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Review Article

The Effect of Licorice and Probiotics on Nonalcoholic Fatty Liver Disease (NAFLD): A Systematic Review

Pouya Rostamizadeh, Zohreh Mazloom*

Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

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*Corresponding author:
Zohreh Mazloom,
Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel: +98-9171111527
Email:
zohreh.mazloom@gmail.com
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ABSTRACT

The present studies showed that utilizing complementary and alternative medicine such as herbal remedies, and the use of beneficial gastrointestinal microorganisms, along with lifestyle modifications can contribute to the improvement of non-alcoholic fatty liver disease (NAFLD). The purpose of this study was to summarize the results of the existing studies on the relationship between licorice and probiotic consumption with fatty liver disease. Databases such as Google Scholar, Scopus, and Pubmed databases were searched to find relevant studies. Clinical and experimental trials were selected to be entered into this review article. The articles were evaluated for duplication, title, type of study, study population and variables. Of the 1177 retrieved articles, 17 were selected for full-text review and 5 for structured review. A review of these studies showed that glycyrrhizic acid as an active ingredient of licorice root significantly decreased the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride (TG), free fatty acid (FFA), and hepatic steatosis. Also clinical studies showed that consumption of probiotics significantly decreased the levels of (ALT), (AST), total cholesterol (TC) and low density lipoprotein (LDL.C). The findings of this study indicated that the use of glycyrrhizic acid and probiotics contributed to the improvement of NAFLD through synergistic effects.

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Introduction

Worldwide, Non-Alcoholic Fatty Liver Disease (NAFLD) is one of the leading causes of chronic liver disease (1, 2). The prevalence of the disease in Western countries is between 20 and 30% and about 15% in Asian countries (3). The prevalence of the fatty liver disease in Iran based on two different studies has been reported 15.3% and 21.5%, respectively (4, 5). The main cause of NAFLD is deposited excessive accumulation of triglyceride in hepatocytes, which accelerates inflammation, the progression of steatosis and fibrosis in the liver tissue (6, 7).

This disease encompasses a wide range, which starts with simple hepatic steatosis and can eventually lead to non-alcoholic steatohepatitis (NASH) and hepatic failure (8). The most important causes of this disease are obesity and insulin resistance (1, 3, 9, 10). In general, the development of simple steatosis to steatohepatitis and advanced fibrosis, are the result of the two processes: the former being caused by excessive accumulation of fat in the liver caused by insulin resistance, and the second is the development of oxidative stress, which is caused

by the accumulation of fat in the liver that causes inflammation (7, 11).

NAFLD if left untreated, progresses to fibrosis, hepatic cirrhosis and hepatic carcinoma (3, 12). Currently, there is no definitive medical treatment for non-alcoholic fatty liver disease. Lifestyle changes, including a combination of improved diet quality, increased physical activity, and gradual weight loss has been identified as the most effective ways to control and treat these patients (3, 13). The use of phytochemicals and herbs with antioxidant properties is one of the new therapeutic approaches. Complementary and alternative medicine can also be used to speed up the control and treatment of patients with NAFLD. Licorice is one of these compounds. The root of licorice is a triterpenoid compound called glycyrrhizic acid, which exerts its anti-inflammatory, antioxidant, antimicrobial/antibacterial and anti-cancer effects by improving fat metabolism and reducing lipid peroxidation (14-19).

Another effective compound in improving NAFLD is probiotics (20). Since obesity is one of the major causes of non-alcoholic fatty liver disease and based on the relationship between the gut and the liver, known as the gut-liver axis, the gut microbiota, as an environmental risk factor, can indicate the association of pathological conditions, such as obesity, with probiotics through its effect on metabolism (21). Two types of probiotics, including Bifidobacterium and Lactobacillus, can work through mechanisms, including improved intestinal epithelial barrier function, alterations in intestinal microbial flora, regulation of gastrointestinal lymphatic immune system function, and effect on cellular signaling pathways and act like insulin-related signaling pathways and nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB) inflammatory factor (22, 23). Therefore, it is possible that licorice and probiotics (supplements or food products) can be effective in improving the metabolic factors of patients with NAFLD through synergistic effects.

Materials and Methods

English-language databases including Google Scholar, Scopus, and Pubmed were searched to find relevant resources. This search was time-limited until April 2019. The following keywords were used to search the English language databases: (Non-alcoholic fatty liver disease) OR (Non-alcoholic steatohepatitis) OR (Hepatic steatosis) OR (Metabolic syndrome) AND (Licorice) OR (Glycyrrhiza glabra) OR (Probiotics) OR (Synbiotics). After preparing the initial list of articles, their titles were first reviewed and duplicates were removed. Then, the title and abstract of the remaining articles were evaluated and some unrelated articles were eliminated.

Subsequently, the full text of the remaining articles was reviewed and the relevant and eligible articles were selected. The studies could be either a clinical trial or an experimental one. The exclusion criteria for this systematic review included articles in a non-English language, cross-sectional studies, case-control studies, and studies whose results were inconsistent with the purpose of the current study. In the next step, information about articles, including, the first author's name, year and place of the study, type of study, age, gender, number of participants, the purpose of study, method of diagnosis and evaluation of NAFLD were collected and analyzed.

Results

By searching through the databases, 1177 articles were identified. After removing the duplicate articles, 584 articles remained for review by title and abstract. By reviewing the titles, abstracts, and considering the inclusion and exclusion criteria, 17 articles remained for full-text review. Ultimately, 12 articles were eliminated and 5 articles that met all the inclusion criteria remained. Their time span was from 2012 to 2018 (Table 1).

Glycyrrhizic Acid and NAFLD

During a clinical trial, Haji Agha Mohammadi et al. conducted a study in 66 patients with NAFLD and found that a daily 2 g capsule containing aqueous licorice root extract which contained 20% glycyrrhizic acid, equivalent to 400 mg of glycyrrhizic acid, could significantly ($P<0.001$) decrease the activity of hepatic transaminases including ALT and AST. However, no significant change was observed in the control group receiving 2 grams of placebo (starch) capsules. In this study, licorice capsules contained 20% glycyrrhizic acid, which is equivalent to 400 mg of glycyrrhizic acid. This high dose of licorice may be problematic for patients.

Since it has been observed that taking more than 200 mg of glycyrrhizic acid for 4 days may cause side effects such as fluid and sodium retention, edema, hypokalemia and thrombocytopenia without a significant increase in the blood pressure (29). In an experimental study, Wang et al. showed that consumption of Glycyrrhiza glabra in male rats with NAFLD treated with methionine and choline-deficient diet for 4 weeks, the level of ALT, and AST enzymes significantly ($P<0.05$) decreased. Besides, the hepatic steatosis, which was diagnosed through histological and biopsy examinations of liver tissue improved.

Table 1: Features of the studies of the effects of licorice and probiotics on non-alcoholic fatty liver disease

Reference	Hajiaghamohammadi et al. 2012 (24)	Wang et al. 2016 (25)	Li et al. 2018 (26)	Nabavi et al. 2014 (27)	Famouri et al. 2017 (28)
Main findings	-No significant change in BMI in the intervention and control groups -Significant decrease in serum ALT and AST in the intervention group	-Significant decrease in ALT, AST, TG, FFA, TC -Significantly reduced fat, inflammation, and fibrosis of liver tissue	-Significant weight loss, hepatic steatosis, ALT, AST and TG in the intervention group -Significant decrease in adipose tissue in the intervention group -No significant change in TC in the intervention group	-Significant weight loss, BMI ALT, AST, TC, LDL.C in the probiotic intervention group -No significant change in HDL.C in the probiotic intervention group and its significant increase with standard yogurt	-No significant changes in weight, BMI, and HDL.C in probiotic intervention group -Significant decrease in WC, ALT, AST, TC, TG, LDL.C and the grade of adipose tissue in the probiotic intervention group
Studied variables	BMI, ALT and AST	ALT, AST, TG, FFA, TC and liver histology	Weight, fatty tissue, liver steatosis, ALT, AST, TG and TC	Weight, BMI, ALT, AST, Glucose, TC, TG, LDL.C, and HDL.C	Weight, BMI, WC, ALT, AST, TC, HDL.C, LDL.C and TG (Fatty liver grade)
Method of diagnosis	Ultrasound and high levels of ALT and AST enzymes	Induction of disease with a limited diet of methionine and choline	Induction of high-fat diet (60% fat)	Ultrasonography	Sonography
Purpose of the study	The effect of licorice root aqueous extract on liver transaminase in non-alcoholic fatty liver disease patients	The effect of glycyrrhizic acid on rats with nonalcoholic fatty liver disease	The effect of diammonium glycyrrhizinate on rats with the non-alcoholic fatty liver disease through affecting the intestinal microbial flora and repairing the intestinal mucosal barrier	Effects of probiotic yogurt consumption on metabolic factors in patients with nonalcoholic fatty liver disease	Effects of probiotics on obese children and adolescents with non-alcoholic fatty liver disease
Number, gender, and age	66 males and females, mean age of control: 39.9 years, mean age of intervention: 40.5 years	56 male rats aged 8-9 weeks	22 male rats aged 4 weeks	72 males and females, Age range: 23-63 years	64 girls and boys, Age range: 10-18 years
Place of study	Iran	China	China	Iran	Iran
Types of study and follow-up time	Clinical Trial, 2 months	Experimental, 4 weeks	Experimental, 14 weeks	Clinical trials, 8 weeks	Clinical trials, 12 weeks

BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TG: Triglyceride, FFA: Free fatty acid, TC: Total cholesterol, WC: Waist circumference, HDL.C: High density lipoprotein cholesterol, LDL.C: Low density lipoprotein cholesterol.

Of course, among groups of rats that received glycyrrhiza glabra at low doses (12.5 mg/kg), moderate doses (25 mg/kg) and high doses (50 mg/kg) a reduction in ALT and AST enzymes, and improvement in hepatic steatosis had a direct relationship with the consumed dosage of glycyrrhiza glabra. In an experimental study, Li et al. showed that daily intraperitoneal injection of diammonium glycyrrhizinate (DG) (150 mg/kg) in male rats with NAFLD for 14 weeks with a high-fat diet with 60% fat, significantly reduced ALT and AST enzymes and hepatic steatosis ($P<0.01$).

Therefore, all three studies of Haji Agha Mohammadi et al., Wang et al., and Li et al. confirmed the effect of licorice on the reduction of the liver enzymes. Haji Agha Mohammadi et al. showed no significant decrease in body mass index (BMI) and weight of patients treated with licorice root extract (P>0.05). While the main treatment for fatty liver disease is lifestyle modification through improved diet quality, increased physical activity and gradual weight loss, Haji Agha Mohammadi et al., instead of using licorice as an alternative treatment, used licorice as a complementary treatment, and provided dietary advice and appropriate physical activity to patients with NAFLD, which was likely to have more significant effects, through a reduction in BMI and weight loss, on improving the condition of these patients.

Wang et al. showed that oral gavage administration of glycyrrhizic acid in the male rats with NAFLD inhibited hepatic lipogenesis and increased the metabolism of triglycerides and fatty acids through having an effect on the expression of constitutive genes, fatty acid, and triglyceride in the liver. This process is done by affecting the expression of the lipoprotein lipase (LPL) gene and enhancing the lipolysis process of triglycerides in the liver. The severity of these effects is directly related to the amount of glycyrrhizic acid used; in other words, the higher the dose of glycyrrhizic acid (50 mg/kg), the greater the effect.

Li et al. showed that in a group of rats receiving DG by intraperitoneal injection, both the weight and amount of adipose tissue decreased significantly. But in the study of Haji Agha Mohammadi, no significant change in BMI was observed, whereas, in the two experimental studies of Wang et al. and Li et al., a significant decrease in hepatic steatosis, adipose tissue, and body weight were reported. As a result one of the weaknesses of Haji Agha Mohammadi et al.'s clinical trial was that they did not measure and evaluate the lipid profile in NAFLD patients.

Wang et al. showed that consumption of glycyrrhizic acid in NAFLD rats reduced triglyceride, free fatty acids and total cholesterol significantly (P<0.05). Besides, a significant decrease (P<0.05) in serum inflammatory markers including monocyte chemotactic protein-1(MCP-1) and mouse keratinocyte-derived chemokine (MKC), which in turn reduces inflammation of the liver tissue was observed. The decrease in the MCP-1 and MKC was dependent on the dose of glycyrrhizic acid so that in the group receiving higher glycyrrhizic acid (50 mg/kg), a greater decrease in the above parameters was observed. Glycyrrhizic acid also reduced the activity of hepatic stellate cells, resulting in decreased collagen production and improved hepatic fibrosis.

Li et al. also showed that DG intake in NAFLD rats significantly decreased serum triglyceride levels (P<0.05), but no significant change was observed in the total cholesterol in the DG group (P>0.05). Although a slightly decreasing trend was noted in total cholesterol in the group receiving DG, Li et al. found that the consumption of DG in rats with NAFLD, through increased production of probiotics in the intestine, could improve obesity and associated metabolic disorders such as NAFLD.

DG can also modify the gut microbiota by increasing the production of short chain fatty acids such as butyrate. These fatty acids can repair intestinal epithelial barrier cells and prevent the entrance of endotoxin produced by intestinal pathogens through portal circulation to the liver and prevent inflammatory reactions in the liver and intestine. Therefore, from the study of Li et al., it can be concluded that glycyrrhizic acid, in addition to exerting its anti-inflammatory and antioxidant properties through the production of probiotics, improved intestinal microbial flora, and intestinal barrier repair, prevented the entry of endotoxins produced by pathogens to the liver and thereby reduced the level of inflammation in the liver and improved NAFLD.

Probiotics and NAFLD

Nabavi et al. showed that the consumption of 300 g daily probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* for 8 weeks in NAFLD patients could significantly (P<0.01) reduce the weight and BMI in comparison to the group consumed 300 g of conventional yogurt. While Famouri et al. indicated that daily intake of a probiotic capsule containing *L. acidophilus*, *B. lactis*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum* in the obese children and adolescents with NAFLD for 12 weeks reduced waist circumference, but there was no significant change in the placebo group.

Also, no significant change in the weight, BMI and BMI z score was observed in any of the treatment groups, including probiotic capsule and placebo. If, however, the studies were performed in a way that, for example, in the study of Nabavi et al., there was a control group with no yogurt consumption; and in the Famouri et al.'s study, in addition to the probiotic capsule and the placebo capsule groups, another group of probiotic diet products such as probiotic yogurt was considered, the findings would be more complete and reliable. Nabavi et al. showed that daily consumption of 300 g of probiotic yogurt for 8 weeks in NAFLD patients could significantly (P<0.02) decrease ALT and AST liver enzymes, total

cholesterol (P<0.001) and LDL.C (P<0.01). However, no significant change in the above parameters was seen in the control group.

Famouri et al. showed that daily consumption of a probiotic capsule for 12 weeks in obese children and adolescents with NAFLD could significantly (P<0.05) decrease ALT, AST, TC, and LDL.C. Therefore, based on the above two studies, the consumption of probiotic yogurt and probiotic capsule can both significantly reduce these parameters and improve NAFLD. In the study of Nabavi et al., no significant changes were observed in serum glucose, TG and HDL.C levels in the group consuming probiotic yogurt. But in the control group that consumed conventional yogurt, there was a significant increase (P<0.05) in HDL.C levels. But there was no significant change in serum TG and glucose levels. While Famouri et al. reported a significant decrease in TG levels (P<0.001) in the group receiving the probiotic capsule, but there was no change in HDL.C.

Also, in the Famouri et al.'s study, serum glucose was not included in the measured parameters. In the placebo group, only TG significantly decreased (P<0.001). There are some inconsistencies in the results associated with lipid profile parameters, such as TG and HDL.C, due to differences in the recommendations and ways of improving lifestyle or the participants' failure in following the recommendations. Moreover, the fatty liver grade was also found to be significantly reduced in the probiotic capsule-treated group as liver enzymes decreased, indicating improved hepatic steatosis. Based on the above findings and results, it can be concluded that the use of glycyrrhizic acid in licorice root with probiotics has synergistic effects in improving NAFLD.

Discussion

This review is the first review study on the synergistic relationship between licorice consumption and probiotics on NAFLD. Several factors are involved in the pathogenesis of this disease. Symptoms of this disease appeared as metabolic syndrome and impact on anthropometric characteristics, which is itself an underlying factor for various diseases (30). Given that, until now, proven medical treatment for NAFLD is not known, then, research on the discovery of new compounds for the treatment of this disease is essential. In general, NAFLD treatment was based on three goals of (i) Reducing the process of lipogenesis and increase the metabolism of fatty acids and triglycerides, (ii) Reduction of inflammation of the liver tissue by decreasing the gene expression of inflammatory cytokines and (iii) Reducing the liver tissue fibrosis by restricting the activity of hepatic stellate cells and preventing their production of collagen because fibrotic tissue can replace normal liver tissue.

Failure to reach a single conclusion about the effect of probiotics on weight loss and BMI in this review study may be due to the following reasons: (i) No use of similar probiotic bacterial species in Nabavi et al. and Famouri et al. studies; the use of one probiotic bacterial species could have resulted in the study being specifically related to one probiotic species. Because the effects of different probiotic species may be different. (ii) Differences in the type of probiotic product in the two Nabavi et al. and Famouri et al. studies: according to the above studies, consumption of probiotic diet products such as probiotic yogurt can have a significant effect on the weight loss and BMI than probiotic capsules. (iii) Differences in treatment duration between the two Nabavi et al. and Famouri et al. studies.

In two experimental studies, Li et al. and Wang et al. found that all tested rats were male. Since the prevalence of NAFLD among men is higher than in women, both men and women had to be used to generalize their results to humans. In future studies, it is recommended that more sample sizes be used to increase the accuracy of the study and to obtain more reliable results. In addition to sonography, tests such as biopsy or fibrous scans, which measure liver fibrosis in addition to liver steatosis, can also be used to better evaluate the liver.

Conclusion

Based on the findings of this review study, it can be concluded that glycyrrhizic acid in licorice root can in addition to antioxidant and anti-inflammatory effects, by increasing the production of probiotics cause to change in intestinal microbial flora. Glycyrrhizic acid and probiotics, respectively, can play a role in improving NAFLD alone, with similarities in their effects. Now, if these two compounds are used together, their synergistic effects will not be unexpected. However, further studies are needed to increase the generalizability of the results.

Conflict of Interest

None declared.

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