ANTIDIABETIC EFFECT OF *CINNAMON* (CINNAMONUM ZEYLANICUM) USED TO CONTROL DIABETES MELLITUS IN ALLOXAN INDUCED DIABETIC MALE RABBITS

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ABSTRACT

This study was carried out to check the effect of Cinnamon (Cinnamonum zeylanicum) aqueous extract oral administration on serum glucose, cholesterol, and urea level and body weight in normal and Alloxan-induced diabetes male rabbits. Alloxan monohydrate (120mg/kg) was used to induce diabetes mellitus in twelve hours fasted male rabbits. After seven days of alloxan monohydrate induction diabetes mellitus was confirmed animals with fasting serum glucose level more than 250mg/dl and were considered as diabetes. 50% mortality rate was noted. In 1st step of experimental work, twenty one male rabbits were divided in to seven experimental groups each group contains three male rabbits, 1st group normal and 2nd group diabetic control and 3rd to 7th group containing male rabbits were treated with 0.50%, 0.75%, 01%, 1.25%, 1.50% Cinnamon aqueous extract to check the effective dose against diabetes. In 2nd step of experimental work nine male rabbits were selected and each group contains three male rabbits 1st and 2nd group contains normal and diabetic controls and 3rd group is treated with most effective dose of Cinnamon to check its effect against serum glucose level and together with serum cholesterol level, serum urea level and body weight. Whole experiment was designed for the period of two months. Blood serum was used to determine all selected biochemical parameters, on every third day. It was observed that in 1st step 1% Cinnamon treated male rabbits showed significant hypoglycemic effect which decreased 52.38% serum glucose level where as in 2nd step of experimental work 1% Cinnamon controlled 54.11% serum glucose level, 35.25% serum cholesterol level and 34.55% serum urea level and body weight was gradually decreased. It is concluded that oral administration of Cinnamon aqueous extract decreases serum glucose, cholesterol and urea level in diabetes induced male rabbits.

INTRODUCTION

Diabetes mellitus is a metabolic disorder, which increases blood glucose levels and disturb the carbohydrates, fats protein metabolism. Metabolic and abnormalities are resulting from defects in insulin secretion and insulin action or both (Fajans, et al., 1997). According to World Health Organization estimates, one in 20 of world's adult population now suffers from diabetes. At least one in ten deaths among adults between 35-64 years age is related to diabetes (Aurangzeb, et al., 2008). The largest number of diabetic people in the year 2025 will be noted in India, China and United States (Ramachandran et al., 2002). Diabetes mellitus is a potentially devastating, disease with high morbidity and mortality rates. The main identifying feature of diabetes is chronic and highest rate of the circulating glucose concentration. The long-term hyperglycaemia is very important in the development and progression of microvascular and microvascular complications (Sen, et al., 2005). Serious side effects can be produced by using synthetic hypoglycemic agents, which are costly. It is necessary to search more effective and

safer hypoglycemic agents and it is the prime need to continue search in this important area. It is clear from the above facts that an immediate prevention and treatment of diabetes must be proposed globally. Since centuries the diabetics patients have been treated with different medicinal plants or their extracts based on the folklore medicine (Akhtar and Ali (1984). In the various investigations, the oral anti-hyperglycemic agents from different medicinal plants have been used in traditional medicine and many of these plants possess highly active biological activity (Marles and Fransworth, 1995; Kesari et al., 2007). Nowadays, interest has been increased in herbal remedies due to the fewer side effects with the oral hypoglycemic agents (therapeutic agent) for the diabetes mellitus treatment (Kim et al., 2006). The well established fact is that cinnamaldehyde possesses large number of bioactive components. The very large numbers of traditional healers have reported that Cinnamon is very effective to reduce blood glucose level (Qin et al., 2003). Oral administration of cinnamaldehyde (20mg/kg bw) highly glycosylated hemoglobin decreases serum cholesterol. (HbA1C). total triglyceride levels and at the same time highly increases plasma insulin, hepatic glycogen and high density lipoproteincholesterol levels (Subash et al., 2007). Fasting serum glucose concentration in the age of 60 with type 2 diabetic must take daily Cinnamon or placebo for 40 days (1, 3 or 6g Cinnamon versus an equivalent-appearing placebo). During all three doses, the fasting serum glucose level (from a mean of 236 to 175mg/dl) significantly decreases in subjects taking Cinnamon but not observed with the placebo (Mang et al., 2006).

The main aim of this study was to check optimal extraction parameters of cinnamon behave as antidiabetic agent on alloxan-induced diabetic male rabbits.

MATERIALS AND METHODS

Animals used: Healthy and young male rabbits were purchased from Kacha Kila, Hyderabad city weighing 1-2 kg body weight. Before experimental work rabbits were kept under observation for 15 days in animal house of IBGE, University of Sindh Jamshoro. Animals were offered a balanced diet consisting of green leaves, fodder, pulses and water. All rabbits were kept in wooden cadges during whole experiment.

Plant Material Collection: Cinnamon *(Cinnamonum zeylanicum)* was purchased from the market of Jamshoro and was identified and authenticated in the Institute of Biotechnology and Genetic Engineering (IBGE) and has been stored in laboratory for future reference. Cinnamon converted in to powder by electric grinder for extraction (Akhtar, 2002).

Preparation of plant extract: Cinnamon was ground into fine powder in a Warring commercial blender. For quantitative analysis in 1st step the Cinnamon was made in different concentrations 0.5%, 0.75%, 01%, 1.25%, and 1.50% to check the effective dose against diabetes in male rabbits. In 2nd step of experimental work, 1% Cinnamon aqueous extract was mixed with 500ml of tap water and filtered two times using filter paper through suction pump than made volume up to 900ml as reported by Ismail (2005) and Akhtar (2002).

Chemicals: Alloxan monohydrate $(C_4H_2N_2O_4,H_2O)$ was purchased from Sigma Chemical Company,USA. Glucose oxidase (Human Centronic GmbH-65205,

Germany), cholesterol (Human Centronic GmbH-65205 Germany) and urea, (Biomerieux, France) kits were used for performing the respective tests.

Biochemical and Biological Parameters: Blood glucose, Cholesterol and urea level were estimated from the serum by kit methods (Lopes-Virella et al., 1977; McGowan et al., 1983). Body weight was measured after every third day.

Administration of extract: Three times in a day 300ml (Total 900ml) of plant extract was administrated to three rabbits treated with Cinnamon. Both groups of diabetic control and normal control rabbits were left on normal tap water, administrated same dose with respective group.

Preparation and induction of diabetes mellitus in male rabbits: Alloxan Monohydrate was used to induce diabetes mellitus in normoglycemic young male rabbits. Animals were allowed in fasting condition for 12 hours and than were injected 120mg/kg alloxan monohydrate through marginal ear vein with freshly prepared in 0.9% normal saline and this dose is sufficient to destroy the β cells of pancreas. Normal rabbits were injected 0.9% normal saline (NaCl). 50% mortality rate in alloxan induced male rabbits was observed. Rabbits having blood serum glucose level ≥250mg/dl were considered as diabetes rabbits After 72 hours of induction of alloxan in healthy rabbits Blood glucose level was checked by the spectrophotometeric method (Demerdesh et al., 2005, Akhtar et.al. 2007).

Experimental design: All rabbits were divided into three different groups; normal control, diabetic control, treated with aqueous extracts of Cinnamon plant. Rabbits were divided into different groups as mentioned blow:

1st step of experiment:

GROUP–I: 0.9% (NaCl) normal saline, normal diet (Normal Control)

GROUP-II: 120mg/kg (Alloxan), Diabetic control (patients)

GROUP–III: 120mg/kg (Alloxan), Diabetic treated with effective plant (0.50%)

GROUP–IV: 120mg/kg (Alloxan), Diabetic treated with effective plant (0.75%)

GROUP–V: 120mg/kg (Alloxan), Diabetic treated with effective plant (01%)

GROUP–V1: 120mg/kg (Alloxan), Diabetic treated with effective plant (1.25%)

GROUP–V11: 120mg/kg (Alloxan), Diabetic treated with effective plant (1.50%)

2nd step of experiment:

GROUP–I: 0.9% (NaCl) normal saline, normal diet (Normal Control)

GROUP-II: 120mg/kg (Alloxan), Diabetic control (patients)

GROUP–III: 120mg/kg (Alloxan), Diabetic treated with Cinnamon (1%)

Treatment of rabbits: Diabetic rabbits were treated with 1% aqueous extract of Cinnamon orally with total 900ml tap water for 21 days for qualitative analysis. Effective medicinal plant (Cinnamon) was selected for 2^{nd} step of research (quantitative analysis), different concentrations of Cinnamon were taken 0.5%, 0.75%, 1%, 1.25% and 1.50% per day for 21 days after the induction of Alloxan Monohydrate and Diabetic Mellitus was confirmed (Meral1, 2004).

Collection of blood and Analytical Procedure: The procedure for collection of blood was adopted for glucose, cholesterol and urea estimation. The blood was collected from marginal ear veino. After collection of blood, pricked site of the ear was rubbed with cotton wool soaked with 70% ethanol to protect the rabbit against infection. 1.0ml blood sample was collected in appendrof and samples were labeled and stored for future analysis at 4°C.

Statistical Analysis: Data were calculated as mean values and then final value minus initial value, finally divided by initial value. The answer was multiplied by 100. The data were presented as \pm standard error means (S.E.M).

RESULTS AND DISCUSSION

The data obtained from normal control. Cinnamon treated and diabetic control male rabbits presented in Table 1-5. The effect of various doses of Cinnamon on the blood glucose levels of diabetic male rabbits is given in Table-I, which demonstrates the levels of glucose controlled by using different concentrations of Cinnamon aqueous extracts (0.50%, 0.75%, 01%, 1.25%, and 1.50%) used compared with normal control and diabetic control male rabbits (Table-1). After seven days of alloxan administration serum glucose level was checked, \geq 250mg/dl serum glucose level containing rabbits were selected for further experimental work. The actual rabbit blood glucose levels could vary from 190mg/dl to 260mg/dl. These results are partially in accordance with the results of Nilüfer et al., (2006). Mean initial serum glucose level with S.E of normal control rabbits was noted (90.90 ± 2.21) , diabetic control (316.53±5.87) and Cinnamon treated 0.50% (305.75±2.42), 0.75% (316.50± 3.17), 01% (315.87±5.26), 1.25% (299.9 ± 2.54), 1.50% (330.00±4.61). After eighteen days serum glucose level of both normal and diabetic control (106.25±1.36) and Cinnamon treated (299.9±2.16) remains more or less same. Mean final serum glucose level with SE of Cinnamon treated rabbits decreased 0.50% (200.5± 5.3/34.42%), 0.75% (160.4±2.61/49.34%), 01% (150±2.08/52.38%), 1.25% (175.7± 2.45/41.47%) and 1.50% (200±4.84/ 39.39%). It is clear from the results that 1% Cinnamon aqueous extract controlled significant level of serum glucose compared with their respective normal and diabetic controls.

As shown in **Table-2**, alloxan monohydrate increases serum glucose level after seven days of induction. Initial mean plus SE values of normal and diabetic control male rabbits are (123.50 ± 0.46) and (314.93 ± 1.50) but any effective change was not observed till the final reading. The starting mean and standard error value of serum glucose of Cinnamon treated male rabbits was 315.99 ± 1.80 , which gradually decreased till the 15th day.

According to the data shown in Table-3, the 1% Cinnamon aqueous extract possessed significant hypolipidemic effect, which observed during fifteen days of treatment. It is observed that the mean Cholesterol level \pm SE in normal control was noted (90.90 ± 2.21) , and remains same on 15th in Diabetic controls (140.41 ± 4.72) and in cinnamon (139±1.94). treated group Serum cholesterol level remains same in normal but significantly increased in diabetic control was observed after fifteen days of interval, normal control (79.12±0.93) and diabetic control (165.25 ± 2.18) ,

The test samples were taken from Alloxan-induced diabetic rabbits till 15 days. On day 3, 6, 9, 12 and 15 blood urea level was determined. The data shows that 1% Cinnamon aqueous extract has possessed remarkable effect against serum urea. Mean normal value of serum urea in rabbits is 42-80mg/dl blood as reported by Jones (1975). Normal control male rabbits contain serum urea level (61.04±1.15mg/dl) and diabetic control contains serum urea level (122.28±2.63 mg/dl) and diabetic treated rabbits contain (120.47±2.76mg/dl) respectively. Diabetic rabbit' having initial serum urea level high as compared to normal values because of alloxan induction urea level also increased. Cinnamon aqueous extract 1% controlled serum urea level 43.55% (68.00±1.90mg/dl) and results are presented in Table-4.

Table-5 shows the effect of Cinnamon aqueous extract oral administration on the body weight of alloxan induced diabetic male rabbits compared with their respective controls. Initial body weight of normal and diabetic control male rabbits is (1545.9 ± 8.11) and (1258.3 ± 8.46) , which gradually changed on 15th day, body weight of normal control was noted and (1555.0±6.11) diabetic control (1150.0 ± 5.50) . The initial value of body weight of Cinnamon treated male rabbits was (1230.6±5.07), which gradually decreased on the final day of test (1119.9 ± 10.20) . Alloxan, which induces diabetes mellitus resultant destroy the insulin-producing pancreatic B-cells without affecting other cells (Malaisse et al., 1982). The high increase in the level of serum blood glucose. cholesterol and urea was observed after seven days of induction of alloxan in young male rabbits compared to their respective controls. Administration of 1% Cinnamon aqueous extract significantly decreased the blood Glucose, Cholesterol and urea level.

The data from the experimental work on diabetes control in rabbits shows that Cinnamon has significant hypoglycemic effect. It is reported that cinnamon increases the insulin sensitivity and glucose uptake in adipocytes (Jarvull-Taylor et al., 2001). Cinnamon contains hydroxylchalcone compounds and their function is to block tyrosine phosphatase, which act on the insulin receptor and these compounds have the potential to increase insulin signaling (Wang et al. 2009). It is demonstrated that Cinnamon polyphenols has insulin-like activity in cells, animals and people with type II diabetes. Initially, a water-soluble Cinnamon Extract (CE) act like insulin and increases the activity of autophosphorylation the insulin of receptor of β cells and decreases the activity of tyrosine phosphatase in vitro (Imparl, et al., 1998). Cinnamon extract significantly reduces blood glucose level in mice after 2 weeks of treatment (Kim et al., 2006). The beneficial effect of Cinnamon to control glucose is due to the presence of doubly-linked polyphenol type -A compounds. Our findings indicate that the use of 1% Cinnamon aqueous extract orally for two to three weeks leads to significant improvements against blood sugar level may be insulin activated the beta cells in pancreas or behaved insulin like characteristics. It is reported that the 90 days supplementation with 1.0g of daily Cinnamon lowers HbA1C by 0.83% in patients with poorly controlled diabetes (Paul Crawford, 1909). Cinnamon is mostly used to increase the flavor and taste in food preparation. The Cinnamon and perhaps other spices may have additional roles in glucose metabolism and blood pressure regulation (Harry, et al., 2006). The cholesterol mean is given in the range of 10-80mg/100ml, whereas these experiments gave a mean of 76mg/ 100ml, range 50-110mg/100mm (Jones, 1975). The optimum phosphorylation of the insulin receptor is connected with the increased of insulin sensitivity that is associated with improvement of glucose and lipid concentration (Radosevich, et al., 1988). It is observed that the diet of rabbits mixed with fenugreek decreases total serum lipid level. The curry leaf and mustard seeds in rat's diet lowered total

serum cholesterol, LDL cholesterol and VLDL cholesterol but increases HDL cholesterol level (Khan, et al., 1996). The serum glucose, triglyceride, total cholesterol and LDL cholesterol levels in people with type 2 diabetes decreased with Cinnamon. Those who have type 2 diabetes or elevated glucose, triglyceride, LDL cholesterol or total cholesterol levels may benefit from the regular inclusion of Cinnamon in their daily diet because Cinnamon would not contribute to caloric intake (Alam, et al., 2003).

Mean normal value of serum urea in rabbits is 42-80ml/100ml as reported by Jones (1975). In STZ induce diabetic male rabbits after fifteen days, the rise in blood urea and sugar are accompanied with the increase in blood urea, serum creatinine, cholesterol and glycogen in liver and muscle with loss of body weight. Bitter gourd seed at a dose 3g proved to be hypoglycaemic on par with glibenclamide. The probable mechanism is stimulation of insulin release by pancreas. But, bitter gourd seed does not help in lowering blood urea and creatinine. However, it shows the loss of weight in bitter gourd seed treatment (Kedar et al., 1982).

Whereas, 1% Cinnamon treated diabetic rabbits body weight decreased gradually during the fifteen days treatment although at the end of the experiment their body weights was significantly less than those of normal rabbits. In contrast, the control diabetic rats showed significant weight loss when compared to both the normal and control rabbits may be due to intake of Cinnamon, which increases body heat and speeds up metabolism with the results of gradual weight loss.

In addition to this, Cinnamon can reduce the level of cholesterol of bad LDL cholesterol. With the passage of time period cause several other complications, including coronary heart diseases and heart attacks, which are common health problem in obese people with diabetes and Cinnamon can help in controlling this condition too. It has been observed that Cinnamon can reduce the level of blood sugar by increasing the insulin level, which controls diabetes and body weight.

CONCLUSION

It is concluded that oral administration of cinnamon aqueous extract decreases serum glucose, cholesterol and urea level in diabetic induced male rabbits. It was observed in 1^{st} step that using different doses of Cinnamon treated male rabbits showed significant hypoglycemic effect, which decreased 52.38% serum glucose level where as in 2^{nd} step of experimental work 1% Cinnamon controlled 54.11% serum glucose, 35.25% serum cholesterol and 34.55% serum urea level and body weight was gradually decreased.

Test	Mean blood glucose concentration ±SE (mg/dl)							
Sample	1 st day	3 rd day	6 th day	9 th day	12 th day	15 th day	18 th day	
Normal control	90.90± 2.21	109.9±4.02	115.05±2.55	105.60±1.69	106.25±1.27	106.25±1.36	112.6± 4.37 (34.42%)	
Diabetic control	316.53±5.87	317.23±6.53	330.00±2.16	325.25±3.83	310.22±3.29	306.6±2.97	299.9±2.1 (49.34%)	
0.50%	305.75±2.42	282.72±2.49	260.08±4.75	250.30±3.85	246.3±4.09	210.±2.37	200.5±5.3 (34.5 %)	
0.75%	316.50±3.17	281.74±3.51	250.80±5.12	230.30±5.14	210.40±2.29	190.5±2.66	160.4± 261 (49.36%)	
01%	315.87±5.26	254.62±1.54	199.00±4.58	187.92±0.66	162.53±1.14	155.99±1.24	150.± 2.08 (52.38%)	
1.25%	299.9±2.54	281.9±6.62	250.8± 5.13	235.8±5.14	220.7±2.86	200.±2.32	175.7±2.45 (41.47%)	
1.50%	330.00±4.61	293.62±1.04	275.70±2.65	250.80±5.27	245.00±2.39	230.±3.71	200.± 484 (39.39%)	

Table-1: Effect of different concentrations of Cinnamon aqueous extract on Serum

 Glucose level in alloxan-induced diabetic male rabbits.

Table-2: Effect of 2 % aqueous extract of, cinnamon on serum glucose level of alloxan-induced diabetic and normal male rabbits

Test Sample	Mean blood glucose concentration ±SE (mg/dl)						
	1 st day	3 rd	6 th day	9 th day	12 th	15 th day.	
		day			day		
Normal	123.50±0.46	119.6 ± 0.30	122.37±0.81	115.70±0.60	125.27±0.43	130.06±0.93	
control							
Diabetic control	314.93 ± 1.50	332.3 ± 0.65 (-5.51%)	331.25±1.38 (-5.18%)	295.85±0.71 (6.05%)	299.90±1.43 (4.77%)	300.33±2.42 (4.63%)	
Cinnamon treated	315.99 ± 1.80	225.2±2.40 (28%)	210.50±0.82 (33.94%)	199.25±4.54 (36%)	185.43±2.23 (41%)	145.±2.52 (54.11%)	

Table-3: Effect of 3% aqueous extract of, cinnamon on serum cholesterol level of alloxan-induced diabetic and normal male rabbits

Test	Mean blood cholesterol concentration \pm SE (mg/dl)							
Sample	1 st day	3 rd day	6 th day	9 th day	12 th day	15 th day.		
Normal	72.18±	71.96 ± 0.77	76.10±0.91	90.15±1.68	87.18±2.13	79.12±0.93		
control	2.31							
Diabetic	140.41±	147.28±0.18	152.26±0.57	145.55±1.37	160.31±3.24	165.25±2.18		
control	4.72							
Cinnamon	139±	125.97±0.51	136.35±4.19	120.25±2.86	98.22±1.00	89.99±2.41		
treated	1.94	(9.42%)	(1.9%)	(13.4%)	(29.33%)	(35.25%)		

induced diabetic and normal male rabbits								
Test	est Mean blood urea concentration ±SE (mg/dl)							
Sample	1 st day	3 rd day	6 th day	9 th day	12 th day	15 th day.		
Normal	61.04 ± 1.15	60.66± 1.25	63.18±1.28	60.12 ± 2.10	68.16±1.24	65.12±1.32		
control								
Diabetic	22.28 ± 2.63	119.5 ± 2.26	113.9 ± 0.91	111.5 ± 2.11	129.97±7.35	120.0 ± 3.61		
control								
Cinnamon	120.47±	115 ± 2.17	100 ± 2.09	96.95± .54	90.20 ± 2.62	68.00± 1.90		
treated	2.76	4.54%)	(16.99%)	(19.52%)	5.29%)	(43.55%)		

Table-4: Effect of 1% aqueous extract of, cinnamon on serum urea level of alloxan induced diabetic and normal male rabbits

Table-5: Effect of 1 % aqueous extract of, cinnamon on body weight of alloxan induced diabetic and normal male rabbits

Test	Mean body weight of Diabetic and normal male rabbits ±SE (grams)						
Sample	1 st day	3 rd day	6 th day	9 th day	12 th day	15 th day.	
Normal control	1545.9± 8.11	1737.5± 2.50	1706.63±15.39	1549.87±6.57	1569.97±8.64	1555.0±6.11	
Diabetic control	1258.3 ± 8.46	1362.2± 2.50	1299.97 ± 10.17	1200.00± 5.14	1180.00 ± 7.33	1150.0± 5.50	
Cinnamon treated	1230.6±5.07	1207.5± 2.50	1201.6±4.41	1149.9±8.67	1129.9± 8.61	1119.9±10.20	

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