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A New Healer in the Treatment of Diabetes and Diabetic Wounds: *Stevia rebaudiana*

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Abstract: Diabetes, one of the most common diseases in the world, causes a decrease in the formation of macrophages, endothelial cells, keratinocytes, platelets, and fibroblasts, which play a role in the cellular response to tissue damage in wound healing, and a decrease in the cytokines they secrete, inflammatory mediators, or growth factors, making wound healing difficult. As the healing period of the wounds increases, the psychology of the patients is adversely affected by the inability to return to their daily routines, the loss the of workforce increases, and the country's economy is adversely affected. In the last decades, because of the increase in many diseases such as diabetes and diabetes-related wounds, the use of calorie-free foods and herbal treatment methods has been preferred. Plants are increasingly being used as a source of pharmaceutical medications since they are simple to obtain, have no negative side effects, are affordable, and are simple to utilize. In order to meet these needs, sweeteners containing stevia extracts or components, obtained from the *Stevia rebaudiana* plant, that are calorie-free and 300-fold sweeter than cane sugar, have been on the market for some time. Despite the fact that *Stevia rebaudiana*, often known as sugar grass, is not a commonly utilized plant around the globe, it is possible to find literature that claims it is used as a preventive and curative for a variety of diseases. Although *Stevia rebaudiana* has various biological effects such as antioxidant, antidiabetic, antitumor, and antimicrobial, knowledge of diabetes and its effects on diabetic wound healing are limited. The purpose of this review is to evaluate how effectively *Stevia rebaudiana* treats diabetes and diabetic wounds.

Keywords: Diabetes, diabetic wound, *Stevia rebaudiana*.

Diyabet ve Diyabetik Yaraların Tedavisinde Yeni Bir Şifacı:*Stevia rebaudiana*

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Öz: Dünya'nın en yaygın hastalıklarından biri olan diyabet, yara iyileşmesinde doku hasarına karşı verilen hücresel cevapta rol alan keratinositler, fibroblastlar, endotelyal hücreler, makrofajlar ve trombositlerin ortaya çıkışında, salgıladıkları sitokinlerde, inflamatuar medyatörlerde veya büyüme faktörlerinde azalmaya yol açarak yara iyileşmesini zorlaştırmaktadır. Yaraların iyileşme süresi uzadıkça, hastaların günlük rutinlerine dönememeleri ile psikolojileri olumsuz yönde etkilenmekte ve iş gücü kaybı artmakta, ülke ekonomisi de olumsuz yönde etkilenmektedir. Son yıllarda diyabet ve diyabete bağlı yara gibi bir çok hastalığın artışına bağlı olarak kalorisiz gıdaların kullanımına ve bitkisel tedavi yöntemlerine yönelinmiştir. Bitkilerin kolay bulunması, yan etkilerinin olmaması, uygun maliyetli olmaları ve kullanımlarının kolay olması nedeniyle tıbbi ilaç kaynağı olarak kullanımları da artmaya başlamıştır. Bu ihtiyaçların karşılanabilmesi amacıyla *Stevia rebaudiana* bitkisinden elde edilen, kalorisiz ve şeker kamışından 300 kat daha tatlı doğal tatlandırıcı bileşenlere sahip stevia ekstraktları ya da bileşenlerini içeren tatlandırıcılar bir süredir piyasaya sürülmektedir. Şeker otu olarak da bilinen *Stevia rebaudiana* bitkisi dünyada yaygın olarak kullanılmasa da literatürde birçok hastalığa karşı koruyucu ve küratif ajan olarak kullanıldığını belirten yayınlara rastlamak mümkündür. Yapılan çalışmalarda, *Stevia rebaudiana* bitkisinin antioksidan, antidiyabetik, antitümör ve antimikrobiyal gibi çeşitli biyolojik etkilere sahip olduğu belirlenmesine rağmen diyabet ve diyabetik yara iyileşmesi üzerindeki etkisine dair bilgiler kısıtlıdır. Bu derleme, *Stevia rebaudiana* bitkisinin diyabet ve diyabetik yaraların tedavisi üzerindeki etkisini değerlendirmeyi amaçlamaktadır.

Anahtar kelimeler: Diyabet, diyabetik yara, *Stevia rebaudiana*.

INTRODUCTION

From the 1980s to the present, diabetes has increased from 4.7% to 8.5% in the adult population. In 2030, diabetes will be the seventh most common reason of death globally, according to the World Health Organization. (Hussein, 2020). Most patients who have diabetes, an associated metabolic condition that affects more than 340 million people worldwide, develop diabetic wounds. The loss of workforce increases with the length of time that it takes for the wounds to heal, which has a negative impact on the country's economy.

In diabetic patients, the ability to metabolize glucose decreases and there are delays in the wound healing process with the resulting hyperglycemic conditions (Patel et al., 2019)

A complex and special cellular reaction to tissue damage is wound healing. This event involves platelets, macrophages, endothelial cells, keratinocytes, fibroblasts, and collagens. Diabetes causes a decrease in cytokines, inflammatory mediators, or growth factors secreted by these cells, causing abnormalities in wound healing processes such as inflammation, collagen deposition, intercellular matrix differentiation, fibroblast proliferation, and wound contraction, and impair wound healing (Kolluru et al., 2012).

Factors such as infections, hypoxia, immunosuppression, aging, and Diabetus Mellitus (DM) inhibit the wound healing process and may lead to an increase in mortality and morbidity. The reason for the delays in wound healing in individuals with DM is the prevention of cell proliferation and collagen production because of high blood sugar levels, reduction of fibroblast formation and growth factors, increase in apoptosis in scar tissue cells, decrease in angiogenesis, granulation tissue formation, chemotaxis, and phagocytosis, and thus increase in infection formation. (Blakytny & Jude, 2006; Young & McNaught ,2011).

Plants can be used as a source of medicinal drugs because they are easily accessible, have no negative side effects, have low costs, and have practical uses (Alsarayreh et al., 2022). For many years, herbs have been used as a therapeutic for many diseases and to heal wounds around the world. So that they can be used in scientific investigations for pharmaceutical development, these plants' activities are thoroughly studied. Due to economic and social concerns, it is important to undertake research and develop natural products as novel therapeutics and wound healing agents (Suntar, 2014).

The small and perennial herb, stevia has a weak stem and a deep root system. There are 150 different species of stevia, which is also known by other names including honey, sugar, and sweet leaf (Singh et al., 2019). Stevia products containing steviol glycoside components that are approximately 300 times sweeter than sugar are used in food products such as tea, medicine, cakes, and most desserts as a healthy alternative (Özdemir et al., 2014).

Şekil 1. Şeker Enstitüsü Etimesgut Deneme İstasyonunda yetiştirilmekte olan *Stevia rebaudiana* bitkisine ait bir görüntü.
Figure 1. An image of the *Stevia rebaudiana* plant being grown at the Sugar Institute Etimesgut Testing Station.

Although stevia, a medicinal plant, has been used for therapeutic purposes for a long time, interest in it has grown recently as a result of a greater knowledge of its bioactive qualities. Extensive study is being done on stevia's antidiabetic (glucagonostatic antihyperglycemic, and insulinotropic), antioxidant, antibacterial, anticancer, anticariogenic, and antiplatelet effects in addition to its sweetening capabilities. (Salehi et al., 2019).

The use of stevia plant, which has various advantages in terms of functional properties and effects, is especially important for diabetic patients and people with calorie restriction (Goyal et al., 2010). In this review the healing potential of stevia that natural sweetener used to treat diabetes and diabetic wounds was aimed.

Diabetes and Diabetic Wound Healing: Because it is one of the leading causes of morbidity and mortality worldwide, the metabolic disease DM is well-studied both in vivo and in vitro (Güleç Peker et al., 2021). About 20% of people with diabetes develop diabetic wounds, such as leg or foot ulcers. Hyperglycemic states and complex wound healing processes occur with diabetic patients' reduced ability to metabolize glucose. Wounds can be in two different forms: chronic and acute. Tissue injuries that take more than 12 weeks to heal are called chronic wounds. Diabetes delays the healing process as it impairs every stage of normal wound healing, such as hemostasis, inflammation, proliferation, and remodeling (Patel et al., 2019). Due to immune system abnormalities in diabetes patients, minor wounds might develop into large, infected wounds due to their being unable to fight infection. Atherosclerotic vascular disease is also common in these patients. This reduces blood perfusion, leading to impaired wound healing. Diabetes reduces or impairs nitric oxide

(NO) production, which regulates wound repair during the healing process due to nitric oxide synthase (eNOS) phosphorylation and arginase insufficiency. Many studies have revealed that wound healing is delayed with an increase in reactive oxygen species (ROS) levels, and healing can be achieved in non-advanced diabetic wounds with eNOS. It has also been reported that some antioxidants accelerate diabetic wound healing (Kolluru et al., 2012).

Stevia rebaudiana: The perennial plant Stevia rebaudiana, a member of the Asteraceae family, is indigenous to Paraguay and Brazil. The leaf parts are very rich in diterpenoid steviol glycoside compounds. These compounds are 300 times sweeter than sucrose, with the most dominant being Rebaudioside A and Stevioside (Sardar et al., 2022). Stevia, which has been widely used in food products in recent years, is thought to be used widely in health products in the coming years due to its antioxidant, antimicrobial, anti-inflammatory, anti-hyperglycemic, anti-hypertensive, antifibrotic, antiglycemic, anti-diarrhea, hypolipidemic, and anti-tumor properties. Since it is safe, calorie-free, inexpensive, and easily available, it can also be used to control body weight and prevent blood sugar spikes (Wang et al., 2020).

Chemical Composition of Stevia rebaudiana: Stevia leaves are sweetened by diterpene glycosides such as stevioside, rebaudioside (A, B, C, D), steviol, dulcoside A and steviolbiocid (Singh et al., 2019). Stevia leaves contain high concentrations of phenolic compounds (hydroxybenzoic acids, hydroxycinnamic acids and flavonoids). Flavonols and flavones are the main flavonoids found in this plant species. In some studies, it has been stated that stevia leaves contain approximately 24.01 mg/g of total phenol and 19.93 mg/g of total flavonoids. These compounds contribute to total antioxidant activity and other positive effects on health. Besides, stevia leaves contain high concentrations of tannin compounds (average 5.43-5.91g/100g). Tannins have anticancer, anti-inflammatory, anti-apoptosis, and antioxidant effects and decrease the risk of atherosclerosis (Bursać Kovačević et al., 2018). In Table 1, some of the steviol glycosides found in *Stevia rebaudiana* are listed according to their biological action against various disorders.

Table 1. Activities of steviol glycosides (Singh et al., 2019a).

Substance	Activity attempt	Test material	Doses	Result
Steviol	Genotoxic effect	Mice (oral)	250 mg/kg 500 mg/kg 1000 mg/kg 2000 mg/kg	Negatory
Stevioside	Mutagenicity	Cell Culture	50 mg	Negatory
Steviol	Mutagenicity	Cell Culture	2 mg	Negatory
Stevioside	Activity of antireproductive	Hamster (Oral, F)	0.5 g/kg 1 g/kg 2.5 g/kg	Negatory
Stevioside	Activity of antireproductive	Rat (Oral)	0.025 g/kg	Negatory
Stevioside	Insulin Boosting	Rat	0,025 g/kg	Affirmative
Stevioside	Activity of Insulintropicity	In vitro-Mouse islent cell	1nmol/L	Affirmative
Stevioside	Stimulating beta-cell of pancreas	Cell Culture	1-100 micromole/L	Affirmative

Difference of Stevia rebaudiana from Other Sweeteners: Sweeteners are attracted by obesity and diabetes patients who want to reduce the cost of the food industry and to eliminate the need for sweetening. Sweeteners can be divided into three groups: sugar alcohols (sorbitol, mannitol, erythritol, etc.), artificial sweeteners (saccharine, aspartame, sucralose, etc.) and natural sweeteners (stevia, molasses, honey, etc.). Naturally occurring in many fruits and vegetables, sugar alcohols include calories but have fewer than sucrose. Contrarily, the calories in artificial sweeteners are minimal or nonexistent (Özdemir et al., 2014). Studies on human and mice have been conducted because artificial sweeteners are not always efficient for regulating weight and may have negative effects. It is thought that non-caloric artificial sweeteners may cause some obesity-related metabolic changes as a result of adversely affecting the intestinal microbiota.

Nowadays the possible cancer risk factor associated with the use of artificial sweeteners in animal and human studies is frequently discussed (Schiano et al., 2020). Studies comparing stevia, a calorie-free natural sweetener, to aspartame and sucrose found postprandial glucose levels to be lower with stevia. Stevia has gained more importance as an alternative sweetener with the emergence of data that artificial sweeteners are carcinogens (Özdemir et al., 2014). Herbal medicine is preferred because of some advantages such as low incidence of side effects and low cost. Metformin, obtained from the medicinal plant Galega officinalis, has long been used for the treatment of diabetes and is the only ethically approved drug. This situation requires the search for antidiabetic and antioxidative agents of natural origin. Since *S. Rebaudiana* is known to have important antihyperglycemic, antidyslipidemic and antioxidative properties, more studies are required to investigate and elucidate the action mechanisms of its active ingredients, to establish complete safety profiles, and especially for diseases such as diabetes (Singh et al., 2013).

Antioxidant Activity of Stevia rebaudiana: In diabetes, which is known to be related to oxidative stress and inflammation, especially ROS produced by mitochondria leave a permanent accumulation of oxidative damage in biomolecules. ROS formation can be prevented or neutralized after formation by several antioxidant defense mechanisms such as superoxide dismutase, catalase and glutathione reductase (Cannizzo et al., 2011). If the ROS concentration exceeds the capacity of these mechanisms, free radicals in consequence of oxidative reactions damage the compounds in the body such as DNA, protein lipid. It is very important to maintain a balance between ROS levels and antioxidants so that cells can function (Ma, 2014). In some studies, it has been shown

that low ROS levels and an increase in antioxidants can reduce oxidative stress, thus prolonging life expectancy (Calabrese et al., 2011). The presence of high concentrations of phenolic compounds in the stevia plant contributes to the total antioxidant activity (Kovačević et al., 2018). It has been reported that Endothelial Progenitor Cells (EPCs) are exposed to premature aging due to oxidative stress in diabetic patients (Rosso et al., 2006; Yuan et al., 2015). In the light of these data, antioxidants are thought to have therapeutic properties in preventing endothelial aging (Brodsky et al., 2004). The contents of tannins, carbohydrates, diterpenes, flavonoids and polyphenolic compounds were determined by preliminary phytochemical analysis of the aqueous *Stevia rebaudiana* extract. It has been understood that flavonoids reduce lipid peroxidation by preventing or slowing the onset of cell necrosis or by improving vascularity. By inhibiting lipid peroxidation, cell damage is prevented, and DNA synthesis is promoted. This increases the strength and vitality of collagen fibrils (Das, 2013). *Stevia rebaudiana*, which has a high phenolic content, is thought to be a natural antioxidant source due to its ability to inhibit 1-1-diphenyl 2-picryl hydrazil (DPPH) radical, which is a lipophilic radical, and to clear NO, hydroxyl radical, superoxide anion and hydrogen peroxide from the environment. It has been proven to be a stronger antioxidant than standard ascorbic acid (Shukla et al., 2009). It is also known that flavonoids and tannins support the wound healing process due to their antimicrobial properties (Deshmukh et al., 2009). There are in vitro studies showing that stevia leaves reduce the risk of oxidative stress. In a study conducted in diabetic rats, it was concluded that stevia extract had positive effects on oxidative and histological changes (Özdemir et al., 2014).

Anti-Inflammatory Activity of Stevia: The anti-inflammatory effect of *Stevia rebaudiana* has been demonstrated both in vivo and in vitro, and the stevioside it contains has been shown to be effective in inhibiting skin inflammation caused by the application of 12-O tetradecanoylphorbol-13-acetate (TPA) (Yasukawa et al., 2002). Additionally, it has been claimed that the isosteviol component it contains has the ability to inhibit DNA polymerase and human DNA topoisomerase II (Mizushina et al., 2005). In one of the studies, the effect of these components on IL-8 release in human colon cells was investigated by using non-toxic doses of stevioside and steviol, which are known to have anti-inflammatory effects. It has been shown that steviol suppresses TNF-α-induced IL-8 release and decreases nuclear factor-κ (NF-k)B expression (Boonkaewwan et al., 2008). Another study has shown that stevioside stimulates phagocytic activity and B and T cell proliferation (Sehar et al., 2008). This shows that stevioside promotes infection resistance. Stevia demonstrated antioxidant and anti-inflammatory effects in a different study. It shielded the livers against fibrosis brought on by chronic thioacetamide use. In addition to the ability of stevia therapy to induce nuclear erythroid factor 2 and block several profibrogenic pathways to reduce NF-k, it inhibits the activation of hepatic stellate cells and normalizes cellular redox, resulting in protection against inflammation and fibrosis and thus chronic liver damage. It is thought that it may contribute to the treatment (Ramos-Tovar et al., 2019).

Antihyperglycemic Activity of Stevia rebaudiana: In a study on whether rebaudioside A, one of the steviol glycosides, can prevent type 2 diabetes, it has been proven that it induces stimulating of insulin at excessive levels of glucose in the presence of Ca^{+2}. Similarly, stevioside has been shown to have direct effects on insulin sensitivity in 3T3-L1 cells (Vaghela & Soni, 2020). One of the steviol glycosides found in stevia leaves, stevioside has an important potential in glucose metabolism. There are also studies in humans showing the positive benefits of stevia on insulin sensitivity and postprandial glucose levels (Salehi et al., 2019). Its antihyperglycemic and blood pressure lowering effects have long been studied in type 2 diabetic rats. It is thought that insulin secretion can be increased by inducing genes involved in glycolysis by stevioside. Because it possesses both antihyperglycemic and blood pressure reducing properties, stevioside has therapeutic potential in the cure of type 2 diabetes (Jeppesen et al., 2003).

The Role of Stevia rebaudiana in the Treatment of Diabetes: Type 2 diabetes, a chronic metabolic disorder, is linked to microvascular and macrovascular complications. Chronic hyperglycemia, hypertension, dyslipidemia, obesity, and smoking are some of the determinants of these complications. Several scientific studies have been conducted with the extract of the leaves of the *Stevia rebaudiana* plant, which has been used for many years in the traditional South American diabetes treatment. There is evidence of mild suppression of plasma glucose when the extracts are taken orally in healthy subjects, while there is a 35% reduction in blood glucose in diabetic subjects (Jeppesen et al., 2003). In a report on stevia, which is considered to be safe as a drug alternative for diabetic patients, it was stated that human insulin secretion is increased by steviol glycosides. This indicates that steviol glycosides can be used as potent antihyperglycemic agents. In addition, this information is supported by increased glucose intolerance and decreased plasma glucose level in animal and human subjects consuming aqueous stevia extract. It was reported that stevioside given at a dose of 1.000 mg caused approximately 18% reduction in glucose level compared to control in a study in diabetic patients. Another study

reported that 200 and 400 mg/kg *S. rebaudiana* leaf extract caused a significant decrease ($P < 0.01$) in glucose level in rats (Singh et al., 2019).

The Role of Stevia rebaudiana in Diabetic Wound Healing: Pattanayak and colleagues (2008) have been shown that the turnover of collagen, which is an important protein of the extracellular matrix and contributes to wound strength, and accordingly the hydroxyproline content of the granulation tissue increases in wounds treated with aqueous *Stevia rebaudiana* extract (Pattanayak & Sunita, 2008). As a result of the breakdown of collagen, free hydroxyproline and its peptides are released. Therefore, it is thought that the measurement of hydroxyproline can be used as an index for collagen turnover. Studies revealed that *Stevia rebaudiana* exhibited wound healing-promoting activity in mice undergoing an excision wound model, but the effect was concentration-related. It has been observed that the epithelization period decreases, granulation tissue formation, collagen synthesis and wound contraction rate increase at appropriate concentrations (Das, 2013). It was revealed that the flavonoids contained in stevia support the wound healing process due to its astringent and antimicrobial properties, which are responsible for wound healing and increased epithelialization rate in a study using 20 mg/kg stevia (Babakhanyan et al., 2017). Wound treatment with *S. rebaudiana* aqueous extract was found to be more effective than control, basal cream, and tetracycline groups in the rats. A significant reduction in wound area was observed. Significant changes were observed in epithelialization compared to other groups. In addition, the wound surface area, lymphocyte, and macrophage counts decreased and blood vessel and fibrocyte counts increased in the groups treated with *S. rebaudiana* on the 10th day. Therefore, the use of stevia in the treatment of wounds can be recommended (Abbasi et al., 2021). One group of wound-formed male rats was treated by administering 1 ml of Stevia leaf aqueous extract suspended in 90 g of Eucerin for 20 days. The controls were injured but not treated. It was observed that the lymphocyte count decreased in the injured rats treated with stevia compared to the injured control group. It showed that blood vessels, fibrocytes and fibroblasts increased over 20 days. According to the findings, stevia plant affects wound healing in rats (Nafaji et al., 2017).

CONCLUSION

There is a line of evidence to show that stevia has anticancer, anti-inflammatory, anti-apoptosis, anti-diabetic, and, antioxidant effects. There is also been established to stevia has also beneficial effects on wound healing in this review. Stevia leaves contain high concentrations of phenolic and tannin compounds and these compounds contribute to total antioxidant activity and other positive effects on health. In this context, more clinical trials with long-term follow-up studies be conducted to examine the anti-diabetic and wound-healing properties of stevia, as an alternative natural way to lower blood sugar and thereby contribute to the general prevention of diabetes.

Authors' Contributions

SCC: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing, **NK:** Investigation, Resources, Writing – original draft, Writing – review & editing.

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Statement of Conflicts of Interest

There is no conflict of interest between the authors.

Statement of Research and Publication Ethics

The authors declare that this study complies with Research and Publication Ethics.

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