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Physiological effects of *Cinnamomum cassia* bark extract on β-cells of Islets of Langerhans in alloxan induced diabetic rats

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Abstract : *Cinnamomum cassia* (*C. cassia*) is a culinary spicy herb. Use of *C. cassia* for blood glucose regulation has been known since ancient days. The study was conducted to investigate effects of *Cinnamomum* cassia bark extract (CCBE) & Sitagliptin on β-cell of islets of Langerhas as evaluated by serum insulin and blood glucose. 30 Albino rats of either sex were studied. Blood samples were collected, stored and processed in postgraduate laboratory. Data was analyzed on SPSS version 21.0. (IBM, corporation, USA). P-value of significance was defined at ≤0.05. The *C. cassia* bark extract showed blood glucose lowering and insulin releasing effects comparable to sitagliptin. The effect was observed at both low and high doses of C.cassia. It is concluded that the *C. cassia* bark extract regulates blood glucose homeostasis and enhances insulin secretion from β-cells of islets of Langerhans.

Keywords: CinnamomumCassia Blood Glucose Insulin Alloxan Diabetic Rats.

1. INTRODUCTION

Cassia is a member of plant family known as *Cinnamon*. It is also known as "*Java cinnamon*", *Saigon cinnamon*", "*Padang cassia*" or as the "*Chinese cinnamon*". In botanical taxonomy, the Cassia is termed as *C. cassia blume*, *C. cassia*, *C. aromaticum (nees) syn*, *C. burmannii*, C b*urmannii blume*, C. *obtusifolia*, *C. cassia (nees)* ex b*lume*, C. *tora* and *C. loureini nees*.(Thakare, 2004) (European Medicine Agency, 2011)

The cassia and cinnamon (dalchini) are not obtained from same plant, and are not similar regarding content of coumarins. Both must be taken as separate foods, from both health standpoint and nutritional values. "*Ceylon cinnamon*" is the only and one scientifically true cinnamon, obtained from the *Cinnamomum zeylanicum* plant. (Thakare, 2004). It is publicly known fact that the Cinnamon is primarily used as herbal spice, taste enhancer, and food additive, and to some extent in liquors preparation. Coumarins are a natural component of cassia which belongs to benzopyrene family. The coumarins are present in sufficient quantities in cassia which may be health hazardous. But it is well known fact that the *Ceylon cinnamon* contains little amounts of coumarins and is thus free of health hazards. Cassia and cinnamon vary too much in their biochemical composition. Ceylon cinnamon is rich in benzyl-benzoate and eugenol but lacks coumarin. Coumarins are present in Bark of cassia considerably. However, amount depends upon species, sub-species of cinnamon and more over climate conditions. (Aaresrup, *et al.*,2002) (Cheng, *et al* .,2013) (Blevins, *et al* .,2007) *Cinnamomum cassia* (*C. cassia*) is a culinary spicy herbal agent used before centuries back. Use of *C. cassia* for blood glucose regulation has been known since ancient days. Use of *C. cassia* as medicine dates back 5000 years, when it was primarily used for stomach and digestive problems, as appetizer, as anti-nauseating, anti-gas, anti-spasmodic, anti-flatulent, and anti-diarrhea. (Hoehn, *et al.*,2012) (Meletis, 2002) It is reported that the *C. cassia* significantly helps type 2 diabetics to manage their glycaemic status. Type 2 diabetics having problems in controlling blood glucose even with insulin therapy are normalized with concomitant use of cinnamon. (Kirkham, *et al.,* 2009) (Khan, *et al.*,2003) (Davis, *et al* .,2011) (Baker, *et al.*,2008) Active compound of *C. cassia* capable of exerting insulin like activity is debatable. The original active compound regulating blood glucose was recognized as "*methylhydroxy chalcone polymer (MHCP)*". The MHCP is suggested of exerting glucose lowering effect through *molecular mimicry*. It is demonstrated in *in-vitro* experiments that the MHCP activates a number of cell receptors including *insulin* receptors. (Jarvill-Taylor, *et al* .,2001) Anderson investigated MHCPs effectiveness as insulin mimetic in 3T3-L1 adipocytes of rats (Anderson, 2008) and reported positive results. Recent reports claim that the blood glucose regulating effects are exerted by polyphenols, in particular "*Polyphenol A*". (Jia, *et al* .,2009) (Curtis, *et al* .,2012) (Anderson, 2008) *C. cassia* is reported in a few clinical trials and animal studies of regulating blood glucose. Sitagliptin is an FDA approved drug used to treat diabetes mellitus. The

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present study was conducted to evaluate physiological effect of *C.cassia bark extract* (CCBE) on β-cell physiology in comparison to Sitagliptin as evaluated by serum insulin and blood glucose.

2. MATERIALS AND METHODS

An experimental study was conducted at the animal house of Isra University, Hyderabad, Sindh from January - December 2014. 30 male albino rats of weight 200-250 grams were selected. Sick non-feeding rats were excluded. Rats were divided into 3 groups;

Animal Grouping: Group A1 (n=5) controls, Group A2 (n=5) Diabetic controls, Group B1 (n=5) diabetics rats received low dose (3 grams) of C.cassia bark extract (CCBE), Group B2 (n=5) diabetics rats received high dose (6 grams) of CCBE, Group C1 diabetics rats received low dose (50 mg) of sitagliptin and Group C2 diabetics rats received high dose (100 mg) of sitagliptin orally per day.

Induction of Diabetes mellitus: DM was induced by single intraperitoneal injection of Alloxan (Sigma Company) at dose of 120mg/kg dissolved in 0.5ml of acetate buffer. DM was defined as blood sugar >200mg/dl on three successive days. On 30th post experiment period, 2-3ml of blood was drawn from the tail of rats, collected in vacutainers and centrifuged at 4000 rpm for 5 minutes to obtain serum. Body weight was measured simultaneously.

Ethanol Extract of Cinnamomum cassia: Stem bark of *C. cassia* was purchased from the local market. The taxonomy of Plant material was identified and authenticated by the Department of Botany, University of Sindh, Pakistan. Barks of C.cassia stem were washed thoroughly in running tap water. Materials were placed and spread properly on cotton cloth and were fully covered from all sides by net cloth to minimize the entry of dust and other foreign particles. The room temperature was maintained between 35-40^{o}C during day time and 25-30^{o}C during night time. The humidity was minimized by keeping exhaust fan open in the morning and switch off at night. This procedure was performed continuously for 6 weeks, till the plant materials were completely dried. The filtered solution was transferred in the round flask of the rotary evaporator for separating the alcohol form plant materials. The solution was continuously heated below 50^{o}C and also under negative pressure of 2 bar to minimize the boiling point. This separated the ethanol from the plant extract.

Blood glucose and serum insulin: The blood glucose test was performed on HITACHI ANALYZER 902 (Roche, USA) and serum insulin by ELISA method. The study was approved by the ethics committee of the institute, the Isra University. Data collected was analyzed on SPSS version 21.0. (IBM, incorporation,

USA). The normality of data was checked with Shapiro-Wilk test. Continuous variables which followed normal Gaussian curve were analyzed by analysis of variance. Variables which yielded significant F-ratio and p-value were analyzed by Fischer`s LSD testing.

3. RESULTS

The present study was an experimental study conducted at animal house of Isra University. The primary goal of study was to evaluate effects of Cinnamomum cassia bark extract (CCBE) on β-cell of islets of Langerhans as evaluated by serum insulin and blood glucose comparable to sitagliptin. The study observed significant effects of CCBE on blood glucose and serum insulin comparable to sitagliptin. Cumulative results for blood glucose and insulin are shown in **Table I to 4).** Blood glucose lowering activity of CCBE was observed comparable to sitagliptin. Insulin levels were found elevated in CCBE animals compared to controls.

Table. 1. Blood glucose (mg/dl) in animal groups (n=30)

	Mean	SD	p-value
Group A1. Controls	122.0	9.33	<0.001
Group A2. Diabetic controls	420.1	66.92	
Group B1. Sitagliptin (low dose -50 mg)	353.2	64.89	
Group C1. CCBE (low dose - 3 g/day)	359.0	64.48	

CCBE- *C.cassia bark extract*

Table. 2. Blood glucose (mg/dl) in animal groups (n=30)

	Mean	SD	p-value
Group A1. Controls	122.0	9.33	<0.02
Group A2. Diabetic controls	420.1	66.92	
Group B2. Sitagliptin (High dose- 100 mg)	270.4	61.92	
Group C2. CCBE (High dose- 6 g/day)	251.4	70.24	

Table. 3. Serum Insulin (µU/ml) in animal groups (n=30)

	Mean	SD	p-value
Group A1. Controls	23.0	2.73	<0.002
Group A2. Diabetic controls	3.40	1.14	
Group B1. Sitagliptin (low dose -50 mg)	7.0	1.58	
Group C1. CCBE (low dose - 3 g/day)	6.40	1.34	

CCBE- *C.cassia bark extract*

Table. 4. Serum Insulin (µU/ml) in animal groups (n=30)

	Mean	SD
Group A1. Controls	23.0	2.73
Group A2. Diabetic controls	3.40	1.14
Group B2. Sitagliptin (High dose- 100 mg)	9.8	4.20
Group C2. CCBE (High dose- 6 g/day)	10.4	4.61

CCBE- *C.cassia bark extract*

4. DISCUSSION

Cinnamomum cassia is a culinary spicy herbal agent used since centuries back. Cinnamon use for lowering plasma glucose has been known since ancient days. Use of Cinnamon as medicine dates back 5000 years approximately, when it was primarily used for stomach and digestive problems, as appetizer, as anti-nauseating, anti-gas, anti-spasmodic, anti-flatulent, and for diarrhea.(Hoehn, *et al* .,2012) (Meletis, 2002)

It is reported that the Cinnamon significantly helps type 2 diabetics to manage their glycaemic status. Type 2 diabetics having problems in controlling glucose levels even with insulin therapy are normalized with concomitant use of cinnamon. (Kirkham, *et al* .,2009) (Khan, *et al* .,2003) (Davis, 2011)

Active compound of Cinnamon capable of exerting insulin like activity is debatable. The original active compound regulating blood glucose level was recognized as "*methylhydroxy chalcone polymer (MHCP)*". (Jarvil-Taylor, *et al* .,2001) Anderson investigated MHCPs ability to function as insulin mimetic in 3T3-L1 adipocytes. Recent reports had claimed of glucose regulatory effects exerted by polyphenols, in particular "*Polyphenol A*". (Jia, *et al* .,2009) (Curtis, *et al* .,2012) (Anderson, 2008) A search of Pubmed, Medlip, Google scholars and a number of websites revealed limited number of literature on the effects of Cinnamomum cassia on blood glucose levels in diabetes mellitus in both animal and human studies. *Cinnamomum cassia* is reported in a few clinical trials and animal studies, of possessing glucose regulating effects and antioxidant effects.

Kamble, *et al* .,(2013) recently performed an experimental study in alloxan induced albino diabetic rats at Al-Ameen Medical College, Karnataka, India to investigate the effects of *C. cassia* on glucose homeostasis. Study compared effects of aqueous extract of *C. cassia* (60 mg/kg), glibenclamide (5 mg/kg) and Metformin (0.5gm/kg) in diabetic rats. All the agents under study were given orally as single morning dose. Fasting blood glucose was checked with glucometer on days 0, 10 and 15. Study reported that the aqueous extract of *C. cassia* (60 mg/kg) alone produced significant effects on glucose homeostasis compared to glibenclamide and metformin ($p<0.05$). Similar are the results of present study as CCBE exerted glucose lowering effect in rat model. Qin, *et al* .,(2010) had reported that the fructose induced "*insulin resistance*" in male Wistar albino rats was ameliorated by *C.cassia* extract ingestion. The insulin resistance was improved and insulin dependent glucose uptake was enhanced in *C.cassia* extract fed animals. It was concluded that the *C.cassia* extract overcomes insulin resistance and improves glucose uptake through insulin mediated signaling pathways. The present study witnessed similar effects on glucose homeostasis which are almost parallel to the previous study. Kannappan *et al* .,(2006) conducted a study on effects of cinnamon bark extract (CBEt) on insulin sensitivity and glucose tolerance. It was reported by researcher that the CBEt ingested rats revealed enhanced expression of hexokinase. And also the skeletal muscle and liver glycogen content was elevated. The findings are also in agreement with present study in regards of glucose homeostasis. Kim *et al* .,(2006) had reported similar effects of CBBE on glucose homeostasis in type 2 diabetic db/db mice model. The blood glucose was measured on weeks 2, 4 and 6. Significantly positive effects on glucose homeostasis were observed and it was concluded that the CCBE exerts its blood glucose lowering effects through insulin-mediated glucose regulation hence glucose homeostasis was maintained.[19] Babu, *et al* .,(2007) conducted a study with "Cinnamaldehyde" derived from true Ceylon *Cinnamomum zeylanicum.* Cinnamaldehyde was administered at different doses (5, 10 and 25 mg/kg) for 45 days to streptozocin-induced diabetic male Wistar rats. The results were highly yielding regarding glucose and blood lipids homeostasis, and yielding effects were significantly dose dependent. After 6 weeks of experimental period a significant reduction was observed in total cholesterol, triglycerides and enteric α-glycosidase activity. Overall, it was concluded that the cinnamaldehyde exerts hypoglycemic and hypolipidemic activity. Several recent studies reported that the "*Cinnamon oil*" and "*Polyphenolic oligomers*" extracts had shown promising hypoglycemic, hypolipidemic and anti-oxidant activities in streptozocin induced diabetic rat models.(Talpur, *et al* .,2013) (Babu, *et al* .,2007) The findings are in agreement with present study. CCBE proved more effective than Sitagliptin in present study. Overall, blood glucose lowering and insulin secreting activity of Cinnamomum cassia bark extract was proved in present study.

5. CONCLUSION

It is concluded that the *Cinnamomum cassia* bark extract regulates blood glucose primarily through augmentation of insulin secretion from β-cells of islets of Langerhans.

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