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Antidiabetic Activities of *Rhazya stricta* Decne: A Review

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Abstract

The plant sources play an important role in combating most diseases including diabetes. *Rhazya stricta* Decne is a folkloric medicinal plant being used in the traditional medicine systems against many ailments including diabetes mellitus. Various extracts of the plant have shown promising antidiabetic activities in various bioassays including successful researches on the animal models. The role of animal models in experimental researches directed at identification of the useful plants possessing antidiabetic properties is elaborated. A detailed account of the antidiabetic properties of the plant is presented. This is for the first time that only one activity of the plant is exclusively discussed in any review.

Introduction

The diabetes mellitus is a chronic disease characterized by hyperglycemia that may occur due to genetic, environmental or lifestyle factors and considered among the top five causes of death in most high-income countries and half of patients died from diabetes mellitus were under 60 years of age [1]. The rise in the number of patients of type 2 diabetes mellitus is associated with obesity, hypertension mainly in the elderly population. One of the main causes for the occurrence of the disease is the unhealthy lifestyle with no adherence to improved diet and poor exercise [2]. Even though a wide range of therapeutics are available to counter diabetes, medical science is still facing a challenge of management of diabetes mellitus with fewer side effects [3,4]. The use of plants and herbal medicine is very frequent in Asia and developing countries for the treatment of diseases including diabetes due to their efficiency, fewer side effects and cost-effectiveness [5]. In particular, medicinal plants with antihyperglycemic activities are more important and around 800 plant species have been investigated and reported for their glucose lowering effects [6,7]. However, the exploration of plant material in search of effective antidiabetic agents with less or no side effect is still continuing [8].

An array of secondary metabolites is well-known for the treatment of diabetes reported from plant species. The in vitro, in vivo and enzyme based assays were considered strong tools to assess the antidiabetic potential of the plant. A variety of the compounds of different phytochemical classes were identified in the plants. Particularly, the compounds identified in the chloroform soluble fraction have demonstrated antihyperglycemic activities [9-21].

The use of therapeutic agents and changes in lifestyle are the strategies that can prevent or at least delay the development of diabetes mellitus in patients with impaired glucose tolerance [22]. The use of synthetic drugs for the treatment of diabetes mellitus leads to secondary complications, therefore, an alternate medicines system based on natural products is being considered by the health-care professionals due to their efficacy, fewer side effects and cost-effectiveness [22]. The anti-hyperglycemic property of the medicinal plants entirely depends on the chemical constituents present in them and many antidiabetic compounds have been isolated from a number of plants [23-25].

For the diabetes mellitus therapy, advancement of medical care uses a different array of lifestyle and pharmaceutical interventions [26]. The use of alpha-glucosidase inhibitors like acarbose, miglitol, and voglibose can hinder the release of glucose from complex carbohydrates in the small intestine, consequently suppressing postprandial hyperglycemia.

Along with beneficial effects, use of alpha-glucosidase inhibitors is associated with gastro-intestinal disorders [27]. Likewise, glucagon-like peptide-1 (GLP-1) is an incretin hormone that plays different roles in blood glucose regulation in the gut (28). This hormone is rapidly inactivated by an enzyme dipeptidyl peptidase-IV (DPP-IV) also present in the gut within less than a minute after being secreted [29].

In the treatment of diabetes mellitus, the inhibition of the DPP-IV enzyme is a novel strategy that could potentially affect glucose regulation through multiple functions [30-32]. The beta-amyloid cleaving enzyme (BACE1) levels may also play an important role in glucose and lipid homeostasis in conditions of chronic nutrient excess [33]. The central BACE-1 level was reported to be higher after insulin deficiency produced through the streptozotocin injection [34].

It has been reported that BACE1 is a regulator of insulin signaling and the amount of insulin receptor in liver during diabetes. The amount of insulin receptor is found to be reduced due to the degradation by the BACE1 enzyme. It may be suggested that insulin signaling can be improved with the use of BACE1 inhibitors during diabetes. The enzyme is also found to be involved in the regulation of the insulin receptor in the liver [35]. Hence, considering the BACE1 as a therapeutic target, efforts to discover and develop the BACE1 inhibitors have been pursued in the last few years [36]. The extract of the plant also demonstrated significant antidiabetic activity by inhibiting the dipeptidyl peptidase-IV and β -secretase enzymes, resulting in an increase in the glucagon-like peptide-1 secretion [36].

To address many biological and biomedical questions and to increase human knowledge, the role of animal models in experimental research cannot be denied. Many of the animal species are being used in the field of biology due to their phylogenetic proximity to humans [37]. Animal models have been playing a major role in the field of diabetic research and valuable information about pathways that contribute to the induction of diabetes mellitus in humans may be accessed [38]. Moreover, animal models are considered as an essential tool to understand the molecular basis, pathogenesis of diabetes and to evaluate the different therapeutic agents [39].

As mentioned above, the diabetes mellitus is a chronic disease characterized by hyperglycemia that may occur due to genetic, environmental or lifestyle factors. The natural remedies have been used to treat diabetes since long and many antidiabetic compounds of varied efficacies have been isolated from the medicinal plants. *Rhazya stricta* has been used for decades for the treatment of diabetes mellitus and associated ailments. The extract of different part of the plant, particularly the chloroform soluble fraction of the roots of the plant possesses a potent antidiabetic activities.

Diabetic Activity Spectrum of *Rhazya Stricta*

Generally, diabetes is categorized into type 1 and type 2 on the basis of production of insulin in body and mechanism by which it produces. The type 1-insulin dependent diabetes mellitus causes an autoimmune destruction of the pancreatic β cells. The type 2 is non-insulin dependent diabetes mellitus is characterized by the insulin resistance in the target tissues. The current focus of drugs' discovery research in diabetes includes exploration of the alternative medicines, discovery of new synthetic antidiabetic agents as well as isolation of active compounds from the natural sources which have been the source of traditional medicines and are documented and described for their antidiabetic properties [6-9].

The diabetes mellitus is a group of metabolic disorders in which patients suffer from high blood glucose level as a result of their inability to produce insulin or due to insulin resistance in the peripheral tissues. It is one of the most common diseases in the world and it is estimated that the number of adult sufferers will increase up to 69 % and 20 % in the developing and developed countries, respectively till 2030 [40]. The disease is reaching epidemic proportions and will account for 12 % of the total health expenditure [41]. The persistent high blood glucose level in uncontrolled diabetes is associated with a number of complications including retinopathy, neuropathy, nephropathy, and accelerated the cardiovascular diseases [42].

As the diabetes mellitus is the most common human disease and there is growing interest for the plant based therapy in managing diabetes mellitus specifically in the developing world. One of such plants, *Rhazya stricta* Decne belongs to the Apocynaceae family, is a folkloric medicinal plant being used in traditional medicine systems against many diseases including diabetes. The plant has shown a significant anti-diabetic properties in various bioassays and animal models. A number of researches have been carried out to exploit the full antidiabetic properties of the plant [43-45]. An exclusive account of the antidiabetic activities of the plant is presented.

The effects of the water extract of *Rhazya stricta* on glucose homeostasis in normal and streptozotocin diabetic rats were studied [46]. The water extract of the plant was administered to the normal and diabetic rats to study the fasting glucose level. The extract did not show any effect on the fasting glucose levels in normal and diabetic rats up to 7 hours after its oral administration. It also did not produce any significant effect on an oral glucose tolerance test in the normal and diabetic rats. The chronic administration of the plant in drinking water for 37 days did not produce any effect on the parameters of glucose homeostasis studied like plasma glucose, body weight, feed and fluid intake and plasma fructosamine in the normal or diabetic phase of the experiment. The LD₅₀ of plant in mice was 2.36 mg/ kg body weight of the lyophilized extract and a daily administration of the plant to the rats for 5 days did not produce any signs of organ damage. The water extract of the plant showed no noticeable impact on a glucose concentration introduced orally to rats with and without diabetes. Frequent treatment of the plant in a water supply had no effect on the glucose

homeostasis measures investigated the plasma glucose, body mass, feed and fluid intake, and blood fructosamine during a 37-day period in either the normal or diabetic stage of this study. *Rhazya stricta* is claimed to contain various medicinal properties including antihyperglycemic.

The pharmacologic and toxicologic studies on *Rhazya stricta* Decne in rats, mice and rabbits showed that the extract of the plant possesses antidiabetic activities [47]. The administration of the plant extracts to the animals resulted in an increase in the insulin concentration and reduction in glucose levels. An acute treatment of rats with the lyophilized extract of the plant at a dose of 4.0 g/ kg produced a significant rise in insulin concentration. In the streptozotocin-diabetic rats loaded orally with glucose at a dose of 1.0 g/ kg, the plant at dose of 8 g/ kg produced a significant decreases in plasma glucose concentration at 0.5 hour and 1.0 hour after the treatment. However, the chronic treatment of rats and mice for 28 days with the lyophilized extract of the plant did not affect the plasma glucose or insulin concentration or any of the hematological or biochemical indices measured. The acute oral treatment with the extract at a dose of 4.0 g/ kg produced a significant and short-lived increase in the plasma insulin concentration accompanied by a significant reduction in the plasma glucose concentration. The time dependent dose response is presented in Table 1.

Dose of Extract	Time	Insulin Concentration	Plasma Glucose Concentration
1.0 g	0.5 hour	Increased	Decreased
4.0 g	1.0 hour	Increased	Decreased
6.0 g	1.5 hour	Increased	Decreased
8.0 g	2.0 hour	Increased	Decreased

Table 1: Effect of Doses of Extracts on Concentration of Insulin and Plasma Glucose [47].

The effects of *Rhazya stricta* alone and its combination with glibenclamide on plasma glucose, insulin and glucagon levels of treatment of diabetic rats were examined [48]. The study revealed that many diabetic patients in the United Arab Emirates use the medicinal plants as a supplement to treatment with insulin or oral hypoglycaemic agents. The treatment of the control rats with the extract at the oral doses of 0.5 g/kg, 2.0 g/ kg and 4.0 g/ kg did not show any effect on the concentration of glucose, insulin or glucagon for up to 4 hours after administration of the extract. The same doses to the diabetic rats reduced the glucose level in one hour at the dose of 0.5 g/ kg and 2.0 g/ kg and in two hours at the dose of 4.0 g/ kg after administration of the extract. This was accompanied by significant increases in the insulin concentration 1, 2 and 4 hours after the administration of the extract at the doses of 0.5 g/ kg, 2.0 g/ kg and 4 g/ kg. The glibenclamide at the rate of 2.5 mg/ kg, 5.0 mg/kg and 10.0 mg/ kg reduced glucose and glucagon levels and increased level of insulin in the normal and diabetic rats. Simultaneous treatment of the normal and diabetic rats with the plant extract at the doses at the rate of 0.5 g /kg, 2.0 g/ kg and 5.0 g/ kg and glibenclamide at a dose of 5.0 mg/ kg increase the effects on glucose, insulin and glucagon induced by the extract or by the glibenclamide when given separately. When the plant extract was given at the doses of 0.5 g/ kg, 2 g/ kg and 4 g/ kg per day for 6 consecutive days the glucose level was reduced by approximately 6 %, 8 % and 30 %, respectively. These results imply that co-administration of the extract with glibenclamide might adversely interfere with the glycaemic control in the diabetic patients. The effect of doses to glucose level are presented in Figure 1.

The effects of different doses of the extract of plant on the rat adiponectin gene and insulin resistance were studied [49]. The oral administration of aqueous extracts of the leaves of the plant indicated fluctuations in the adiponectin levels during eighteen weeks period of treatment. The serum adiponectin levels showed a significant increase after 2 and 4 weeks of the treatment.

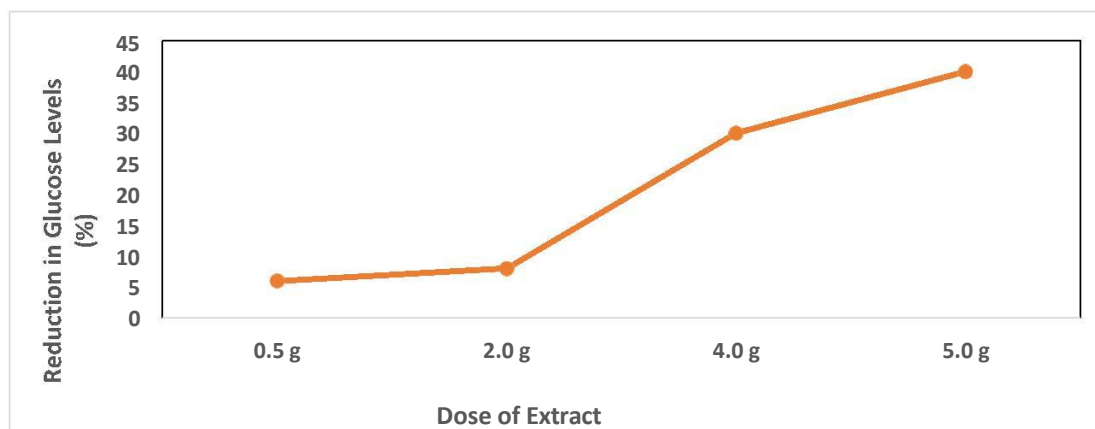


Figure 1: The Effect of the Doses of the Extract of Plant on Glucose Level [49].

Also a highly significant increase in the adiponectin level compared to the control group was detected in rats treated with 0.125 gm/ ml and 0.150 gm/ ml after eighteen weeks of treatment. Insulin resistance is an important risk factor for type II diabetes mellitus and cardiovascular disease. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was performed to check the degree of insulin resistance in the rats. The results showed an inverse highly significant correlation between adiponectin levels and insulin resistance after two weeks of the treatment with the extracts of the plant. The studies published to date indicate that polymorphisms at the adiponectin gene (exon 3) are indeed predictors of circulating adiponectin levels. However, the results showed a significance increase in the adiponectin levels, and no indication of any rare mutation in this locus using CSGE technique observed. Such effects of the plant extract could prove useful in treating diabetes, carbohydrate metabolism, hypertension, as well as inflammatory conditions.

The effects of the extracts of the plant on the concentrations of adiponectin have not been identified, so far. The literature evidences however showed similarities in the effects of the plant and adiponectin on diabetes, carbohydrate metabolism, hypertension, as well as inflammatory conditions. The leaves of the plant have been used for the treatment of various ailments including diabetes mellitus. The people of the Arabian Gulf region commonly use water extracts of the leaves for the treatment of diabetic patients [40].

The serum adiponectin levels were significantly ($p < 0.05$) lower ($15.77 \pm 3.84 \mu\text{g/ml}$) than the control after one week of treatment in the rats receiving 0.150 gm/ml of the aqueous extracts of the plant. The serum adiponectin levels showed a significant increase ($p < 0.05$) after 2 and 4 weeks of the treatment. The increase was clear in the rats of the group 4 receiving 0.150 gm/ml dose (33.40 ± 8.38) and after 4 weeks of the treatment in the group 2 receiving 0.1 gm/ml dose (33.89 ± 5.46). A significant ($p < 0.01$) increase in the adiponectin level compared with the control group was clear in the rats of group 3 ($20.77 \pm 7.03 \mu\text{g/ml}$) after eighteen weeks of the treatment. A highly significant ($p < 0.001$) increases in the adiponectin concentration was recorded with the same dose in the group 4 ($24.06 \pm 4.65 \mu\text{g/ml}$).

The analysis of the data using the Pearson correlation showed an inverse highly significant correlation between the adiponectin levels and insulin resistance degrees after two weeks of treatment with the plant. Recently, adiponectin has been identified as one of the adipocytokines with important metabolic effects. It plays an important role in the development of insulin resistance and atherosclerosis [50].

It was important to realize that adipocytokine is circulating in concentrations exceeding the concentrations of any other known hormone, though still there is much uncertainty with regard to its primary physiological role especially in healthy subjects [51]. The biochemical effects of the aqueous extract of the leaves of the plant were examined in liver and kidney of rats [52].

Week	Variables	Group1 Control 10 rats	Group 2 (0.1 gm/ml) 15 rats	Group 3 (0.125 gm/ml) 15 rats	Group 4 (0.150 gm/ml) 15 rats	p-value
01	Insulin ($\mu\text{U/ml}$)	22.42 $\pm$ 18.08	18.35 $\pm$ 15.97	21.81 $\pm$ 20.77	46268 $\pm$ 24.82	<0.01 ^(c)
	Homa-IR ($\mu\text{U/ml. mmol/l}$)	3.93 $\pm$ 9.42	4.37 $\pm$ 4.16	4.95 $\pm$ 4.94	9.68 $\pm$ 5.23	<0.01 ^(c)
	Adiponectin ($\mu\text{U/ml}$)	19.1 $\pm$ 2.76	18.60 $\pm$ 2.00	17.46 $\pm$ 2.94	15.77 $\pm$ 3.84	<0.05 ^(c)
02	Insulin ($\mu\text{U/ml}$)	4.62 $\pm$ 2.50	14.81 $\pm$ 9.66	14.92 $\pm$ 21.01	9.53 $\pm$ 9.4	NS
	Homa-IR ($\mu\text{U/ml. mmol/l}$)	0.92 $\pm$ 0.48	3.70 $\pm$ 2.82	3.41 $\pm$ 5.18	2.15 $\pm$ 2.52	<0.05 ^(c)
	Adiponectin ($\mu\text{U/ml}$)	27.7 $\pm$ 7.35	24.12 $\pm$ 4.80	24.11 $\pm$ 5.75	33.40 $\pm$ 8.38	<0.05 ^(c)
04	Insulin ($\mu\text{U/ml}$)	8.76 $\pm$ 8.71	9.03 $\pm$ 8.13	19.24 $\pm$ 14.60	20.70 $\pm$ 12.72	<0.05 ^(b,c)
	Homa-IR ($\mu\text{U/ml. mmol/l}$)	1.62 $\pm$ 1.96	1.95 $\pm$ 1.96	4.22 $\pm$ 4.31	5.50 $\pm$ 3.73	<0.01 ^(c)
	Adiponectin ($\mu\text{U/ml}$)	30.41 $\pm$ 8.96	33.89 $\pm$ 5.46	28.20 $\pm$ 3.33	27.58 $\pm$ 5.93	NS
08	Insulin ($\mu\text{U/ml}$)	29.70 $\pm$ 25	16.39 $\pm$ 9.96	12.83 $\pm$ 7.97	8.88 $\pm$ 3.54	<0.05 ^(a) <0.01 ^(b) <0.001 ^(c)
	Homa-IR ($\mu\text{U/ml. mmol/l}$)	8.30 $\pm$ 7.32	3.89 $\pm$ 29.55	2.56 $\pm$ 1.64	1.51 $\pm$ 0.65	<0.01 ^(a) <0.001 ^(b,c)
	Adiponectin ($\mu\text{U/ml}$)	22.85 $\pm$ 5.38	24.21 $\pm$ 4.78	23.53 $\pm$ 6.22	24.28 $\pm$ 5.26	NS
12	Insulin ($\mu\text{U/ml}$)	17.36 $\pm$ 18.72	12.76 $\pm$ 7.73	16.44 $\pm$ 20.83	15.86 $\pm$ 13.93	NS
	Homa-IR ($\mu\text{U/ml. mmol/l}$)	4.71 $\pm$ 6.20	2.86 $\pm$ 2.08	3.99 $\pm$ 5.67	3.48 $\pm$ 3.25	NS
	Adiponectin ($\mu\text{U/ml}$)	19.62 $\pm$ 4.54	21.6 $\pm$ 4.21	18.40 $\pm$ 4.64	18.77 $\pm$ 4.58	NS
18	Insulin ($\mu\text{U/ml}$)	10.86 $\pm$ 8.53	7.82 $\pm$ 3.65	9.11 $\pm$ 5.95	8.52 $\pm$ 6.65	NS
	Homa-IR ($\mu\text{U/ml. mmol/l}$)	2.29 $\pm$ 1.96	1.57 $\pm$ 0.83	1.84 $\pm$ 1.39	1.60 $\pm$ 1.41	NS
	Adiponectin ($\mu\text{U/ml}$)	14.61 $\pm$ 3.91	16.28 $\pm$ 2.93	20.77 $\pm$ 7.03	24.06 $\pm$ 4.65	<0.01 ^(b) <0.001 ^(c)

Table 2: The Relationships between the Adiponectin and Insulin Levels [49].

NS: Not significant; Values were represented as the mean $\pm$ SD (a: control vs group 2, b: control vs group 3, c: control vs group 4); p-value ≤ 0.05 was used as a criterion of significance; p-value ≤ 0.01 was used as a criterion of high significance ($p < 0.01$, $r = 0.35$).

The same condition of the previous experiment was conducted in the present experiment to determine the effects of oral administration of the aqueous extract of the leaves of the plant on the serum adiponectin concentrations and to study its molecular effects on exon 3 of adiponectin gene in the rats. The relationship between the serum adiponectin and insulin resistance after treatment with the aqueous extracts of the leaves of the plant in rats were also estimated and the same is presented in the Table 2.

This increase in the adiponectin concentration induced by the extract of the plant show the importance of using this plant as a medicinal treatment. However, the mode of modulating adiponectin concentration by the plant is still not clear. The results showed inverse significant correlations between adiponectin levels and serum insulin levels after week 1 and 2 of treatment with the plant extract.

An inverse significant correlation between adiponectin levels and insulin levels in a British South-Asian population with a high incidence of type 2 diabetes, cardiovascular disease, central obesity and metabolic syndrome was reported [53]. The insulin resistance is an important risk factor for the type II diabetes mellitus and cardiovascular disease [54].

The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was carried out to evaluate the degree of insulin resistance in each of the rats. This method has been supported by other studies as a precise method for the assessment of insulin resistance [55,56]. The study showed an inverse significant correlation between adiponectin and insulin resistance degrees in all treated rats after one week of treatment with the leaves of the plant. The finding were in consistent with the previous studies that observed inverse correlation between adiponectin levels and insulin resistance [57,58].

This is for the first time that the effects of treatment with the leaves of the plant on adipoQ gene (exon 3) and its protein (adiponectin) were reported. The study clearly shows that oral administration of the leaves of the plant for eighteen weeks produced highly significant increases in adiponectin concentrations in the treated rats especially on rats that were treated with the highest dose of the plant extract. The adiponectin gene was shown to be associated with the adiponectin levels in the healthy caucasians [59].

An earlier report showed that in the presence of at least 1 non-synonymous mutation in exon 3 showed evidence of association with adiponectin levels [60]. The significance of the genetic variations in human adiponectin gene on its plasma concentrations and obesity were also examined in the Japanese population [61].

The mutations in the adiponectin gene were screened by direct sequencing or restriction fragment polymorphism. The levels of plasma adiponectin were determined by the enzyme linked immunosorbent assay (ELISA). The results showed that, two nucleotide changes have been identified in the adiponectin gene. The G/T polymorphism in exon 2 was neither associated with plasma adiponectin concentrations nor with the presence of obesity. A subject carrying missense mutation in the exon 3 (R112C) showed markedly low plasma adiponectin concentration. The frequency of the adiponectin gene mutations in exon 3 of Polish origin patients with type 2 diabetes was 3.9 %, while in the control group it was 0.98 %, and this difference was not statistically significant. It was also observed that the adiponectin level is significantly lower in patients with the C.331 TC mutation [62].

In summary, the studies published to date indicate that polymorphisms at the adiponectin locus (exon 3) are indeed predictors of circulating adiponectin levels, insulin sensitivity, and atherosclerosis, highlighting the pivotal role of this adipokine in the modulation of metabolism and atherogenesis [63].

Under the initially described conditions, no single-base mismatches (heteroduplexes) were detected by the CSGE in a 713-bp is a polymerase chain reaction (PCR) product that contains sequences for exon 3 of the AdipoQ gene. The mean adiponectin levels were found to be significantly higher ($p < 0.01$ -p) Therefore, it was necessary to study the effects of this plant using doses similar to those used by humans in the folk medicine. The results indicated that no mutagenic action was practiced by the plant extracts on exon-3 of adipoQ gene. This does not exclude the possibility of mutagenic elsewhere in the genome of the rat [64-67].

The report revealed that a screening of the total genome of the rat for mutagenic action of the aqueous extract of the leaves of the plant will be revealing. It is also noted that the knockout mutation of the adipoQ gene may be more revealing and required further investigations. The adiponectin has drawn much attention because of its insulin-sensitizing and antiatherogenic actions which suggests that genetic deficits in its production or action may contribute to the insulin resistance and coronary artery disease [68].

A number of bioactive compounds have been isolated from plants which are the potent α -glycosidase and /or α -amylase inhibitors and have shown good antidiabetic properties. The main phytochemicals with reported antidiabetic activities are flavonoids, polyphenolic compounds, tannins, glycosides, alkaloids and terpenoids. A potent α -glycosidase inhibitor which helps in prevention of diabetes was isolated from the water extract of leaves of *Morus alba*, mulberry trees [69]. It is known that the extract of the leaves of *Rhazya stricta* contains the main phytochemicals with reported antidiabetic activities such as alkaloids, glycosides, flavonoides, tannins and triterpenes [70,71].

The possibility that some of the claimed therapeutic actions of the extract of *Rhazya stricta* may be due to its immunomodulatory capacity. The alkaloidal fraction of the plant significantly increased the production of IL-1 and TNF- α [72]. It has also been reported that there is a highly significant correlation between IL-1 and TNF α levels and adiponectin concentrations [73].

The effect of extract of the leaves of *Rhazya stricta* on the rat adiponectin level concentration could be a promising issue (after avoiding its possible mutagenic effects) in treating human diabetes, coronary artery disease, as well as inflammatory conditions. Future studies are required to be conducted to ascertain the mode of action of the alkaloidal extract of the plant on whole adipo Q gene, adiponectin receptor loci and the identification of additional genes which might be involved in the regulation of the serum adiponectin levels.

The indole alkaloidal fraction of *Rhazya stricta* has shown improvement in the key biochemical parameters associated with the metabolic syndrome in rats [74]. The plant has traditionally been used in the Asian countries as herbal remedy for the treating of various animal and human diseases. The study was focused on identifying and characterizing metabolic syndrome (MetS; also called Syndrome X or insulin-resistance syndrome), combinations of the metabolic disorders, and increases vulnerability to the development of cardiovascular diseases, obesity and diabetes. Because of lack of drugs to treat MetS and proper preventive strategies it has become global health concern, particularly in the Western countries where 25 % of the population might develop MetS and the risk increases with age. The effect of the whole aqueous extracts, alkaloid and non-alkaloid containing fraction extracted from the extracts of the leaves was evaluated on biochemical parameters associated with the metabolic syndrome in animals.

The Wistar rats were treated daily for 5 months with different concentrations of the extracts. The sera samples were analyzed at monthly intervals to determine the lipid profile, insulin level, insulin resistance level, and two key enzymes depicting the normal kidney and liver functions. The treatment with the alkaloidal fraction of the plant resulted in significant increases in the levels of insulin and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), as compared to the treatment with the non-alkaloidal fraction.

The indole alkaloid containing fraction not only improved the lipid profile and liver functions in the rats but also led to improvements in the insulin levels, most likely by modulating insulin resistance. The aqueous extract of the plant caused a significant increase in the serum adiponectin levels and resulted in considerable improvement in insulin resistance in rats [74]. The variations in insulin concentrations during 1-5 months of treatment with the plant extract, alkaloidal and non-alkaloidal fractions are presented in Figure-2 through Figure-4.

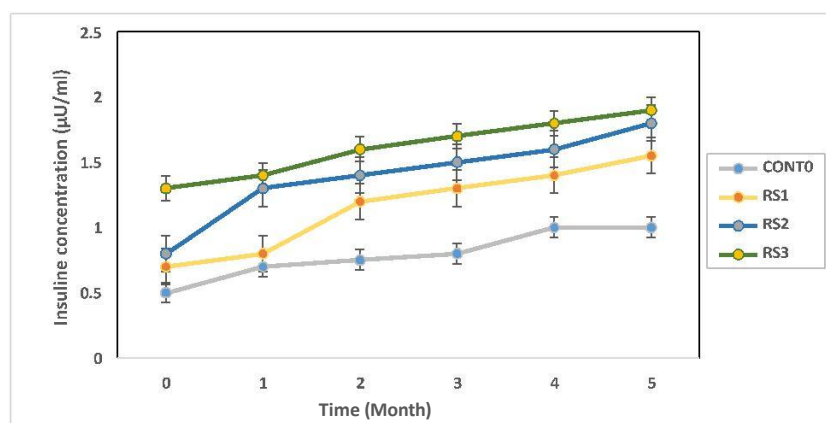


Figure 2: The Insulin Concentrations during Treatment with Water Extract of the Plant [74].

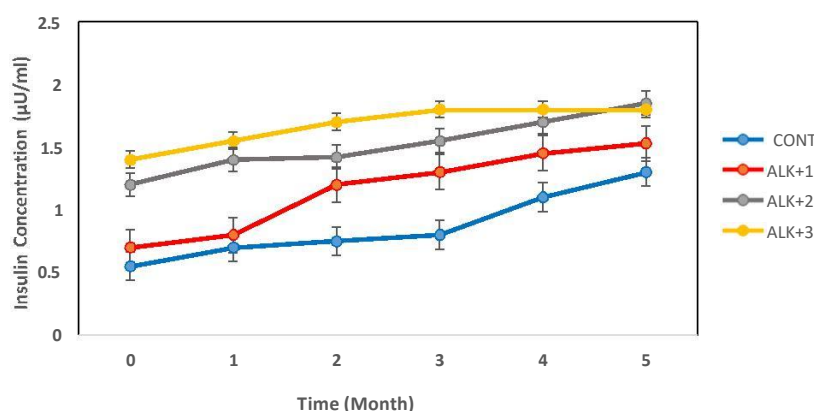


Figure 3: Insulin Concentrations during Treatment with Alkaloid Fraction of Plant [74].

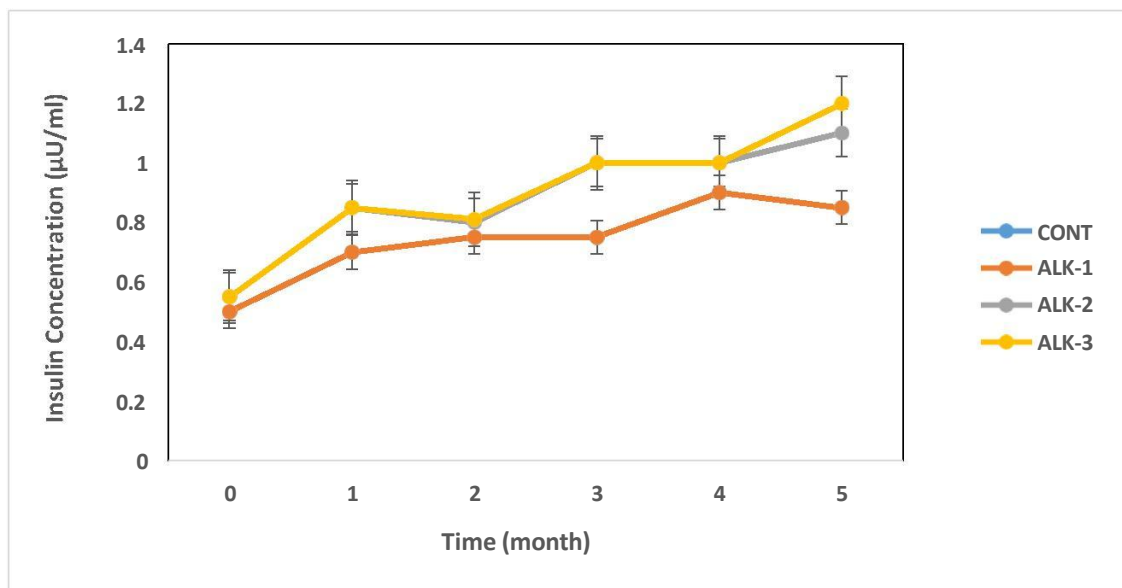


Figure 4: Insulin Concentrations during Treatment with Non-Alkaloidal Fraction of Plant [74].

The plant-induced effects on insulin and insulin-resistance over time. The serum insulin levels increased in the groups treated with the water extract of the plant and also in the groups treated with the alkaloid fraction. Similarly, the HOMA-IR insulin resistance levels increased in the groups treated with the water extract and the groups treated with the alkaloid fraction. Overall, no significant changes in triglycerides, serum insulin, HOMA-IR insulin resistance or aspartate aminotransferase (AST) enzyme levels were observed in the non-alkaloid extract-treated groups. The variations in HOMA-IR levels during 1-5 months of treatment with plant extract, alkaloidal and non-alkaloidal fractions of the plant are presented in Figure 5 through Figure 7.

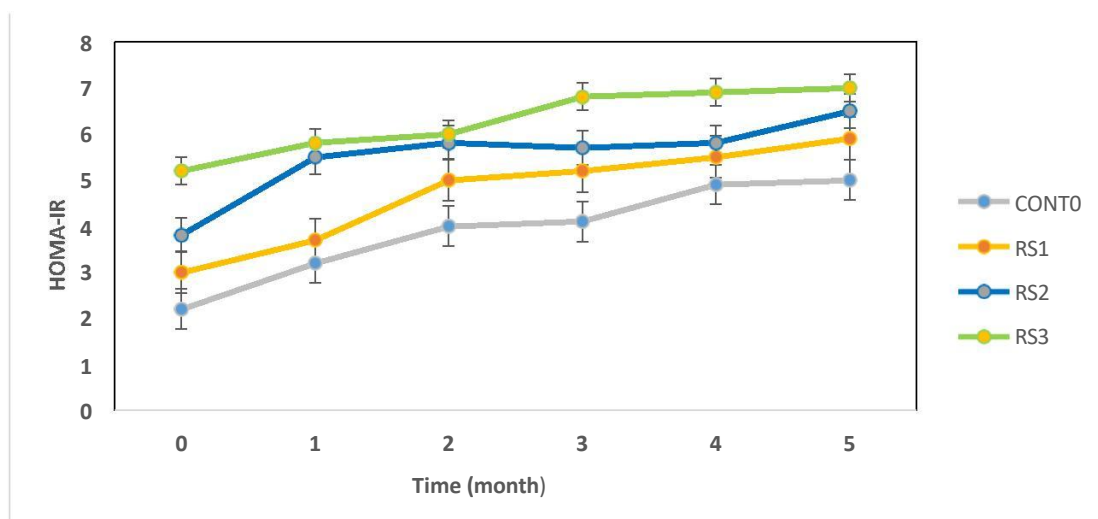


Figure 5: The HOMA-IR Levels during Treatment with Water Extract of the Plant [74].

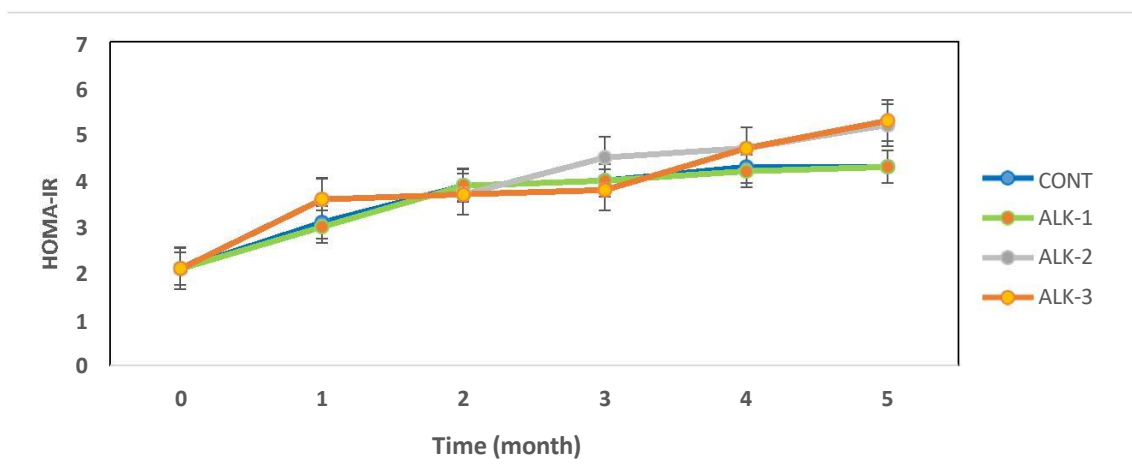


Figure 6: HOMA-IR Levels during Treatment with Non-Alkaloid Fractions of Plant [74].

The metabolic syndrome characterized by insulin resistance, obesity, high blood pressure, erratic blood sugar homeostasis and unhealthy cholesterol levels has become a major health concern worldwide. There is no specific drug treatment for the metabolic syndrome itself. Metformin, thiazolidinediones and acarbose have been commonly used for improving the metabolic syndrome or just for delaying the onset or progression of type 2 diabetes. Recent safety concerns do not favor thiazolidinediones and hence, there is a vast unmet medical need to develop new drugs with better efficacy and safety profile. A study from the United Arab Emirates revealed that water extracts of *Rhazya stricta* were unable to show any beneficial effect on the biochemical parameters of diabetes in streptozotocin-treated rats [46].

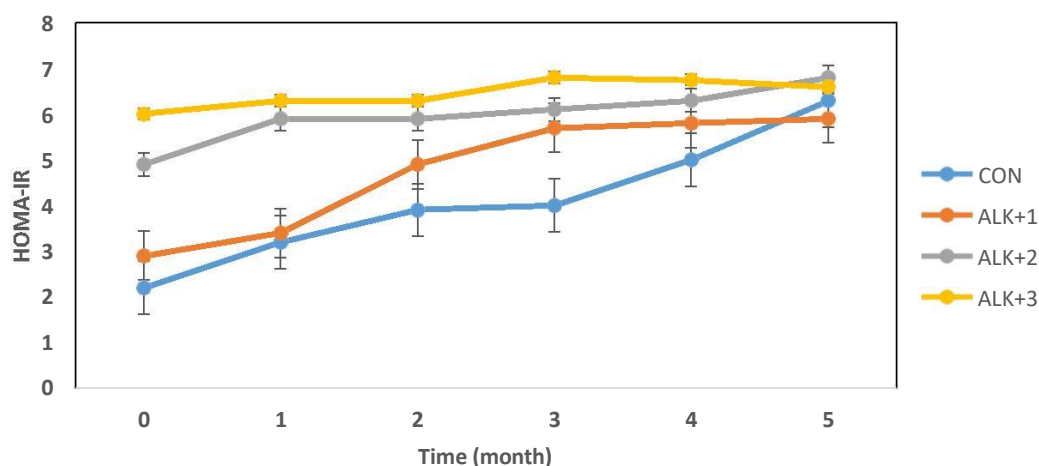


Figure 7: The HOMA-IR Levels during Treatment with Alkaloid Fraction of Plant.

It has since been established that the streptozotocin-treated diabetic rats do not respond to the sulphonylurea group of hypoglycaemic agents, as streptozotocin is known to kill >90% of insulin producing cells in the islets. In a human clinical trial involving 116 patients in China, the alkaloid berberine was shown to be effective against type 2 diabetes and dyslipidaemia [75]. Therefore, proof-of-concept for the efficacy and safety of plant alkaloids has already been established in humans. Pharmaceutical intervention in a complex disease like MetS may require a combination of small molecule inhibitors, biotech and herbal therapeutic approach.

A targeted delivery of estrogen along with glucagon-like peptide 1 (GLP-1) reversed the molecular pathological symptoms of metabolic syndrome, particularly obesity, hyperglycemia and dyslipidemia in mice, has brought renewed hope for the combination therapy [76].

In this study, the biochemical effects of this plant using lower doses, i.e., 0.1, 0.125 and 0.150 gm/ml with daily oral administration for five months, similar to those usually prescribed by the herbal medicine practitioner in Saudi Arabia. The whole water extract of the plant showed a negative correlation between adiponectin levels and HOMA-IR in the rats treated with the extract. The results of the study were found similar to those reported earlier [65].

In a recent study with WNIN/ob obese rats, carbenoxolone-a specific inhibitor of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), ameliorated MetS in this animal model, whereas 11 β -HSD1 induced severe fat loss and glucose intolerance in the lean rats [77]. It will be interesting to examine whether 11 β -HSD1 could be the target of a specific alkaloid(s) from the plant. The short-term treatment (4 weeks) of rats with intermediate concentrations of the whole water extracts of the plant did not show any effects on vital body functions [78].

In this study, the medium-term use (up to 5 months) of alkaloids was observed to understand the safety aspects of the alkaloid fractions on various MetS parameters. The result showed that both insulin secretion and insulin resistance were significantly higher in animals treated with the purified total alkaloid fractions as compared to the control animals or those treated with the water extracts of the plant.

Based on the results of the study, it is concluded the extracts of the plant caused improvement in insulin levels and insulin resistance. This suggested that the therapeutic potential of the plant should be further assessed employing more rigorous new drug discovery analytical tools.

The antidiabetic and hypolipidemic potential of the extract of *Rhazya stricta* Decne and its fractions was evaluated [79]. The oral administration of the extract and fractions of the plant showed a considerable decline in the blood glucose levels in the diabetic mice. The crude methanol extracts of different parts of the plant were tested in vivo on albino mice balb-C, for the reduction of blood glucose, urea, cholesterol, triacylglycerides and the glycosylated haemoglobin. The results showed that leaves of the plant have best antidiabetic effects by reducing the blood glucose level, glycosylated haemoglobin, triacylglycerides and cholesterol in the hyperglycaemic mice. As the crude extract of the leaves has shown potent antidiabetic activity, it was further fractionated by solvent extraction with n-hexane, ethyl acetate, chloroform

and water. All fractions were also tested for their antidiabetic and hypolipidemic potential. The results showed that the ethyl acetate fraction was most effective in the reduction of the blood glucose level in fasting and random conditions and the blood glucose reduction was comparable to glucophage, a standard antidiabetic drug. The study suggests that the extract of the leaves of the plant and the ethyl acetate fraction possesses great potential for the development of an antidiabetic medicine.

The oral glucose tolerance test was performed to check which animals can develop diabetes more rapidly. Among tested animals, those male mice were used to develop for diabetes whose blood glucose level was more than 130 mg/dl while those female mice were used to develop diabetes whose blood glucose level was more than 220 mg/dl in the OGTT. The blood glucose levels of the selected mice for assessment of oral glucose tolerance test (OGTT) are presented in the Table 3.

Group	Sex	Blood Glucose Level (mg/dl)				
		0 min	30 min	60 min	90 min	120 min
1 (Negative control)	M	110.34±56.88	136±78.9	117±60.00	130.34±54.81	91±21.74
	F	186.67±59.09	212.34±21.36	203.67±14.46	195.67±29.02	166.67±32.25
2 (Diabetic control)	M	151.67±14.64	313.34±63.50	236.34±68.38	245.67±87.37	120.67±51.29
	F	259.67±53.45	234±17.22	237.34±14.21	249±76.39	185.67±24.54
3 (Antidiabetic control)	M	218±40.58	183±35.38	223.34±67.30	110.34±57.735	152.67±40.69
	F	198.67±57.07	244.67±37.93	233.34±14.20	218±44.69	233.67±84.60
4 (<i>R. stricta</i> Fruit)	M	218±40.58	183±35.38	223.34±67.30	110.34±57.7	152.67±40.69
	F	186.67±59.07	212.34±21.36	203.67±14.46	195.67±29.02	166.67±32.25
5. (<i>R. stricta</i> leaves)	M	110.34±56.88	136±78.93	117±60.008	130.34±54.81	120.67±51.99
	F	259.67±53.45	234±17.22	237.34±14.21	249±79.39	185.67±24.54

Table 3: Blood Glucose Levels of Selected Mice for Assessment of Oral Glucose Tolerance Test [79].

± = Value obtained after triplicate analysis, M= Male, F= female.

Results of Blood glucose concentration of tested animals showed that in males during fasting condition, leaves of the plant reduced blood glucose level more rapidly than other plants parts and then its own fruit because blood glucose concentration was found to be 146.00±40.36 mg/ dl and 162.32±41.078 mg/ dl in male and female mice, respectively in fasting conditions while it was found to be 125.34±63.79 mg/dl and 107.34±18.00 mg/dl in male and female mice, respectively in random conditions. These blood glucose was lowered almost as much as the glucophage has done in which blood glucose was lowered up to 84.67±21.78 mg/dl and 85.00±25.06 in male and female mice, respectively in fasting conditions while it was found to be 104.67±36.29 mg/dl and 92.95±9.5 mg/dl in male and female mice, respectively in random conditions. The concentrations of glucose (mg/ dl) in various groups of animals after the induction of the extracts of the plant and standard are given in the Table 4. The concentration of glucose (mg/ ml) in various groups of animals are presented in the Figure 8.

Groups	Sex	Normal		STZ		Glucophage		Plant extract	
		Random	Fasting	Random	Fasting	Random	Fasting	Random	Fasting
Group 3 (Glucophage)	M	221.33±50.16	200±21.79	262±81.26	212.667±67.26	104.67±36.29	84.67±21.78		
	F	210.34±11.15	169±31	169.33±33.86	97.34±48.41	92.95±9.5	85±25.06		
Group 4 (<i>R. stricta</i> Fruit)	M	143.23±55.05	228.67±38.53	303.34±52.12	359.34±34.19			226.67±14.51	263.61±61.62
	F	173.66±49.09	206.65±6.65	289±53.55	283.34±5.68			192.34±28.92	219±77.62
Group 5 (<i>R. stricta</i> Leaves)	M	230±40.14	316.67±15.04	348.67±51.82	344±31			125.34±63.79	146.00±40.36
	F	171.67±21.36	206.34±28.29	260.67±51.04	289.67±64.36			107.34±18.00	178.34±17.03

Table 4: Concentration of Glucose (mg/dl) in Various Groups of Animals after the Induction of Antidiabetic Standard and Plant Extract [79].

± = Value obtained after triplicate analysis, M= Male, F= female.

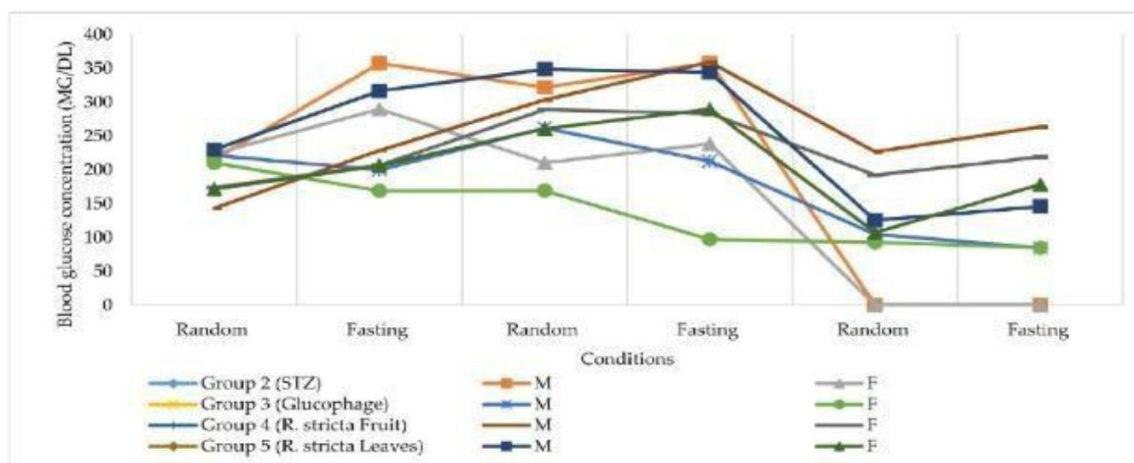


Figure 8: The Concentration of Glucose (mg/ ml) in Various Groups of Animals [79].

The glycosylated haemoglobin was more strongly reduced by the extract of the leaves of the plant in which its amount was found to be $6.3 \pm 0.7\%$ in males. The amount of glycated haemoglobin (1HBA1c, %) in various groups of animals after the induction of the extracts of the plant and standard are presented in the Table-5. The fruits of the plant were less effective in the reduction of glycosylated haemoglobin in male and female mice. The statistical analysis showed that the fruits of the plant have equal ability to reduce glycosylated. The glycated haemoglobin (HBA1C, %) in various groups of animals after the induction of the extracts of the plant and Standard are presented in the Figure 9.

Groups	Sex	Buffer	STZ	Glucophage	R.stricta	
					Leaves	Fruit
Group 1	M	6+0.3				
(Negative control)	F	6.1+1.56				
Group 2	M		10.84+3.94			
(Diabetic control)	F		10.27+2.12			
Group 3	M			6.1+1.13		
(Antidiabetic control)	F			6.17+1.58		
Group 4	M				6.3+0.7	
(<i>R.stricta</i> Leaves)	F				6.6+0.1	
Group 5	M					8.54+0.94
(<i>R.stricta</i> Fruits)	F					9.54+1.53

Table 5: Amount of Glycated Haemoglobin (HBA1c, %) in Various Groups of Animals after the Induction of Antidiabetic Standard and Plant Extract [79].

$\pm$ = Value obtained after triplicate analysis, M= Male, F= female.

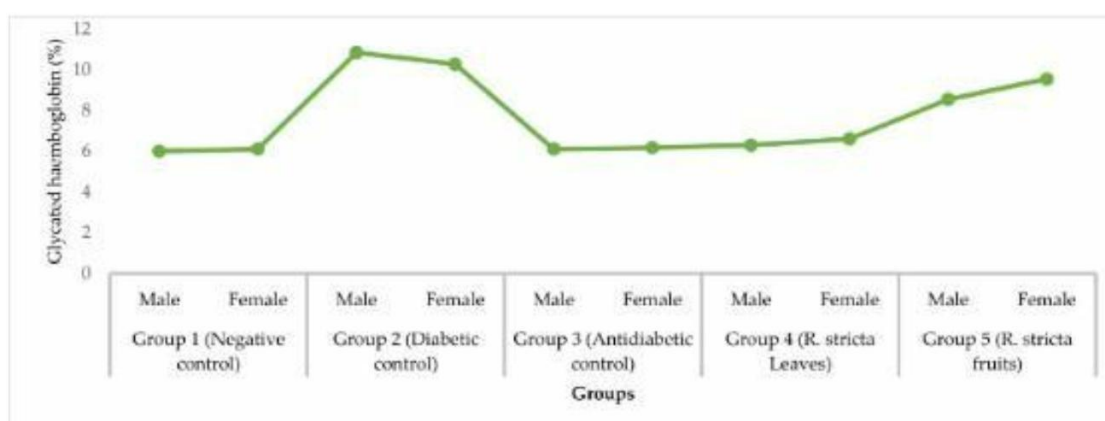


Figure 9: Glycated haemoglobin (HBA1C, %) in Various Groups of Animals after the Induction of the Plant Extracts and Standard [79].

The antidiabetic activity of the extracts on polarity basis were also examined. Although all extracts of the leaves of the plant exhibited the activity of reduction in blood glucose, blood cholesterol, and urea, and glycosylated haemoglobin levels. However, leaves of the plant were found more effective. On the basis of this activity, leaves of the plant were used to check their blood glucose lowering activity in the n-hexane, ethyl acetate, chloroform and water extracts. The blood glucose lowering activity of these extracts were also compared with negative control, positive diabetic control and positive antidiabetic controls. It was found that ethyl acetate extract was more effective in the reduction of life blood glucose level at fasting condition (200 ± 67.45 mg/dl and 153.67 ± 21.08 mg/dl, respectively) and random conditions

(226.67±14.14 mg/dl and 231±48.66 mg/dl) in both males and female mice and the amount of blood glucose was closed to the amount of blood glucose reduced by glucophage at fasting condition (84.67±21.78 mg/dl and 85±25.96 mg/dl, respectively) and random conditions (104.67±36.29 mg/dl and 92±9.5 mg/dl) in both male and female mice. The blood glucose concentrations (mg/ dl) after treatment with polarity based extracts of the leaves are given in the Table-6.

GROUPS	Sex	Blood glucose concentration (mg/dl) (normal)		Blood glucose concentration (mg/dl) (STZ)		Blood glucose concentration (mg/dl) Glucophage)		Blood glucose concentration (mg/dl) (Plant extract)	
		Random	Fasting	Random	Fasting	Random	Fasting	Random	Fasting
Group 3 (Glucophage)	M	219±70.71	195±28.28	81.26±26	212.67±67.26	104.67±36.29	84.67±21.78		
	F	223±2,821	74.5±41.72	169.34±33.85	9737±48.42	92±9.5	85±25.96		
Group 4 (<i>R.stricta</i>) n - Hexane	M	200±36.6	209±25.45	275.34±32.47	312.34±32.81			226.67±14.14	252.34±43.62
	F	145.5±14.85	207.5±9.19	282±33.95	289±17.45			231±48.66	196.34±50.06
Group 5 (<i>R.stricta</i>) Ethyl acetate	M	209.34±38.14	232.17±85.17	254.67±52.29	236±42.32			152±11.53	200±67.45
	F	133.67±53.16	111.67±23.02	287.67±29.19	251±36.67			168.34±29.57	153.67±21.08
Group 6 (<i>R.stricta</i>) Chloroform	M	176.67±27.02	223±46.23	295±3034	280±29.46			203.67±6.43	208±32.36
	F	100±45.03	118±28.05	290±29.71	300±37.64			231.67±74.61	203.34±42
Group 7 (<i>R.stricta</i>) Water	M	207.34±77.15	192±8	303.34±45.36	319.34±32.25			236.67±23.63	233.67±9.61
	F	128±6.55	131.67±50	268.67±33.97	306.67±20.11			215.67±61.04	155.34±45.62

Table 6: Blood Glucose Concentration (mg/ dl) after Treatment with Polarity Based Extracts of Plant Leaves [79].

N = 3 and data obtained after triplicate analysis

The results of the blood glucose lowering activity of the ethyl acetate extract was almost similar to those reported earlier [80]. The earlier reports showed found likenesses in the properties of *Rhazya stricta* and adiponectin on diabetes, hypertension, carbohydrate metabolism, as well as inflammatory situations and animal studies for the conformation of antidiabetic effects of the plant and adiponectin have proved that adiponectin eases elevated blood glucose levels in diverse models of fatness/diabetes mellitus. Water and n-hexane extracts of *R. stricta* leaves were almost equally effective in the reduction of blood glucose levels of diabetic male and female mice. The blood glucose concentration (mg/ dl) of the polarity based extracts of the leaves of the plant are presented in the Table 7 and Figure 10.

GROUP	DMRT RESULT
Group 1 (buffer)	151.0 ^C
Group 2 (STZ)	323.9A
Group 3 (Glucophage)	226.6 ^B
Group 4 (n-Hexane extract of <i>R. stricta</i> (Leaves)	184.3 ^{BC}
Group 5 (Ethyl acetate extract of <i>R. stricta</i> (Leaves)	91.58 ^o
Group 6 (Chloroform extract of <i>R. stricta</i> (Leaves)	195.8 ^{BC}
Group 7 (Water extract of <i>R. stricta</i> (Leaves)	210.3 ^B

Table 7: Blood Glucose Concentration (mg/ dl) of Polarity Based Extracts of Leaves of Plant.

N = 3 and date obtained after triplicate analysis; A = Maximum/ Highest blood glucose concentration; B = blood glucose concentration, higher than C but lower than A; C = blood glucose concentration higher than D but lower than C; D = Least/ Lowest blood glucose concentration.

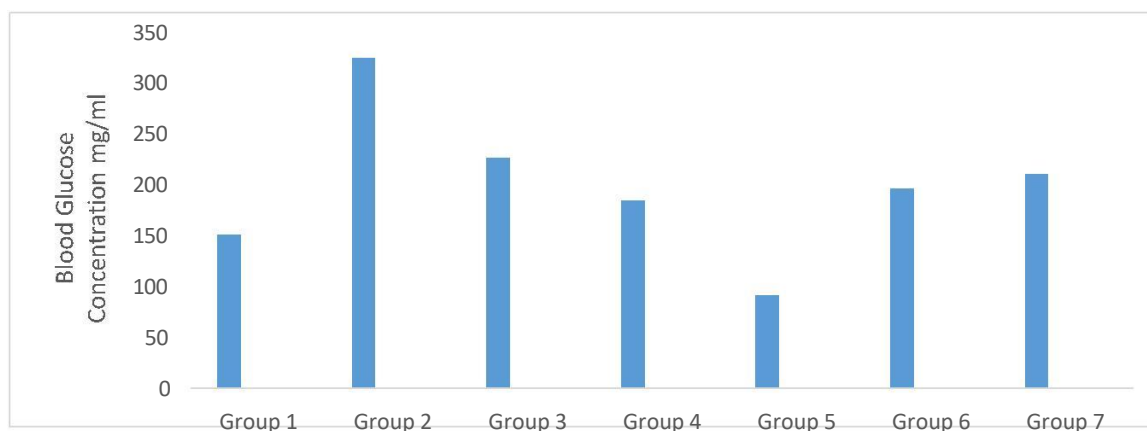


Figure 10: Blood Glucose Concentration (mg/ dl) of Polarity Based Extracts of Leaves of the plant.

The above discussion showed that the leaves of *Rhazya stricta* were most effective in reducing blood glucose, blood cholesterol, urea and glycosylated haemoglobin while its ethyl acetate fraction was most effective in the reduction of blood glucose level at fasting condition and random conditions in both male and female mice and that the amount of blood glucose was close to the amount of blood glucose reduced by glucophage. Based on the findings, the leaves of the plant and particularly the ethyl acetate fraction may be subjected to the activity directed isolation of the most effective phytochemical against hyperglycaemia.

The methanol extract of the leaves of the plant was analyzed for their hypoglycemic and Hypocholesterolemic activities against the streptozotocin induced hyperglycemia [81]. The methanol extract of the leaves of the plant was evaluated for its hypoglycemic and hypolipidemic in blood of the male and female albino mice balb C. The extract of the leaves have shown anti-diabetic activity by reducing cholesterol, glucose and triglycerides in the blood samples. The results showed that the leaves of the plant were best for the hypoglycemia at 125.34 ± 63.79 mg/dl, 107.34 ± 18.00 mg/dl, 146.00 ± 40.36 mg/dl and 178.34 ± 17.03 mg/dl while the hypocholesterolemia at 147.88 ± 21.83 mg/dl and 125.89 ± 14.03 mg/dl and triglycerides at 103 ± 8.88 mg/dl and $89. \pm 43.4$ mg/dl in random and fasting conditions of the male and female mice respectively. The extract of the plant were most effective for the hypoglycemia and hypocholesterolemia in the female mice as compared to the male mice. The statistical analysis showed that leaves of the plant are more effective than other plants. So the combination of different parts of the plant with other plant may be further evaluated for their use against hyperglycemia and hypercholesterolemia in females.

The phytochemical analysis, antimicrobial screening and hypoglycemic effect of the extracts of some selected medicinal plant from Oman was carried out to investigate the medicinal potential of the plants including *Rhazya stricta* [82]. In particular, the extracts of the plant was analyzed for their antidiabetic activities. The oral administration of plant extract of the plant reduced the blood sugar level of the treated mice. The blood sugar level was started reducing after 1 week of treatment and continued till 21 days of the exposure as compared to the control. The phytochemical screening of the plant indicated that it contains many of the chemical substances which had important role in the reducing blood sugar level.

The blood sugar level of the experimental mice was analyzed after 21 days of treatment. The extracts of *Rhazya stricta* have shown hypoglycemic effect. The extracts were found effective in reducing blood sugar level and all the tested concentration of this extract effectively reduced the blood glucose level. The mice treated by all the concentrations of the plant showed reduction in blood sugar level and the effect was more pronounced with the increasing the doses of the extract. It was reported at 0.1% (0.12 mmol), 0.5% (0.27mmol) and at 1.0% (0.37mmol). The hypoglycemic effect of the extract of the plant may be due to its positive effect on the insulin releasing mechanism which showing resembling with the mechanism of sulfonylureas [83,84].

Findings of this study suggested that the extract of *Rhazya stricta* have remarkable effect on the decreasing serum glucose level. This research supports the inclusion of this plants in formulation of traditional antidiabetic, and the formulations made using the identified effective extract and fraction of this plant could serve the purpose better than the existing formulations with crude aqueous extract since the experimental plants used in this study are used all over the Sultanate of Oman as blood sugar control plant material traditionally. The effects of the ethanol extract of the plant on blood sugar level are presented in Table 8.

Concentration of Extract	Before	Blood Sugar Level in m mol After 21 Days	Mean
0.1%	5.30±0.61	4.80±0.13	0.50↓
0.5%	6.30±0.63	4.90±0.05	1.40↓
1.0%	5.30±1.57	5.25±0.09	2.35↓

Table 8: Effect of Ethanol Extracts of *Rhazya stricta* on Blood Sugar Level of Mice [82].

All values expressed are the SEM ± of 3 replicates calculated with descriptive statistics maintained for 21 days with plant.

The assessment of the antidiabetic potential and phytochemical profiling of the extracts of the roots of *Rhazya stricta* was carried out to evaluate the biological activities of the roots of the plant including their antidiabetic activities [85]. The extracts were subjected to the in vitro and in vivo assays by using animal models. The fractions obtained from the extracts of the plant were evaluated for a variety of assays including α -glucosidase, dipeptidyl peptidase-IV (DPP-IV), β -secretase and glucagon-like peptide-1 (GLP-1) secretion. The alloxan-induced diabetic mice were treated with the extract of the root of the plant for in vivo studies and blood glucose levels, HbA1C, and other biochemical markers along with the histological study of the liver. A majority of the fractions showed excellent results against diabetes by inhibiting enzymes DPP-IV (up to 61%) and β -secretase (up to 83%) with IC₅₀ values of 979 μ g/ml and 169 μ g/ml, respectively with increase in the GLP1 secretion.

The results of the in vivo studies indicated a marked reduction in the blood glucose and HbA1c levels along with positive effects on other parameters like lipid profile, liver functions and renal functions of the extract-treated mice as compared to the control. The histological examination of the liver demonstrated hepatoprotective effects against diabetes led changes in the mice. The results further indicated a potent antidiabetic activity of the roots of the plant with the potential to protect body organs against diabetic changes. A variety of phytochemicals has also been identified that might be responsible for the antidiabetic potential of the roots of the plant.

The roots of the plant were evaluated for their antidiabetic effects through various assays including animal studies. The alloxan induced diabetic mice were treated with the extracts of the roots and their effects on blood glucose and other biochemical parameters were evaluated. The liver histology of mice was also done to determine the hepatoprotective/hepatotoxic effects of the extract on the liver as it is the vital organ involves in the detoxification of metabolites, synthesis of various proteins and other biochemicals necessary for digestion [85].

The in vivo studies showed a significant increase in glucose concentration observed in the mice of the untreated diabetic control group as compared to the normal control group. After 28 days of oral administration of the extract fractions, an observable reduction was noted in the glucose level of almost all groups in comparison with the untreated control group. Similar results were observed in glycosylated hemoglobin (HbA1C) level and the noticeable decrease was shown by all treated groups of mice as compared to the untreated diabetic control groups. Overall, maximum activity has been shown by the second chloroform layer and its glucose-lowering effects are comparable with the results of the treated control group with a standard drug glibenclamide. The results are presented in the Figure 11 and Figure 12.

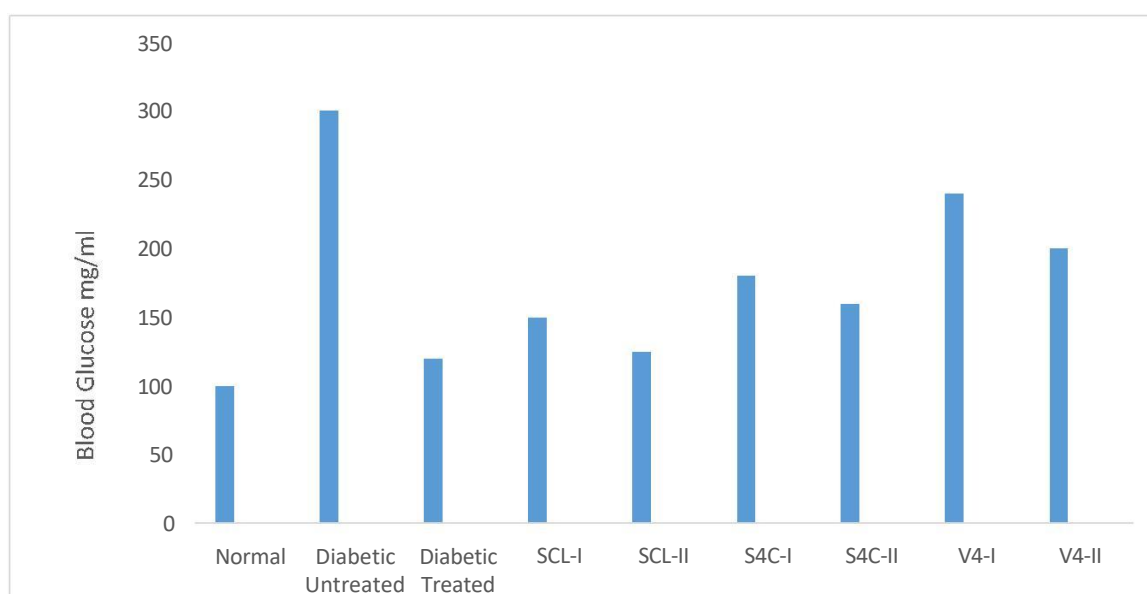


Figure 11: The Blood Glucose Levels of All Groups of Mice after Treatment [85].

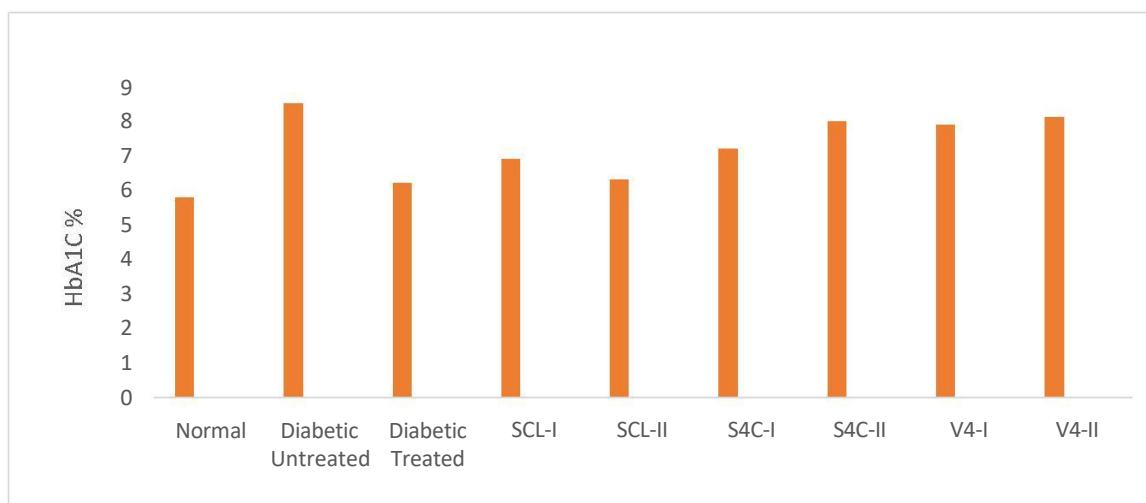


Figure 12: Glycosylated Hemoglobin Levels of All Groups of Mice after Treatment [85].

Like other members of the Apocynaceae family, *Rhazya stricta* is claimed to contain various medicinal properties including antihyperglycemic effects [86]. The extracts of the roots of the plant inhibited α -glucosidase enzyme that can lead to better glycemic control through a reduction in disaccharide hydrolysis [87]. The inhibition of the DPP-IV enzyme is another strategy to keep incretin hormones available in the blood for insulin-dependent disposal of glucose from the blood. This study proved that roots of the plant has dual activity to cope with diabetes mellitus as it inhibited the DPP-IV enzyme as well as stimulated GLP1 secretion. Despite the availability of many synthetic DPP-IV inhibitors, various studies have been conducted on medicinal plants and several plants were found to possess the DPP-IV enzyme activity [88]. The extracts of the roots of *Rhazya stricta* showed a remarkable inhibition of β -Secretase in a dose-dependent manner that is supposed to be involved in diet-induced obesity and related complications including diabetes. An earlier report revealed that the BACE1 is a regulator of insulin signaling and the amount of insulin receptor is found to be reduced due to the degradation by the BACE1 enzyme. In this connection, the report suggested that the insulin signaling can be improved with the use of BACE1 inhibitors during diabetes [89].

The monitoring of the blood glucose levels of diabetic patients and HbA1c levels are considered important factors in the treatment of diabetes mellitus. The extracts of the roots of the plant considerably reduced the blood glucose level and HbA1c in accordance with previous reports where aerial parts of the plant were seen reducing blood glucose levels and HbA1c accordingly [79-81]. Another study reported that long-term oral administration of the alkaloids rich fractions of the plant significantly improved the insulin level and insulin resistance which showed insulin secretagogue activity of the plant for the disposal of blood glucose [74].

Several studies reported the link of reactive oxygen species with diabetes and oxidative stress is considered as one of the main factors that have an important role in beta-cells dysfunction, resulting in diabetes [90]. The role of oxidative stress has also been determined in the pathogenesis and complication of diabetes [91,92]. In this regard, various reports suggested the use of antioxidants in the aetiology of diabetes and its associated complications [93,94]. Up-till now, many plants have been investigated extensively to search natural antioxidants to prevent/minimize the destructive process caused by the oxidative stress [95]. The *Rhazya stricta* root extracts displayed its potential for diabetes mellitus by lowering blood glucose level through different mechanisms that might be a synergistic effect of many of the phytoconstituents present in the extracts.

In this study, positive effects of the extracts on other biochemical parameters like lipid profile, renal function tests, liver function tests, total protein and serum albumin of mice have also been observed. The outcome of these biochemical parameters pointed out lipid-lowering potential and beneficial effects of the root extract on kidneys and liver functions of the mice. The extract of the leaves of *R. stricta* was reported in lowering the levels of cholesterol and triglycerides in animals [96]. The histological examination of the mice liver has shown that the administration of the root extract fractions has not posed any substantial alterations of liver cells and any kind of known hepatic variations like dilation, congestion, necrosis or hypertrophy were not seen in all treated groups. These results suggested that the root extracts of *R. stricta* has potential to preserve the hepatic cells against diabetes led changes and its associated complaints.

The pharmacological evaluation of the extract of the roots of *Rhazya stricta* was carried out to assess their medicinal potential including the antihyperglycemic activities [97]. The extract was subjected to the enzyme inhibition assays. The extract showed their glucose-lowering effects by inhibiting the enzyme activity which could reduce post-prandial blood glucose level. The dipeptidyl peptidase-IV (DPP-IV) inhibition assay results showed the novel DPP-IV inhibition activity of the plant extract and all fractions showed significant enzyme inhibition and antihyperglycemic activity. The study also revealed that the extract of the roots indicated antihyperglycemic potential due to the presence of various classes of phytochemicals and micronutrients in the plant.

The high blood glucose levels stimulate the formation of reactive oxygen species and production of the free radicals [26]. The reactive oxygen species (ROS) are chemically active derivatives of oxygen including free radicals that pose detrimental effects on cells by the enzyme inactivation and damage to vital cellular machinery [98,99]. As oxidative stress from hyperglycemia may also play an important role in several associated complications (26). Therefore, to maintain health and for the prevention and treatment of diseases, the use of antioxidants have been attracting the attention of scientists [100].

The extract and fractions of the roots of the plant were subjected to the α -Amylase inhibition assay to determine their α -Amylase inhibition activity: The crude extract of root and its fraction showed good α -amylase inhibition activity. All fractions including the crude extract were examined for their activity against enzyme initially at 1mg/ ml concentration. Acarbose was used as a positive control for the purpose. All fractions exhibited reasonable activity against the enzyme and all were then re-analyzed with lower concentrations for the calculation of IC_{50} value. The α -amylase inhibition by the extracts and fractions of the plant at 1 mg/ml concentration are presented in the Figure 13.

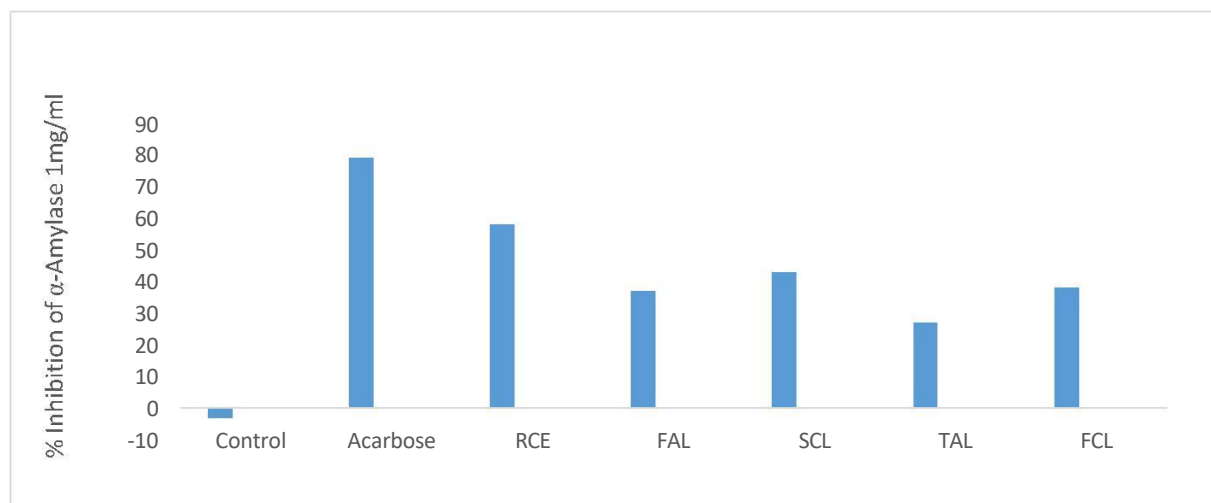


Figure 13: The α -Amylase Inhibition by Extracts and Fractions of Plant at 1 mg/ml Concentration [97].

At 1 mg/ml concentration, the crude extract of the roots inhibited 52 % enzyme (IC_{50} 1.175 mg/ ml) while the second chloroform layer was the second most potent fraction with 45 % inhibitory activity (IC_{50} 1.327 mg/ ml) in comparison to the aqueous extract fractions, first aqueous layer and third aqueous layer. The both fractions showed moderate activity with IC_{50} 2.762 and 3.038 mg/ml, respectively. The extract of the roots of the plant was subjected to the α -glucosidase inhibition assay to determine its α -glucosidase inhibition activity. The α -glucosidase inhibition activity of the extract of the roots and its fractions was not good as α -amylase inhibition while the crude extract inhibited 47 % α -glucosidase at 1 mg/ ml. The second chloroform layer and fourth chloroform layer again proved to be the second and third most successful fractions after the crude extract by inhibiting 44 % and 28 % enzyme activity at the same concentration.

The crude extract of the roots, second chloroform layer and fourth chloroform layer were analyzed again at different concentrations for the calculation of IC_{50} which were found as 1.596, 2.266 and 3.075 mg/ ml, respectively. The chloroform fractions, second chloroform layer and fourth chloroform layer have exerted better inhibitory effects while the aqueous fractions, first aqueous layer and third aqueous layer displayed very little activity like 10.2 % and 13.6 %, respectively. Therefore, further assessment of the aqueous layers at lower concentration was considered unnecessary. The α -glucosidase inhibition by the extracts and Fractions of the plant at 1 mg/ml concentration are presented in the Figure 14.

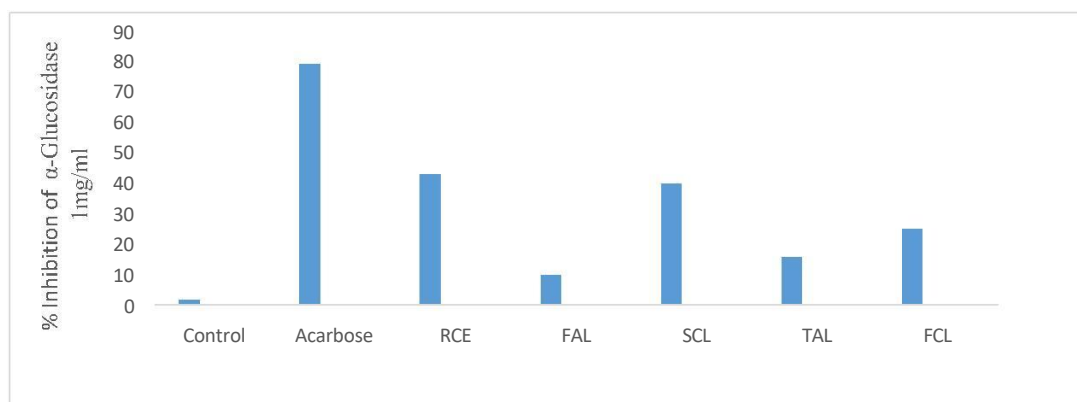


Figure 14: The α -Glucosidase Inhibition by Extracts and Fractions of Plant at 1 mg/ml Concentration [97].

The extract of the root extract and fractions were evaluated for their potential against DPP-IV enzyme which has the ability to degrade incretin hormone in the gut resulting in a high glucose level in the blood. The fractions obtained from the extract of the roots was subjected to the dipeptidyl peptidase-IV (DPP-IV) inhibition assay. All fractions were examined at 1mg/ ml and then re-examine at lower concentrations for determination of the IC₅₀ value. The crude extract of the roots showed 70 % DPP-IV inhibition activity while the second chloroform layer and fourth chloroform layer fractions displayed good results by inhibiting 64 % and 40 % enzyme activity at the 1 g/ ml concentration. The DPP-IV percentage inhibition by the extracts and fractions of the roots of the plant at 1 mg/ml concentration are expressed in the Figure 15.

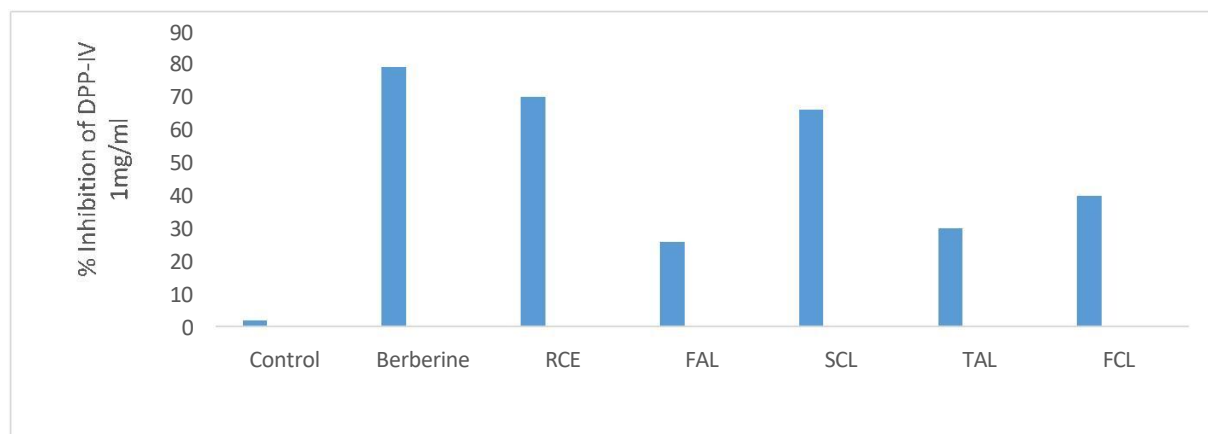


Figure 15: The DPP-IV Percentage Inhibition by Extracts and Fractions of Plant Roots at 1 mg/ml Concentration [97].

The aqueous fractions, first aqueous layer and third aqueous layer also inhibited the enzyme activity by 27 % and 31 %, respectively. For the calculation of the IC₅₀, all fractions including the crude extract of the root were evaluated at 0.25 mg/ ml, 0.5 mg/ ml, 1.0 mg/ ml and 2.0 mg/ ml concentrations. Of all tested fractions, the crude extract of the roots and second chloroform layer exhibited good inhibitory activities as IC₅₀ 0.520 and 0.853 mg/ ml while the second chloroform layer, first aqueous layer and third aqueous layer showed the IC₅₀ as 1.804, 2.797 mg/ml and 2.394 mg/ ml, respectively.

The roots of the plant has the potential to bring down the glucose level in many different ways. The crude extract of the roots and its fractions inhibited α -amylase and α -glucosidase enzymes significantly ($p < 0.05$). The extract of roots and chloroform fractions showed good enzymes inhibition while aqueous fraction inhibited enzyme activity moderately. The earlier report showed that the ethanolic extract of another member of the Apocynaceae family, *Picrolima nitida* also contains the α -glucosidase inhibition activity with the IC₅₀ value 6.15 mg/ml [101].

The inhibitory effects of the extract of the plant against dipeptidyl peptidase-IV (DPP-IV) were evaluated. Recent advancements in the diabetes therapeutics have resulted in the development and clinical use of incretin-based therapies. These therapies stimulate insulin secretin either by increasing circulating level of glucagon-like peptide-1 (GLP-1) or by inhibiting the dipeptidyl peptidase-IV enzyme that is involved in the degradation of incretin hormones. Therefore, as an alternative to drug therapies, DPP-IV inhibitors from natural sources should be sought [102].

In the initial screening, the crude extract and fractions of the roots of the plant were able to inhibit DPP-IV significantly ($p < 0.01$). Of all the fractions, the crude extract and its second chloroform layer fraction exhibited potent DPP-IV inhibition activity while all other fractions also inhibited enzyme activity significantly ($p < 0.05$) with varying percentages. All fractions were further evaluated at lower concentrations for the calculation of IC₅₀ value and the crude extract of the roots exhibited remarkable DPP-IV inhibition with IC₅₀ 0.520 mg/ml.

The study showed that the roots of *Rhazya stricta* have an excellent antihyperglycemic activity to cope with diabetes with different modes of action as it inhibited the carbohydrate digesting enzymes on one side and on the other side it inhibited the DPP-IV enzyme activity. The inhibition of the DPP-IV helps incretin hormone (functional form) to be available in the bloodstream for the release of insulin from the pancreas. The plant is also reported to be an insulin secretagogue as in many of the animal studies carried out by different groups, an increase in insulin concentration after treatment with the plant and insulin-dependent glucose disposal has been reported [47,81]. Hence, the DPP-IV enzyme inhibition might be one of the reasons for the insulin secretion through incretin hormone stimulation.

The results of in-vitro antihyperglycemic enzyme inhibition assays confirmed the presence of antidiabetic compounds in the roots of the plant. The earlier reports also confirmed that the extracts exhibited the DPP-IV inhibition activity. Therefore, it can be a good source of the DPP-IV inhibitors for the treatment of diabetes mellitus.

The efficient antidiabetic drugs are always in great demand because of an increasing number of diabetic patients worldwide and medical science is still facing a challenge of management of diabetes mellitus with fewer side effects [103,104]. *Rhazya stricta* is an important medicinal plant of Apocynaceae family that is little investigated for its biological activities although it produces a large number of terpenoid indole alkaloids [105]. The crude extract and fractions of the roots of the plant obtained through the solvent-solvent extraction were evaluated for their antihyperglycemic potential using different enzyme inhibition assays and all were found to be effective in lowering glucose level by inhibiting α -amylase, α -glucosidase, and DPP-IV enzymes in a dose-dependent manner.

Conclusions

Above reports showed that the natural remedies have been used to treat diabetes since long and many anti-diabetic compounds of varied efficacies have been isolated from medicinal plants. *Rhazya stricta* has been used for decades for the treatment of diabetes mellitus and associated ailments. Considering the folkloric use of the plant against diabetes, researches carried out on its extracts showed the effectiveness of its root extracts against diabetes through in vitro assays and in vivo studies using animal models. The results revealed strong antidiabetic activity of the roots of the plant with the potential to protect body organs against diabetic changes. The reports confirmed that the roots of the plant is a potential source for the treatment of diabetes mellitus as it has demonstrated its effectiveness by inhibiting various key enzymes involved in the hyperglycemia. The results of the assays clearly indicated the role of the roots in lowering of blood glucose levels with a positive impact on the associated biochemical parameters and liver cells. Besides, a variety of natural products including alkaloids, heterocyclic compounds are identified in the extracts of the plant which showed a potent antidiabetic activity.

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