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Antidiabetic Activity of Aqueous Extract of *Cinnamomum cassia* in Alloxan- Induced Diabetic Rats

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ABSTRACT

To study the antidiabetic activity of aqueous extract of *Cinnamomum cassia* in alloxan induced diabetic albino rats. The aqueous extract of cinnamon 60mg/kg was studied alone and in combination with conventional oral antidiabetic drugs like Glibenclamide 5mg/kg and Metformin 0.5gm/kg in alloxan-induced diabetic *albino rats*. Treatment with drugs were started on the 6th day (i.e.day 0) of alloxan treatment. All the drugs were given orally as a single dose in the morning for 15days. The fasting blood glucose levels were determined on day 0, 10, and 15 by using Glucometer. Blood sample for glucose estimation was collected from rat tail vein. Data were statistically analyzed by ANOVA followed by Bonferroni Multiple Comparisons Test. Administration of aqueous extract of Cinnamon alone, Glibenclamide alone and Metformin alone led to a decrease in blood glucose levels which was statistically significant ($P<0.01$) when compared to control group. But a combination of Glibenclamide and Cinnamon led to a decrease in blood glucose levels which was statistically significant ($P<0.05$) when compared to Glibenclamide alone . A combination of Metformin and *Cinnamomum cassia* does not significantly ($P>0.05$) decrease the blood glucose level when compared to Metformin alone. This study shows that Cinnamon extract produced a significant hypoglycemic effect and the combination of Cinnamon with glibenclamide when given for 15days caused more significant reduction in blood glucose level than either drug is given alone. Increased activity in combination may be due to potentiation or synergism.

Keywords: Diabetes mellitus; albino rats; alloxan monohydrate; *Cinnamomum cassia*; Glibenclamide; Metformin; Hypoglycemia.

INTRODUCTION

Diabetes was described more than 2000 years ago. It is a syndrome characterized by disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin secretion or due to a combination of insulin resistance and inadequate insulin secretion to compensate. India has now been declared by WHO as the 'Diabetes capital of the world'[1]. Experts opine that, in the not so distant future, India would host the largest population of diabetes in the world. The currently used hypoglycemic drugs in the treatment of diabetes are not completely effective and are associated with adverse effects both in the short and long run[2]. Therefore there is a need to continue the search for more effective and safer drugs for the treatment of diabetes. An important area of this search is to screen plant extracts for potential hypoglycemic properties. Traditional herbs and spices also can be used to control blood glucose concentrations. Allspice, Cinnamon, bay leaf, cloves, nutmeg, witch hazel, oregano, and black and green tea have been shown to have an insulin-like biological activity; of these substances, Cinnamon has been shown to have the highest bioactivity[3].

At least 8 different species of Cinnamon have been identified, but there are 2 main types. The species most known and most widely cultivated throughout the world are,

i) *Cinnamomum zeylonicum*(Ceylon Cinnamon) or True *Cinnamon* (*Cinnamomum verum*)
ii) *Cinnamomum Cassia* (*Chinese Cinnamon*)

Although both type of Cinnamon have an effect on blood sugar regulation, Ceylon Cinnamon is the safest one to use medicinally, but *C. cassia* has stronger effect on blood sugar regulation. Cinnamon extract also has cholesterol-lowering action, blood pressure lowering effect, anti-inflammatory and anti-oxidant effects, antimicrobial activity, *H. pylori* inhibition, antifungal activity, anticancer action, antinocieptive activity, Pro-healing activity.

The present study is undertaken to evaluate the anti-diabetic activity of aqueous extract of cinnamon in alloxan induced albino rats.

MATERIAL AND METHODS

Plant material and drug preparation

Cinnamomum cassia was obtained from the local market, Raichur and authenticated. The cinnamon bark was washed, dried and reduced to powder with electric grinder. The powder(10g) was extracted in 100ml double distilled water with revolving evaporator in vacuum state using vacuum pump till the volume of water reduced to 50ml.The supernatant was then filtered through Whatman paper no-1 to obtain the Cinnamon water extract. The final concentration was 0.2gm/ml[4].

Experimental procedure

The antidiabetic effect of aqueous extract of cinnamon was assessed using adult albino rats weighing 250 – 300 gms of either sex. The animals were maintained with standard pellet diet and water ad libitum. They were further divided into 6 groups consisting of 6 animals each. Group I: diabetic rats received saline/ gum acacia(2%) suspension, which served as the control. Group II: diabetic rats received Cinnamon extract, 60mg/kg. Group III: diabetic rats received Glibenclamide 5mg/kg. Group IV: diabetic rats received Cinnamon extract, 60mg/kg + Glibenclamide, 5mg/kg. GroupV: diabetic rats received Metformin 0.5gm/kg and Group VI: diabetic rats received Cinnamon extract, 60mg/kg+ Metformin, 0.5gm/kg. Treatments with drugs were started on the 6th day (i.e.day 0) of alloxan treatment. The aqueous extract of Cinnamon, glibenclamide, metformin and normal saline/gum acacia were administered orally as a single dose in the morning for 15days to all the diabetic rats by using polythene tubing sleeved on an 18-20 gauge blunted hypodermic needle. All the experiments were conducted as per the norms approved by Institutional Animal Ethics Committee.

Induction of *Diabetes mellitus*

Alloxan monohydrate was used to induce diabetes mellitus. After an overnight fast, the rats were injected single dose (125mg/kg) of freshly prepared 5% solution of alloxan monohydrate in 0.9% sodium chloride (normal saline) intraperitoneally. The induction of diabetes was confirmed after the 5th day of alloxan treatment by estimation of elevated fasting blood glucose level. Only those rats with blood glucose level >150mg/dl was included in the study.

Method of blood collection

Blood glucose readings were recorded in all rats after an overnight fasting. Blood samples were obtained from rat tail vein**5**, after applying xylene to make vein prominent. Blood glucose was estimated by glucose oxidase-peroxidase reactive strips and a glucometer.

Statistical analysis

The results were expressed as “mean ±SEM” (n=6). Analysis of variance (ANOVA) followed by Bonferroni Multiple Comparisons Test for controls with standard and test group comparisons were used for statistical evaluation. P value of less than ($P<0.05$) was considered statistically significant and $P>0.05$ not significant.

RESULTS

Effect of *Cinnamomum cassia* extract on blood glucose levels in alloxan-induced diabetic rats

Results of present study clearly indicate that 15 days treatment with aqueous extract of Cinnamon (60mg/kg) orally exhibited a highly significant ($P<0.001$) decrease in mean fasting blood glucose level, 203.5 ± 13.47 on 10th and 191.5 ± 12.72 on15th day as compared to mean fasting blood glucose level, 279.33 ± 10.13 on 10th

day and 287 ± 8.43 on 15th day in control animals (Table1; Fig.1).

Effect of Glibenclamide on blood glucose levels in alloxan-induced diabetic rats

Glibenclamide treated group had significant (P<0.01) decrease in mean fasting blood glucose level, 171.33 ± 13.95 on 10th and 161.33 ± 14.41 on 15th day as compared to mean fasting blood glucose level, 279.33 ± 10.13 on 10thday and 287 ± 8.43 on 15th day in control animals (Table 1; Fig. 1).

Effect of Cinnamon in combination with Glibenclamide on blood glucose levels in alloxan-induced diabetic rats

Combination of aqueous extract of Cinnamon (60mg/kg) with Glibenclamide (5mg/kg) orally for 15 days significantly (P<0.05) enhanced the glucose lowering effect of glibenclamide with mean of 119.83 ± 11.92 on 10th day and 110.0 ± 10.83 on 15th day when compared to glibenclamide (5mg/kg) given alone with mean of 171.33 ± 13.95 on 10th and 161.33 ± 14.41 on 15th day. This

Table 1: Effect of cinnamon extract alone and in combination with Glibenclamide on blood glucose level in alloxan (125mg/kg I.P)-induced diabetic rats

Group	Groups Treatment	Blood glucose concentration(mg/dl)		
		0th day	**10th day**	**15th day**
I	Control (vehicle 2% *Gum acacia*)	273 ± 11.01	279.33 ± 10.13	287 ± 8.43
II	Cinnamon (60mg/kg)	263.83 ± 13.15 NS	203.5 ± 13.47 **	191.5 ± 12.72 **
III	Glibenclamide (5mg/kg)	248.33 ± 16.70	171.33 ± 13.95**	161.33 ± 14.41**
IV	*C. cassia* (60mg/kg)+ Glibenclamide (5mg/kg)	249.50 ± 15.10 NS	119.83 ± 11.92 *	110.0 ± 10.83 *
	F – ratio	0.704	28.78	39.70
	P – value	0.56	<0.0001	<0.0001

All values are given as mean ± SEM (n=6); **p<0.001 when Group II was compared with Group I ,*p<0.05 when Group IV was compared with Group III, (ANOVA followed by Bonferroni Multiple Comparisons Test).

Table 2: Effect of cinnamon extract alone and in combination with Metformin on blood glucose level in alloxan (125mg/kg I.P)-induced diabetic rats

Group	Groups Treatment	Blood glucose concentration(mg/dl)		
		0th day	**10th day**	**15th day**
I	Control (vehicle 2% gum acacia)	273 ± 11.012	279.3 ± 10.13	287 ± 8.43
II	*C. cassia* (60mg/kg)	263.83 ± 13.15 NS	203.5 ± 13.47 **	191.5 ± 12.72 **
V	Metformin (0.5gm/kg)	259.33 ± 15.50	179.5 ± 13.55	167.17 ± 13.51
VI	*C. cassia* (60mg/kg) + Metformin (0.5gm/kg)	261.67 ± 15.08 NS	148.33 ± 10.86 NS	136.83 ± 9.71 NS
	F – ratio	0.188	21.35	33.05
	P – value	0.903	<0.0001	<0.0001

All values are given as mean ± SEM (n=6); **p<0.001 when Group II was compared with Group I ,*p<0.05 when Group IV was compared with Group III, (ANOVA followed by Bonferroni Multiple Comparisons Test).

indicates that cinnamon enhances the therapeutic efficacy of glibenclamide when given in combination (Table 1; Fig.1).

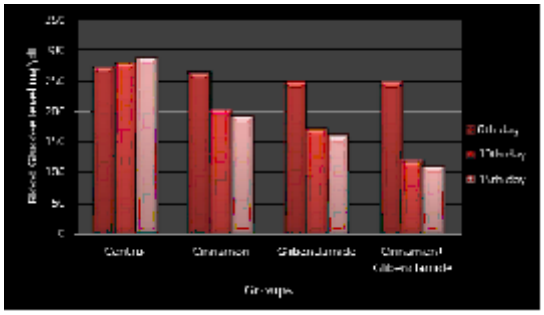

Fig. 1 : Effect of cinnamon alone and in combination with Glibenclamide

Effect of Metformin on blood glucose levels in alloxan-induced diabetic rats

Metformin treated group had significant (P<0.01) decrease in mean fasting blood glucose level, 179.50 ± 13.55 on 10th and 167.17 ± 13.51 on 15th day as compared to mean fasting blood glucose level, 279.33 ± 10.13 on 10th day and 287 ± 8.43 on 15th day in control animals (Table 2; Fig. 2)

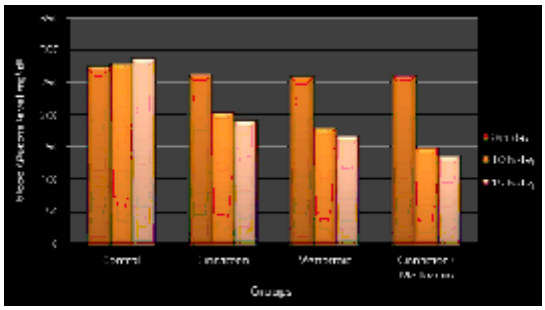

Fig. 2 : Effect of cinnamon alone and in combination with Metformin

Effect of Cinnamon in combination with Metformin on blood glucose levels in alloxan-induced diabetic rats

Combination of aqueous extract of Cinnamon (60mg/kg) with metformin(0.5gm/kg) orally for 15 days exhibited no significant (P>0.05) decrease in fasting blood glucose level with mean of 148.33 ± 10.86 on 10th and 136.83 ± 9.71 on 15thday when compared to Metformin alone (0.5gm/kg) with mean of 179.5 ± 13.55 on 10th day and 167.17 ± 13.51 on 15th day. This indicates that Cinnamon does not enhance the therapeutic efficacy of metformin when given in combination (Table 2; Fig. 2).

DISCUSSION

The results of present study show that the aqueous extract of cinnamon produced a significant hypoglycemic effect and the combination of Cinnamon with glibenclamide when given for 15days in alloxan induced diabetic albino rats caused more significant reduction in blood glucose level than either drug is given alone.

Phytochemical analysis revealed the presence of alkaloids, proteins, tannins, cardiac glycosides, flavonoids, saponins and steroids as probable inhibitory compounds[6]. The active ingredient present in the bark is flavonoids (antioxidant) or the methylhydroxy chalcone polymer which increased the glucose metabolism and also have the property of stimulating cell sensitivity to insulin. Traditionally cinnamon was used as antiseptic and astringent, to treat nausea and flatulence, diarrhoea. In diabetes cinnamon decreases the blood glucose level by Enhancing the insulin activity this effect is due to factor" Methylhydroxy chalcone polymers"(MHCP), prevents the development of insulin resistance by increases the expression of peroxisome proliferator-activated receptors γ and α (PPARγ/α)7,8, improves glucose metabolism and glucose uptake by water soluble polyphenol polymers9, by delaying the gastric emptying rate reduces post-prandinal blood glucose level 10, increases pancreatic secretion of insulin from existing beta cells. Water soluble polyphenol polymers from Cinnamon are reported to increase insulin-dependent glucose metabolism.

Our findings also agree with the recent studies of Khan *et al.,* 11 who concluded that intake of 3 gram or 6 gram of Cinnamon daily for a period of 40 days led to a major reduction in fasting serum glucose (18–29%), reduction in triglyceride (23–30%), reduction in LDL (7–27%), and total cholesterol (12–26%) concentrations in people with type 2 diabetes.

This trend was justified as Cinnamon was potentiating the function of insulin in carbohydrate metabolism. Khan *et al.* 12 have reported that an unidentified factor present in Cinnamon that potentiates the action of insulin in carbohydrate metabolism. They termed this factor as insulin potentiating factor. Anderson *et al* 13 characterized this unidentified factor present in Cinnamon as methylehydroxy chalcone polymers (MHCP).

Cinnamon with Glibenclamide combination therapy showed significant decrease in fasting blood glucose level than those observed with glibenclamide alone, indicating that the combination therapy results in an additive glucose lowering effect. Thus it seems likely that, apart from its pancreatic actions like, - Insulin potentiating action (khan et al and Jarvill-Taylor et al)12,9

Increase in secretion of insulin from existing beta cells of pancreas and increasing the expression of peroxisome proliferator-activated receptors γ and α (PPARγ/α).Cinnamon also possess extrapancreatic actions like, it increases insulin-dependent glucose metabolism in vitro and in experimental animal[13] and delays the gastric emptying rate that reduces post-prandinal blood glucose level 10 which could have contributed to its hypoglycemic action with glibenclamide.

From our study we found that Cinnamon with glibenclamide can produce better glycemic control; therefore the combination of these drugs could be synergistic leading to a potentiation of action in the decrease of blood glucose level in diabetic rats, so that dose and side effect of glibenclamide can be reduced when given in combination and so it is worthwhile to try Cinnamon with glibenclamide in the treatment of Type-II diabetes.

Thus *Cinnamomum cassia* shows a promise in the development of a new antidiabetic drug. So, Cinnamon can be used by type-2 diabetes patients on regular basis. It can be added to foods by sprinkling over it or food is prepared with Cinnamon added as spice. It can be chewed or Cinnamon tea without sugar can be prepared. Recent studies have determined that consuming as little as one-half teaspoon of Cinnamon each day may reduce blood sugar, cholesterol and triglyceride levels by as much as 20% in type 2 diabetes patients. However further extensive studies need to be done to confirm this activity in animal models as well as human trials.

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