Comparative analysis of metformin alone and in combination with caffeic acid in diabetic rats

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Abstract

The study aims to assess the impact of metformin combined with caffeic acid on diabetic rats induced with STZ. In this experiment, the animals were categorized into six groups: Group I consisted of normal control rats, Group II included diabetic control rats, Group III comprised metformin standard rats, Group IV was given caffeic acid, Group V received metformin 125 mg/kg plus caffeic acid, and Group VI was administered metformin 250 mg/kg plus caffeic acid. Measurements were taken for fasting blood glucose levels, oral glucose tolerance, lipid profile, SOD, and MDA. In the diabetic control group, fasting blood glucose, MDA, cholesterol, and triglyceride levels were notably elevated. However, in diabetic rats treated with metformin and caffeic acid, there was a significant reduction in fasting blood glucose and MDA levels, along with a decrease in body weight, cholesterol, and triglyceride levels. The combination of metformin and caffeic acid effectively normalized all the aforementioned biochemical parameters in diabetic rats. Our findings indicate that the combination of metformin 250 mg/kg and caffeic acid exhibits antidiabetic and antioxidant properties in diabetic rats.

1. Introduction

Diabetes mellitus is characterized by high blood sugar levels due to insufficient or absent insulin production by the pancreas, and it may also involve reduced insulin effectiveness. This condition ranks among the most prevalent metabolic disorders, impacting a significant portion of the global population. Symptoms and signs of diabetes mellitus include hyperglycemia, increased hunger, frequent urination, blurred vision, and fatigue, among others (Hashim *et al.,* 2024; Hashim *et al.,* 2023).

Metformin is an oral antihyperglycemic medication belonging to the biguanide class, used either alone or alongside other treatments to manage type 2 diabetes (T2D). While the exact mechanism by which it lowers blood glucose and HbA1c levels is not fully understood, metformin reduces glucose production in the liver and enhances insulin sensitivity by promoting the uptake and use of glucose in peripheral tissues. It aids in re-establishing the body's insulin response by decreasing the liver's sugar production and the absorption of sugar in the stomach or intestines. Beyond its blood sugar-lowering effects, metformin is also used with dietary and exercise modifications to prevent diabetes in individuals at high risk. Additionally, it is prescribed for women with polycystic ovarian syndrome, where it may help regulate menstrual cycles and boost fertility (Goldberg *et al.,* 2022).

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Caffeic acid, also known as 3,4-dihydroxycinnamic acid, is a significant phenolic acid commonly present in fruits, grains, and various dietary items. This compound is found in a range of fruits and vegetables, both in its free and conjugated forms. It is also present in sweet potatoes, green coffee beans, apples, and more (Yusuf *et al.,* 2019). Caffeic acid exhibits both antioxidant and antidiabetic properties. It notably reduces fasting glucose levels when compared to control db/db mice. Additionally, caffeic acid aids in decreasing glycosylated hemoglobin levels, a reliable indicator of chronic diabetes. An increase in hepatic glucokinase (GK) leads to enhanced blood glucose utilization for energy production or glycogen storage in the liver.

2. Material and Methods

2.1 Chemicals

Streptozotocin (STZ), metformin, caffeic acid, ethanol, formaldehyde, and other chemicals were purchased from Sigma Aldrich.

2.2 Animals

Adult male SD rats, each weighing between 120 and 200 g, were housed in the Experimental Animal House at the Faculty of Pharmacy, Integral University. The animals were placed in polypropylene cages, with five rats per cage. The laboratory environment was controlled with a 12 h light and 12 h dark cycle, and the rats were provided with a standard pellet diet and unlimited access to drinking water. The temperature in the animal house was kept at $23 \pm 2°C$, and the relative humidity was maintained at $50 \pm 15\%$. The rats were allowed a seven-day period to acclimate. Ethical approval was secured from the Institutional Animal Ethical Committee (IAEC) (Approval No: IU/IAEC/18/17) at Integral University, Lucknow.

2.3 Induction of type 2 diabetes in rats

Rats were kept without food but had access to water starting the previous evening. Streptozotocin (STZ) was dissolved in ice-cold citrate buffer (pH 4.5, 0.1 M) and administered intraperitoneally at a dose of 65 mg/kg body weight within 5 min. This was followed by an intraperitoneal injection of NIC (110 mg/kg) 15 min later. Blood glucose levels were measured 72 h post-injection. To prevent death from hypoglycemia, diabetic animals were provided with water and 5% glucose 24 h after the STZ injection. Blood samples were collected from the tail vein 72 h later and analyzed using a glucometer (Accu-Chek). Animals with plasma glucose levels exceeding 250 mg/dl were classified as diabetic and included in the diabetic studies.

2.4 Experimental design

To assess the impact of metformin (125, 250 mg/kg) combined with caffeic acid (40 mg/kg) on STZ-induced diabetic rats, diabetic animals were utilized post-induction. SD rats were organized into six groups, each containing five animals, and their initial body weights were documented. The treatment spanned 28 days for each group (Table 1). Upon conclusion of the study, the final body weights of all animals were measured. Subsequently, the animals were anesthetized using thiopentone sodium, and blood samples were obtained *via* retro-orbital puncture to measure blood sugar and other biochemical parameters.

Table 1: Treatment schedule

Groups (n = 5)	Treatment	Dosage, route of administration and duration
I (NC)	Vehicle (normal saline)	10 ml/kg, p.o. once a day for 28 days
II (DC)	STZ	65 mg/kg, i.p. STZ (single dose)
III (STD)	Diabetic rat + Metformin	250 mg/kg, p.o. once a day for 28 days
IV	Diabetic rat + Caffeic acid	40 mg/kg, p.o. once a day for 28 days
V	Diabetic rat + Metformin + Caffeic acid	125 mg/kg + 40 mg/kg, p.o. once a day for 28 days
VI	Diabetic rat + Metformin + Caffeic acid	250 mg/kg + 40 mg/kg, p.o. once a day for 28 days

(N = Number, NC = Normal control, DC = Diabetic control, STD = Standard, i.p. = intraperitoneal, STZ = Streptozotocin, p.o. = per oral)

2.5 Determination of blood glucose

At initial and final day of the treatment blood sugar measurements were taken by using tail's vein blood (by ACCUCHEK- ACTIVE kit made by Roche, Germany).

2.6 Oral glucose tolerance test (OGTT)

To assess glucose tolerance, an OGTT was conducted. Following a night of fasting, a dextrose solution with a concentration of 40% wt/vol. was given to rats *via* intra-gastric administration at a dosage of 2.5 g/kg of body weight. Blood glucose levels were then measured at intervals of 0, 30, 60, and 120 min. The glucose tolerance was evaluated by determining the area under the curve (AUC) for glucose using the trapezoidal method.

AUC = (basal glycaemia + glycaemia 0.5 h) × 0.25 + (glycaemia 0.5 h + glycaemia 1 h) × 0.25 + (glycaemia 1 h + glycaemia 2 h) × 0.5

2.7 Body weight changes

At initial and final day of the treatment body weight were taken and change in body weight were calculated.

2.8 Estimation of lipid profile (TG, Cholesterol, HDL, LDL, VLDL)

Lipid profile was estimated by using commercial kit.

2.9 Assessment of oxidative biomarkers in pancreas (SOD, TBARS)

Oxidative biomarkers were estimated in pancreas supernatant (Marklund and Marklund, 1974; Ohkawa *et al.,* 1979).

2.10 Statistical analysis

The data were expressed as mean ± SEM for each group of four animals. Statistical analysis was conducted using one-way ANVOA, followed by Dunnett's test to compare all groups against the control (Graph Pad Instat, USA).

3. Results

3.1 Effect of metformin with caffeic acid on the blood glucose level

In Table 2, the glucose level in the diabetic control group (DC) showed a significant increase ($p < 0.01$) compared to the normal control group (NC). Conversely, all treated groups exhibited a significant reduction in glucose levels ($p < 0.01$) when compared to the diabetic control. Notably, the combination of metformin 250 mg/kg with caffeic acid 40 mg/kg resulted in a significantly greater decrease ($p < 0.01$) in glucose levels compared to metformin 250 mg/kg alone.

3.2 Effect of metformin with caffeic acid on the OGT

In Table 2, the area under the curve (AUC) for the diabetic control group (DC) showed a significant increase ($p < 0.01$) compared to the normal control group (NC). Conversely, all treated groups exhibited a significant decrease in AUC ($p < 0.01$) when compared to the diabetic control (DC). Notably, the combination of metformin 250 mg/kg with caffeic acid 40 mg/kg resulted in a significantly greater reduction ($p < 0.01$) in AUC compared to metformin 250 mg/kg alone.

All values were expressed as mean ± SEM. Significant difference between various groups (ANOVA) and individual comparison was done by Dunnett's t-test. **$p < 0.01$=Significant, when compared with normal control (NC), ##$p < 0.01$=Significant when compared with diabetic control (DC). a$p < 0.01$=Significant when compared with metformin 250 mg/kg.

3.3 Effect of metformin with caffeic acid on the body weight change

In Table 3, the body weight of the diabetic control group (DC) shows

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a decrease ($p<0.01$) when compared to the normal control group (NC). All treated groups exhibited a significant increase in body weight ($p<0.01$) compared to the diabetic control (DC). Notably, the combination of metformin 250 mg/kg with caffeic acid 40 mg/kg resulted in a significantly greater increase ($p<0.01$) in body weight than metformin 250 mg/kg alone.

Table 2: Effect of metformin with caffeic acid on the blood glucose level and OGT

Groups/ treatment	Blood glucose concentration (mg/dl)		AUC (mg/dl)
	Initial blood glucose level	Final blood glucose level	
NC	65.7 ± 0.85	67.71 ± 2.00	77.5 ± 2.1
DC (STZ 65 mg/kg)	395.7 ± 64.7	350.05 ± 5.2**	311.23 ± 1.0**
Metformin 250 mg/kg	338.7 ± 6.2	230.2 ± 08##	154.51 ± 0.8##
Caffeic acid 40 mg/kg	333.2 ± 19.6	326.2 ± 2.5##	188.16 ± 1.0##
Metformin 125mg/kg + Caffeic acid 40 mg/kg	315 ± 1.0	284.7 ± 1.5##	165.84 ± 1.4##
Metformin 250 mg/kg + Caffeic acid 40 mg/kg	356.7 ± 11.3	208.0 ± 1.4##a	128.77 ± 0.8##a

Table 3: Effect of metformin with caffeic acid on the body weight change

Groups/ Treatment	Change in body weight (g)			
	At week 0	At week 4 (g)	% body weight variation	
			% weight gain	% weight loss
NC	137.5 ± 5.20	153.7 ± 6.25	11.78 ± 2.6	-
DC (STZ 65 mg/kg)	138.2 ± 2.6	129 ± 2.61	-	5.2 ± 1.4
Metformin 250 mg/kg	130.00 ± 2.0	138 ± 2.16	6.5 ± 2.3	-
Caffeic acid 40 mg/kg	126.7 ± 3.1	156 ± 1.5	23.12 ± 1.3	-
Metformin 125 mg/kg + Caffeic acid 40 mg/kg	136.2 ± 1.2	152 ± 4.0	11.60 ± 5.8	-
Metformin 250 mg/kg + Caffeic acid 40 mg/kg	132.5 ± 4.7	140 ± 6.12	5.6 ± 1.6	-

All values were expressed as mean ± SEM. Significant difference between various groups (ANOVA) and individual comparison was done by Dunnett's t-test. **$p<0.01$=Significant, when compared with normal control (NC), ##$p<0.01$=Significant when compared with Diabetic control (DC). a$p<0.01$=Significant when compared with metformin 250 mg/kg.

3.4 Effect of metformin with caffeic acid on the serum cholesterol

In Table 4, the cholesterol levels in the diabetic control group (DC) showed a significant increase ($p<0.01$) compared to the normal control group (NC). However, these levels significantly decreased ($p<0.01$) in all treated groups when compared to the diabetic control DC. Notably, there was a significant increase ($p<0.01$) in cholesterol levels in the group treated with a combination of metformin 250 mg/kg and caffeic acid 40 mg/kg compared to the group treated with metformin 250 mg/kg alone.

3.5 Effect of metformin with caffeic acid on the serum triglycerides

Table 4 shows that the triglycerides level in the diabetic control group (DC) was significantly higher ($p<0.01$) compared to the normal control group (NC). The HDL level was notably lower ($p<0.01$) in all treated groups when compared to the diabetic control (DC). However, a significant decrease ($p<0.01$) in HDL level was observed in the group treated with a combination of metformin 250 mg/kg and caffeic acid 40 mg/kg compared to the group treated with metformin 250 mg/kg alone.

3.6 Effect of metformin with caffeic acid on the serum HDL

In Table 4, the diabetic control group (DC) exhibited a significant reduction in HDL levels ($p<0.01$) compared to the normal control group (NC). All treated groups showed a significant increase in HDL levels ($p<0.01$) when compared to the diabetic control DC. Notably, the combination of metformin 250 mg/kg with caffeic acid 40 mg/kg resulted in a significantly higher increase ($p<0.01$) in HDL levels compared to metformin 250 mg/kg alone.

3.7 Effect of metformin with caffeic acid on the LDL in blood serum

In Table 4, the LDL level in the diabetic control group (DC) showed a significant increase ($p<0.01$) compared to the normal control group (NC). Conversely, all treated groups exhibited a significant decrease ($p<0.01$) in LDL levels when compared to the diabetic control. However, the combination of metformin 250 mg/kg with caffeic acid 40 mg/kg resulted in a significant increase ($p<0.01$) in LDL levels compared to metformin 250 mg/kg alone.

3.8 Effect of metformin with caffeic acid on the serum VLDL

In Table 4, the VLDL level in the diabetic control group (DL) showed a significant increase ($p<0.01$) compared to the normal control group (NC). The VLDL level was notably lower ($p<0.01$) across all treated groups when compared to the Diabetic control. However, a significant decrease ($p<0.01$) was observed in the group treated with a combination of metformin 250 mg/kg and caffeic acid 40 mg/kg compared to the group treated with metformin 250 mg/kg alone.

Table 4: Effect of metformin with caffeic acid on the serum level

Groups	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
NC	184.00 ± 1.13	74.06 ± 16.62	72.75 ± 1.49	96.7 ± 2.7	36.88 ± 022
DC (STZ 65 mg/kg)	330.42 ± 13.52[**]	209.15 ± 5.4[**]	20.75 ± 2.81[**]	267.5 ± 11.7[**]	66.08 ± 2.70[**]
Metformin 250 mg/kg	272.64 ± 5.7[##]	135.6 ± 4.5[##]	44.25 ± 2.28[##]	163.1 ± 5.6[##]	46.90 ± 1.21[##]
Caffeic acid 40 mg/kg	234.5 ± 6.0[##]	151.9 ± 1.4[##]	38.75 ± 1.1[##]	197.2 ± 10.9[##]	54.52 ± 1.15[##]
Metformin 125mg/kg + Caffeic acid 40 mg/kg	224.63 ± 1.5[##]	130.08 ± 4.5[##]	41.25 ± 1.54[##]	157.2 ± 2.10[##]	44.92 ± 0.30[##]
Metformin 250 mg/kg + Caffeic acid 40 mg/kg	209.68 ± 1.2[##a]	111.39 ± 1.5[##a]	55.75 ± 1.1[##a]	131.5 ± 1.7[##a]	41.93 ± 0.24[#a]

All values were expressed as mean ± SEM. Significant difference between various groups (ANOVA) and individual comparison was done by Dunnett's t-test. [**]$p<0.01$ = Significant, when compared with normal control (NC) [#]$p<0.05$ and [##]$p<0.01$ = Significant when compared with Diabetic control (DC). [a]$p<0.01$ = Significant when compared with metformin 250 mg/kg.

3.9 Effect of metformin with caffeic acid on SOD level in pancreas tissue

In Table 5, the SOD level in the diabetic control group (DC) showed a significant decrease ($p<0.01$) compared to the normal control group (NC). Conversely, all treated groups exhibited a significant increase ($p<0.01$) in SOD levels when compared to the diabetic control DC. Notably, the combination of metformin 250 mg/kg with caffeic acid 40 mg/kg resulted in a significantly higher increase ($p<0.01$) in SOD levels compared to metformin 250 mg/kg alone.

3.10 Effect of metformin with caffeic acid on MDA level in pancreas tissue

Table 5 shows that the MDA level in the diabetic control group (DC) was significantly higher ($p<0.01$) compared to the normal control group (NC). In contrast, all treated groups exhibited a significant reduction in MDA levels ($p<0.01$) when compared to the diabetic control. Notably, the combination of metformin 250 mg/kg with caffeic acid 40 mg/kg resulted in a significantly greater decrease ($p<0.01$) in MDA levels compared to metformin 250 mg/kg alone.

Table 5: Effect of metformin with caffeic acid on SOD level in pancreas tissue

Groups	Concentration of SOD (U/mg of protein)	Concentration of MDA (nmoles/mg of protein)
NC	140.6 ± 0.8	26.83 ± 0.68
DC (STZ 65 mg/kg)	72.0 ± 0.4[**]	48.01 ± 0.67[**]
Metformin 250 mg/kg	120.3 ± 0.8[##]	36.24 ± 0.64[##]
Caffeic acid 40 mg/kg	127.7 ± 0.55[##]	29.7 ± 0.5[##]
Metformin 125 mg/kg + Caffeic acid 40 mg/kg	133.2 ± 1.0[##]	32.6 ± 0.6[##]
Metformin 250 mg/kg + Caffeic acid 40 mg/kg	135.4 ± 1.21[#a]	30.0 ± 0.7[#a]

All values were expressed as mean ± SEM. Significant difference between various groups (ANOVA) and individual comparison was done by Dunnett's t-test. [**]$p<0.01$=Significant, when compared with normal control (NC), [#]$p<0.05$ and [##]$p<0.01$=Significant when compared with Diabetic control (DC). [a]$p<0.01$=Significant when compared with metformin 250 mg/kg.

4. Discussion

Diabetes mellitus (DM) is classified as a metabolic disorder, primarily characterized by prolonged elevated blood sugar levels. It is considered one of the world's major diseases due to its widespread impact on the global population and is divided into two main types: I and II (Anwar *et al.,* 2024). Complications arising from diabetes can include potential blindness, lower limb amputation, kidney failure, and heart attack or stroke. This study aims to investigate the glucose-lowering effects of metformin combined with caffeic acid in a diabetic rat model induced by STZ.

Metformin is a medication taken orally to reduce blood sugar levels in individuals with type 2 diabetes, especially those who are overweight or obese and have normal kidney function. It is classified under the biguanide group of antidiabetic medications. Metformin primarily alleviates high blood sugar by inhibiting the liver's glucose production, known as hepatic gluconeogenesis (Szymczak-Pajor *et al.,* 2022). Caffeic acid has been found to significantly decrease fasting blood sugar levels, aligning with previous research findings (Oršoliæ *et al.,* 2021). Recent studies indicate that caffeic acid lowers blood sugar levels and boosts insulin secretion in diabetic rats. This compound reduces blood glucose by inhibiting glucose-6-phosphatase activity, affecting liver glucose production, and enhancing glucokinase (GK) activity in the liver. Hepatic GK plays a crucial role in maintaining glucose balance and is a potential target for treating type 2 diabetes pharmacologically. An increase in hepatic GK can lead to greater use of blood glucose for energy production or glycogen storage in the liver (Sharma *et al.,* 2022).

The current research indicates that a combination of metformin (250 mg) and caffeic acid leads to a significant reduction in blood glucose

levels. Metformin notably enhances hypolipidemia in individuals with type 2 DM, likely due to its ability to sensitize insulin. Caffeic acid effectively lowers total cholesterol and triglycerides while boosting HDL levels.

The current research indicates that administering metformin (250 mg) alongside caffeic acid leads to a significant reduction in total cholesterol, triglyceride, LDL, and VLDL levels, while it elevates HDL levels in diabetic rats induced with STZ. Previous studies have shown that metformin and caffeic acid possess antioxidant properties by boosting enzymatic antioxidant levels (SOD, catalase) and reducing MDA levels. Our findings reveal that metformin and caffeic acid notably enhance SOD activity and decrease MDA levels, thereby mitigating oxidative stress.

5. Conclusion

The study investigated the effects of metformin combined with caffeic acid on streptozotocin (STZ)-induced diabetic rats. Treatment with metformin and caffeic acid significantly reduced fasting blood glucose, MDA, body weight, cholesterol, and triglyceride levels in diabetic rats. The combination of metformin and caffeic acid effectively normalized all the biochemical parameters in diabetic rats, demonstrating anti-diabetic and antioxidant properties.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Mohd Yusuf: Contributed to investigation, data curation, and methodology; **Badruddeen:** Contributed to conceptualization, supervision, project administration, validation, and overall guidance of the study; **Juber Akhtar:** Contributed to investigation and data curation; **Mohammad Irfan Khan:** Contributed to methodology and formal analysis; **Anas Islam:** Contributed to software handling, data analysis, and visualization of results; **Asad Ahmad:** Contributed to investigation and validation of experimental data; **Gazala Noor:** Contributed to literature survey and drafting of the manuscript; **Mohammad Ahmad:** Contributed to resources and critical review of the manuscript; **Akash Srivastava:** Contributed to writing the original draft, reviewing, and editing of the manuscript; **Mohd Ajmal:** Contributed to validation, critical revision, and final approval of the manuscript.

Consent for publication

All authors gave their full consent for publication and submission to this journal.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Ethics approval

Approved by the Institutional Animal Ethics Committee (IAEC), Protocol No. IU/IAEC/18/17.

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References

Anwar, K.R.; Badruddeen; Akhtar, J.; Khan, M.I. and Ahmad, M. (2024). An outlook on pathological pathways of diabetes and molecular mechanisms of antidiabetic phytobioactives. Lett. Funct. Foods, 1(1):e180723218858.

Goldberg, R.B.; Orchard, T.J.; Crandall, J.P.; Boyko, E.J.; Budoff, M.; Dabelea, D.; Gadde, K.M.; Knowler, W.C.; Lee, C.G; Nathan, D.M. and Watson, K. (2022). Effects of long-term metformin and lifestyle interventions on cardiovascular events in the diabetes prevention program and its outcome study. Circulation, 145(22):1632-1641.

Hashim, M.; Badruddeen; Akhtar, J.; Khan, M.I.; Ahmad, M.; Islam, A. and Ahmad, A. (2024). Diabetic neuropathy: An overview of molecular pathways and protective mechanisms of phytobioactives. Endocr. Metab. Immune Disord. Drug Targets, 24(7):758-776.

Hashim, M.; Badruddeen; Akhtar, J.; Khan, M.I.; Ahmad, M.; Islam, A.; Ahmad, A. and Zahra, F. (2023). Diabetic nephropathy: An outline on molecular mechanism and protective pathways of phytoconstituents. J. Phytonanotech. Pharmaceut. Sci., 3(3):1-16.

Marklund, S. and Marklund, G (1974). Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. Eur. J. Biochem., 47(3):469-474.

Ohkawa, H.; Ohishi, N. and Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal. Biochem., 95(2):351-358.

Oršoliœ, N.; Sirovina, D.; Odeh, D.; Gajski, G; Balta, V.; Šver, L. and Jazvinšœak Jembrek, M. (2021). Efficacy of caffeic acid on diabetes and its complications in the mouse. Molecules, 26(11):3262.

Sharma, P.; Singh, S.; Sharma, N.; Singla, D.; Guarve, K. and Grewal, A.S. (2022). Targeting human glucokinase for the treatment of type 2 diabetes: an overview of allosteric glucokinase activators. J. Diabetes Metab. Disord., 21(1):1129-1137.

Szymczak-Pajor, I.; Wenclewska, S. and Œliwiñska, A. (2022). Metabolic action of metformin. Pharmaceuticals, 15(7):810.

Yusuf, M.; Nasiruddin, M.; Sultana, N.; Akhtar, J.; Khan, M.I. and Ahmad, M. (2019). Regulatory mechanism of caffeic acid on glucose metabolism in diabetes. Res. J. Pharm. Technol., 12(10):4735-4740.