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Original Research Article

Assessment of Antioxidant Activity of *Stigma maydis* Extract/Corn Silk Extract and Exploring its Efficacy Against Hyperglycemia in Diabetic Rats

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ABSTRACT

Diabetes Mellitus (DM) is a major health issue characterized by hyperglycemia and is still on its upsurge. Corn silk extract (CSE) can be used as a remedy against hyperglycemia due to its rich antioxidant activity. This study was designed to assess the antioxidant potential of aqueous and ethanol corn silk extracts and to assess the efficacy of the selected extract against hyperglycemia in diabetic rats. For this purpose, aqueous and ethanol corn silk extracts were prepared and their antioxidant potential was assessed by performing TPC, DPPH, and ABTS assay. Based on the antioxidant tests results, ethanol corn silk extract was selected and given to rats. For the trial, 20 male rats with average weight 250 ± 5 g were divided into three groups. Group 1 was non-diabetic, non-treated (control) while Group 2 and group 3 were diabetic, non-treated and diabetic, treated respectively. Group 2 and group 3 were injected 3 mL streptozotocin at the rate of 60 mg/kg with the final concentration of 5 mg/mL intraperitoneally. Group 3 received 1.5 mL ethanol corn silk extract while other two groups were given 1.5 mL water. Out of the three groups, Group 1 and group 2 had an inconsequential decline in mean blood glucose level at $p < 0.05$ while group 3 showed a significant decline in mean blood glucose level at $p < 0.05$. The polyphenols and antioxidants present in the corn silk extract impart functional as well as therapeutic properties to corn silk.

Keywords: Corn silk, Hyperglycemia, Antioxidant activity, Diabetes Mellitus, Ethanol extract

Introduction

Diabetes mellitus (DM) also known as diabetes, is one of the five leading causes of death globally.[1] It is an international health issue with an expected rise in prevalence from 171 million to 336 million in 2030. Due to its severe complications and higher prevalence, it is becoming 3rd most fatal disease worldwide.[2] According to International Diabetes Federation, every 11th adult has diabetes and by 2040 every 10th adult will have diabetes. Moreover, 327 million individuals have diabetes at present, which is being estimated to boom up to 438 million in the near 2045, out of which type 2 diabetes is predominantly prevalently depicting 90% of the affected population globally[3, 4] and out of these 27.4 million populations is just from Pakistan.[5] Thus, diabetes is considered a pandemic as its cases keep on surging from the previous two decades till now, from 5.32 million to 27.4 million.[5]

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Diabetes type 2 is 12.14% and 9.83% in males and females, respectively, in Punjab, Pakistan.[6]

Change in lifestyle, dietary modification, and physical exercise are key components to treat diabetes without the influence of any pharmacological drug. High fiber diet, diet low in saturated fats, and overall low carbohydrate diet therapies are quite beneficial to attenuate blood glucose level.[7] Treatment of diabetes mellitus through pharmacological drugs is also possible. In this case, anti-diabetic drugs like metformin and glucosidase inhibitors are used but they have side effects including liver disease and kidney failure.[8]

Hyperglycemia is a condition caused by elevated blood glucose level over a period. Serum glucose level more than 140 mg/dl indicates hyperglycemia. It is not only associated with critically ill patients but also with non-critically ill patients admitted to the hospital.[9] About 22% to 46% of such admitted patients suffer from hyperglycemia.[10] Hyperglycemia causes damage to vascular tissue at a cellular level which quickens the process of atherosclerosis.[11] The development of hyperglycemia involves three major processes: accelerated glycogenolysis, increased gluconeogenesis, and impaired glucose utilization by peripheral tissues.[12]

Stigma maydis is a renowned customary Chinese herbal medicine that has the potential benefits to curb the complications of hyperglycemia.[13] The female flower of maize contains yellowish thread-like structures known as stigmas which develop into corn silk. Corn silk extract contains active compounds like flavonoids, tannins, stigmasterol, sitosterol, alkaloids, saponins, and both fixed and volatile oils.[14] Flavonoids are further categorized into six main classes; flavonols, flavanols, isoflavones, flavones, flavanones, and

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anthocyanins.[15] Potential benefits of corn silk include lowering blood pressure, treatment of obesity and edema, alleviating urinary tract infections, minimizing prostate inflammation and stimulating relaxation, and preventing gall and kidney stones. Proximate analysis of corn silk revealed that aqueous and ethanol extracts differ in composition so they have different antioxidant capacities.[16]

Antioxidants present in corn silk are very useful to minimize the effects of hyperglycemia as they inhibit further oxidation and formation of reactive oxygen species. Hyperglycemia induces oxidative stress by promoting the radical-generating system and suppressing the radical-scavenging system. These antioxidants decrease oxidative stress and provide safety from these complications. This shows a strong relationship between antioxidants and diabetes.[17] The body's natural defense mechanisms nullify the effects of radicals produced inside the body. If free radicals are produced at a higher rate, as seen in diabetic patients, then our body is not able to diffuse these free radicals on its own and requires external influence in the form of antioxidants to minimize the damage.[18] Diet derivative antioxidants which are most commonly used are Vitamin C, Vitamin E, and Vitamin A.[19]

Keeping in view the antioxidant potential of corn silk extract, we designed this study assess and compare the antioxidant activity of aqueous and ethanol extracts and evaluate the bio-efficacy of the selected extract with higher antioxidant potential against hyperglycemia in diabetic rats.

Materials and Methods

Location

This study was carried out in the Food Analysis Lab of Food Science and Human Nutrition (FSHN) Department, University of Veterinary and Animal Sciences (UVAS), Lahore. Whereas efficacy trial was conducted in the Animal Room of Epidemiology & Public Health, UVAS, Lahore.

Experimental Design

Corn silk (Voucher No. 24367) was obtained from the corn processing industry (GPS coordinates- 32.0456395, 72.7249458) on 13th August, 2017. The plant was collected by Mr. Hammad Tahir, Lecturer, Lahore University of Biological and Applied Sciences, Lahore, Pakistan. Further, identified and authenticated by Prof. Dr. Sanaullah Iqbal, Chairman, Department of Food Science and Human Nutrition, UVAS, Lahore, Pakistan and Dr. Muhammad Hassan Mushtaq, Assistant Professor, Department of Epidemiology and Public Health, UVAS, Lahore, Pakistan. Aqueous and ethanol extracts were prepared separately by following the standard methods and their antioxidant potential was compared by performing DPPH assay, ABTS assay, and total phenolic content. Extract having higher antioxidant potential was selected for randomized control trial and given to diabetic rats for thirty days. To carry out our efficacy trial 20 male rats were purchased and categorized into three groups with each group having 6 rats. The distribution of rats and action on each group is tabulated in Table 1.

Corn Silk Extract Preparation

Aqueous extract preparation

Corn silk (100 g) was cleaned and cut into small pieces followed by drying at room temperature. After drying, corn silk sample was soaked in distilled water (500 mL) for 10 minutes. The soaked sample was homogenized using waring blender for two minutes followed by filtration. The filtrate was concentrated to dryness using a rotary evaporator in vacuum at 50°C. At last, the concentrated extract was stored at 4°C. [16]

Ethanol extract preparation

To prepare ethanol extract, a 100 g sample was soaked in 500 mL 97% ethanol for 24 hours. The soaked sample was placed in a shaker for 2 hours followed by filtration using Whatman filter paper no 1. The filtrate was concentrated to dryness using rotary evaporator at 50°C. The concentrated extract was stored at 4°C until used. [16]

Assessment of Antioxidant Activity

Prepared extracts were subjected to the following tests for the assessment of antioxidant potential.

Total phenolic content

In this method, 0.25 mL of Folin Ciocalteu Reagent (FCR) was mixed with 0.25 mL of (20 % w/v) corn silk extract. Then 0.5 mL of distilled water was dissolved in this solution along with 4.5 mL, 7% sodium bicarbonate. The absorbance was checked at 765 nm. Each mL of gallic acid solution in methanol was added to different concentrations of 0, 50, 100, 150, 200, and 250 mg to obtain the standard curve. The absorbance of extract measured by spectrophotometer was compared with the standard Gallic acid curve whereas TPC was expressed as mg GAE/100g dried extract. [20]

DPPH

In this method, 3 mL of 0.1 mM ethanolic DPPH solution was prepared and its absorbance was checked at 515 nm which is denoted by AWE. Then 3 mL (20 % w/v) corn silk extract was added to 50 mM phosphate buffer to maintain the pH of 7.5 and mixed with already prepared DPPH solution. Absorbance was checked and measured at 515 nm which is denoted by AE. The decline in absorbance was calculated using the following equation.

Absorbance reduction (%) = [(AWE – AE) / AWE] * 100
AWE = Absorbance without extract
AE = Absorbance with extract [21]

ABTS

This method involved the addition of 7.4 mM ABTS solution in 2.6 mM potassium per-sulfate solution. The resulting solution was allowed to react for 12 hours in the dark. After that 1 mL ABTS°+ was added to the previous solution to dilute it along with 60 mL methanol and absorbance was obtained at 734 nm. 1 mL of both aqueous and ethanolic extracts were added one by one to ABTS°+ solution under dark conditions for 1 hour and absorbance was recorded at 734 nm. The scavenging capacity of both extracts was compared with standard ascorbic acid and % inhibition was calculated as that for the DPPH method.

Absorbance reduction (%) = [(AWE – AW) / AWE] * 100
AWE = Absorbance without extract
AE = Absorbance with extract [22]

Table 1: Animal Grouping and Treatment

No. of Groups	Label of Groups	Detail of Group	No. of Rats	Action
Group 1	Normal Control (NC)	Non-Diabetic, Non-treated	N = 6	3 mL Normal Saline + 1.5 mL Water
Group 2	Diabetic Control (DC)	Diabetic, Non-Treated	N = 6	3 mL Streptozotocin (STZ) + 1.5 mL Water
Group 3	Treatment (T)*	Diabetic, Treated	N = 6	3 mL Streptozotocin (STZ) + 1.5 mL Ethanol Corn Silk Extract

*Treatment = Corn Silk Extract

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Animal Study
Selection of animals
20 male Sprague Dawley healthy rats having an average weight of 250g ± 5g were purchased from the University of Lahore (UVAS-03-2018-BeST-255-M). They were transported to the animal facility of Epidemiology and Public Health, UVAS, Lahore. They were housed and kept in a room providing 12 hours of light and 12 hours of the dark period. The temperature was maintained around 20 °C to 25 °C. They had access to commercial feed and water for one week to acclimatize to the environment.[23]

Induction of diabetes
After one week, 14 rats were injected with 3 mL of streptozotocin solution each having a final concentration of 5 mg/ml. Rats with blood glucose level (BGL) > 200 mg/dl were selected for the study. After 48 hours BGL was measured, and all 14 rats had blood glucose level higher than 200 mg/dl. Among these 14 rats, six rats were placed in diabetic, non-treated group and six rats were placed in diabetic, treated group randomly. Six rats were placed in the non-diabetic, non-treated group.

Feed and water Intake
All groups were given the same commercial feed once a day for consecutive 30 days orally. Group 1 and group 2 were given 1.5 mL of water once a day. Group 3 was given 1.5 mL (20 % w/v) corn silk extract, once a day for consecutive 30 days orally.

Biochemical Analysis
The biochemical analysis involves the estimation of blood glucose level. Blood sample from the tail was collected initially, after 15 days, and after 30 days, and BGL was measured by using a glucometer on each mentioned day.[13]

Statistical Analysis
Obtained data were analyzed statistically using Statistical Package for Social Science for Windows Version 21.0. One-way ANOVA was used to analyze data at significance level $p < 0.05$. Group difference was equated using the Least Significance Difference at $p < 0.05$.

Ethics
Ethical Approval was obtained from the Independent Institutional Ethics Committee (IIEC) of the Bioequivalence Study Center, UVAS Lahore (UVAS-03-2018-BeST-255-M).

Results and Discussion

Total phenolic content
Both aqueous and ethanol extracts of corn silk possess a significant quantity of phenolic compounds but ethanol extract surpasses the aqueous extract as aqueous extract contains 1303.33 ± 170.20 mg GAE / 100 g dried sample and ethanol extract contains 1856.33 ± 117.40 mg GAE / 100 g dried sample. Figure 1 shows that ethanol corn silk extract has more total phenols indicating more antioxidant potential as compared to the aqueous extract.

DPPH
Ethanol extract exhibits a higher amount of DPPH as compared to aqueous extract. DPPH value for aqueous corn silk extract was 68.5 ± 1.01 %. In the same way % inhibition of DPPH for ethanol corn silk extract was 71.8 ± 0.7%. Percent inhibition of DPPH for ethanol and aqueous extract can be seen in Figure 2.

ABTS
Ethanol extract proves to have a higher value of ABTS as compared to aqueous extract. For aqueous extract, the concentrations used were 100, 200, 400, 800, and 1600 µg/mL at which % inhibition was 18, 23, 30, 42, and 57 respectively. For ethanol extract, the concentrations used were 100, 200, 400 800, and 1600 µg/mL and it showed the % inhibition of 23, 30, 36, 46, and 63 respectively. The higher percent inhibition of ethanol extract can be seen in Figure 3.

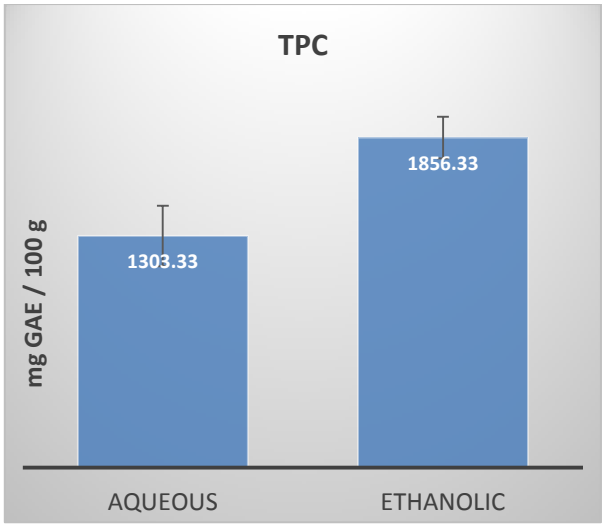

Figure 1: Comparison of the total phenolic content of aqueous and ethanolic corn silk extract

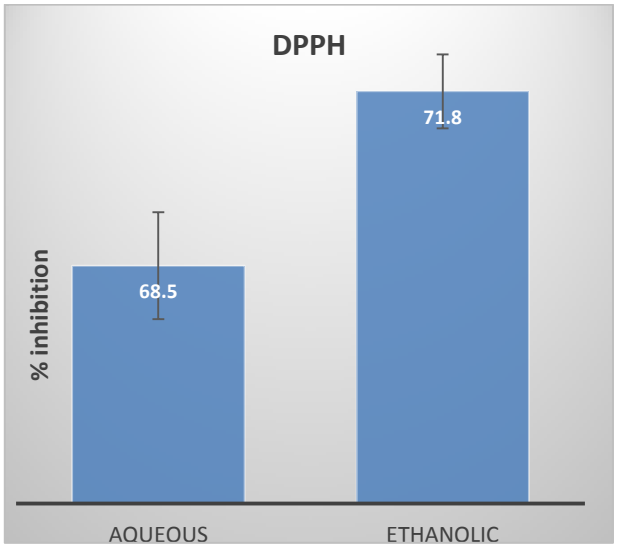

Figure 2: Comparison of the % inhibition of DPPH radical of aqueous and ethanolic corn silk

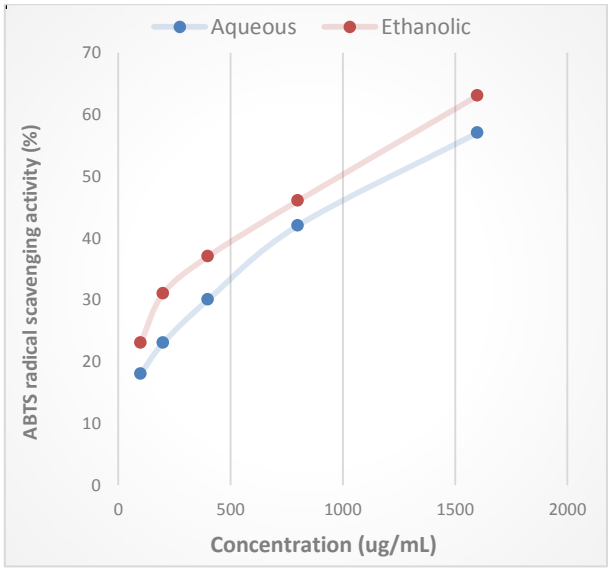

Figure 3: Comparison of the ABTS radical scavenging activity of aqueous and ethanol corn silk

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Table-2: Mean blood glucose level at different time intervals

	Blood Glucose level (mg/dl) at Day 0	Blood Glucose level (mg/dl) at Day 15	Blood Glucose level (mg/dl) at Day 30
Normal Control*	97.33 ± 4.13	115.50 ± 17.91	113.33 ± 16.40
Diabetic Control**	304.17 ± 54.31	341.67 ± 66.44	388.83 ± 51.84
Treatment***	286.67 ± 24.48	224.33 ± 33.66	192.50 ± 47.74

*Non-Diabetic, Non-Treated; **Diabetic, Non-Treated; ***Diabetic, Treated

Table 3: ANOVA Table

Groups	F	Significance
Normal Control (NC)	2.920	.085^{NS}
Diabetic Control (DC)	3.224	.068^{NS}
Ethanol Corn Silk Extract (1.5 mL)	10.297	.002*

* = Significant at p< 0.05; NS = non-Significant

Table 4: Multiple Comparison Analysis

Groups	(I)	(J)	Significance
Normal Control	Day 0	Day 15	.043^{NS}
		Day 30	.070^{NS}
	Day 15	Day 0	.043^{NS}
		Day 30	.795^{NS}
	Day 30	Day 0	.070^{NS}
		Day 15	.795^{NS}
Diabetic Control	Day 0	Day 15	.279^{NS}
		Day 30	.023^{NS}
	Day 15	Day 0	.279^{NS}
		Day 30	.179^{NS}
	Day 30	Day 0	.023^{NS}
		Day 15	.179^{NS}
Ethanol Corn Silk Extract	Day 0	Day 15	.010*
		Day 30	.000*
	Day 15	Day 0	.010*
		Day 30	.152^{NS}
	Day 30	Day 0	.000*
		Day 15	.152^{NS}

* Significant at p < 0.05; NS = non-significan

Selection of Corn Silk Extract

Based on results of these antioxidants tests, it is evident that ethanol extract has more antioxidant potential as compared to aqueous extract. So, ethanol extract was selected for efficacy trial.

Biochemical Analysis

All eighteen (18) rats were anesthetized at the end of the 30th day and BGL was measured by collecting the blood from the tail vein using a glucometer. The results of mean blood glucose level are presented in Table 2

A linear line was obtained in the case of the non-diabetic, non-treated group showing an insignificant change in mean blood glucose level at p < 0.05. Similarly, the diabetic, non-treated group showed a gradual increment depicting the increase in blood glucose whereas the diabetic, treated group showed a significant decline in blood glucose level at p < 0.05 as depicted in Figure 4.

The analysis of variance (ANOVA) in Table 3 indicates that the difference in mean blood glucose level from day 0 to day 30 for non-diabetic, non-treated (normal control) group was non-significant at p < 0.05. Similarly, the difference in mean blood glucose level from day 0 to day 30 for diabetic, non-treated (diabetic control) group was also non-significant at p < 0.05. But the difference in mean blood glucose level for diabetic, treated (ethanol corn silk extract) group was significant at p < 0.05, or we can say that there was significant decline in mean blood glucose level in our corn silk extract group from day 0 to day 30. The significant decline was due to the treatment with ethanol corn silk extract. Table-4 shows the multiple comparison test by least significance difference indicating a significant difference in mean blood glucose level from Day 0 to Day 15 in the treatment group.

Corn silk has numerous functional and therapeutic effects which are very beneficial for the prevention of certain diseases and the promotion of health. Antioxidants present in corn silk are very useful to minimize the effects of hyperglycemia as they inhibit further oxidation and formation of reactive oxygen species.[24] Diabetes leads to hyperglycemia and hyperglycemia induces oxidative stress by promoting the radical-generating system and suppressing the radical-scavenging system. These antioxidants decrease oxidative stress and provide safety from these complications. So, we can say that antioxidants and diabetes have a strong relationship.[17] The body's natural defense mechanisms nullify the radicals produced inside the body. If free radicals are produced at a higher rate as seen in diabetic patients, then our body is not able to overcome these free radicals on its own and requires external influence in the form of antioxidants to minimize the damage caused by free radicals.[18] These studies were designed to evaluate the efficacy of *Stigma maydis* against hyperglycemia and the results confirm the significant implications of corn silk.[16, 25-27]

The study revealed that the treatment group which received ethanol extract for consecutive 30 days had a significant decline in mean blood glucose level compared to the non-diabetic and the diabetic non-treated groups at p < 0.05. One-way ANOVA showed that the mean blood glucose level of the treatment group had a significant difference between groups at p < 0.05. Hence, the mean blood glucose level of the non-diabetic, non-treated (normal control) group remains constant throughout the trial with a linear stabilized line from day 0 to day 30. However, in the case of the diabetic, non-treated (diabetic control) group, mean blood glucose level increased from day 0 to day 15 up to the 30th day with a steep upward line. The ethanol corn silk extract group showed a steep downward line from day 0 to day 15 and then a gradual downward trend from day 15 to day 30 showing a significant decline in mean blood glucose level at p < 0.05 (Figure 4). The LSD multiple comparison analysis in Table-4 highlights mean differences were insignificant for both the normal control and diabetic control group. However, the treatment group showed a different trend. It showed that the mean difference was significant between day 0 and day 15 but from day 15 to day 30 mean blood glucose level was insignificant at p < 0.05. So, ethanol corn silk extract has significant potential to curb blood glucose level. A rat model was used to confirm the effect of corn silk on cholesterol metabolism and had similar results.[28] The effect of *Eugenia jambolana* and *Tinospora cordifolia* plant extract was assessed in ameliorating diabetic gastropathy neuropathy and in rats.[29] The rats were given acetaminophen to induce renal damage and evaluated the improvement in renal damage by giving corn silk extract.[30]

This study focused on the anti-diabetic effect of corn silk. Results showed that corn silk ethanol extract significantly decreased blood glucose (p <0.05) which was comparable with other studies done on corn silk.[13, 31-33]. Results were also comparable with the studies done on antioxidant potential of leaf extract of *Stachytarphyta jamaicensis* and root bark extract.[34, 35] Results also showed that blood glucose

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significantly reduced in the group which received 20 g/ kg corn silk polysaccharide at $p < 0.05$.[13]

Conclusion

Antioxidants present in the extract have a hypoglycemic effect. Ethanol corn silk extract proves to be beneficial for health in terms of alleviating blood glucose level i.e., for combating hyperglycemia.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

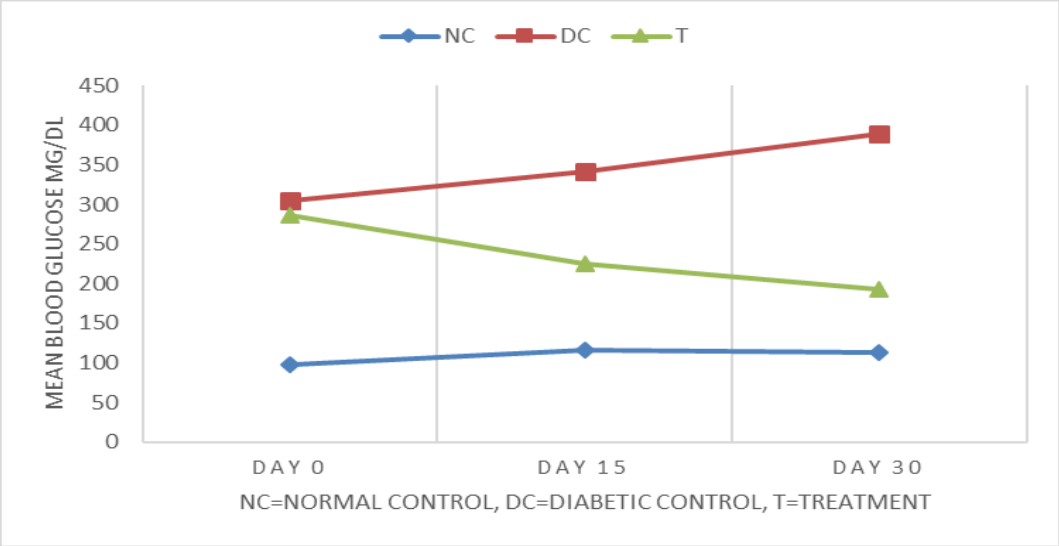

Figure 4: Comparison of mean blood glucose level at Day 0, Day 15 and Day 30

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