International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

The Effect of *Stevia Rebaudiana* on Nonalcoholic Fatty Liver Disease (NAFLD): A Review

Tahereh Ranjbar[1], Seyed Jalil Masoumi[2,3]*

1. Student Research Committee, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
2. Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
3. Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Keywords:
Stevia
Diabetes
Dyslipidemia
Obesity
Inflammatory cytokines

**Corresponding author:*
Seyed Jalil Masoumi,
Nutrition Research Center,
Department of Clinical Nutrition,
School of Nutrition and Food Sciences,
Shiraz University of Medical Sciences,
Shiraz, Iran
Tel: +98-71-32300050
Email: masoumi7415@gmail.com
Received: March 16, 2017
Revised: October 1, 2017
Accepted: November 22, 2017

ABSTRACT

Due to the increasing prevalence, indefinite proven treatment for nonalcoholic fatty liver disease (NAFLD) as well as the correlation between NAFLD and metabolic disease including obesity, diabetes and dyslipidemia, researchers are trying to evaluate treatment methods of these types of diseases in order to treat NAFLD. This review aims to discuss the effects of *Stevia rebaudiana* on NAFLD. A literature search in Pubmed, Science direct and Google scholar was undertaken using the keywords "Stevia", "steviol glycoside", "diabetes", "insulin resistance", "blood glucose", "dyslipidemia", "cholesterol", "obesity", "food intake", "inflammatory cytokines", and then qualified articles were used. Several studies have shown the beneficial effects of stevia on improving fasting blood sugar (FBS) levels, glucose intolerance, and insulin resistance. Moreover, some studies have expressed that stevia decreases the food intake. Results about the efficacy of stevia on serum cholesterol and HDL-c are controversial; however, almost all support the useful effects of stevia on triglyceride level. Furthermore, its reducing effect on the inflammatory factors was previously clarified. Stevia was shown to have certain health benefits on diabetes, dyslipidemia, obesity and inflammation. Although there have been few studies, which evaluated the impact of *Stevia rebaudiana* on NAFLD, it is likely that *Stevia rebaudiana* improves NAFLD.

Please cite this article as: Ranjbar T, Masoumi SJ. The Effect of *Stevia Rebaudiana* on Nonalcoholic Fatty Liver Disease (NAFLD): A Review. Int J Nutr Sci 2018;3(1):2-6.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is growing rapidly around the world as the prevalence of obesity increases (1). According to a meta-analysis study, the global NAFLD outbreak identified by imaging is estimated to be 25.24%, with the highest prevalence in the Middle East and South America and the lowest incidence in Africa (2). Also, Nonalcoholic fatty liver with a prevalence of 19-46% in the United States is the most common liver disease in Western countries (3). According to other reports, the incidence of NAFLD in other parts of the world ranges from 6% to 35%, with an average of 20% (4). According to Iranian Ministry of Health, NAFLD is responsible for 1% of mortality in individuals older than 15 years (5).

NAFLD is a spectrum of liver diseases that ranges from steatosis to steatohepatitis and cirrhosis.

The early stage of the disease is NAFLD, which is characterized by a simple accumulation of fat in the liver. The next stage is nonalcoholic steatohepatitis (NASH) that is distinguished by the presence of hepatic steatosis and inflammation with hepatocyte injury which can be with or without fibrosis (6). The dominant feature of NAFLD is cell damage in such a way that it causes bulking, apoptosis, necrosis and mitochondrial enlargement, as well as inflammation and liver fibrosis. The mechanism of this disease is not fully understood, but it is linked to insulin resistance, inflammatory cytokines, and oxidative stress also commonly associated with metabolic comorbidities such as diabetes mellitus, dyslipidemia and obesity (2, 7).

According to the studies, there is not any approved medicinal therapy for NAFLD but American Association for the Study of Liver Diseases (AASLD) presents some recommendation to manage NAFLD such as weight loss, insulin-sensitizing drugs and vitamin E (8, 9). Over the past decade, herbal medicines have attracted more attention because of their potential effects on NAFLD prevention and treatment, as well as effectiveness and low risk of side effects (10). One of the medicinal plants widely used as an alternative medicine especially in the treatment of hyperglycemia is Stevia. *Stevia rebaudiana* that grows in South America does not contain usable carbohydrates for humans. It contains Stevioside, Rebaudiosides A, B, C, D, E, and F, dulcoside A, and Steviolbioside (11).

Besides natural sweeteners, stevia contains a complex mixture of compounds like terpenes, tannins, sterols, vitamins, carotenes, flavonoids, enzymes, organic acids, polysaccharides, hormones, etc. According to studies glycosides of *S. rebaudiana* and its extracts have pharmacological and therapeutic features that include antioxidant, antihypertensive, antimicrobial, anticancer and antidiabetic effects (12). In this work, we review the possible effects of *S. rebaudiana* on the NAFLD.

Stevia and Obesity

As mentioned, obesity is associated with the NAFLD. Prevalence of simple steatosis in obese people has been reported to be 30-37% and NAFLD prevalence in obese and overweight individuals to be 57% to 98% (13). One study showed that over 95% of bariatric surgery patients had fatty liver, 20–30% had NASH, and 10% suffered from advanced fibrosis (14). According to AASLD, weight loss can be a suggested treatment for NAFLD (8). Thus, replacing sugars with calorie-free sweeteners is an effective strategy (15). Some studies have reported that administration of stevia significantly decreased the food intake over the entire day (16, 17).

Stevia and Diabetes Mellitus

NAFLD seems to enhance the risk of type 2 Diabetes mellitus, in addition to worsening glycemic control. Also, T2DM may promote NAFLD progression. The prevalence of T2DM or impaired fasting glucose in NAFLD patients is 18-33%; conversely, NAFLD is presented in 49-62% of patients with T2DM. Also, insulin resistance occurs in 66-83% of NAFLD patients. The correlation between NAFLD and T2DM has stimulated researchers to do several clinical studies in which anti-diabetic drugs have been evaluated in NAFLD (18, 19). The natural sweet-tasting glycosides in stevia not only are 200 to 350 times sweeter than sucrose, also is calorie-free and is widely used as an alternative medicine in hyperglycemia treatment (11, 12). Some studies showed that stevia has desirable effects on glycemic control (Table 1).

Stevia and Dyslipidemia

Dyslipidemia is a condition with an alteration in lipid metabolism that may cause an excess of triglyceride, total cholesterol or both as well as low content of HDL-C (12). Free fatty acid and accumulation of triglyceride in the liver is a feature of NAFLD. The liver injury usually occurs because of these features, inflammatory cytokines and oxidative stress (23). Most studies investigating the effects of stevia on lipid profile indicate that it can reduce triglyceride but the results regarding cholesterol are contradictory. According to one meta-analysis, there is no significant difference in total cholesterol, LDL and HDL between steviol glycoside and placebo (24). Table 2 summarizes some studies about the effects of stevia on lipid profile.

Stevia and Inflammatory Cytokines

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that organizes the synthesis, secretion, and activity of other pro-inflammatory molecules. The increase in serum levels of TNF-α in both animal models of NAFLD and NAFLD patients might be due to lipotoxic effects of excess fat. In fact, oxidative stress and activation of NF-kB pathway, leading, in turn, to an increase in TNF- α production (27, 28). Because of physiological and pathophysiological functions of TNF-α, which include transcriptional regulation, fatty-acid metabolism, hormone-receptor signaling, glucose metabolism, and adipocyte differentiation, it has become the main focus of many studies. Many recent studies have found that the levels of TNF-α mRNA are closely connected to the prevalence of obesity

Table 1: Stevia and Diabetes mellitus.

Author/ Year	Model	Methodology	Results	Reference
Shivanna N/2013	Inbred Wistar rats	Eighty rats were divided into 8 groups; They were supplemented with stevia polyphenols or leaves powder (4%) or fiber extracted from stevia in a one-month intervention	Reduction of blood glucose, increment in insulin level, Glucose tolerance and insulin sensitivity were improved by their feeding.	(20)
Akbarzade/2015	Pathogen-free male Wistar rats	40 rats were divided into 5 groups; 2 control groups (diabetic and non-diabetic) and the other groups were diabetic rats that were supplemented with 250, 500 and 750 mg/kg of stevia.	Significant reductions in fasting blood sugar (FBS) and insulin resistance index (HOMA-IR) in groups with 250 and 500 mg/kg of stevia supplementation in comparison with rats in the diabetic control group.	(11)
Ritu M/2016	Subjects with T2DM	20 subjects were divided into two groups, the experimental group were given 1 g stevia leaf powder biochemical parameters were studied initially followed by two periods of 30 and 60 days.	Stevia significantly reduced post-prandial and fasting blood glucose levels.	(21)
Gregersen S/2004	T2DM patients	12 T2DM patients took part in this acute, paired cross-over study. A standard test meal was supplemented with either 1 g of stevioside or 1 g of maize starch (control).	Stevioside significantly reduced postprandial blood glucose levels in T2DM patients.	(22)

Author/ Year	Model	Methodology	Results	Reference
Park J/2010	C57BL/6J mice	40 mice were divided into 4 groups: normal diet, high-fat diet, high-fat diet with 1 mL/kg/day sucrose and high-fat diet with1 mL/kg/day stevia extract	Significant reduction in serum and liver concentration of triglyceride and serum level of cholesterol in group with stevia supplementation in comparison with the group with a diet containing sucrose	(25)
Aghajanyan/2017	Hyperglycemia-induced by immobilization stress in rabbits	Rabbits were divided into 3 groups: non-hyperglycemic, control hyperglycemic and the experimental hyperglycemic groups that received 100 mg/kg stevia extract.	Stevia administration caused a significant reduction in serum levels of TG, total Chol, LDL-c and an increase in HDL-C	(26)
Ritu M/2016	Subjects with T2DM	20 subjects were divided into two groups, the experimental group received 1 g stevia leaf powder. Biochemical parameters were studied initially following two periods of 30 and 60 days.	The serum VLDL-C and triglycerides levels significantly reduced in the experimental group.	(21)

and hyperlipidemia. Also, in vivo testing revealed that the decrease in TNF-α level is related to weight loss (29).

Some studies showed that IL-6 and IL-8 levels increased in patients with NAFLD in comparison with healthy controls (27). In another research, the effects of stevioside on insulin resistance and the pro-inflammatory state in male C57BL6J mice fed a high-fat diet were investigated. Interestingly, stevioside not only improved fasting glucose and insulin sensitivity, but also decreased expression levels of several inflammatory cytokines like TNF-α, interleukin 6 and 10, Interleukin 1 beta, macrophage inflammatory protein 1-alpha (MIP-1α), CD11b and CD14 (30).

Conclusion

Pieces of evidence showed that NAFLD is usually

related to obesity, diabetes, insulin resistance and dyslipidemia. Considering the association between NAFLD and metabolic disorders, researchers are trying to evaluate anti-obesity, antidiabetic and anti-hyperlipidemic drugs to treat NAFLD. The ideal effects of stevia on such disorders have been supported. Finally, as there is little research investigating the direct effects of stevia on NAFLD, we recommend researchers to carry out further interventional studies.

Conflict of Interest

None declared.

References

1 Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol*. 2013;10:686-90. DOI:1038/nrgastro.2013.171. PMID:24042449.

2 Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the study of liver diseases. *Hepatology*. 2017;67:328-57. DOI:1002/hep.29367.

3 Cusi K, Sanyal AJ, Zhang S, et al. Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab*. 2017;19:1630-1634. DOI:1111/dom.12973. PMID:28417532.

4 Vernon G, Baranova A, Younossi Z. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011;34:274-85. DOI:1111/j.1365-2036.2011.04724.x.

5 Kani AH, Alavian SM, Haghighatdoost F, et al. Diet macronutrients composition in nonalcoholic Fatty liver disease: a review on the related documents. *Hepat Mon*. 2014;14. DOI:5812/hepatmon.10939.

6 Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American gastroenterological association, American association for the study of liver diseases, and American college of gastroenterology. *Gastroenterology*. 2012;142:1592-609. DOI:1053/j.gastro.2012.04.001.

7 Paknahad Z, Zeraei-Bidgoli H. Metabolic syndrome and nonalcoholic fatty liver disease: nutritional approach for prevention. *J Isfahan Med School*. 2013;31.

8 Mahan LK, Raymond JL. Krause's Food & the Nutrition Care Process-E-Book. Elsevier Health Sciences; 2016.

9 Sherafatmanesh S, Ekramzadeh M, Moosavi L. The role of carbohydrate related factors in pathogenesis of nonalcoholic fatty liver disease. *Int J Nutr Sci*. 2017;2:52-7.

10 Yao H, Qiao YJ, Zhao YL, et al. Herbal medicines and nonalcoholic fatty liver disease. *World J Gastroenterol*. 2016;22:6890-905. DOI:3748/wjg.v22.i30.6890. PMID:27570425.

11 Akbarzadeh S, Eskandari F, Tangestani H, et al. The effect of stevia rebaudiana on serum omentin and visfatin level in STZ-induced diabetic rats. *J Diet Suppl*. 2015;12:11-22. DOI:3109/19390211.2014.901999. PMID:24689449.

12 Carrera-Lanestosa A, Moguel-Ordóñez Y, Segura-Campos M. Stevia rebaudiana Bertoni: A natural alternative for treating diseases associated with metabolic syndrome. *J Med Food*. 2017;20:933-43. DOI:1089/jmf.2016.0171. PMID:28792778.

13 Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34:274-85. DOI:1111/j.1365-2036.2011.04724.x. PMID:21623852.

14 Ong JP, Elariny H, Collantes R, et al. Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. *Obes Surg*. 2005;15:310-5. DOI:1381/0960892053576820. PMID:15826462.

15 Majchrzak D, Ipsen A, Koenig J. Sucrose-replacement by rebaudioside a in a model beverage. *J Food Sci Technol*. 2015;52:6031-6. DOI:1007/s13197-014-1624-z.

16 Duran Aguero S, Vasquez Leiva A, Morales Illanes G, et al. Association between stevia sweetener consumption and nutritional status in university students. *Nutr Hosp*. 2015;32:362-6. DOI:20960/nh.1060.

17 Anton SD, Martin CK, Han H, et al. Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. *Appetite*. 2010;55:37-43. DOI:1016/j.appet.2010.03.009. PMID:20303371.

18 Fruci B, Giuliano S, Mazza A, et al. Nonalcoholic Fatty liver: a possible new target for type 2 diabetes prevention and treatment. *Int J Mol Sci*. 2013;14:22933-66. DOI:3390/ijms141122933. PMID: 24264040.

19 Smith BW, Adams LA. Nonalcoholic fatty liver disease and diabetes mellitus: pathogenesis and treatment. *Nat Rev Endocrinol*. 2011;7:456-65. DOI:1038/nrendo.2011.72. PMID:21556019.

20 Shivanna N, Naika M, Khanum F, et al. Antioxidant, anti-diabetic and renal protective properties of Stevia rebaudiana. *J Diabetes Complications*. 2013;27:103-13. DOI:1016/j.jdiacomp.2012.10.001. PMID:23140911.
21 Ritu M, Nandini J. Nutritional composition of Stevia rebaudiana, a sweet herb, and its hypoglycaemic and hypolipidaemic effect on patients with non-insulin dependent diabetes mellitus. *Biomed Res Int*. 2016;96:4231-4. DOI:1002/jsfa.7627.
22 Gregersen S, Jeppesen PB, Holst JJ, et al. Antihyperglycemic effects of stevioside in type 2 diabetic subjects. Metabolism: clinical and experimental. *Metabolism*. 2004;53:73-6. PMID:14681845.
23 Townsend SA, Newsome PN. Non-alcoholic fatty liver disease in 2016. *Br Med Bull*. 2016;119:143-56. DOI:1093/bmb/ldw031. PMID:27543499.
24 Onakpoya IJ, Heneghan CJ. Effect of the natural sweetener, steviol glycoside, on cardiovascular risk factors: a systematic review and meta-analysis of randomised clinical trials. *Eur J Prev Cardiol*. 2015;22:1575-87. DOI:1177/2047487314560663. PMID:25412840.
25 Park JE, Cha YS. Stevia rebaudiana Bertoni extract supplementation improves lipid and carnitine profiles in C57BL/6J mice fed a high-fat diet. *J Sci Food Agric*. 2010;90:1099-105. DOI:1002/jsfa.3906. PMID:20393989.
26 Aghajanyan A, Movsisyan Z, Trchounian A. Antihyperglycemic and antihyperlipidemic activity of hydroponic stevia rebaudiana aqueous extract in hyperglycemia induced by immobilization stress in rabbits. *Biomed Res Int*. 2017;2017:9251358. DOI:1155/2017/9251358. PMID:28758125.
27 Fasshauer M, Blüher M. Adipokines in health and disease. *Trends Pharmacol Sci*. 2015;36:461-70. doi: 10.1016/j.tips.2015.04.014. PMID:26022934.
28 Diehl AM. Tumor necrosis factor and its potential role in insulin resistance and nonalcoholic fatty liver disease. *Clin Liver Dis*. 2004;8:619-38. DOI:1016/j.cld.2004.04.012. PMID:15331067.
29 Mohd-Radzman NH, Ismail WI, Adam Z, et al. Potential roles of stevia rebaudiana Bertoni in abrogating insulin resistance and diabetes: A Review. *Evid Based Complement Alternat Med*. 2013;2013:718049. DOI:1155/2013/718049. PMID:24324517.
30 Wang Z, Xue L, Guo C, et al. Stevioside ameliorates high-fat diet-induced insulin resistance and adipose tissue inflammation by downregulating the NF-kappaB pathway. *Biochem Biophys Res Commun*. 2012;417:1280-5. DOI:1016/j.bbrc.2011.12.130. PMID:22240021.