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ORIGINAL ARTICLE

Antiobesity Effects of Lycii Fructus in High-Fat Diet/Fructose-Induced Obese Rats

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ABSTRACT

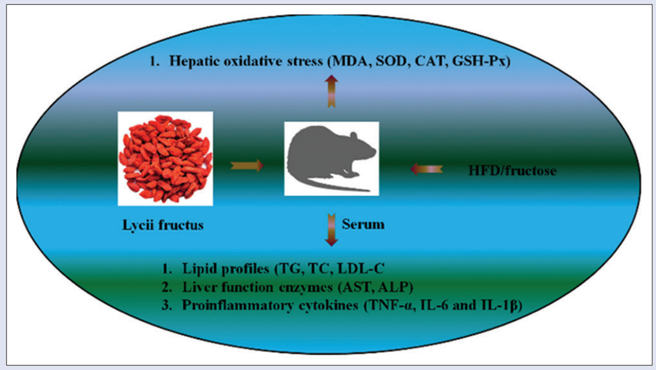
Background: The prevalence of obesity is increasing at an enormous rate among all age groups which makes it one of the foremost health problems. **Objective:** This study was aimed at investigating the effect of the ethyl acetate extract from Lycii fructus (ETLF) against high-fat diet (HFD)/fructose-induced obesity in rats. **Materials and Methods:** Obesity was induced in rats by feeding them with HFD and 15% fructose for 8 weeks, while the animals in ETLF groups were administered with 100 and 400 mg/kg of ETLF once daily from the 5th to the 8th week. **Results:** ETLF displayed antiobesity by significantly reducing body weight gain, serum lipid levels as well as alleviating increased serum insulin and glucose levels. In addition, ETLF treatment when compared to the HFD/fructose fed group significantly alleviated oxidative stress and inflammation by reducing malondialdehyde, tumor necrosis factor alpha, interleukin 1 beta (IL-1 β) and IL-6 levels as well as enhancing the activities of superoxide dismutase, catalase, and glutathione peroxidase. **Conclusion:** Thus, these results portrayed that ETLF had protective effects against metabolic disorders induced by HFD/fructose through its antioxidant, anti-inflammatory, and antihyperlipidemic activities.

Key words: Anti-inflammation, antioxidant, high-fat diet, lycii fructus, obesity

SUMMARY

- The ethyl acetate extract of lycii fructus ameliorative high-fat diet/fructose-induced obesity
- The ethyl acetate extract of lycii fructus significantly improved metabolic and renal functions in obese rats.

Abbreviations used: ETLF: Ethyl acetate extract from lycii fructus; HFD: High fat diet; TNF-α: Tumor necrosis factor alpha; IL-1s β: Interleukin 1 beta; IL-6: Interleukin 6; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; MDA: Malondialdehyde; GSH-Px: Glutathione peroxidase; CAT: Catalase; SOD: Superoxide dismutase.



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INTRODUCTION

The prevalence of obesity is increasing at an enormous rate in adults and children which makes it one of the foremost health problems. The World Health Organization reported that the global occurrence of obesity has nearly tripled since 1975. An estimated number of 1.9 billion adults were considered overweight in 2016, out of which 650 million were obese. Furthermore, an alarming number of adolescents and children (340 million) were either overweight or obese. Obesity is one of the prevailing metabolic disorder that is becoming a global public health concern due to its strong correlation to some life threatening disorders like stroke, type 2 diabetes mellitus, cardiovascular disease, hypertension, reproductive and gastrointestinal cancers, and osteoarthritis.[1-3] Obesity is a medical condition that is characterized by accumulation of extreme body fats and lipids in the adipose tissue and chronic low grade inflammation which induces the increase in inflammatory mediators such as tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1, interleukin 6 (IL-6) and leptin.[4,5] Obese people have body mass index >30 kg/m^2 and this can be majorly attributed to an imbalance between the intake and use of energy.[6]

The most commonly prescribed therapy for obesity is the use of drugs that can decrease the body weight by reducing appetite, regulating the absorption of fat as well as modulating the peptide receptors in the gut.[7-9] However most of the drugs approved as antiobesity agents have shown very limited efficacy including several unpleasant side effects. For instance, orlistat, lorcaserin, and sibutramine are some of the antiobesity drugs currently in the market, but side effects such as cardiovascular disease, thirst, constipation, headache, insomnia, and strokes have greatly limited their success stories.[10-12] As such, the

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search for antiobesity agents with better efficacy and limited toxicity is imperatively needed.

Recently, natural products have become one of the emerging approach widely used for treating obesity, owing to their perceived safety, efficacy, and ease of accessibility. In addition, several of these natural medicines are an arsenal of cocktails of phytochemicals which work synergistically to effect the desired pharmacological response.[13-15] Lycii fructus is the dried fruit of *Lycium barbarum* or *Lycium chinense*, a very important and popular traditional Chinese medicine and one of the most common components of functional foods and health tonic teas in China.[16,17] Interestingly, lycii fructus is gaining more interest and its popularity is increasing especially in western nations due to its nutritional and medicinal importance.[17-19] It has been pharmacologically explored as having potent anti-aging, anti-fatigue, neuroprotective, retinal protection, hepatoprotective, antioxidant and antidiabetic, antiglaucoma, immunomodulation, antitumor, and cytoprotective effects.[17,20] Lycii fructus is a rich source of phytochemicals such as polyphenols, polysaccharides, Vitamins B, C and E, amino acids and organic acids.[20-23] However, the antiobesity effect of lycii fructus in high-fat diet (HFD)-fed obese rats have not yet been reported. Therefore, this present study investigated the effects of lycii fructus extract on HFD/fructose-induced obesity in rats.

MATERIALS AND METHODS

Plant extraction

Lycii fructus (400 g) was crushed into smaller pieces and extracted with 80% CH_3OH (2.5 L × 3) under reflux for 2 h. The hydromethanolic extract obtained was filtered with Wattman No. 3 filter paper and evaporated to dryness under reduced pressure with a rotary evaporator to obtain a crude hydro methanolic extract (12.8g), which was further reconstituted in distilled water and partitioned with EtOAc (1 L × 2). The EtOAc soluble extract ethyl acetate extract from lycii fructus (ETLF) was concentrated to dryness and stored until further use.

Experimental animal studies

Healthy male Wistar rats weighing 140–180 g were used for this study. The rats were acclimatized for 7 days prior to the start of the experiment under the following conditions of temperature of 24°C ± 2°C with 55% ± 5% relative humidity and a 12-h light and 12-h dark period. During the period of acclimatization, the animals were allowed unrestricted access to standard regular rat diet and water. The procedure used during the animal experiment received approval from the Ethic Committee of the First People's Hospital of Yunnan Province (ethics number: 20180930). After 7 days of acclimatization, the animals were randomly allotted into five groups as stated below:

- Normal control group: Fed with standard rat chow and water *ad libitum*
- HFD control group: Fed with HFD comprising of 27.5% kcal of carbohydrate, 58.7% kcal of fat and 14.4% kcal of protein and 15% fructose solution
- HFD-ETLF100 group: Fed with HFD, 15% fructose solution and ETLF extract (100 mg/kg)
- HFD-ETLF400 group: Fed with HFD, 15% fructose solution and ETLF extract (400 mg/kg).

The body weights and food intake was recorded. After 8 weeks of HFD/fructose and treatment, the animals were fasted overnight, sacrificed, and blood samples were obtained for the determination of serum biochemical parameters.

Determination of serum biochemical parameters

The serum levels of lipids (total cholesterol [TC], triglyceride [TG]), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were assayed by an automatic biochemistry analyzer.

Determination of serum and liver oxidative stress and inflammatory markers

Hepatic levels of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and malondialdehyde (MDA) were assayed in the liver homogenate with the aid of commercially available kit according to the manufacturer's instructions. Analyses of the levels of TNF-α, IL-1 β, and IL-6 in the serum were determined by commercially available ELISA kit based on the manufacturer's instructions.

Statistical analysis

All data were analyzed with ANOVA (one-way analysis of variance) followed by Turkey's multiple comparison test (Graph pad Prism 7.0; San Diego, USA). Results were expressed as mean ± standard deviation, and values with $P < 0.05$ were considered as statistically significant.

RESULTS

Effect of ethyl acetate extract from lycii fructus on body weight, epididymal fat, and food intake

The effect of ETLF on the body weight, epididymal fat, and food intake in the HFD/fructose fed rats are shown in Figure 1. The average body weight of rats fed with HFD after 8 weeks was significantly higher than the body weight of the rats in the control group. The body weight gain of the HFD control group increased by approximately 66% when juxtaposed to the normal group. However, treatment with ETLF remarkably prevented excessive body weight gain in ETLF 100 and ETLF 400 groups. Furthermore, in the ETLF treated groups, the epididymal fat weight was observed to be significantly lower than the corresponding weight in the HFD control group. As regards the food intake, there was no significant difference in the consumption of food of the normal control, HFD control and ETLF-treated groups [Figure 1].

Effect of ethyl acetate extract from lycii fructus on serum biochemical parameters

The HFD/fructose fed animals displayed significantly higher levels of serum lipid values (TG, TC and LDL-C) as compared to the normal control group. The HFD/fructose fed control group had approximately 2-, 1.7-, and 2.5-fold increase in TG, TC, and LDL-C values respectively relative to the normal control group [Figure 2a-c]. In addition, glucose and insulin levels in HFD/fructose fed group were also markedly higher [Figure 2d and e]. Interestingly, ETLF treatment alleviated the altered lipid profiles as observed by the reduced level of TC, TG and LDL-C levels as well as significantly reduced glucose and insulin levels when compared to the HFD/fructose fed group [Figure 2]. Furthermore, when compared with the normal control group, AST and ALT levels in the HFD/fructose fed group were significantly increased, whereas supplementation with ETLF (100 and 400 mg/kg) attenuated AST and ALT levels [Figure 3].

Effect of ethyl acetate extract from lycii fructus on oxidative stress and antioxidant enzymes

As shown in Figure 4, the activities of CAT [Figure 4a], SOD [Figure 4b] and GSH-Px [Figure 4c] in the liver tissues of the HFD/fructose-fed control group were notably reduced when compared with the normal control group. However, ETLF treatment significantly increased the activities of liver CAT, SOD and GSH-Px compared with the HDF/fructose fed control group. In addition, MDA level [Figure 4d] in the HFD/fructose fed control group was higher compared to the normal

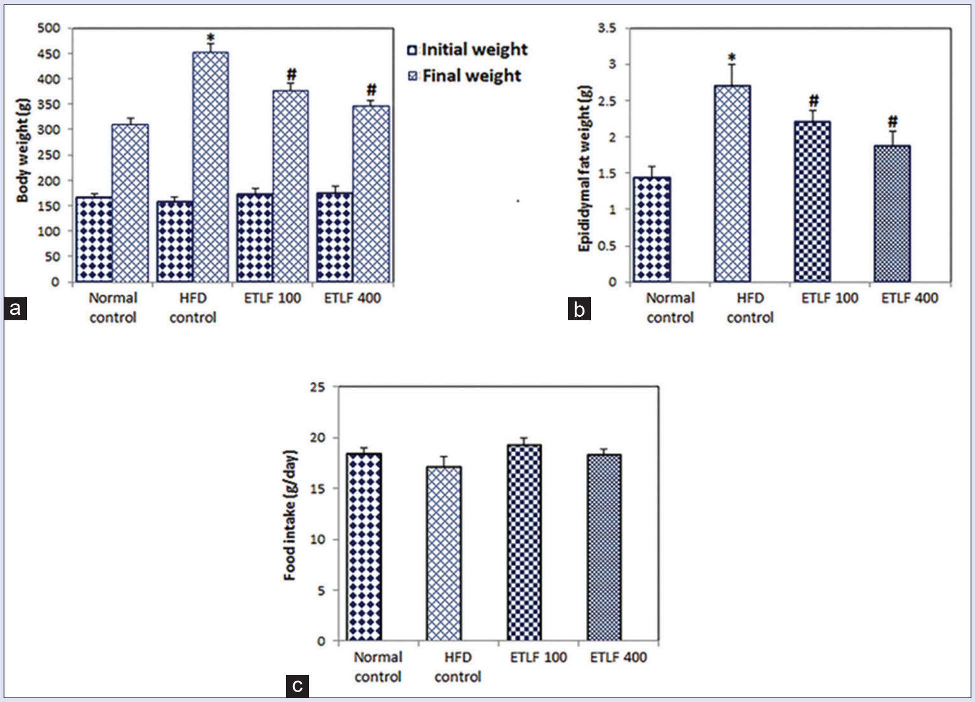

Figure 1: Effect of ethyl acetate extract from Lycii fructus on (a) body weight, (b) epididymal fat weight and (c) food intake in high fat diet/fructose fed rats. Values are expressed as means ± standard deviation (n = 6) and considered statistically significant at P < 0.05 *Compared to normal control; #Compared to high-fat diet control. High-fat diet control: High-fat diet control group; ethyl acetate extract from lycii fructus 100: obese rats treated with lycii fructus (100 mg/kg); ethyl acetate extract from lycii fructus 400: obese rats treated with lycii fructus (400 mg/kg)

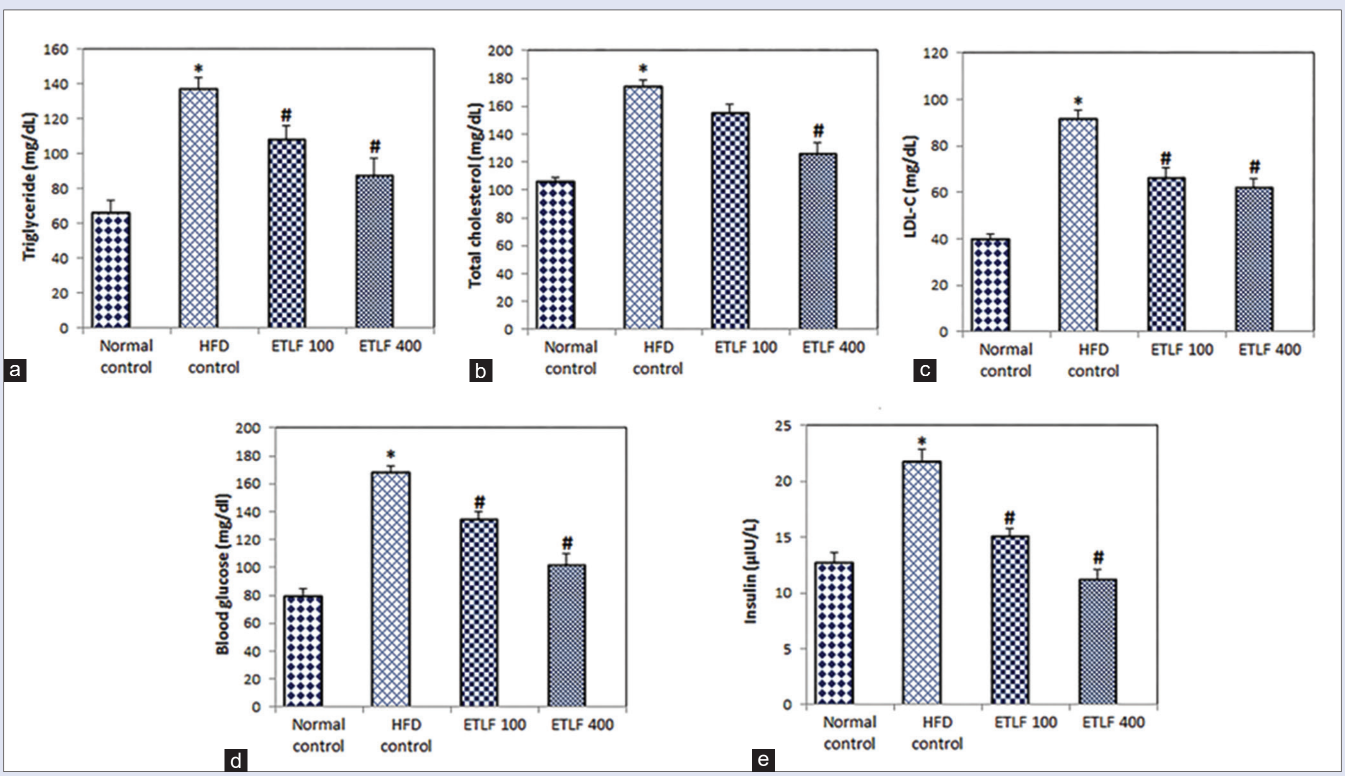

Figure 2: Effect of ethyl acetate extract from lycii fructus on serum biochemical parameters in high-fat diet/fructose-fed rats. (a) Triglyceride levels, (b) total cholesterol levels, (c) low density lipoprotein cholesterol levels, (d) blood glucose levels, and (e) insulin levels. Values are expressed as means ± standard deviation (n = 6) and considered statistically significant at P < 0.05 *Compared to normal control; #Compared to high-fat diet control. High-fat diet control: high-fat diet control group; ethyl acetate extract from lycii fructus 100: obese rats treated with lycii fructus (100 mg/kg); ethyl acetate extract from lycii fructus 400: obese rats treated with lycii fructus (400 mg/kg)

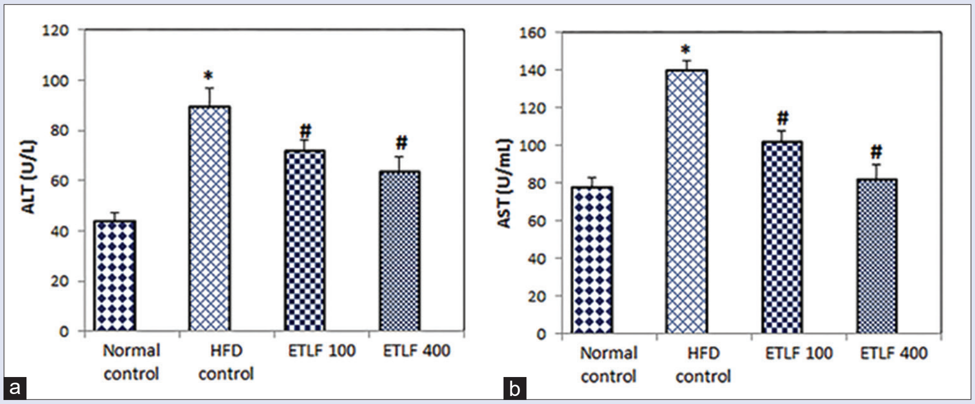

Figure 3: Effect of ethyl acetate extract from lycii fructus on serum (a) alanine aminotransferase levels and (b) aspartate aminotransferase levels high fat diet/fructose fed rats. Values are expressed as means ± standard deviation ($n = 6$) and considered statistically significant at $P < 0.05$. *Compared to normal control; #Compared to high-fat diet control. High-fat diet control: high-fat diet control group; ethyl acetate extract from lycii fructus 100: obese rats treated with lycii fructus (100 mg/kg); ethyl acetate extract from lycii fructus 400: obese rats treated with lycii fructus (400 mg/kg)

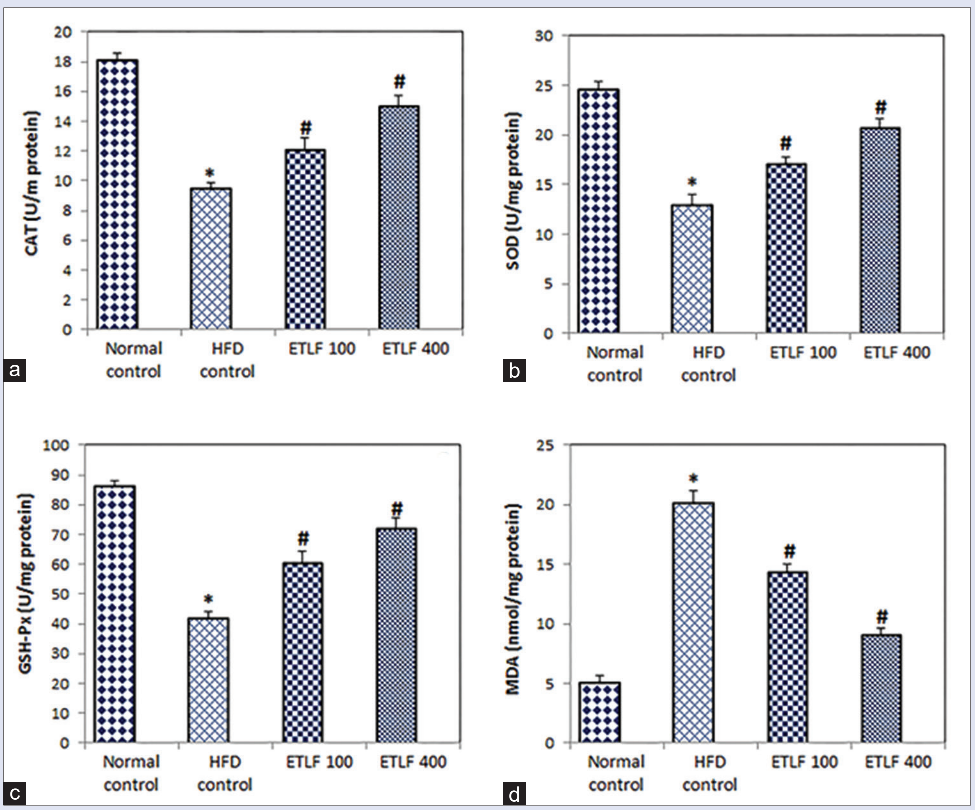

Figure 4: Effect of ethyl acetate extract from lycii fructus on hepatic oxidative stress in high fat diet/fructose fed rats. (a) Catalase levels, (b) superoxide dismutase levels, (c) glutathione peroxidase levels and (d) malondialdehyde levels. Values are expressed as means ± standard deviation ($n = 6$) and considered statistically significant at $P < 0.05$. *Compared to normal control; #Compared to high-fat diet control. High-fat diet control: High-fat diet control group; ethyl acetate extract from lycii fructus 100: obese rats treated with lycii fructus (100 mg/kg); ethyl acetate extract from lycii fructus 400: obese rats treated with lycii fructus (400 mg/kg)

control group. Moreover, ETLF (100 and 400 mg/kg)-treated groups displayed reduced levels of MDA when compared to the HDF/fructose control group.

Effect of ethyl acetate extract from lycii fructus on inflammatory markers

The animals in the HFD/fructose fed control group showed significantly higher levels of serum TNF-α [Figure 5a], IL-6 [Figure 5b] and IL-1 β [Figure 5c] than the normal control. Whereas, in groups treated with ETLF, these inflammatory markers were markedly reduced.

DISCUSSION

The prolonged consumption of HFD as well as the long-term intake of high amount of fructose has been indisputably proven to be closely linked to the onset and progression of obesity, insulin resistance and metabolic syndrome.[24-26] This study describes for the first time the

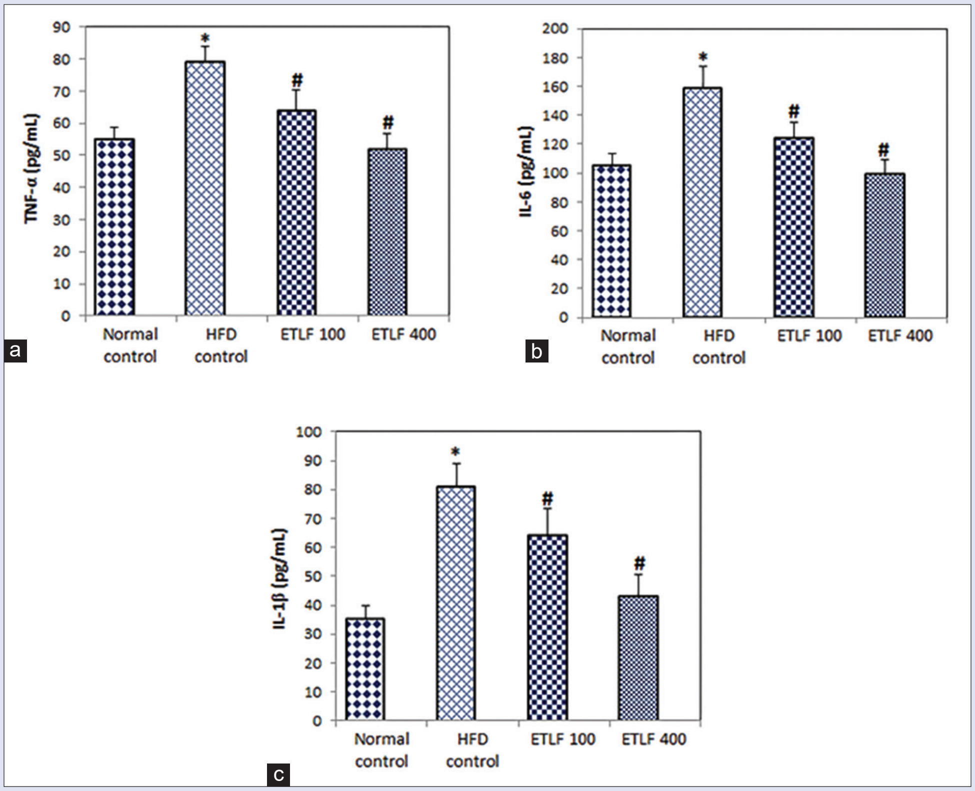

Figure 5: Effect of ethyl acetate extract from lycii fructus on serum inflammatory cytokines in high fat diet/fructose fed rats. (a) Tumor necrosis factor α levels, (b) Interleukin 6 levels and (c) Interleukin 1 beta levels. Values are expressed as means ± standard deviation (n = 6) and considered statistically significant at $P < 0.05$. *Compared to normal control; #Compared to high-fat diets control: high-fat diet control group; ethyl acetate extract from lycii fructus 100: obese rats treated with lycii fructus (100 mg/kg); ethyl acetate extract from lycii fructuss 400: obese rats treated with lycii fructus (400 mg/kg

antiobesity effects of lycii fructus in an HFD/fructose fed obese rat model. The increase in the awareness and use of substances from natural origin for health promotion and/or treatment of various diseases has led to extensive investigations different traditional medicinal plants for their possible pharmacological role and mechanism of action. Although a number of researches have illustrated the usefulness of lycii fructus as an antioxidant, anti-aging, anticancer, antidiabetic, and kidney protection, no study to the best of our knowledge has assessed its protective effect on HFD-fructose induced obesity. In this present study, the HFD-fructose feeding for 8 weeks led to rapid body weight gain as well as significant increase in fat weight of the rats and the administration of ETLF significantly led to body and epididymal fat weight loss.

Dyslipidemia, a condition associated with high levels of lipids is one of the vital markers in the pathogenesis of metabolic syndrome including obesity. Dyslipidemia has been reported to be closely associated with increased risk of cardiovascular diseases, insulin resistance and nonalcoholic fatty liver as a result of increased levels of TG and TC.[14,27,28] It is an undisputable and well-established fact that the consumption of diet with high fat can instigate elevated levels of TG, TC and LDL-C.[29,30] It was observed in this study, that the treatment with the extract of Lycii fructus lowered serum TG, TC, and LDL-C concentrations.

Insulin resistance is considered as one of the major hallmark associated with obesity, resulting in high levels of serum insulin and glucose[29,31] It has been previously reported that the consumption of HFD in animal models instigates hyperglycemia and insulin resistance.[28,32] In this present study, treatment with lycii fructus displayed decreased blood glucose level and ameliorated insulin sensitivity.

In liver damage or injury, serum liver markers such as ALT and AST are usually observed to be increased.[33,34] Consumption of HFD over a prolong period of time can initiate liver abnormalities, which may result in increase of ALP and AST due enzyme leakage as from cellular membranes.[35,36] In line with other previous studies, we noticed significant upregulation in the concentration of AST and ALT in the serum of HFD/fructose fed group. ETLF effectively suppressed the levels of these liver function enzymes, suggesting that Lycii fructus protected against HFD/fructose induced liver injury.

Oxidative stress and increase in inflammatory mediators has been strongly associated with obesity and insulin resistance.[37,38] Oxidative stress occurs due to increased generation of reactive oxygen species and local and/or systemic pro-inflammatory cytokines, in addition to decrease in the activity of enzymatic antioxidants (SOD, CAT and GSH-Px) during obesity.[39] In addition, the elevated production of cytokines in adipose tissue results in oxidative stress which can further stimulate systemic inflammation.[40-42] In this study the HFD/fructose fed animals had decreased level of SOD, CAT and GSH-Px and high levels of MDA, TNF-α, IL-6 and IL-1 β indicating reduction of the antioxidant defense system and initiation of inflammation. Whereas, ETLF treatment enhanced the activities of SOD, CAT and GSH-Px, as well as reduced MDAs, TNF-α, IL-6, and IL-1 β levels. Therefore, reducing oxidative stress and inflammation may alleviate obesity associated metabolic complications.

CONCLUSION

In conclusion, our study portrayed that lycii fructus extract displayed antiobesity and anti-hyperlipidemic properties in HFD/fructose-fed rats. These effects is thought to be associated with ability of the extract to alleviate insulin resistance, oxidative stress, inflammatory response and enhance antioxidant defenses system. Thus, lycii fructus may be considered to have potentially useful application in management of obesity, hyperlipidemia, and metabolic disorders.

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Nil.

Conflicts of interests

There are no conflicts of interest.

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