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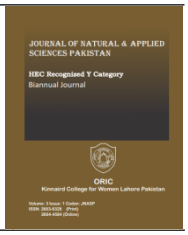

HYPOGLYCEMIC AND HYPOLIPIDEMIC ACTIVITY OF STEVIA

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Abstract

There are more than 150 different types of stevia but Stevia rebaudiana Bertoni is used for therapeutic purposes. Stevia rebaudiana Bertoni is also known as natural sweeter because it contains increased amount of steviol glycosides. Stevia leaves contain more steviol glycosides as compare to other parts. As a functional food it is used to cure many health abnormalities such as diabetes, hyperlipidemia, cancer and obesity. Stevioside is responsible for translocation of Glut4 to plasma membrane. Glut4 helps in the regulation of insulin and glucose. Basically, it is an insulin-regulated glucose channel.t primarily present in striated muscles and adipose tissues. With the help of Glut 4 glucose enters into the cells from bloodstream. When insulin is secreted it travels cytosolic store to plasma membrane.

Keywords
Stevia rebaudiana Bertoni, Steviol glycosides, Glut4, Stevioside, Insulin.

1. Introduction

Stevia rebaudiana Bertoni belongs to plant family Asteraceae family (Ahmad *et al*., 2020). Its common name is Stevia and use for many therapeutic purposes since thousands years (Karaköse *et al*., 2015). Stevia rebaudiana Bertoni is considered as native plant of Argentina, Paraguay and Brazil.

Stevia has many therapeutic benefits such as anti-inflammatory, anti-oxidative, anti-viral and anti-microbial properties (Mondaca *et al*., 2018; Ferrazzano *et al*., 2015). Stevia rebaudiana Bertoni is also known as natural sweeter because it contains 250-300 times more sweetness as compare to sucrose. Basically Stevia leaves are extensively

used for medicinal purposes (Hossain *et al*., 2017). Stevia Leaves also help to improve liver and kidney functions (Ranjbar & Masoumi 2018; Ameer *et al*., 2020). There are no side effecters' different health ailments. Nowadays its demand has been increasing due to wei of stevia has been observed in previous studies. There are more than 150 different types of stevia but Stevia rebaudiana Bertoni is used for therapeutic purposes. Stevia rebaudiana Bertoni is also known as natural sweeter because it contains increased amount of steviol glycosides. Stevia leaves contain more steviol glycosides as compare to other parts.

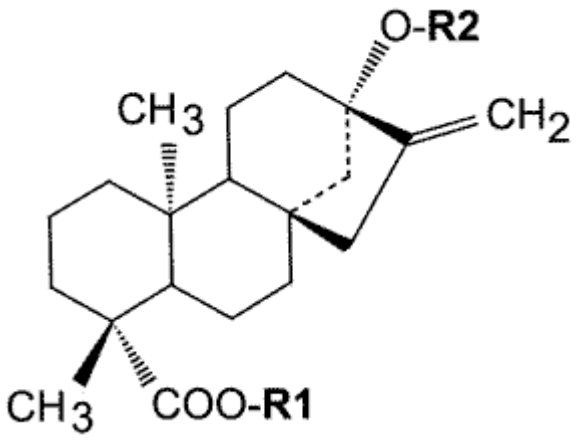

Figure 1: Structure of Steviol Glycosides

Stevia leaves also contain several important phytochemical constituents such as alkaloids, flavonoids, chlorophyll, xanthophyll, oligosaccharides, amino acids, essential oils, lipids, proteins, free sugars, trace elements and hydroxycinnamic acids (chromogenic acid, caffeic acid) (Gupta *et al*., 2013). As a functional food it is used to cure many health abnormalities such as diabetes, hyperlipidemia, cancer and obesity (Aghajanyan *et al*., 2017). Many studies proved that stevia helps to improve blood glucose and lipids levels as well as reduces gain weight gain in humans and animals. Stevia with zero-calories as a sweeter provide sweet taste without any increase in serum glucose level. Sativoside is responsible for translocation of Glut4to plasma membrane. Glut4 helps in the regulation of insulin and glucose. Basically it is an insulin-regulated glucose channel.t primarily present in striated muscles and adipose tissues. With the help of Glut 4 glucose enters into the cells from bloodstream. When insulin is secreted it travels cytosolic store to plasma membrane (Yamashita *et al*., 2016). Term diabetes mellitus is defined as a heterogeneous group of disorders with different etiologies. It is basically characterized by hyperglycemia. Reason behind its occurrence is inadequate insulin production or improper insulin functioning. Insulin is a hormone, helps to regulate glucose, protein and fat metabolism (Ramachandran, 2010). Diabetes not only effect blood glucose levels but it also leads toward organ failure and other complications. Beta cells failure may be caused by some injury or genetic factors (Cole & Florez, 2020; Redondo *et al*., 2018). Different environmental factors are also linked with the development of diabetes such as diet, physical activity, weight, lifestyle and medications. According to International Diabetes Federation globally 425 million individuals were suffering from diabetes globally. Different factors are involved in the development of diabetes mellitus such as epigenetics, environment, genetics, diet and life-style (Lambrinou *et al*., 2019; Ganesan *et al*., 2018). Several medicines are used to increase insulin sensitivity within muscles. Due to various

side effects many herbal products are used to manage diabetes and other abnormal health conditions (Kumar *et al*., 2021). Role of genetics in insulin resistance is unclear. Glucose and weight these two factors are important in the management of diabetes. Lifestyle modifications may help to control its complications. In diabetes major sites of insulin resistance are skeletal muscles, adipose tissues and liver. Glycated hemoglobin (HbA1c) is an important indicator to diagnose and treat diabetes (Knowler, 2015). In food industries stevia glycosides are used as a substitute of sweeteners and therapeutic purposes (Acharya & Srivastava, 2008).

2. Hypoglycemic and Hypolipidemic Effect of Stevia

Anti-diabetic effect of Stevia leaves was determined in a study among albino rats. In this study rats were first induced with diabetes by administration of 40mg/kg streptozotocin. These diabetic rats were given different doses of Stevia aqueous extract (200ppm, 300ppm, 400ppm, 500ppm/kg body weight) for two-months. Study findings showed that stevia extract improved weight and blood glucose levels. At the end of study fasting blood glucose levels were reduced about 73.24% and random blood glucose levels were reduced about 66.09%. There was significant association between blood glucose levels and stevia extract consumption. On the other hand, liver glycogen and insulin levels were also improved in intervention group. Reduction in glycosylated (HbA1c) hemoglobin was 5.3%. So this study concluded that glycosylated (HbA1c) hemoglobin helps in the management of blood glucose levels among diabetic rats (Talevi, 2021). Globally incidence rate of diabetes is much more frequent, different nutraceuticals are used for its prevention and treatment. Gupta and his colleagues conducted a study to find anti-diabetic effect of Rebaudioside A and Steviol Glycosides. In this study a mixture of 9 steviol glycosides was used, named as Steviol Glycosides System Suitability (SGSS). Diabetes was induced with the help of alloxan monohydrate injection (150 mg/kg body weight). After disturbance of antioxidant functions due to alloxan monohydrate induction blood glucose levels were increased. Rats were fed with 20 and 30mg of Reb A and SGSS per kg body weight orally for 21 days of study time period. After completion of study period there was significant reduction in blood glucose levels with p value less than 0.05. Whereas oxidative stress was also reduced and lipids levels were also improved in intervention group (Ahmad & Ahmad, 2018). Hypoglycemic effect of stevia extract was also determined in another study. In this study diabetic rats were divided into three groups. Group 1 was provided with 300mg/kg of stevia extract, second group with 1mg/kg glimepiride and third group with the combination of glimepiride and stevia extract. After 21 days of study all treatment groups showed more significant reduction in blood glucose, triglycerides, LDL, ALT ans AST levels. But stevia also reduced eNOS expression in diabetic rats as compare to other groups. So this study concluded that stevia and glimepiride can be as new therapeutic agents for the treatment of diabetes (Gupta *et al*., 2021). Beside anti-diabetic

activity Steviol Glycosides also have lipid lowering potential by reducing blood cholesterol levels it also helps to improve HDL levels (Assi *et al*., 2020). Stevia as a calorie free plant has efficacy to reduce weight, blood cholesterol and glucose levels. In a review many studies are used to describe anti-diabetic effect of stevia and its byproducts. Through literature it has been proved that stevia is a safe therapeutic herb use to control hyperlipidemia and hyperglycemia (Anker *et al*., 2019). Zhao and his colleagues conducted a study to explore the effect of *Stevia* residue extracts (SRE) on impaired glucose regulation (IGR). In this study mice were fed with high fructose and fat diet for the induction of impaired glucose regulation. Chemical characterization of SRE was done through LC/MS/MS. Chemical Characterization analysis showed that SREs is loaded with flavonoids and chromogenic acids. At the end of study biochemical markers showed that liver fat storage, antioxidants levels and lipids levels were improved. Significant reduction in blood glucose levels was observed after daily use of 200mg/kg SRE. So results suggested that SRE have great potential to improve metabolic activities (Masoumi *et al*., 2020). In 2010 Kujur and his colleagues found the hypoglycemic effect of Stevia rebaudiana Bertoni. In this study they found that stevia consumption for one-month helps to lower blood glucose levels among diabetic rats. When alloxan monohydrate induced diabetic rats were provided 50mg/kg stevia extract there was a significant reduction in blood glucose levels observed, blood glucose level decreased from 220 to 161 mg/dL after 28 days. On the other hand, when they were provided with 100mg/kg of stevia extract, blood glucose levels were reduced from 220 to 137 mg/dL. There was no significant difference among both these groups. Third group of rats was provided with an oral diabetic medication, glyburide. In this group glucose levels were decreased from 211 to 101 mg/dL. Stevia had more beneficial effect on blood glucose levels as compare to anti-diabetic drug (Zhao *et al*., 2018; Kujur *et al*., 2010). In 2017 Prata and his co-workers determined the relation between sativoside and Glut-4 translocation among neonatal rat cardiac fibroblasts. Glut4 translocation analysis was done with the help of confocal microscopy and Glut4- specific antibody targeting. They investigated that 1 mg/mL steviol glycosides shows similar effect on Glut-4 translocation as 100 nM insulin. They also compare glucose uptake by cells in both groups. Findings showed that glucose uptake was 139% when incubated with insulin. On the other hand, glucose uptake was 117% in the case of steviol glycosides close to insulin incubation (Ray *et al*., 2020). Globally prevalence rate of obesity is increasing day by day. Oxidative stress, inflammation and insulin resistance are common complications among obese individuals. To combat obesity and its comorbidities different herds or neutraceutical are used. Many studies support anti-obesity effect of stevia. Through anti-inflammatory, anti-oxidative and anti-hyperlipidemic potential it helps to prevent obesity. Stevia leaves are also responsible for fat burning (Prata *et al*., 2017; Ray *et al*., 2020). In a study therapeutic potential of stevia was compared with

fructose. In this study total 36 rats were divided into three main groups. First group (control) rats had free access to water. Second group provided 0.2% stevia solution whiles the last one with fructose. All groups were consumed standard food for 13 weeks of study time period. After completion of study time period blood glucose, lipids and insulin levels were examined. Results showed that there was significant weight reduction observed in stevia group. In this group cholesterol levels were also reduced while HDL levels were improved (Salehi *et al*., 2019). In a study pharmacological effect of *Uncaria Tomentosa* and *Stevia rebaudiana* was determined. In this study hypolipidemic and hypoglycemic effect of *Uncaria Tomentosa* and *Stevia rebaudiana* was evaluated among three rat models (hyperlipidemic, hyperglycemic and hypertensive). After 28 days of study toxicity and blood parameter levels were measured. Data analysis revealed that there was a significant difference among blood parameters before and after study. Blood cholesterol and LDL levels were significantly were decreased in Stevia rebaudiana group (Galindo *et al*.,2019).

Table 1: Study Population, Study Time-period, Doses and Effects

Sr no.	Study population	Study time period	Doses	Effect	References
1.	Diabetic rats	Two months	Stevia aqueous solution (200ppm, 300ppm, 400ppm, 500ppm/kg) body weight	Reduced fasting glucose about 73.24% and random glucose about 66.09% HbA1c also reduced 5.3%.	[19]
2.	Alloxan monohydrate induced Diabetic rats	21-days	Reb A 20mg and SGSS 30mg/kg body weight	Blood glucose levels were significantly reduced with p value less than 0.05.	[20]
3.	Mice (with abnormal metabolic activities)	1-month	Stevia residue extracts 200mg/kg body weight	Metabolic activities were improved including glucose regulation.	[24]

4.	Diabetic rats	1-month	50mg, 100mg/kg body weight stevia extract and oral medicine	More blood glucose levels were reduced in stevia groups as compare to medicine group	[25]
5.	Neonatal rat	8weeks	1 mg steviol glycosides	Improved glucose uptake by Glut-4 translocation about 117%	[27]
6.	Hyperlipidemic rats	13weeks	0.2% stevia	Cholesterol levels were reduced which HDL levels were increased.	[30]
7.	Diabetic rats	21-days	300mg/kg body weight stevia extract.	Blood glucose, LDL and cholesterol levels were reduced.	[22]

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