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COMPLETE RECOVERY FROM DIABETES TYPE 2 IN STREPTOZOTOCIN INDUCED DIABETIC ALBINO RATS BY (E) 4-HYDROXYBUT-2-ENOIC ACID

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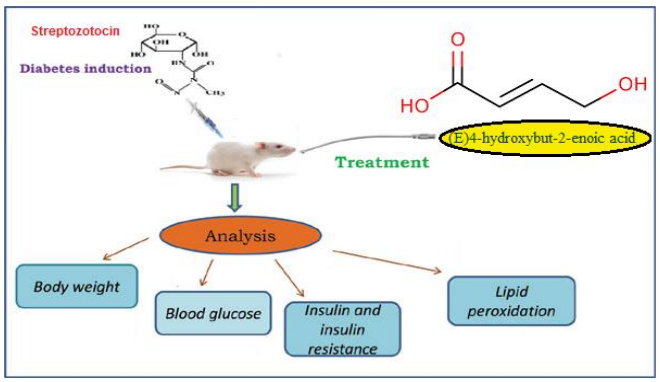
ABSTRACT

(E)4-hydroxybut-2-enoic acid (HBA) used to test its antidiabetic activity in Streptozotocin (STZ) induced diabetic albino rats. (HBA) is given to the STZ induced diabetic rats at the concentration of 0.01 mg/kg body weight in different groups of 6 diabetic rats each orally once a day for 15 days. Body weight showed significant increase ($p<0.05$) after 15 days of treatment with (HBA) when compared with the control. Blood glucose level on 15th day of treatment become significantly low ($p<0.05$). At the termination of the experiment (on 15th day) the urine glucose and ketone were absent in (HBA) group which was present in the diabetic control. Findings of the present study suggest that (HBA) at the dose of 0.01 mg/kg body weight brings about significant beneficial effects in various physiological parameters altered during diabetic manifestation. The treatment was continued for an additional 4 weeks. The result was the disappearance of sugar in the urine sample, the treatment was stopped for (HBA) Group, the sugar level was followed up in the urine after 2 weeks, a month, then 6 months, the results showed that glucose in the urine sample of (HBA) group completely disappeared.



KEYWORDS: Antidiabetic activity, (E)4-hydroxybut-2-enoic acid, *Streptozotocin*, albino rats.

INTRODUCTION

Diabetes mellitus is a complex and a multifarious group of disorders that disturbs the metabolism of carbohydrates, fat and protein. It results from shortage or lack of insulin secretion or reduced sensitivity of the tissue to insulin. Several drugs such as biguanides and sulfonylureas are presently available to reduce hyperglycemia in diabetes mellitus. These drugs have side effects and thus searching for a new class of compounds is essential to overcome diabetic problems.[1] Management of diabetes without any side effect is still a challenge to the medical community. There is continuous search for alternative drugs. Therefore it is prudent to look for options in herbal medicines for diabetes as well. Although, herbal medicines have long been used effectively in treating diseases in Asian communities and through out the world. The mechanism of most of the herbals used has not been defined. Many traditional plants treatments for diabetes are also used. But most of the evidence for their beneficial effects is anecdotal.[2] Traditional antidiabetic plants might provide new oral hypoglycemic compounds, which can counter the high cost and poor availability of the current medicines/ present day drugs for many rural populations in developing countries. India is well known for its herbal wealth. Medicinal plants like Syzigium cumini has been studied[3] for treatment of diabetes mellitus. However, detailed studies on the efficacy, mechanism of action and safety of plant extract are needed.

Diabetes mellitus is a major endocrine disorder affecting nearly 10% of the population all over the world.[4] Diabetes is one of the leading causes of death in humans and animals. In animals it occurs most frequently in the dog with an incidence of approximately 0.2%. In the indigenous Indian system of medicine good number of plants were mentioned for the cure of diabetes and some of them have been experimentally evaluated and active principle were isolated.[5] WHO (1980) has also recommended the evaluation of the effective of plants in conditions where there are no safe modern drugs.[6] The ethnobotanical information reports state that about 800 plants may possess antidiabetic potential (Aguilara *et al*., 1998).Recently the medicinal values of various plants extracts have been studied by many scientists in the field of diabetic research.[7]

Various parts of herbs have been used formedicinal purposes including the treatment of diabetes mellitus.Streptozotocin (STZ) is a naturally occurring nitrosourea product of *Streptomyces achromogenes.* Usually, the intraperitoneal injection of a single dose (60 mg/kg body weight) of it exerts direct toxicity on $ cells resulting in necrosis within 48-72 h and causes a permanent hyperglycemia. STZ breaks nuclear DNA strand of the islet cells.[8]

Diabetes was confirmed by the determination of fasting glucose concentration on the third day post administration of streptozotocin. There is no final cure for diabetes type 2 yet, which causes the pancreas to deteriorate and sometimes turns into diabetes type 1 . This causes patients to suffer from insulin injection and medications, which exhausts them financially and health-wise. Therefore, we searched to find a cure for this disease and reached accurate and successful results.[9] Loss of functional β-cell mass is the key mechanism leading to diabetes mellitus — as long as β-cells are able to compensate, for instance, for insulin resistance, normoglycaemia is preserved1.[9] The American Diabetes Association (ADA) defines type 1 diabetes mellitus (T1DM) as autoimmune β-cell destruction, usually leading to absolute insulin deficiency, and type 2 diabetes mellitus (T2DM) as progressive loss of β-cell insulin secretion frequently occurring on the background of insulin resistance.[10]

Diabetes mellitus (DM) is chronic, lifelong progressive metabolic disease characterized by hyperglycaemia due to absolute or relative insulinopaenia. There are several different types of DM and each are caused by a complex interplay between genetic predisposition and environmental factors. The metabolic dysregulation that contributes to hyperglycaemia includes diminished insulin secretion, impaired glucose utilization or increased glucose production, and eventually causes pathophysiological changes in multiple organs and organ systems.[11,12] Despite all the scientific advances in the field of pathophysiology, diagnosis and treatment, the prevalence of DM has shown a dramatic rise over the past 200 years. , and this number is expected to rise, mostly due to type 2 DM.[13]

MATERIALS AND EXPERIMENTATION

Animals: Adult albino rats weighing about 180-200 g were used in the present investigation. All the rats were given a period of acclimatization for 15 days beforestarting the experiment. They were fed standard chow diet and were given free access to water.

Animals described as fasting were deprived of food for at least 16h but were allowed free access to drinking water. Streptozotocin (Batch No.4564523) was purchased from Sigma Aldrech and was freshlydissolved in 0.1 M citrate

Streptozotocin (Batch No.4564523) was purchased from Sigma Aldrech and was freshly dissolved in 0.1 M citrate buffer (pH = 4.5) at the dose of 650 mg/kg body weight and injected intraperitoneally within 15 min of dissolution in a vehicle volume of 0.4 mL with 1 mL of tuberculin syringe fitted with 24 gauge needle, whereas normal control group was given citrate buffer only (0.4 mL).

Diabetes was confirmed by the determination of fasting glucose concentration on the third day post administration of streptozotocin.

(E)4-hydroxybut-2-enoic acid: (Batch No 538753),

Experiments

Rats were divided into the following groups.

Group I

Consisted of 12 rats which served as normal control and were given only distilled water daily.

Group II

Consisted of 12 STZ induced diabetic rats and served as diabetic control and were given distilled water only.

Group III

Consisted of 12 STZ induced diabetic rats and were treated orally with (HBA) at the dose of 0.01 mg/kg body weight for 15 days, once a day.

After 15 days of 0.01 mg/kg (E)4-hydroxybut-2-enoic acid treatment, body weight was measured before and after the aid balance single unit. Blood glucose level was classified on day 0,15, a month, then 6 months of the aid experiment glucometer using the strip method and blood was taken from the withers. The body and back of the rat were collected from dust. ketones were examined on videotape keto-diastix on day 0 , 15, a month, Then the treatment was stopped after 4 months and then measured after 6 months of the experiment.

Basic analyses were performed with the help of Student's "t" test). Animal housing and care were applied experimental experiments according to the rules of local animal origins.

Induction of diabetes: Streptozotocin (Batch No.S0130) was purchased from Sigma Aldrech and was freshly dissolved in 0.1 M citrate buffer (pH = 4.5) at the dose of 50 mg/kg body weight and injected intraperitoneally within 15 min of dissolution in a vehicle volume of 0.4 mL with 1 mL of tuberculin syringe fitted with 24 gauge needle, whereas normal control group was given citrate buffer only (0.4 mL).

The following parameters were assayed

Glucose level (Direct Enzymatic Colorimetric

Method.

Insulin level (Immunoassay).

Insulin resistance

MDA (Colorimetric Method using)

TG (Enzymatic Colorimetric Method ..

LDL

HDL (Enzymatic Colorimetric).

Urea level (Enzymatic Colorimetric Method).

RESULTS AND DISCUSSION

Body weight

Diabetes is characterized by weight loss and it was also seen in this study. Streptozotocin administration brought about marked reduction in body weight of rats. This reduction was found to be statistically significant ($p<0.05$) when compared with normal control group. These reduced body weights were found to be increased when compared to their respective diabetic control group and this increase was found to be statistically significant in rats treated with *HBA*,

Blood glucose

Streptozotocin causes selective destruction of $ cells of islets of pancreas and brings an increase in blood glucose levels. It is evident from the present investigation that streptozotocin administration at the dose of 50 mg/kg body weight causes significant diabetogenic response in albino rats. Blood glucose levels to 3.5 fold as compared to their respective normal control group rats, These raised levels of blood glucose in diabetic rats were declined sharply after oral feeding of HBA. Fig (1).

Lipid peroxidation, insulin and insulin resistance

significant increase in the serum insulin level and a significant decrease in insulin resistance and lipid peroxidation when compared to that of the diabetic non treated group after 6 months of oral feeding of HBA. Fig (2).

Urea

administration to diabetic rats resulted in decrease in the serum level of urea which was

significant when compared to diabetic non treated group.

HDL, TGs and LDL

Significant decrease in the serum levels of TGs and LDL with significantly increased serum level of HDL as compared to the diabetic non treated group.

MDA

Significant lower level of serum MDA when compared to the diabetic non treated group.

Urine glucose and ketone

Urine analysis on 0 day showed the presence of glucose and traces of ketone in urine. But on 15th day glucose and ketone traces were absent in HBA treated groups.

Table 1: Effect of HBA on urine glucose and ketone in streptozotocin induced diabetic rats.

	Glucose and Ketone level in urine		
	0 day	6 monthes	
Groups	Glucose	Ketone	Glucose
Normal control Diabetic control *HBA*	- +++ +++	- Trace -	- +++ -

Glucose: - = absence of glucose, +++ = 1 g/dL. Ketone: - = absence of ketone, Trace = 5 mg/dL

Table 2: Effects of HBA on glucose, insulin, insulin resistance, TGs, LDL, HDL, Urea, and MDA in the diabetic rats 'serum.

Parameters	**Groups**		
	I	**II**	**III**
Glucose (mg/dl)	97.3±1.98	290.3±16	95.1 ±4.1
Insulin (**µIU/ml**)	7.2±0.12	4.6±0.21	7.23±0.1
Insulin resistance	1.83±0.04	3.4±0.06	1.7±0.02
Urea (mg/dl)	21.6±0.8	46.4±1.2	20.9±0.4
TGs (mg/dl)	95±1.9	170.3±1.1	96.2±0.9
LDL (mg/dl)	23.1±1.2	74.43±2.1	22.8±2.3
HDL (mg/dl)	48.1±1.3	29.24±0.2	48.±0.9
MDA (nmol/ml)	5.2±0.3	10.4±0.41	5.8±0.889

Data are expressed as the mean difference between groups was considered statistically significant when P value < 0.05. I: Control group. II: Diabetic non treated groupII: Diabetic + HBA treated group.

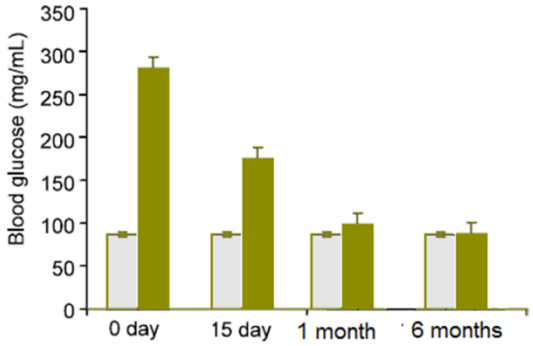


Fig. 1: Effect of (E)4-hydroxybut-2-enoic acid on urine glucose in streptozotocin induced diabetic rats.

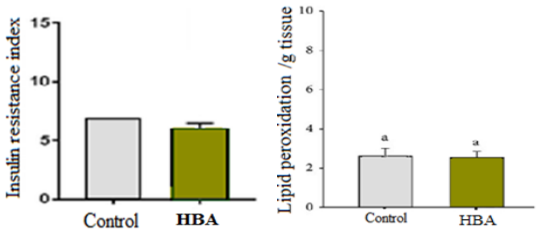


Fig. 2: Effect of (E)4-hydroxybut-2-enoic acid on lipid peroxidation and insulin resistance in streptozotocin induced diabetic rats after 6 monthes.

Oral administration of HEA significantly increased the levels of plasma insulin in STZ-induced diabetic rats when compared with diabetic control rats. HEA stimulate the secretion of insulin from β-cells of pancreas showed significant decrease in the activities of glucose-6-phosphatase.

The results of the present study indicated that HEA has a beneficial effect on normalizing glucose level in STZ-induced diabetic rats.

This suggests the efficacy of HEA in the maintenance of glucose may be used as a therapeutic agent in the management of diabetes mellitus.

CONCLUSION

The present study concluded that (E) 4-hydroxybut-2-enoic acid has anti-diabetic effects in albino rats, and therefore could be promising nutraceutical therapy for the management of diabetes and its associated complications in lipid peroxidation, insulin resistance, HDL, TGs, LDL, MDA and urine glucose and ketone

A model resembling type 2 diabetes in humans. treatment with HBA at a dose of 0.5 mg/kg/day for four months can completely reverse glycemic changes to normal healthy levels. Furthermore, pancreatic beta cell function can be fully activated, allowing treatment to be discontinued after four months.

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