulin levels were detected using an insulin radioimmunoassay (RIA) commercial kit. The samples were analyzed in a double assay format, and the intra-assay coefficient of variation was 1.4%.

2.4. Plasma Adiponectin and leptin concentrations

The leptin and adiponectin levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) commercial kits. Specifically, for adiponectin concentrations, the Alpco ELISA kit was used (Promega Corporation), and for leptin levels measurements, the R&D Systems ELISA kit was used. Insulin was quantified using the Mouse Insulin ELISA by ALPCO Diagnostics. The intraassay and inter-assay coefficients of variation were 5.3 and 7.2, respectively, for insulin and 4.3 and 7.8 for leptin.

2.5. Hepatic 11β-HSD1 and C/EBP-α genes mRNA

2.5.1. Total RNA extraction

About 100 mg of liver were ground in liquid N_2. According to the manufacturer's instruction, a portion of about 50 to 100 mg was used to extract RNA using TRIzol total RNA kit (Invitrogen, Biotechnology Co, Ltd, Carlsbad CA, USA). Total RNA concentration was then quantified by measuring the absorbance at 260 nm in a photometer (Eppendorf Biophotometer, Germany). Ratios of absorptions (260/280 nm) were between 1.8 and 2.0 for all preparations. Aliquots of each RNA sample were subjected to electrophoresis through a 1.4% agarose-formaldehyde gel to verify their integrity. Total RNAs samples 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.

2.5.2. Reverse transcription

Two μg of total RNA was reverse transcribed by incubation at 37°C for 1 h in a 25 μL mixture consisting of 1 × RT-buffer (Promega, USA), 100 U Moloney Murine Leukemia Virus reverse transcriptase (M-MLV) (Promega, USA), 8 U RNase inhibitor (Promega, USA), 5.3 μmol/L random hexamer primers (TaKaRa Biotechnology, China) and 0.8 mmol/L dNTP (TaKaRa Biotechnology, China). The reaction was terminated by heating at 95°C for 5 min and quickly cooling on ice. RT was performed in a Bio-Rad DNA Engine Peltier Thermal Cycler PTC0200 (Bio-Rad, USA).

2.5.3. Real-Time PCR

The primers for the reference gene 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. For hepatic 11β-HSD1 and C/EBP-α mRNA expression, real-time PCR was performed in Mx3000P (Stratagene, USA) according to the previous publication (Ahmed et al., 2015). Mock RT and No Template Controls 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. Melting curves were performed to insure a single specific PCR product for each gene. Two μL of 16-fold dilution of RT product was used for PCR in a final volume of 25 μL containing 12.5 μL SYBR Green Realtime PCR Master Mix (TOYOBO Ltd., Japan) and 0.2-0.8 μM of each forward and reverse primers for 11β-HSD1 and C/EBP-α (Table 3) were synthesized by Geneary (Shanghai, China). The PCR products were sequenced to validate the identity of the amplicons. Primers specific for A mouse GAPDH were used as a reference gene for normalization purposes. The method of $2^{-\Delta\Delta Ct}$ was used to analyze the real-time PCR data (Livak & Schmittgen, 2001). The mRNA abundances were presented as the fold change relative to the average level of the control group.

2.5.4. Hepatic 11β-HSD1 protein expression

About 50 mg of the liver samples were ground using liquid nitrogen and were homogenized in 300 μL of ice-cold Radioimmunoprecipitation assay (RIPA) buffer 1x in phosphate saline buffer (PBS) (pH 7.5), 1% Nonidet P-40, 0.5% sodium deoxycholate, 0.1% Sodium Dodecyl sulphate (SDS), 3% aprotinin (was added before lysing), and 1% Phenylmethylsulfonyl fluoride (PMSF) / isopropanol (10 mg/mL, added before lysing)] using a tissue grinder (Polytron, Polytron PT1200E; Brinkman Instruments, Littau, Switzerland). After 30 min of incubation on the ice, the homogenate was centrifuged at 10,000xg for 20 min at 4°C to remove all insoluble material. 70% of the supernatant yield was collected, and the protein concentration was measured by the BCA assay (Pierce, Rockford, IL, USA) according to the manufacturer's direction.

15 μg of protein extract from each sample was mixed with loading buffer and denatured by boiling for 5 min before loading on a 12% SDS-PAGE gel. After electrophoretic transfer, the nitrocellulose membranes (BioTrace, Pall, USA) were cut to isolate the 11β-HSD1 band (32 kDa) and β-actin band (43 kDa) band according to the prestained SDSPAGE standards. After five times washing with TBST (Tris Buffered Saline with Tween) (0.1% Tween-20 in Tris-buffered saline), the blotted membranes were blocked with 5% skim milk in TBST for 2 h at 25°C. Followed by five times washing with TBST, the blots were then incubated with rabbit polyclonal antibody against 11β-HSD1 (Cayman Chemical Company, USA, diluted 1:200) and against β-actin (Cayman Chemical Company, USA, and diluted 1:10.000) at 4°C 18 hours. Then blots were washed five

times with TBST and incubated with HRP-conjugated secondary antibody (Abcam, UK; 1:4000) for 2h at 25°C. Finally, the blots were washed and detected by enhanced chemiluminescence (ECL) using the LumiGlo substrate (Super Signal West Pico Trial Kit, Pierce, USA). The band density of 11β-HSD1 was normalized by β-actin. ECL signals recorded on x-ray film were scanned and analyzed with Kodak 1D Electrophoresis Documentation and Analysis System 120 (Kodak Photo Film Co. Ltd., USA).

2.6. Statistical analysis

Descriptive statistics model was used for homogeneity and normality of variances check. Body weight, VAT, blood lipids profile, blood glucose, plasma CORT, plasma leptin, Adiponectin, and insulin, in addition to mRNA and protein expression were analyzed by one-way ANOVA using SPSS 21.0 for Windows 10, then followed by a least-significant difference (LSD) test for groups comparisons. A P-value ≤ 0.05 was considered significant.

3. Results

3.1. Body weight and organs weight

The treatment of HFD significantly ($P<0.01$) increased VAT compared to control group, while treatment of GA significantly decreased the values of VAT in HFD+GA treated mice group (Fig. 1A and 1B). Similarly, the treatment of HFD significantly increased the mice body weight compared to the control group, while the administration of GA significantly ($P<0.01$) reduced mice body weight gain of HFD mice (Fig. 1C).

3.2. Plasma insulin and blood glucose

The treatment of HFD increased blood glucose levels when compared to the control. But the treatment of GA significantly ($P<0.05$) reduced concentrations of blood glucose compared to the control, and HFD treated mice groups (Fig. 2 A). Unlikely, supplementation of HFD increased plasma insulin concentrations compared to the control group, whereas the supplementation of GA significantly decreased insulin concentrations (Fig. 2 B).

3.3. Plasma corticosterone, adiponectin, and leptin concentrations

The treatment of HFD significantly increased plasma CORT concentrations compared to the control group. However, the supplementation of GA significantly ($P<0.05$) decreased plasma CORT levels compared to the control, and HFD treated mice groups (Fig. 2 C). Conversely, the treatment of HFD significantly ($P<0.05$) decreased plasma Adiponectin concentrations when compared to the control group, and HFD treated mice groups (Fig. 2D). However, the supplementation of GA significantly ($P<0.05$) decreased leptin concentrations compared to the control, and HFD treated mice groups (Fig. 2 E).

3.4. Plasma lipid profile

The intake of HFD significantly ($P<0.05$) increased plasma total cholesterol and LDL concentrations compared to control. Yet, GA administration significantly ($P<0.05$) decreased plasma total cholesterol and LDL concentrations. In contrast, the supplementation of GA significantly ($P<0.05$) increased HDL cholesterol concentration compared to the control, and HFD treated mice groups (Table 2).

3.5. Hepatic 11β-HSD1 and C/EBP-α genes mRNA and protein expression

Interestingly, the treatment of GA significantly down-regulated the

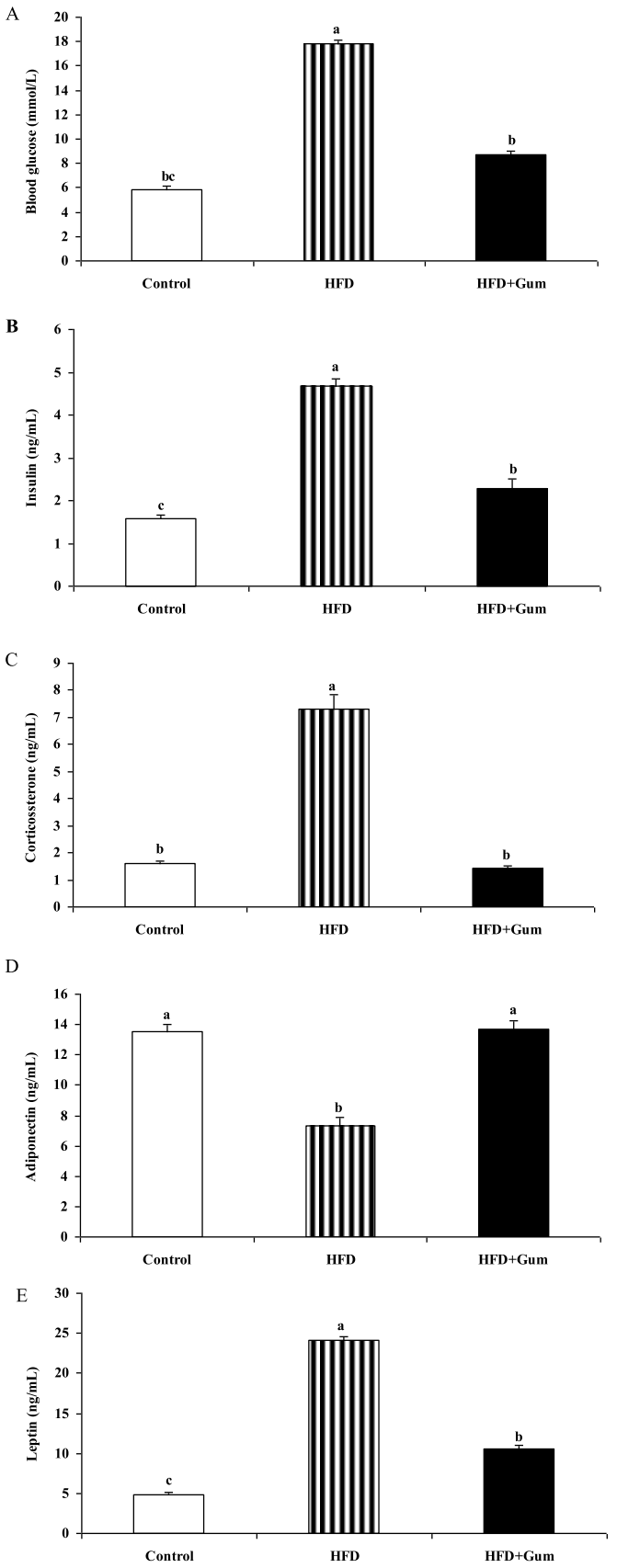

Fig. 2. Effect of GA treatments on blood glucose (A), plasma Insulin (B), plasma CORT (C), plasma Adiponectin (D), and plasma leptin (E). The values are the means ± SEM, n=10/group. Bars with different letters are significantly different at $p<0.05$.

Table 2
Effect of GA treatments on blood lipid profile concentrations. Data were expressed as means ± S.E.M. of 10 /group. Different letters in the rows indicate significantly different mean values at $p<0.05$.

Group	Triglyceride (mg/dL)	Total cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
Control	40.7±3.15a	68.9±4.6 a	49.7 ±4.9 a	48.45 ±5.60a	8. 63 ±6.5a
HDF	39.1±3.7a	97.2±4.8 b	34.1 ±2.2 b	71.45 ±5.60b	13. 81 ±4.7a
HFD+GA	38.7±5.4a	71.2±5.5 a	54.9 ±9.3 a	39.71 ±5.12a	10.41 ±0.15a

Table 3
Primers sequences used for Real-time PCR

Target genes	Gene bank number	Product Size	Primer sequences
GAPDH	NM_008084.2	141	F: 5′-ACATGGTCTACATGTTCCAGTA-3′ R: 5′-GGAGTCTACTGGTGTCTTCA-3′
11β-HSD1	NM_008288.2	302	F: 5′-AGCAACCAGAGATAGGCAGC-3′ R: 5′-ACACCTCGCTTTTGCGTAGA-3′
C/EBP-α	NM_001287521.1	178	F: 5′-AGACATCAGCGCCTACATCG-3′ R: 5′-CCGGTACTCGTTGCTGTTCT-3′

11β-HSD1 protein expression in the liver of mice fed with HFD compared to the control and HFD treated mice groups (Fig. 3C). The intake of HFD increased hepatic 11β-HSD1 mRNA expression compared to the control group. However, the supplementation of GA significantly decreased hepatic 11β-HSD1 mRNA expression compared to the HFD treated mice group (Fig. 3 A). Likewise, treatment of GA significantly decreased hepatic C/EBP-α mRNA expression compared to the HFD treated mice group (Fig. 3 B).

4. Discussion

Obesity is a global public health problem associated with high morbidity and mortality (Abdelaal, le Roux, & Docherty, 2017). Therapeutic approaches such as surgical operations (Jumbe, Hamlet, & Meyrick, 2017), uses of synthetic drugs (Wolfe, Kvach, & Eckel, 2016); ultimately cause adverse complications, health consequences with high economic costs (Tremmel, Gerdtham, Nilsson, & Saha, 2017). Several experimental studies confirmed the association between dietary fibre intake reduction in abdominal obesity (Pilolla, 2018), food intake (Fayet-Moore, Cassettari, Tuck, McConnell, & Petocz, 2018), body weight (Solah et al., 2017), cholesterol (Soliman, 2019) and blood glucose (McRae, 2018). Consistently, supplementation of Gum Arabic (GA) decreased body weight which was associated with reduction of abdominal visceral adipose tissue (VAT). The body weight reduction via GA may be based on the fact that dietary fibre consumption has potential health beneficial including satiety promotion (Dreher, 2018), cleric intake reduction (Adam, Thomson, Williams, & Ross, 2015), stomach hormone secretions (Hervik & Svihus, 2019), thus, could reduces weight. In addition, dietary fibre intake reported changing body composition (Solah et al., 2017).

Leptin, the hormone, a hunger biomarker produced by adipose tissue, communicates information about the organism's energy balance (Barateiro, Mahú, & Domingos, 2017; Rosenbaum & Leibel, 2014). Leptin circulating plasma levels are influenced by the nutritional status of the organism (Alwarawrah, Kiernan, & MacIver, 2018). Deregulations in leptin signaling pathway and biosynthesis have been associated with obesity (Sánchez-Jiménez, Pérez-Pérez, de la Cruz-Merino, & Sánchez-Margalet, 2019). In the present study, the administration of GA decreased plasma leptin concentrations. These results are consistent with previous findings that revealed the consumption of cereal fibre reduced plasm leptin concentrations in mice fed with a high fat diet (Zhang et al., 2016). Several studies reported the effect of dietary fibre consumption on modulating of leptin secretion and its ameliorating effects on leptin resistance in mice (Acharya, Gao, Bless, Chen, & Tetel, 2019; H. Wang, Hong, Li, Zang, & Wu, 2018; Zhang et al., 2016). The majority of those reports based on circulating leptin levels suggest that fibre consumption ultimately has beneficial health effects by improving leptin resistance and sensitivity (Hong et al., 2016; Izadi, Saraf-Bank, & Azadbakht, 2014; Maziarz et al., 2017). However, the mechanism of action through which GA decreases leptin remains unclear. On the other hand, the administration of GA increased plasma Adiponectin concentrations associated with low blood leptin concentrations. The present findings agree with earlier studies that revealed the consumption of cereals dietary fibre increased serum adiponectin levels in mice fed a high-fat diet (Han et al., 2017). In addition, the consumption of fermentable fibre significantly increased plasma adiponectin concentrations in mice fed with high fat and sucrose diet (Jangra, K, Sharma, Pothuraju, & Mohanty, 2019). Yet, the mechanism underlying the increases of plasma adiponectin via dietary fibre, including GA requires further investigation, which will be our future exciting research direction.

Recent studies reported that the consumption of dietary fibre, including GA reduced plasma cholesterol (Soliman, 2019), triglyceride (Hannon et al., 2018) and, bad cholesterol, low-density lipoprotein (LDL) levels both in human and mice (Narayan et al., 2014; Yanai & Tada, 2018). In agreement with earlier publications, the treatment of GA decreases total cholesterol LDL, whereas it increases good cholesterol and HDL concentrations. The reduction in plasma lipid profile was associated with a reduction in blood glucose concentrations. Numerous modes of action have been pointed out to disclose the hypercholesterolemic effects of dietary fibre (McRae, 2017; Rideout, Harding, Jones, & Fan, 2008; Viuda-Martos et al., 2010). One potential elucidation is that dietary fibre increases the viscosity of the intestinal nutritional contents (Grundy et al., 2016; Jha, Fouhse, Tiwari, Li, & Willing, 2019); consequently it is interfering with nutrient absorption (Adams, Sello, Qin, Che, & Han, 2018) and micelle formation (Jesch & Carr, 2017), which in turn, decreases intestinal lipids absorption. Others mechanisms suggested is that the soluble dietary fibers serves through disrupting the bile acids formation (Naumann, Schweiggert-Weisz, Eglmeier, Haller, & Eisner, 2019) the entero-hepatic circulation, enhancing bile acid excretion (Dubey, Toh, & Yeh, 2018; Parnell & Reimer, 2010) and consequently decreases the plasma cholesterol concentrations (Babio, Balanza, Basulto, Bullo, & Salas-Salvado, 2010; Narayan et al., 2014). Furthermore, the viscosity prosperity of fermentable dietary fibres is reported to have significant effects on lowering cholesterol in the rat (Brockman, Chen, & Gallaher, 2014).

11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) an intracellular gate-keepers of tissue GCs action catalyses generation of active glucocorticoids (GCs), which plays a vital role is initiation of abdominal fat deposition (Galitzky & Bouloumié, 2013). CCAAT-enhancer binding protein- α (C/EBP- α) (Sai et al., 2008), the main transcription factor required for the expression of 11β-HSD1 mRNA expression plays a critical role in the induction of obesity via influences on 11β-HSD1 mRNA transcription (Ren et al., 2014). Here we presented the first finding revealing that the administration of GA downregulated hepatic C/EBP- α mRNA expression is associated with downregulation of hepatic 11β-HSD1 mRNA expression in mice. Moreover, downregulation of hepatic 11β-HSD1 mRNA expression was consistent with hepatic 11β-HSD1 protein expression. Interestingly, the downregulation of 11β-HSD1 and its transcriptional enhancer C/EBP- α were associated with a reduction of plasma corticosterone (CORT) concentrations.

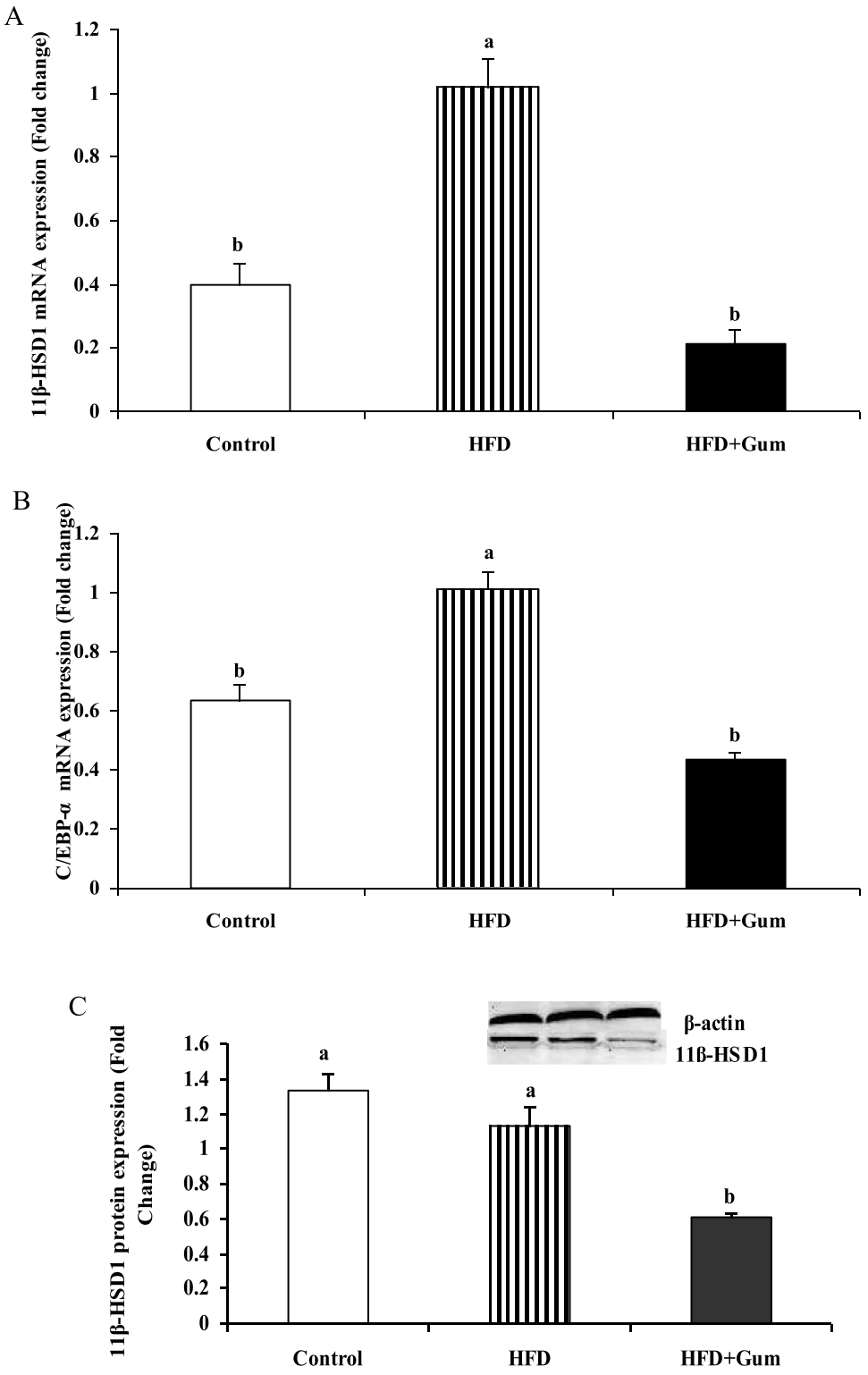

Fig. 3. Effect of GA treatments on hepatic 11βHSD1 (A) and C/EBP-α (B) mRNA expression and hepatic C/EBP-α protein expression (C). The values are the means ± SEM, n=10/group. Bars with different letters are significantly different at $P<0.05$.

5. Conclusion

In conclusion, the administration of GA reduced body weight and abdominal VAT deposition in female mice associated with the reduction of plasma CORT and downregulation of C/EBP- α and 11β-HSD1 mRNA and protein expression. Thus, GA may have a future perspective of their review to suppress obesity by suppressing C/EBP- α gene mRNA expression.

Declaration of Competing Interest

All authors declare that there is no conflict of interest.

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References

Abdelaal, Mahmoud, Roux, le, Carel, W., & Docherty, Neil G (2017). Morbidity and mortality associated with obesity. *Annals of translational medicine, 5*(7), 161. https://doi.org/10.21037/atm.2017.03.107. -161.

Acharya, Kalpana D., Gao, Xing, Bless, Elizabeth P., Chen, Jun, & Tetel, Marc J (2019). Estradiol modulates gut microbiota in female ob/ob mice fed a high fat diet. *bioRxiv.*. , Article 612283. https://doi.org/10.1101/612283

Adam, Clare L., Thomson, Lynn M., Williams, Patricia A., & Ross, Alexander W. (2015). Soluble fermentable dietary fibre (pectin) decreases caloric intake, adiposity and lipidaemia in high-fat diet-induced obese rats. *Plos One, 10*(10), Article e0140392. https://doi.org/10.1371/journal.pone.0140392. -e0140392.

Adams, Seidu, Sello, Cornelius Tlotliso, Qin, Gui-Xin, Che, Dongsheng, & Han, Rui (2018). Does dietary fiber affect the levels of nutritional components after feed formulation? *Fibers, 6*(2), 29.

Aerts, Johan. (2018). Quantification of a glucocorticoid profile in non-pooled samples is pivotal in stress research across vertebrates. *Frontiers in Endocrinology, 9*(635). https://doi.org/10.3389/fendo.2018.00635

Ahmed, Abdelkareem A., Fedail, Jaafar S., Musa, Hassan H., Musa, Taha H., & Sifaldin, Amal Z (2016). Gum Arabic supplementation improved antioxidant status and alters expression of oxidative stress gene in ovary of mice fed high fat diet. *Middle East Fertility Society Journal, 21*(2), 101–108. https://doi.org/10.1016/j.mefs.2015.10.001

Ahmed, Abdelkareem A., Musa, Hassan H., Fedail, Jaafar S., Sifaldin, Amal Z., & Musa, Taha H (2015). Gum arabic decreased visceral adipose tissue associated with downregulation of 11β-hydroxysteroid dehydrogenase type I in liver and muscle of mice. *Bioactive Carbohydrates and Dietary Fibre, 6*(1), 31–36. https://doi.org/10.1016/j.bcdf.2015.06.004

Ahmed, Abdelkareem A., Musa, Hassan H., Fedail, Jafaar S., Sifaldin, Amal Z., & Musa, Taha H (2016). Gum arabic suppressed diet-induced obesity by alteration the expression of mRNA levels of genes involved in lipid metabolism in mouse liver. *Bioactive Carbohydrates and Dietary Fibre, 7*(1), 15–20. https://doi.org/10.1016/j.bcdf.2016.01.002

Ali, B. H., Ziada, A., & Blunden, G. (2009). Biological effects of gum arabic: A review of some recent research. *Food and Chemical Toxicology, 47*(1), 1–8. https://doi.org/10.1016/j.fct.2008.07.001. S0278-6915(08)00394-3 [pii].

Ali, Badreldin H., Al-Husseni, Isehaq, Beegam, Sumyia, Al-Shukaili, Ahmed, Nemmar, Abderrahim, Schierling, Simone, et al. (2013). Effect of Gum Arabic on oxidative stress and inflammation in adenine–induced chronic renal failure in rats. *Plos One, 8*(2), e55242.

Al-Majed, A. A., Mostafa, A. M., Al-Rikabi, A. C., & Al-Shabanah, O. A (2002). Protective effects of oral Arabic Gum administration on gentamicin-induced nephrotoxicity in rats. *Pharmacological Research, 46*(5), 445–451.

Alwarawrah, Yazan, Kiernan, Kaitlin, & MacIver, Nancie J. (2018). Changes in nutritional status impact immune cell metabolism and function. *Frontiers in immunology, 9*, 1055. https://doi.org/10.3389/fimmu.2018.01055. -1055.

Anagnostis, Panagiotis, Katsiki, Niki, Adamidou, Fotini, Athyros, Vasilios G., Karagiannis, Asterios, Kita, Marina, et al. (2013). 11beta-Hydroxysteroid dehydrogenase type 1 inhibitors: novel agents for the treatment of metabolic syndrome and obesity-related disorders? *Metabolism - Clinical and Experimental, 62*(1), 21–33. https://doi.org/10.1016/j.metabol.2012.05.002

Babiker, R., Elmusharaf, K., Keogh, M. B., & Saeed, A. M. (2018). Effect of Gum Arabic (Acacia Senegal) supplementation on visceral adiposity index (VAI) and blood pressure in patients with type 2 diabetes mellitus as indicators of cardiovascular disease (CVD): a randomized and placebo-controlled clinical trial. *Lipids Health Dis, 17*(1), 56. https://doi.org/10.1186/s12944-018-0711-y

Babiker, R., Merghani, T. H., Elmusharaf, K., Badi, R. M., Lang, F., & Saeed, A. M. (2012). Effects of Gum Arabic ingestion on body mass index and body fat percentage in healthy adult females: two-arm randomized, placebo controlled, double-blind trial. *Nutr J, 11*, 111. https://doi.org/10.1186/1475-2891-11-111

Babio, N., Balanza, R., Basulto, J., Bullo, M., & Salas-Salvado, J. (2010). Dietary fibre: influence on body weight, glycemic control and plasma cholesterol profile. *Nutricion Hospitalaria, 25*(3), 327–340. doi: S0212-16112010000300001 [pii].

Baien, Shima Hassan, Seele, Jana, Henneck, Timo, Freibrodt, Christin, Szura, György, Moubasher, Hani, et al. (2020). Antimicrobial and Immunomodulatory Effect of Gum Arabic on human and bovine granulocytes against staphylococcus aureus and Escherichia coli. *Frontiers in Immunology*, 10. https://doi.org/10.3389/fimmu.2019.03119

Barateiro, Andreia, Mahú, Ines, & Domingos, Ana I. (2017). Leptin resistance and the neuro-adipose connection. *Frontiers in endocrinology, 8*, 45. https://doi.org/10.3389/fendo.2017.00045. -45.

Barbe, Alix, Bongrani, Alice, Mellouk, Namya, Estienne, Anthony, Kurowska, Patrycja, Grandhaye, Jérémy, et al. (2019). Mechanisms of adiponectin action in fertility: An overview from gametogenesis to gestation in humans and animal models in normal and pathological conditions. *International journal of molecular sciences, 20*(7), 1526. https://doi.org/10.3390/ijms20071526

Bereshchenko, Oxana, Bruscoli, Stefano, & Riccardi, Carlo (2018). Glucocorticoids, sex hormones, and immunity. *Frontiers in Immunology, 9*(1332). https://doi.org/10.3389/fimmu.2018.01332

Borba, Tássia Karin, Galindo, Lígia Cristina Monteiro, Ferraz-Pereira, Kelli Nogueira, Aragão, da Silva, Raquel, Toscano, Elisa, Ana, et al. (2017). Peripheral and central glucocorticoid signaling contributes to positive energy balance in rats. *Hormone and Metabolic Research, 49*(06), 472–479. https://doi.org/10.1055/s-0043-100383

Bozzetto, Lutgarda, Costabile, Giuseppina, Pepa, Della, Giuseppe, Ciciola, Paola, Vetrani, Claudia, Vitale, et al. (2018). Dietary fibre as a unifying remedy for the whole spectrum of obesity-associated cardiovascular risk. *Nutrients, 10*(7), 943. https://doi.org/10.3390/nu10070943

Brockman, D. A., Chen, X., & Gallaher, D. D. (2014). High-viscosity dietary fibers reduce adiposity and decrease hepatic steatosis in rats fed a high-fat diet. *Journal of Nutrition, 144*(9), 1415–1422. https://doi.org/10.3945/jn.114.191577

Candia, R., Riquelme, A., Baudrand, R., Carvajal, C. A., Morales, M., Solis, N., et al. (2012). Overexpression of 11beta-hydroxysteroid dehydrogenase type 1 in visceral adipose tissue and portal hypercortisolism in non-alcoholic fatty liver disease. *Liver International, 32*(3), 392–399. https://doi.org/10.1111/j.1478-3231.2011.02685.x

Carbone, Salvatore, Canada, Justin M., Billingsley, Hayley E., Siddiqui, Mohammad S., Elagizi, Andrew, & Lavie, Carl J. (2019). Obesity paradox in cardiovascular disease: where do we stand? *Vascular health and risk management, 15*, 89–100. https://doi.org/10.2147/VHRM.S168946

Chapman, Karen, Holmes, Megan, & Seckl, Jonathan. (2013). 11β-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. *Physiological reviews, 93*(3), 1139–1206. https://doi.org/10.1152/physrev.00020.2012

Dreher, Mark L. (2018). Whole fruits and fruit fiber emerging health effects. *Nutrients, 10*(12), 1833. https://doi.org/10.3390/nu10121833

D'Souza, Anna M., Neumann, Ursula H., Glavas, Maria M., & Kieffer, Timothy J. (2017). The glucoregulatory actions of leptin. *Molecular Metabolism, 6*(9), 1052–1065. https://doi.org/10.1016/j.molmet.2017.04.011

Dubey, Rajni, Toh, Yon-Rui, & Yeh, An- I. (2018). Enhancing cellulose functionalities by size reduction using media-mill. *Scientific Reports, 8*(1), 11343. https://doi.org/10.1038/s41598-018-29777-w

Fayet-Moore, Flavia, Cassettari, Tim, Tuck, Kate, McConnell, Andrew, & Petocz, Peter (2018). Dietary fibre intake in Australia. Paper II: Comparative examination of food sources of fibre among high and low fibre consumers. *Nutrients, 10*(9), 1223. https://doi.org/10.3390/nu10091223

Galitzky, Jean, & Bouloumié, Anne. (2013). Human visceral-fat-specific glucocorticoid tuning of adipogenesis. *Cell Metabolism, 18*(1), 3–5. https://doi.org/10.1016/j.cmet.2013.06.008

Grundy, Myriam M. L., Edwards, Cathrina H., Mackie, Alan R., Gidley, Michael J., Butterworth, Peter J., & Ellis, Peter R (2016). Re-evaluation of the mechanisms of dietary fibre and implications for macronutrient bioaccessibility, digestion and postprandial metabolism. *The British journal of nutrition, 116*(5), 816–833. https://doi.org/10.1017/S0007114516002610

Gruzdeva, Olga, Borodkina, Daria, Uchasova, Evgenya, Dyleva, Yulia, & Barbarash, Olga (2019). Leptin resistance: underlying mechanisms and diagnosis. *Diabetes, metabolic syndrome and obesity: targets and therapy, 12*, 191. https://doi.org/10.2147/DMSO.S182406. -198.

Hadoke, Patrick W. F., Kipari, Tiina, Seckl, Jonathan R., & Chapman, Karen E (2013). Modulation of 11β-hydroxysteroid dehydrogenase as a strategy to reduce vascular inflammation. *Current atherosclerosis reports, 15*(5), 320. https://doi.org/10.1007/s11883-013-0320-1. -320.

Hammad, Zeinab Mohamed, & Mohammed, Mohammed Hamed (2018). 2 - management practices of Gum Arabic–producing trees. In A. A. Mariod (Ed.), *Gum Arabic* (pp. 13–21). Academic Press.

Han, Shu-Fen, Jiao, Jun, Zhang, Wei, Xu, Jia-Ying, Zhang, Weiguo, Fu, Chun-Ling, et al. (2017). Lipolysis and thermogenesis in adipose tissues as new potential mechanisms for metabolic benefits of dietary fiber. *Nutrition (Burbank, Los Angeles County, Calif.), 33*, 118–124. https://doi.org/10.1016/j.nut.2016.05.006

Hannon, Bridget A., Thompson, Sharon V., Edwards, Caitlyn G., Skinner, Sarah K., Niemiro, Grace M., Burd, Nicholas A., et al. (2018). Dietary fiber is independently related to blood triglycerides among adults with overweight and obesity. *Current Developments in Nutrition, 3*(2). https://doi.org/10.1093/cdn/nzy094

Harno, Erika, Cottrell, Elizabeth C., Yu, Alice, DeSchoolmeester, Joanne, Gutierrez, Pablo Morentin, Denn, Mark, et al. (2013). 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors still improve metabolic phenotype in male 11β-HSD1 knockout mice suggesting off-target mechanisms. *Endocrinology, 154*(12), 4580–4593. https://doi.org/10.1210/en.2013-1613

Hervik, Astrid Kolderup, & Svihus, Birger (2019). The role of fiber in energy balance. *Journal of nutrition and metabolism, 2019*, Article 4983657. https://doi.org/10.1155/2019/4983657. -4983657.

Hintzpeter, Jan, Stapelfeld, Claudia, Loerz, Christine, Martin, Hans-Joerg, & Maser, Edmund (2014). Green tea and one of its constituents, Epigallocatechine-3-gallate, are potent inhibitors of human 11β-hydroxysteroid dehydrogenase type 1. *Plos One, 9*(1), e84468. https://doi.org/10.1371/journal.pone.0084468. -e84468.

Hong, Jian, Jia, Yimin, Pan, Shifeng, Jia, Longfei, Li, Huifang, Han, Zhenqiang, et al. (2016). Butyrate alleviates high fat diet-induced obesity through activation of adiponectin-mediated pathway and stimulation of mitochondrial function in the skeletal muscle of mice. *Oncotarget, 7*(35), 56071–56082. https://doi.org/10.18632/oncotarget.11267

Hu, Guo-Xin, Lin, Han, Lian, Qing-Quan, Zhou, Shu-Hua, Guo, Jingjing, Zhou, Hong-Yu, et al. (2013). Curcumin as a potent and selective inhibitor of 11β-hydroxysteroid

dehydrogenase 1: Improving lipid profiles in high-fat-diet-treated rats. *Plos One, 8* (3), e49976. https://doi.org/10.1371/journal.pone.0049976

Hu, Lihua, Huang, Xiao, You, Chunjiao, Li, Juxiang, Hong, Kui, Li, Ping, et al. (2017). Prevalence of overweight, obesity, abdominal obesity and obesity-related risk factors in Southern China. *Plos One, 12*(9), Article e0183934. https://doi.org/10.1371/journal.pone.0183934

Hussain, Zulfia, & Khan, Junaid Ali (2017). Food intake regulation by leptin: Mechanisms mediating gluconeogenesis and energy expenditure. *Asian Pacific Journal of Tropical Medicine, 10*(10), 940–944. https://doi.org/10.1016/j.apjtm.2017.09.003

Izadi, Vajiheh, Saraf-Bank, Sahar, & Azadbakht, Leila (2014). Dietary intakes and leptin concentrations. *ARYA atherosclerosis, 10*(5), 266–272.

James, W., & Philip, T. (2018). Obesity: A global public health challenge. *Clinical Chemistry, 64*(1), 24. https://doi.org/10.1373/clinchem.2017.273052

Jangra, S., K, R. S., Sharma, R. K., Pothuraju, R., & Mohanty, A. K (2019). Ameliorative effect of fermentable fibres on adiposity and insulin resistance in C57BL/6 mice fed a high-fat and sucrose diet. *Food Funct, 10*(6), 3696–3705. https://doi.org/10.1039/c8fo02578a

Jesch, Elliot D., & Carr, Timothy P. (2017). Food ingredients that inhibit cholesterol absorption. *Preventive nutrition and food science, 22*(2), 67–80. https://doi.org/10.3746/pnf.2017.22.2.67

Jha, Rajesh, Fouhse, Janelle M., Tiwari, Utsav P., Li, Linge, & Willing, Benjamin P (2019). Dietary fiber and intestinal health of monogastric animals. *Frontiers in Veterinary Science, 6*(48). https://doi.org/10.3389/fvets.2019.00048

Jumbe, Sandra, Hamlet, Claire, & Meyrick, Jane. (2017). Psychological aspects of bariatric surgery as a treatment for obesity. *Current Obesity Reports, 6*(1), 71–78. https://doi.org/10.1007/s13679-017-0242-2

Kaddam, L., Fadl-Elmula, I., Eisawi, O. A., Abdelrazig, H. A., & Saeed, A. M. (2019). Acacia senegal (Gum Arabic) supplementation modulate lipid profile and ameliorated dyslipidemia among sickle cell anemia patients. *J Lipids, 2019*, Article 3129461. https://doi.org/10.1155/2019/3129461

Karnati, Hanuma Kumar, Panigrahi, Manas Kumar, Li, Yazhou, Tweedie, David, & Greig, Nigel H (2017). Adiponectin as a potential therapeutic target for prostate cancer. *Current pharmaceutical design, 23*(28), 4170–4179. https://doi.org/10.2174/1381612823666170208123553

Khan, Saira A., & Jackson, Robert T. (2018). Polyunsaturated fatty acids, inflammation, and metabolic syndrome in South Asian Americans in Maryland. *Food science & nutrition, 6*(6), 1575–1581. https://doi.org/10.1002/fsn3.698

Krause, Matthew P., Milne, Kevin J., & Hawke, Thomas J (2019). Adiponectin-consideration for its role in skeletal muscle health. *International journal of molecular sciences, 20*(7), 1528. https://doi.org/10.3390/ijms20071528

Larson, R., Nelson, C., Korczak, R., Willis, H., Erickson, J., Wang, Q., et al. (2021). Acacia Gum is well tolerated while increasing satiety and lowering peak blood glucose response in healthy human subjects. *Nutrients, 13*(2). https://doi.org/10.3390/nu13020618

Leggio, Massimo, Lombardi, Mario, Caldarone, Elisa, Severi, Paolo, D'Emidio, Stefania, Armeni, Massimo, et al. (2017). The relationship between obesity and hypertension: An updated comprehensive overview on vicious twins. *Hypertension Research, 40* (12), 947–963. https://doi.org/10.1038/hr.2017.75

Leitner, Deborah R., Frühbeck, Gema, Yumuk, Volkan, Schindler, Karin, Micic, Dragan, Woodward, Euan, et al. (2017). Obesity and type 2 diabetes: Two diseases with a need for combined treatment strategies - EASO can lead the way. *Obesity facts, 10*(5), 483–492. https://doi.org/10.1159/000480525

Li, C., Xia, J., Zhu, W., Xin, L., An, C., Yang, S., et al. (2017). Systemic overexpression of the 11betaHSD1 promotes endoplasmic reticulum stress in multiple tissues and the development of metabolic syndrome in mice. *Mol Med Rep, 16*(5), 7738–7744. https://doi.org/10.3892/mmr.2017.7530

Liberman, Ana C., Budziñski, Maia L., Sokn, Clara, Gobbini, Romina Paula, Steininger, Anja, & Arzt, Eduardo (2018). Regulatory and mechanistic actions of glucocorticoids on t and inflammatory cells. *Frontiers in endocrinology, 9*, 235. https://doi.org/10.3389/fendo.2018.00235. -235.

Livak, K. J., & Schmittgen, T. D. (2001). Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods (San Diego, Calif.), 25*(4), 402–408, 10.1006/meth.2001.1262 S1046-2023(01)91262-9 [pii].

Mariod, Abdalbasit A. (2018). 6 - Chemical Properties of Gum Arabic. In A. A. Mariod (Ed.), *Gum Arabic* (pp. 67–73). Academic Press.

Maziarz, Mindy Patterson, Preisendanz, Sara, Juma, Shanil, Imrhan, Victorine, Prasad, Chandan, & Vijayagopal, Parakat (2017). Resistant starch lowers postprandial glucose and leptin in overweight adults consuming a moderate-to-high-fat diet: a randomized-controlled trial. *Nutrition Journal, 16*(1), 14. https://doi.org/10.1186/s12937-017-0235-8

McRae, Marc P. (2017). Dietary fiber is beneficial for the prevention of cardiovascular disease: An umbrella review of meta-analyses. *Journal of chiropractic medicine, 16*(4), 289–299. https://doi.org/10.1016/j.jcm.2017.05.005

McRae, Marc P. (2018). Dietary fiber intake and type 2 diabetes mellitus: An umbrella review of meta-analyses. *Journal of chiropractic medicine, 17*(1), 44–53. https://doi.org/10.1016/j.jcm.2017.11.002

Menzaghi, Claudia, & Trischitta, Vincenzo. (2018). The adiponectin paradox for all-cause and cardiovascular mortality. *Diabetes, 67*(1), 12. https://doi.org/10.2337/dbi17-0016

Mohamed, R. E., Gadour, M. O., & Adam, I. (2015). The lowering effect of Gum Arabic on hyperlipidemia in Sudanese patients. *Front Physiol, 6*, 160. https://doi.org/10.3389/fphys.2015.00160

Myers, J., Kokkinos, P., & Nyelin, E. (2019). Physical activity, cardiorespiratory fitness, and the metabolic syndrome. *Nutrients, 11*(7). https://doi.org/10.3390/nu11071652

Narayan, Shreya, Lakshmipriya, Nagarajan, Vaidya, Ruchi, Bai, Mookambika Ramya, Sudha, Vasudevan, Krishnaswamy, Kamala, et al. (2014). Association of dietary fiber intake with serum total cholesterol and low density lipoprotein cholesterol levels in Urban Asian-Indian adults with type 2 diabetes. *Indian journal of endocrinology and metabolism, 18*(5), 624–630. https://doi.org/10.4103/2230-8210.139215

Nasir, Omaima, Artunc, Ferruh, Wang, Kan, Rexhepaj, Rexhep, Föller, Michael, Ebrahim, Ammar, et al. (2010). Downregulation of mouse intestinal Na+-coupled glucose transporter SGLT1 by Gum Arabic (Acacia Senegal). *Cellular physiology and biochemistry: international journal of experimental cellular physiology, biochemistry, and pharmacology, 25*, 203–210. https://doi.org/10.1159/000276554

Naumann, Susanne, Schweiggert-Weisz, Ute, Eglmeier, Julia, Haller, Dirk, & Eisner, Peter (2019). In vitro interactions of dietary fibre enriched food ingredients with primary and secondary bile acids. *Nutrients, 11*(6). https://doi.org/10.3390/nu11061424

Nemmar, A., Al-Salam, S., Beegam, S., Yuvaraju, P., & Ali, B. H. (2019). Gum Arabic ameliorates impaired coagulation and cardiotoxicity induced by water-pipe smoke exposure in mice. *Front Physiol, 10*, 53. https://doi.org/10.3389/fphys.2019.00053

Nishizawa, H., & Shimomura, I. (2019). Population approaches targeting metabolic syndrome focusing on Japanese trials. *Nutrients, 11*(6). https://doi.org/10.3390/nu11061430

Noakes, Timothy David. (2018). So what comes first: the obesity or the insulin resistance? And which is more important? *Clinical Chemistry, 64*(1), 7. https://doi.org/10.1373/clinchem.2017.282962

Paley, Carole A., & Johnson, Mark I (2018). Abdominal obesity and metabolic syndrome: exercise as medicine? *BMC sports science, medicine & rehabilitation, 10*, 7. https://doi.org/10.1186/s13102-018-0097-1. -7.

Parnell, J. A., & Reimer, R. A. (2010). Effect of prebiotic fibre supplementation on hepatic gene expression and serum lipids: a dose-response study in JCR:LA-cp rats. *British Journal of Nutrition, 103*(11), 1577–1584. https://doi.org/10.1017/S0007114509993539

Peng, Kesong, Pan, Yong, Li, Jieli, Khan, Zia, Fan, Mendi, Yin, Haimin, et al. (2016). 11β-Hydroxysteroid Dehydrogenase Type 1(11β-HSD1) mediates insulin resistance through JNK activation in adipocytes. *Scientific reports, 6*, 37160. https://doi.org/10.1038/srep37160. -37160.

Pilolla, Kari D. (2018). Targeting abdominal obesity through the diet: What does the evidence say? *ACSM's Health & Fitness Journal, 22*(5), 21–28. https://doi.org/10.1249/fit.0000000000000419

Pi-Sunyer, Xavier. (2019). Changes in body composition and metabolic disease risk. *European Journal of Clinical Nutrition, 73*(2), 231–235. https://doi.org/10.1038/s41430-018-0320-x

Polyzos, S. A., Kountouras, J., & Mantzoros, C. S. (2019). Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism, 92*, 82–97. https://doi.org/10.1016/j.metabol.2018.11.014

Rathinasabapathy, Thirumurugan, Jackson, Palatini, Marie, Kimberly, Thor, Yiwen, Buru, Ayuba Sunday, Esposito, Debora, et al. (2017). Thiazolopyridines Improve Adipocyte Function by Inhibiting 11 Beta-HSD1 Oxoreductase Activity. *Journal of Chemistry, 2017*, 10. https://doi.org/10.1155/2017/3182129

Ren, Wei, Guo, Jianjin, Jiang, Feng, Lu, Jun, Ding, Ying, Li, Aimei, et al. (2014). CCAAT/enhancer-binding protein α is a crucial regulator of human fat mass and obesity associated gene transcription and expression. *BioMed research international, 2014*, Article 406909. https://doi.org/10.1155/2014/406909. -406909.

Rideout, Todd C., Harding, Scott V., Jones, Peter Jh, & Fan, Ming Z (2008). Guar gum and similar soluble fibers in the regulation of cholesterol metabolism: current understandings and future research priorities. *Vascular health and risk management, 4* (5), 1023–1033. https://doi.org/10.2147/vhrm.s3512

Rosenbaum, Michael, & Leibel, Rudolph L (2014). 20 years of leptin: role of leptin in energy homeostasis in humans. *The Journal of endocrinology, 223*(1), T83–T96. https://doi.org/10.1530/JOE-14-0358

Ruan, Hong, & Dong, Lily Q. (2016). Adiponectin signaling and function in insulin target tissues. *Journal of molecular cell biology, 8*(2), 101–109. https://doi.org/10.1093/jmcb/mjw014

Sai, Shuji, Esteves, Cristina L., Kelly, Val, Michailidou, Zoi, Anderson, Karen, Coll, Anthony P., et al. (2008). Glucocorticoid regulation of the promoter of 11beta-hydroxysteroid dehydrogenase type 1 is indirect and requires CCAAT/enhancer-binding protein-beta. *Molecular endocrinology (Baltimore, Md.), 22*(9), 2049–2060. https://doi.org/10.1210/me.2007-0489

Sánchez-Jiménez, Flora, Pérez-Pérez, Antonio, de la Cruz-Merino, Luis, & Sánchez-Margalet, Víctor (2019). Obesity and breast cancer: Role of leptin. *Frontiers in Oncology, 9*, 596. https://doi.org/10.3389/fonc.2019.00596. -596.

Sekar, Sunderajhan, Shafie, Siti Raihanah, Prasadam, Indira, Crawford, Ross, Panchal, Sunil K., Brown, Lindsay, et al. (2017). Saturated fatty acids induce development of both metabolic syndrome and osteoarthritis in rats. *Scientific reports, 7*, 46457. https://doi.org/10.1038/srep46457. -46457.

Sena, Cristina M., Pereira, Ana, Fernandes, Rosa, Letra, Liliana, & Seiça, Raquel M (2017). Adiponectin improves endothelial function in mesenteric arteries of rats fed a high-fat diet: role of perivascular adipose tissue. *British Journal Of Pharmacology, 174*(20), 3514–3526. https://doi.org/10.1111/bph.13756

Shukla, Ravindra, Basu, Asish Kumar, Mandal, Biplab, Mukhopadhyay, Pradip, Maity, Animesh, Chakraborty, Satyam, et al. (2019a). 11β Hydroxysteroid dehydrogenase - 1 activity in type 2 diabetes mellitus: a comparative study. *BMC endocrine disorders, 19*(1), 15. https://doi.org/10.1186/s12902-019-0344-9. -15.

Shukla, Ravindra, Basu, Asish Kumar, Mandal, Biplab, Mukhopadhyay, Pradip, Maity, Animesh, Chakraborty, Satyam, et al. (2019b). 11β Hydroxysteroid dehydrogenase –1 activity in type 2 diabetes mellitus: a comparative study. *BMC Endocrine Disorders, 19*(1), 15. https://doi.org/10.1186/s12902-019-0344-9

Slavin, J. (2013). Fiber and prebiotics: mechanisms and health benefits. *Nutrients, 5*(4), 1417–1435. https://doi.org/10.3390/nu5041417. nu5041417 [pii].

Solah, Vicky A., Kerr, Deborah A., Hunt, Wendy J., Johnson, Stuart K., Boushey, Carol J., Delp, Edward J., et al. (2017). Effect of fibre supplementation on body weight and composition, frequency of eating and dietary choice in overweight individuals. *Nutrients, 9*(2), 149. https://doi.org/10.3390/nu9020149

Soliman, Ghada A. (2019). Dietary fiber, atherosclerosis, and cardiovascular disease. *Nutrients, 11*(5), 1155. https://doi.org/10.3390/nu11051155

Stern, Jennifer H., Rutkowski, Joseph M., & Scherer, Philipp E (2016). Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. *Cell metabolism, 23*(5), 770–784. https://doi.org/10.1016/j.cmet.2016.04.011

Stomby, A., Andrew, R., Walker, B. R., & Olsson, T. (2014). Tissue-specific dysregulation of cortisol regeneration by 11betaHSD1 in obesity: has it promised too much? *Diabetologia, 57*(6), 1100–1110. https://doi.org/10.1007/s00125-014-3228-6

Tremmel, Maximilian, Gerdtham, Ulf- G., Nilsson, Peter M., & Saha, Sanjib (2017). Economic burden of obesity: A systematic literature review. *International journal of environmental research and public health, 14*(4), 435. https://doi.org/10.3390/ijerph14040435

Tumminia, Andrea, Vinciguerra, Federica, Parisi, Miriam, Graziano, Marco, Sciacca, Laura, Baratta, Roberto, et al. (2019). Adipose tissue, obesity and adiponectin: Role in endocrine cancer risk. *International journal of molecular sciences, 20*(12), 2863. https://doi.org/10.3390/ijms20122863

Ushida, K. (2012). *Gum Arabic and its Anti-obese Effect Gum Arabic* (pp. 285–290). The Royal Society of Chemistry.

Vara Prasad, Sakamuri S. S., Jeya Kumar, Shanmugam S., Kumar, Putcha Uday, Qadri, Syed S. Y. H., & Vajreswari, Ayyalasomayajula (2010). Dietary fatty acid composition alters 11β-hydroxysteroid dehydrogenase type 1 gene expression in rat retroperitoneal white adipose tissue. *Lipids in health and disease, 9*, 111. https://doi.org/10.1186/1476-511X-9-111. -111.

Vekic, J., Zeljkovic, A., Stefanovic, A., Jelic-Ivanovic, Z., & Spasojevic-Kalimanovska, V. (2019). Obesity and dyslipidemia. *Metabolism, 92*, 71–81. https://doi.org/10.1016/j.metabol.2018.11.005

Viuda-Martos, M., López-Marcos, M. C., Fernández-López, J., Sendra, E., López-Vargas, J. H., & Pérez-Álvarez, J. A. (2010). Role of fiber in cardiovascular diseases: A review. *Comprehensive Reviews in Food Science and Food Safety, 9*(2), 240–258. https://doi.org/10.1111/j.1541-4337.2009.00102.x

Wang, G. C., Yu, J. H., Shen, Y., Leng, Y., Zhang, H., & Yue, J. M. (2016). Limonoids and Triterpenoids as 11beta-HSD1 Inhibitors from Walsura robusta. *Journal of Natural Products, 79*(4), 899–906. https://doi.org/10.1021/acs.jnatprod.5b00952

Wang, H., Hong, T., Li, N., Zang, B., & Wu, X. (2018). Soluble dietary fiber improves energy homeostasis in obese mice by remodeling the gut microbiota. *Biochemical and Biophysical Research Communications, 498*(1), 146–151. https://doi.org/10.1016/j.bbrc.2018.02.017

Wang, Yeli, Meng, Rui-Wei, Kunutsor, Setor K., Chowdhury, Rajiv, Yuan, Jian-Min, Koh, Woon-Puay, et al. (2018). Plasma adiponectin levels and type 2 diabetes risk: a nested case-control study in a Chinese population and an updated meta-analysis. *Scientific reports, 8*(1), 406. https://doi.org/10.1038/s41598-017-18709-9. -406.

Winnick, J. J., Ramnanan, C. J., Saraswathi, V., Roop, J., Scott, M., Jacobson, P., et al. (2013). Effects of 11β-hydroxysteroid dehydrogenase-1 inhibition on hepatic glycogenolysis and gluconeogenesis. *American journal of physiology. Endocrinology and metabolism, 304*(7), E747–E756. https://doi.org/10.1152/ajpendo.00639.2012

Wolfe, Bruce M., Kvach, Elizaveta, & Eckel, Robert H (2016). Treatment of obesity: Weight loss and bariatric surgery. *Circulation research, 118*(11), 1844–1855. https://doi.org/10.1161/CIRCRESAHA.116.307591

Woods, C. P., Corrigan, M., Gathercole, L., Taylor, A., Hughes, B., Gaoatswe, G., et al. (2015). Tissue specific regulation of glucocorticoids in severe obesity and the response to significant weight loss following bariatric surgery (BARICORT). *Journal of Clinical Endocrinology and Metabolism, 100*(4), 1434–1444. https://doi.org/10.1210/jc.2014-4120

Woodward, Lavinia, Akoumianakis, Ioannis, & Antoniades, Charalambos (2017). Unravelling the adiponectin paradox: novel roles of adiponectin in the regulation of cardiovascular disease. *British journal of pharmacology, 174*(22), 4007–4020. https://doi.org/10.1111/bph.13619

Xu, Baoji, & Xie, Xiangyang. (2016). Neurotrophic factor control of satiety and body weight. *Nature reviews. Neuroscience, 17*(5), 282–292. https://doi.org/10.1038/nrn.2016.24

Yanai, Hidekatsu, & Tada, Norio. (2018). *Effects of Glycemic Index and Intake of Dietary Fiber on Serum HDL-Cholesterol Levels*.

Yanai, Hidekatsu, & Yoshida, Hiroshi (2019). Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: Mechanisms and perspectives. *International journal of molecular sciences, 20*(5), 1190. https://doi.org/10.3390/ijms20051190

Zhang, Ru, Jiao, Jun, Zhang, Wei, Zhang, Zheng, Zhang, Weiguo, Qin, Li-Qiang, et al. (2016). Effects of cereal fiber on leptin resistance and sensitivity in C57BL/6J mice fed a high-fat/cholesterol diet. *Food & nutrition research, 60*, 31690. https://doi.org/10.3402/fnr.v60.31690. -31690.