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## INSULIN SECRETING ACTIVITY OF CAMELLIA SINENSIS ON ALLOXAN INDUCED DIABETES MELLITUS IN MALE WISTAR ALBINO RATS.

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### ABSTRACT

**BACKGROUND:** Camellia Sinensis belongs to *Theaceae* family. It may be black tea, brown tea, green tea or oolong tea; all are derived from Camellia Sinensis. Camellia sinensis contains polyphenols, flavonoids, and catechins. Polyphenols possess antioxidant, anti-inflammatory and anti-microbial activity, and show probiotic properties. Growing interest has diverted the researchers to natural herbs for diabetes mellitus as complementary alternative therapy. **OBJECTIVE:** The present study is conducted to determine the insulin releasing effects of Camellia Sinensis in Alloxan induced diabetes mellitus in male Wistar Albino rat model. **MATERIAL AND METHODS:** The present experimental study was carried out at Department of Biochemistry LUMHS Jamshoro and animals were kept at Sindh agricultural university Tando Jam. Laboratory investigations were performed at the Diagnostic and Research Lab, LUMHS. Rats were purchased from the animal house of Agriculture University fulfilling the inclusion and exclusion criteria. Rats were housed in stainless steel cages with saw dust bedding. Animal housing and handling was in accordance to the NIH Guide (Care and Use of Laboratory Animals). A sample of n= 60 Albino Wistar rats were divided into negative control (A) and positive controls (B) and experimental group C (Diabetic rats given Alloxan 120 mg/kg body weight (bwt) i. p + C.sinensis 100 mg/kg bwt). Blood samples were collected from all 3 groups (A, B & C) through cardiac puncture after 4 weeks of experiment. Samples were taken in EDTA – containing tubes and plain tubes. Samples were centrifuged and sera collected for biochemical measurement of serum insulin. Data was analyzed on SPSS version 22.0 (IBM, Incorp, USA). Variables were analyzed using one – way ANOVA (analysis of variance) and Fischer's LSD post-Hoc testing. Level of statistical significance was at confidence interval 95% ( $p \leq 0.05$ ). **RESULTS:** Fasting Insulin (FI) in control group A  $10.49 \pm 1.06$   $\mu\text{U/L}$  compared to low levels in positive control group B noted as  $3.44 \pm 0.81$   $\mu\text{U/L}$ . Camellia sinensis treated experimental group C shows  $5.60 \pm 1.64$   $\mu\text{U/L}$  fasting insulin.  $F=176.2$  value and  $P=0.0001$  reveals Camellia sinensis therapy (30 days) increases the insulin secretion. **CONCLUSION:** In conclusion, the *Camellia sinensis* exerts significant insulin secretory potential in Alloxan induced male albino rat model. The findings are of clinical significance for treating an ever increasing diabetes health problem. However, further human studies are recommended with large sample size to validate the findings.

**KEYWORDS:** Camellia sinensis, Alloxan, Diabetic rats, Diabetes Mellitus, Insulin

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**INSULIN SECRETING ACTIVITY OF CAMELLIA SINENSIS ON ALLOXAN INDUCED**

## INTRODUCTION

Diabetic mellitus (DM) is the most common metabolic disorder of glucose. It is increasingly common and potentially devastating. It increases the financial burden of anti – diabetic drug therapy, being treatable but incurable lifelong metabolic disorders.<sup>1,2</sup> DM is primarily metabolic state of chronic hyperglycemia caused by  $\beta$ -cell dysfunctioning associated with partial or absolute insulin deficiency, insulin resistance of target cell organs and defects in insulin signaling pathways. Relative insulin deficiency is characterized by hyperinsulinemia but defective target organ response called the insulin resistance. DM is associated with secondary metabolic defects of lipids and proteins as well. High incidence and prevalence of DM has been observed in economically prosperity of modern societies that resulted in over eating and sedentary lifestyle.<sup>2,3</sup> Globally the prevalence of DM shows increasing trends. Devastating prevalence has been reported from developing countries as Pakistan. South East Asia is notoriously called capital of DM as 2/3 of diabetic populations are living there. A seriously increasing trend of DM prevalence now ranked Pakistan at third position over the Globe.<sup>3</sup> New cases of DM are being diagnosed every day showing exponential growth of this health problem. In fact, the DM will be major most health problem in the near future, particularly in the developing countries.<sup>3,4</sup> Global prevalence of DM is 463 million cases that is estimated to rise by 700 million by 2045 AD.<sup>3,4</sup> Common clinical complaints of DM patients are; polyuria, polydipsia, hyperphagia, weight loss, urination, generalized weakness, and delayed wound healing. Glycemia and insulinemia need to be controlled strictly to halt the long term diabetic complications such as diabetic retinopathy, diabetic neuropathy, and

diabetic nephropathy, hyper-lipidemia, hyper-triglyceridemia, hyper-cholesterolemia, atherogenesis, myocardial ischemia and infarctions, etc.<sup>4-7</sup> Despite increasing prevalence and incidence of DM, there are no effective drug therapies available to cure it. Available anti – diabetic drugs include biguanides, sulfonylureas, etc however, these medicine sometime result in serious side effects.<sup>6,7</sup> Hence there is a space for new safer and more efficacious herb remedies with no or minimal adverse effects to control diabetes. Currently, growing interest has diverted the researchers to natural herbs for use as complementary alternative therapy.<sup>8,9</sup> One of herb, that has been studies and researched for DM therapy is the *Camellia sinensis*, commonly used tea. *Camellia sinensis* belongs to *Theaceae* family. It may be black tea, brown tea, green tea or oolong tea; all are derived from *Camellia sinensis*. Its leaves are oval, dark green with serrated edges, and the blossoms are fragrant and white, appear singly or in clusters.<sup>8-10</sup> Green tea is processed without oxidation of young leaves contrary to black and oolong tea. Green tea does not undergo fermentation while black tea undergoes fermentation. *Camellia sinensis* contains polyphenols, flavonoids, and catechins. Major catechins of green tea include the epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCG). The EGCG is being the highest in concentration in green tea. Polyphenols exert anti – oxidant, anti – inflammatory and anti – microbial activity, and show probiotic, thermogenic properties in in – vivo and in – vitro studies.<sup>8-10</sup> Therefore, the present study was designed to analyze anti-hyperglycemic and insulin secretagogue effects of *Camellia sinensis* in Alloxan induced diabetes mellitus in male Wistar Albino rat model. The study

will provide basic knowledge of *Camellia sinensis* for diabetes therapy.

### OBJECTIVES OF STUDY

The present study is conducted to;

Determine the insulin releasing effects of *Camellia sinensis* in Alloxan induced diabetes mellitus in male Wistar Albino rat model.

### RATIONALE OF STUDY

The present study will benefit the diabetic population, community and doctors. It may pave a path to understanding of commonly used herb and contribution to the medical literature.

### MATERIAL AND METHODS

#### STUDY DESIGN: -

Experimental study

#### STUDY DURATION: -

Six months (after approval of synopsis by ERC)

#### STUDY SETTING: -

The study was carried out at Department of Biochemistry LUMHS Jamshoro and animals were kept at Sindh agricultural university Tando Jam. Laboratory investigations were performed at the Diagnostic and Research Lab, LUMHS

#### SAMPLE SIZE

n= 60 Albino Wistar rats

#### ANIMAL GROUPS

Control rats were divided into negative (A) and positive controls (B) and experimental group C.

#### Control Rat Groups

- **Group A:** Negative control – receive 0.9% N/S (placebo),<sup>11</sup> housed as rats for normal group findings,
- **Group B:** Positive control - Diabetic rats (Alloxan 120 mg/kg bwt. i.p)<sup>11</sup> left untreated, housed as rats for positive control group findings,

#### Experimental Groups – Diabetic Rats (Alloxan 120 mg/kg bwt. i.p)<sup>14</sup>

- **Group C:** Diabetic rats (Alloxan 120 mg/kg bwt. i.p) + *C. sinensis* (100 mg/kg bwt).<sup>52</sup> *Camellia sinensis* therapy was instituted for 30 days,<sup>16</sup>

#### AMPLING TECHNIQUE

In first phase, 20 rats were labelled as negative control group A (no diabetes

induction, no therapy). 40 rats were selected by simple random sampling for Alloxan given at dose 120 mg/kg bwt intraperitoneal (i.p). Successful DM induction was defined as rats achieving glucose levels of >250 mg/dl at 72 hours' interval. Random sampling used 20 diabetic rats allocated and labeled as positive control group B and left untreated. Remaining 20 diabetic rats were labelled experimental group C and treated with *Camellia sinensis* (100 mg/kg bwt/d) for 30 days.<sup>12</sup>

#### SAMPLE SELECTION

A sample of 60 Adult male albino Wistar rats was purchased according to inclusion and exclusion criteria.

#### Inclusion Criteria for negative control (Group A)

- Adult male albino Wistar rats,
- Body weight 150- 200gm body weight,

#### Inclusion Criteria for positive control (Group B) and experimental group (Group C),

- Adult male albino Wistar rats,
- Body weight 150- 200gm body weight,
- Rats achieving glucose level of >250 mg/dl at 72 hours of alloxan therapy,

#### Exclusion Criteria

- Female rats
- Old age, overweight male rats,
- Unsuccessful – induction of DM

#### DATA COLLECTION PROCEDURE

Rats in groups A, B and C were handled for experiment as per protocol. At the end of experiment, rats were anesthetized by Ketamine (10 mg/Kg) and Xylazine (0.5 mg/Kg) as cited.<sup>12</sup> Blood samples were collected from all 3 groups (A, B & C) through cardiac puncture. Samples were taken in NaF (sodium flouride) – containing tubes and plain tubes. Samples were centrifuged and sera collected. Centrifugation was performed at 4°C, 5000 rpm, for 15 min. Supernatant was collected, put in tubes and stored at very low temperature (-80°C) for biochemical measurement of research variables.

#### BIOCHEMICAL ANALYSIS

Blood sera centrifuged were estimated for the biochemical assay using ELECSYS INSULIN kits. Estimates were performed using Standard methods at the Diagnostic and Research Laboratory of Liaquat University.

#### 1. Fasting Insulin.

### ETHICAL COMMITTEE APPROVAL

#### Institute ethical clearance

Approval of institute's ERC (ethical review committee) of Liaquat University was taken for conducting the animal research study. Research proposal showing detailed protocol was presented and submitted for approval.

#### Animal ethical clearance

Research proposal was submitted to the committee of Animal house of Sindh Agriculture University; Tando Jam. Protocol was approved unanimously. Animal handling was in accordance to the NIH Guideline & Local Institutional guideline.

### DATA ANALYSIS

Data was analyzed on SPSS version 22.0 (IBM, Incorp, USA). Data saved in Microsoft Excel sheet was copied and pasted

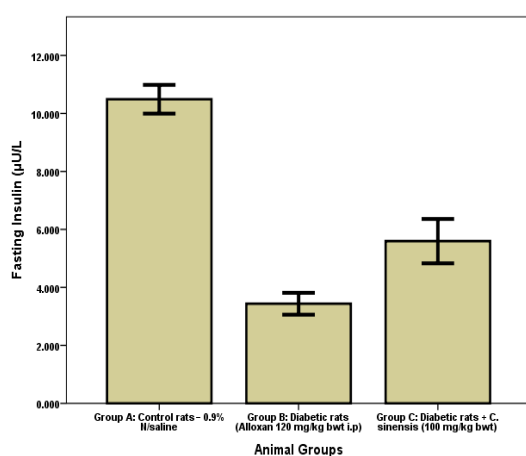
on the SPSS generated sheet ready for analysis. Continuous variables examined for normal distribution. Variables were analyzed using one – way ANOVA (analysis of variance) and Fischer's LSD post-Hoc testing. Level of statistical significance was at confidence interval 95% ( $p \leq 0.05$ ).

### RESULTS

Fasting Insulin (FI) levels are summarized in Table – 1 shows significant insulin levels after *Camellia sinensis* therapy. FI in control group A  $10.49 \pm 1.06$   $\mu\text{U/L}$  compared to low levels in positive control group B noted as  $3.44 \pm 0.81$   $\mu\text{U/L}$ . *Camellia sinensis* treated experimental group C shows  $5.60 \pm 1.64$   $\mu\text{U/L}$  increase in fasting insulin.  $F=176.2$  value and  $P=0.0001$  reveals *Camellia sinensis* therapy (30 days) increases the insulin secretion. Graph – 1 depicts the bars values of fasting insulin.

**Table – 1. Fasting Insulin level ( $\mu\text{U/L}$ )**

	Mean	SD	F- Value	P-value
<b>Group A:</b> Control rats– 0.9% N/saline	10.49	1.06	176.2	0.0001
<b>Group B:</b> Diabetic rats (Alloxan 120 mg/kg bwt)	3.44	0.81		
<b>Group C:</b> Diabetic rats + <i>C.sinensis</i> (100 mg/kg bwt)	5.60	1.64		



**Graph – 1.** Bar graphs show fasting insulin levels in 3 rat groups Compare with table – 1.

### DISCUSSION

Diabetes mellitus is a devastating metabolic disorder victimizing millions of people around the Globe.<sup>21</sup> Oral anti – diabetic drugs and recombinant human insulin are the mainstay of diabetic therapy. Newer drugs; DPP – IV inhibitor, Sodium – glucose transporter (SGLT-4) inhibitor and new insulin formations are other options but at the cost of severe adverse drug effects. Hence a growing research interest is observed for herbal agents and is on climax nowadays.

*Camellia sinensis* (tea) has been used in China, India and various other Eastern and African countries. *Camellia sinensis* (tea) is used as traditional medicine for diabetes. Tea is one of widely used global beverages

that offers a plethora of health benefits such as anti – cancer, anti- oxidant, anti – coronary and anti –diabetic activities.<sup>27,28</sup>

The present experimental rat study shows the 30 days *Camellia sinensis* (green tea) therapy increase serum insulin. Increase in serum fasting insulin is important finding for clinical management of diabetes mellitus patients.

*Camellia sinensis* is commonly used tea plant known of medicinal effects. It is used traditionally for diabetes, hyperlipidemia, coronary artery disease, arthritis, bacterial infections, etc.<sup>36,37</sup>. DPP-IV inhibitory action of *Camellia sinensis* is reported previously.<sup>36-39</sup>

Ansari et al<sup>29</sup> determined the biochemical effects of *C. sinensis* in 3T3-L1 adipocytes in a prospective study and reported glucoregulatory effects and increased insulin secretion similar to present study.

Findings of another recent study by Ansari et al<sup>36</sup> are consistent with present study that revealed similar glucoregulatory and insulin secreting effects of ethanol extract of *Camellia sinensis* (EECS) in mouse, BRIND BD 11 $\beta$  cells, mouse islets cells and 3T3L1 adipocytes. They reported the blood glucose was regulated effectively & insulin secretion was increased.

Zhang et al<sup>32</sup> analyzed the association of tea consumption, glucose metabolism and insulin secretion in a clinical study termed as the “Shanghai High-risk Diabetic Screen (SHiDS) study”. A sample of 237 Chinese subjects was enrolled. Each subject underwent 75 g oral glucose tolerance test (OGTT) and glucose and insulin level were estimated. Results showed tea consumption was positively associated with worsening glucose tolerance and low insulin secretion due to lower pancreatic  $\beta$ -cell function. The findings of above study are contrary to present experimental study and other previous clinical studies.<sup>29,32</sup>

Liu et al<sup>33</sup> has also reported results contrary to present study in type 2 diabetes mellitus in Chinese adults. They reported drinking *Camellia sinensis* (green tea) was associated with increased risk of occurrence of type 2

diabetes mellitus in Chinese adults. Another study by Hayashino et al<sup>34</sup> in 4975 Japanese male workers investigated the association long term tea intake and subsequent risk of developing diabetes. They concluded the long term consumption of Oolong tea was found as a predictive factor of new onset diabetes. The contrary result of above studies are most probably due to the different study population of different geographical areas, different environmental conditions, and dietary factors may have contaminated the results of tea consumption. Xu et al<sup>31</sup> studied 27 trials including 2194 subjects to review the effect of *Camellia sinensis*. Pooled results showed *Camellia sinensis* is utmost at improving the fasting blood glucose levels and HbA1c. The findings are in agreement to present study. However, they further added *Camellia sinensis* has non – significant effect on fasting insulin that is contrary to the findings of present study. Controversial findings are most probably due to different sample population i.e. human clinical trials versus experimental studies. The findings of fasting, random blood glucose and insulin secretion of present study are in agreement with previous studies.<sup>29-31</sup>

In conclusion, this study has demonstrated *Camellia sinensis* exerts significant insulin secreting effects in a commonly used diabetic rat model.

## CONCLUSION

In conclusion, the *Camellia sinensis* exerts significant glucose lowering and insulin secretory potential in Alloxan induced male albino rat model. The findings are of clinical significance for treating an ever increasing diabetes health problem. However, further human studies are recommended with large sample size to validate the findings.

## RECOMMENDATIONS

Further animal and human studies are recommended to validate the findings of present study. *Camellia sinensis* may be used for diabetes mellitus as easily available natural remedy.



**ETHICS APPROVAL:** The ERC gave ethical review approval. **NO: LUMHS/REC/-149 DATED:29/09/2022.**

**CONSENT TO PARTICIPATE:** written and verbal consent was taken from subjects and next of kin.

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#### **AUTHORS' CONTRIBUTIONS:**

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

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