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

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**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.

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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, Rebauidosides 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, carotenoids, 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 stevial 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-κB 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.
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...

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**Table 1: Stevia and Diabetes mellitus.**

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<tr>
<th>Author/ Year</th>
<th>Model</th>
<th>Methodology</th>
<th>Results</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Shivanna N/2013</td>
<td>Inbred Wistar rats</td>
<td>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</td>
<td>Reduction of blood glucose, (20) increment in insulin level, Glucose tolerance and insulin sensitivity were improved by their feeding.</td>
<td>(20)</td>
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<td>Akbarzade/2015</td>
<td>Pathogen-free male Wistar rats</td>
<td>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.</td>
<td>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.</td>
<td>(11)</td>
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<tr>
<td>Ritu M/2016</td>
<td>Subjects with T2DM</td>
<td>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.</td>
<td>Stevia significantly reduced post-prandial and fasting blood glucose levels.</td>
<td>(21)</td>
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<tr>
<td>Gregersen S/2004</td>
<td>T2DM patients</td>
<td>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).</td>
<td>Stevioside significantly reduced postprandial blood glucose levels in T2DM patients.</td>
<td>(22)</td>
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**Table 2: Stevia and dyslipidemia.**

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<th>Author/ Year</th>
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<th>Results</th>
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<tr>
<td>Park J/2010</td>
<td>C57BL/6J mice</td>
<td>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 with 1 mL/kg/day stevia extract</td>
<td>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</td>
<td>(25)</td>
</tr>
<tr>
<td>Aghajanyan/2017</td>
<td>Hyperglycemia-induced by immobilization stress in rabbits</td>
<td>Rabbits were divided into 3 groups: non-hyperglycemic, control hyperglycemic and the experimental hyperglycemic groups that received 100 mg/kg stevia extract</td>
<td>Stevia administration caused a significant reduction in serum levels of TG, total Chol, LDL-c and an increase in HDL-C</td>
<td>(26)</td>
</tr>
<tr>
<td>Ritu M/2016</td>
<td>Subjects with T2DM</td>
<td>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.</td>
<td>The serum VLDL-C and triglycerides levels significantly reduced in the experimental group.</td>
<td>(21)</td>
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</table>
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


