



Evaluating the Efficacy of Berberine Supplement versus Ozempic® Injection in Modulating Glycemic State, Lipid Metabolism and Body Weight in Streptozotocin-Induced Diabetic Rats

WASSAN MHAMMED HUSAIN^{1*}, ISRAA J. MOHAMMAD², DAHLIA N AL-SAIDI¹

¹Medical College, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq; ²College of Health and Medical Technology /Baghdad, Middle Technical university, Baghdad, Iraq.

Abstract | The goal of this study was to see the effect of berberine Hcl supplement versus the effect of Ozempic® injection on body weight, glycemic states, and lipid profile in diabetic rats. The experiment includes two parts: in the first part, forty adult rats with a body weight of 250 ± 50 are randomly divided into two groups. G1: are a control group, twenty rats intraperitoneal (IP) injection of normal saline twice weekly along with a normal (pellet) diet for four weeks. G2: are twenty rats induced diabetes by intraperitoneal injection of a low dose of Streptozotocin (35 mg/kg. BW) twice weekly along with a high-cholesterol diet for four weeks. Rats with fasting blood glucose greater than 190 mg/dl were considered diabetic animals. The second parts include three groups T1: Six diabetic rats were orally administered distilled water and subcutaneously injected with 0.25 mg/kg BW of normal saline for four weeks. T2: Six diabetic rats, orally administered with berberine Hcl 100 mg/kg B.W. and subcutaneously injected with 0.25 mg/kg B.W. normal saline one time per week for four weeks. T3: six diabetic rats treated by subcutaneously injecting Ozempic® 0.25 mg/kg B.W. one dose per week for four weeks with orally administration of distilled water. The result of first part were showed significant ($p \leq 0.00001$) elevation in the body weight from (250 ± 50 gm) of the control group to the (420 ± 30 gm) in the STZ group also elevated in the fasting blood glucose from (90mg/dl) in the control group to the (270 mg/dl) in STZ group. Result of second part of experiment to the body weight and blood collection at three times (zero time, 2nd week, and 4th week) for fasting blood glucose, insulin, insulin C-peptide, and lipid profile measurement were display a significant ($p \leq 0.05$), ($p \leq 0.00001$) decrease in body weight, fasting blood glucose, insulin, insulin C-peptide, and lipid profile in diabetic rats after treatment with berberine supplement and Ozempic® injection. When compared with zero time in the T1 group. At the end of the experiment, we can suggest the ability of 100 mg/kg B.W. of berberine supplement and 0.25 mg/kg B.W. of Ozempic® injection to control unintentional weight gain and improve glycemic status and lipid profile in STZ-induced diabetes within short treatment times (four weeks) and we recommend the further experiments with longer time (three month) for more current result.

Keywords | Ozempic® injection, Semaglutid, Berberine Hcl, Streptozotocin, Type two diabetes, Lipid profile, Insulin resistance

Received | January 03, 2025; **Accepted** | February 14, 2025; **Published** | February 22, 2025

***Correspondence** | Wassan Mhammed Husain, Medical College, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq; **Email:** Wassan.mh.husain@ibnsina.edu.iq

Citation | Husain WM, Mohammad IJ, Al-Saidi DN (2025). Evaluating the efficacy of berberine supplement versus ozempic® injection in modulating glycemic state, lipid metabolism and body weight in streptozotocin-induced diabetic rats. Adv. Anim. Vet. Sci. 13(3): 704-711.

DOI | <https://dx.doi.org/10.17582/journal.aavs/2025/13.3.704.711>

ISSN (Online) | 2307-8316; **ISSN (Print)** | 2309-3331



Copyright: 2025 by the authors. Licensee ResearchersLinks Ltd, England, UK.

This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Diabetes mellitus, is one of the most common metabolic illnesses in the world, is result in decreased insulin secretion, insulin resistance, and increased hepatic glucose production (Rahman *et al.*, 2021). Diabetes increase widely across the world, compared with overweight and obesity epidemic, therefore, it is great importance to find better prevention strategies for Type 2 diabetes. To achieve this aim, appropriate experimental models are critical for understanding the pathogenesis of therapeutic agents' actions and the genetic or environmental impacts that increase the risks of Type 2 diabetes (Zhang *et al.*, 2008). Numerous studies have indicated that the rats feeding on high-fat diet HFD developed insulin resistance (Kumar *et al.*, 2021). It is suggested that a high-fat diet may be an appropriate method to induce insulin resistance, it is an essential characteristic of Type 2 diabetes. Streptozotocin (STZ) induces diabetes mellitus by activating the β cell curtail (Farid *et al.*, 2022). Low-dose STZ has been shown to cause a modest impairment of insulin production, which is similar to the latter stages of Type 2 diabetes (Huo *et al.*, 2025)(Ming Zhang *et al.*, 2008). We are developing rats model to study the natural progression of Type two diabetes, including insulin resistance, β cell dysfunction, and metabolic features (Andonova *et al.*, 2023).

Glucagon-like peptide 1 receptor agonists [GLP-1RAs] seem to have various positive effects on beta cells, potentially helping people with Type 2 diabetes to maintain their glycemic control (Garber, 2011). GLP-1 has been established to suppress glucolipotoxicity in beta cells, allowing them preserve them and enhance their overall function (Costes *et al.*, 2021). Ozempic®, (semaglutide) is a GLP-1 analog, is the 2nd long-acting GLP-1 receptor (GLP-1R) agonist registered for the treatment of obesity (Müller *et al.*, 2022). Ozempic® was first used at lesser dosages to control type 2 diabetes mellitus, but it was recently registered at a larger dose for the treatment of obesity (Wilding *et al.*, 2021).

Folk medicine as a therapeutic alternative are extensively used by the community. According to the World Health Organization (WHO), around the 80% of the world's population uses traditional medicine for primary health needs and enhance quality of life, in fact the plant extracts or active ingredients used in the majority of traditional treatments (Che *et al.*, 2024).

Berberine alkaloids is a natural isoquinoline alkaloid derived from many plant species that has been used to treat dysentery and enteritis for many years. Recent pharmacological study has shown that Berberine has a variety of pharmacological activities, including decreasing insulin resistance, controlling blood lipids, lowering blood pressure,

lowering blood glucose and inflammatory indicators, and enhancing cardiovascular function. With a large number of clinical trials on berberine antidiabetic and anti-inflammatory benefits, it has sparked increased study interest (Ahmad Nazari *et al.*, 2024).

Because the berberine supplements are one of the folk medicines and Ozempic injections are pharmaceutical drugs, they are used for body weight control, with little studies to distinguish which of them is more effective than others in controlling body weight and glycemic status. Therefore, we study their effect on fat and diabetic rats, comparing them with rats without treatment to clarify whether their Ozempic injection is more effective than berberine supplements. The result of investigation may be important for treatment strategy to control the improved severity of type 2 diabetes and control of body weight by using berberine supplements or Ozempic injections.

MATERIAL AND METHODS

CHEMICALS AND KITS

Berberine Hcl by NOW company obtain from local pharmacy, Ozempic® injection shipping from Life MD, fasting blood sugar tested by accu-chek strip, serum insulin and lipid profile was teste by enzyme colorimetric method (spectrophotometer at a wavelength of 500 nm).

ANIMAL DESIGN

Forty adult male rats (4 to 5 month old) with a body weight of 250 ± 50 were put in cages, and placed in a room for one weeks of adaption. During the study, room temperature was kept between 21 °C and 25°C, the air was constantly changed via ventilation vacuum, and the light/dark cycle was set to 12:12 h/day. Animals in current study was followed the ARRIVE criteria (<https://arriveguidelines.org/>) of the animal housed and at the specialized veterinary studies laboratory in Iraq. The study included two part: first part, which is induced diabetes in rats, and the second part, which included treatment of diabetic rats with berberine Hcl and Ozempic®. Forty rats randomly divided to two group:

- G1: are a control group, twenty rats intraperitoneal (IP) injection of normal saline twice weekly along with a normal (pellet) diet for four weeks.
- G2: are twenty rats induced diabetes by intraperitoneal injection of a low dose of Streptozotocin (35 mg/kg. BW)(Jiang and Zhang, 2022) twice weekly along with a high-cholesterol diet for four weeks. The rats were permitted unrestricted access to a high-cholesterol diet consisting of 84.3% regular station chow, 5% fat, 10% yolk powder, 0.2% cholesterol, and 0.5% bile salt (Tang *et al.*, 2006). Rats with fasting blood glucose more than (190 mg/dl) was consider as a diabetic animal and di-

vided to three groups:

- T1: Six diabetic rats were orally administered distilled water and subcutaneously injected with 0.25 mg/kg BW of normal saline for four weeks.
- T2: Six diabetic rats, orally administered with berberine HCl 100 mg/kg B.W. and Subcutaneously injected with 0.25 mg/kg B.W. normal saline one time per week for four weeks.
- T3: six diabetic rats treated by subcutaneously injecting Ozempic® 0.25 mg/kg B.W. (Mahapatra *et al.*, 2022) one dose per week for four weeks with orally administration of distilled water.

PARAMETERS

Rats were weighted by electrical balance in each time of experiment and blood sample were collected in three time (zero time, 2nd week and 4th week) by vein tail and it was put in to EDTA tube for fasting blood glucose measure and gel tube for serum collection. Serum was prepared by centrifugation of collected blood at 2500rpm / 15 min and store in 4 °C (Husain and Alli, 2022) to measure: serum insulin and lipid profile.

STATISTICAL ANALYSIS

By Graph Pad Prism version 8.0.2., the statistically analyzed of data were performed. Comparison between means and variance by Tukey's of Graph Pad Prism and two-way ANOVA analysis for estimation P value (Walters *et al.*, 2021).

RESULTS AND DISCUSSION

FIRST PART OF EXPERIMENT, DIABETIC INDUCED RATS

The successful induced diabetes in rats after administrated with STZ and feeding on high fat diet were showed in Figure 1. The result in Figure 1A and B showed a significant elevation ($P \leq 0.001$) of both body weight and fasting blood glucose in STZ administrated group when compared with control group and a significant elevation ($P \leq 0.005$) when compared with zero time in the same group. Moreover, the result shown in Figure 1C and D demonstrate the significant ($P \leq 0.005$) elevation of serum insulin and insulin C-peptide respectively in STZ administrated group at doze (35 mg/kg. BW) when compared with control group and zero time in the same group.

SECOND PART OF EXPERIMENT, TREATED OF DIABETIC RATS

BODY WEIGHT: A significant ($P \leq 0.05$) decrease of body weight in T2 and T3 treated groups at 4th week of treatment as a compared with 2nd week and zero time compared with T1 group. Whereas, the result of body weight at 4th week in T3 group showed non-significant differences ($P > 0.05$) as a compared with T2 group at the same time. Also, at

the 2nd week of treatment in T3 group showed a significant ($P \leq 0.05$) decrease of body weight when compared with T2 at 2nd week. This results were demonstrated in Figure 2 and the clinical observation of treated rats sport the analytical test.

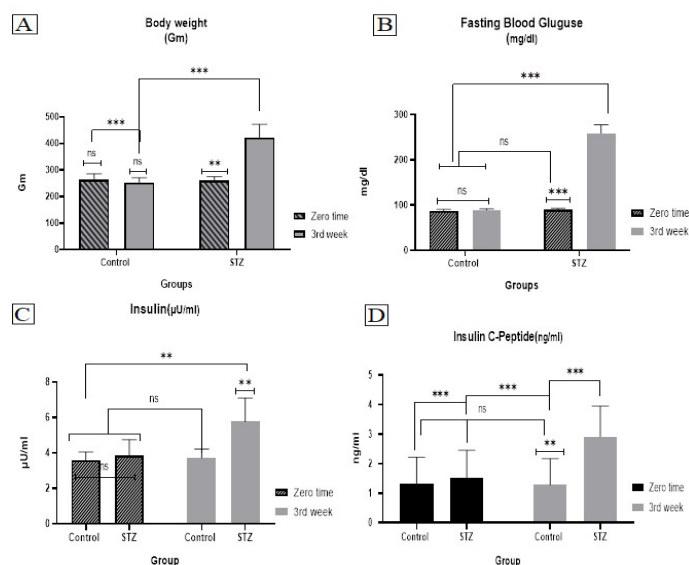


Figure 1: Effect of STZ injection on (A) Body weight; (B) fasting blood glucose; (C) insulin level; (D) insulin C-peptide in a rats at on zero time and 3rd week of part one of experiment. Value represented as M±SE; n=6 Rats; ns: ($P > 0.05$); ** ($P \leq 0.05$); *** ($P \leq 0.001$); **** ($P \leq 0.0001$); Second part of experiment: Treated of diabetic rats.

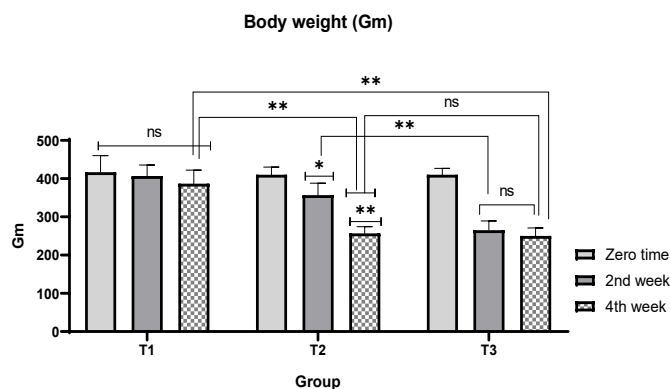


Figure 2: Effect of berberine supplement and Ozempic® injection on Body weight in a rats at on (zero time, 2nd and 4th week) of experiment. **T1:** Diabetic rats; **T2:** rats treated with (35 mg/Kg.B.W.) of berberine supplement; **T3:** rats injected with (0.25 mg/Kg.B.W.) of Ozempic® injection. Value represented as M±SE; n=6 Rats. ns: ($P > 0.05$); ** ($P \leq 0.05$); *** ($P \leq 0.001$); **** ($P \leq 0.0001$).

FASTING BLOOD GLUCOSE: The result showed a significant changes of blood glucose after treated with berberin supplement and Ozempic®, as illustrate in Figure 3, the opposed to T1 group, T2 and T3 showed significant ($P \leq 0.05$) and ($P \leq 0.001$) decrease in fasting blood glucose at 2nd and 4th week of treatment respectively. Moreover,

the rats in T3 group at 2nd and 4th week showed significant ($P \leq 0.05$), ($P \leq 0.001$) decrease respectively when compared with zero time of the same group. Will, the level of fasting blood glucose at 4th week of T3 showed non- significant differences ($P > 0.05$) as a compared with 4th week of T2 treated group. The result indicates the positive response of diabetic rats to the treatment.

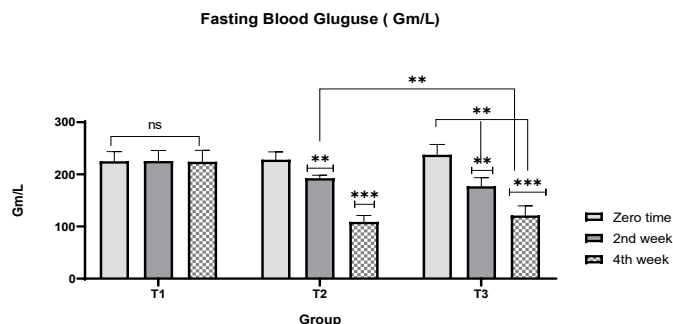


Figure 3: Effect of berberine supplement and Ozempic® injection on Fasting blood glucose in a rats at on (zero time, 2nd and 4th week) of experiment; **T1:** Diabetic rats; **T2:** rats treated with (35 mg/Kg.B.W.) of berberine supplement; **T3:** rats injected with (0.25 mg/Kg.B.W.) of Ozempic® injection. Value represented as $M \pm SE$; $n=6$ Rats. **ns:** ($P > 0.05$); ****** ($P \leq 0.05$); ******* ($P \leq 0.001$); ******** ($P \leq 0.0001$).

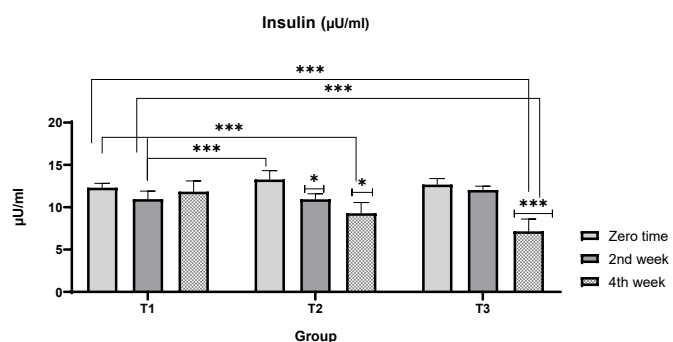


Figure 4: Effect of berberine supplement and Ozempic® injection on insulin in a rats at on (zero time, 2nd and 4th week) of experiment. **T1:** Diabetic rats; **T2:** rats treated with (35 mg/Kg.B.W.) of berberine supplement; **T3:** rats injected with (0.25 mg/Kg.B.W.) of Ozempic® injection. Value represented as $M \pm SE$; $n=6$ Rats. **ns:** ($P > 0.05$); ****** ($P \leq 0.05$); ******* ($P \leq 0.001$); ******** ($P \leq 0.0001$).

SERUM INSULIN AND INSULIN C- PEPTIDE: Level of serum insulin and insulin C-peptide respectively were revealed levels in Figure 4 and Figure 5 respectively. The significant ($P \leq 0.05$) decrease of serum insulin in T2 treated rats at 2nd week of treatment are shown when compared with zero time of T2 group. whereas showed non- significant differences ($P > 0.05$) when compared with 2nd week of T3 rats. Moreover, serum insulin in T3 treated group showed a significant ($P \leq 0.001$) decrease in 4th week as compared with zero time and 2nd week of same group, also, when compared with T1 treated group at all time of treatment.

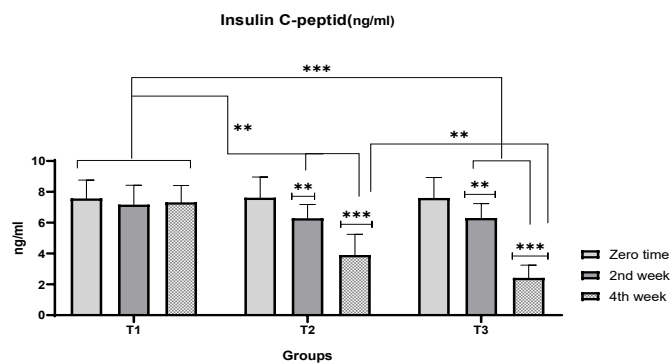


Figure 5: Effect of berberine supplement and Ozempic® injection on insulin C-peptide in a rats at on (zero time, 2nd and 4th week) of experiment; **T1:** Diabetic rats; **T2:** rats treated with (35 mg/Kg.B.W.) of berberine supplement; **T3:** rats injected with (0.25 mg/Kg.B.W.) of Ozempic® injection. Value represented as $M \pm SE$; $n=6$ Rats; **ns:** ($P > 0.05$); ****** ($P \leq 0.05$); ******* ($P \leq 0.001$); ******** ($P \leq 0.0001$).

On the other hand, the result was shown significant ($P \leq 0.001$), ($P \leq 0.005$), decrease insulin C-peptide in T2 and T3 treated rats at 2nd and 4th week of experiment respectively and when compared to the zero time of the same groups and all experiment time of T1 group. Furthermore, at 4th week of T3 showed significant ($P \leq 0.001$) decrease when compared with T2 group at the same time of experiment. The result of insulin C-peptide give us feedback to insulin secretion and working of pancreatic β -cell.

LIPID PROFILE TEST: Lipid profiled in diabetic induced rats after treated with berberine supplement and Ozempic® injection was illustrated in Figure 6. Figure 6A and B shown a significant ($P \leq 0.001$) decrease in cholesterol and triglyceride respectively in T2 and T3 at 2nd and 4th week when compared with T1 treated group, also shown a significant ($P \leq 0.001$) decrease in T2 at 2nd and 4th week as compared with zero time. Rats in T3 group was shown a significant ($P \leq 0.001$) decrease in cholesterol and triglyceride at 4th week when compared with 2nd week and zero time. Figure 6C revealed a significant ($P \leq 0.001$) rise in HDL in T2 when a compared with T1 group, and a significant ($P \leq 0.005$), ($P \leq 0.001$) elevation in HDL in T3 group when compared with T1 and T2 treated groups at 2nd and 4th week of treatment respectively. Moreover, this figure demonstrates the a significant ($P \leq 0.001$) elevation in HDL in T3 treated group at 4th week when compared with zero and 2nd week of treatment.

Furthermore, the Figure 6D depicted a significant ($P \leq 0.001$) decrease in LDL in T3 and T2 group when compared with rats in T1 treated group, also showed a significant ($P \leq 0.05$) decrease in T2 group at on 2nd week and a significant decrease ($P \leq 0.001$) at on 4th week as a compared with zero time in same group, moreover T3 group showed a significant ($P \leq 0.001$) decrease in LDL at 2nd and 4th week

when compared with 2nd and 4th week of T2 group and zero time of the same group.

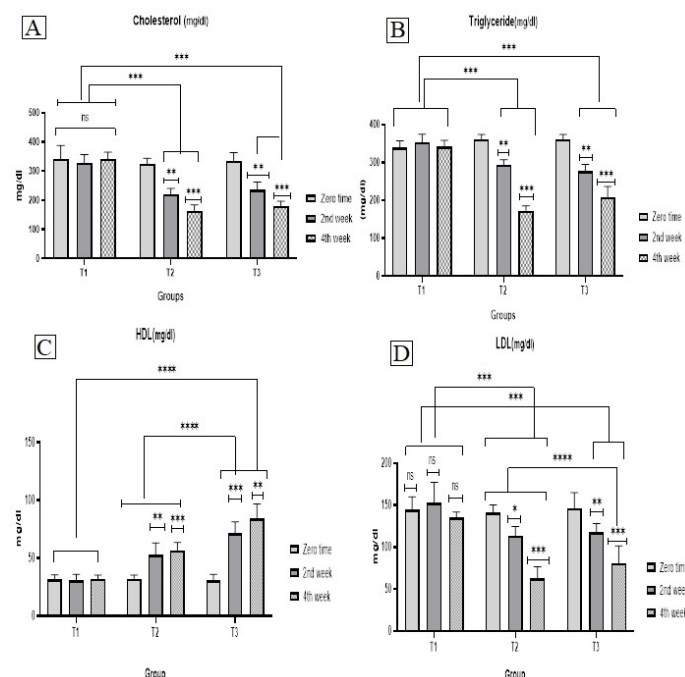


Figure 6: Effect of berberine supplement and Ozempic® injection on (A) cholesterol, (B) Triglyceride, (C) HDL, and (D) LDL in rats at on (zero time, 2nd and 4th week) of experiment; **T1:** Diabetic rats; **T2:** rats treated with (35 mg/Kg.B.W.) of berberine supplement; **T3:** rats injected with (0.25 mg/Kg.B.W.) of Ozempic® injection. Value represented as M±SE; n=6 Rats; ns:(P>0.05); *(P<0.05); ***(P<0.001); ****(P<0.0001).

The rat models are often utilized to investigate the metabolic outline of some features of type two diabetes pathophysiology. Because the rats have a short gestation period and achieve sexual maturity fast (Kottaisamy *et al.*, 2021) there are a quickly adjustments to a variety of diets, ambient circumstances, and manipulations (Domínguez-Oliva *et al.*, 2023). And from the result was shown in Figure 1 a significant elevation in body weight, fasting blood glucose, serum insulin and insulin C-peptide after 3rd week of administration of low dose from STZ. Increase in body weight maybe result from intentional weight gain by using high-fat diet and using the STZ to induce insulin beta cell dysfunction in a mild level (Shehnaz *et al.*, 2023). Furthermore, the result revealed increase in fasting blood glucose, insulin level and insulin C-peptide, this result may be due to the effect of STZ on pancreatic β -cell dysfunction, low dose of STZ cause induce a rise in fasting blood glucose as a result from the body responds to the initial injury caused by STZ to the some insulin-producing beta cells in the pancreas, however the elevation of serum insulin after 3rd week of STZ administration (35 mg/kg.BW) may be result from the compensatory response of remaining healthy pancreatic β -cell to compensate the function the damage

insulin-producing beta cells, this lead to typically increase in insulin C-peptide production because the C-peptide is byproduct of insulin production (Dakroub *et al.*, 2024).

The result from second part of experiment (Figure 2, 3, 4, 5 and 6) showed a significant decrease in body weight, fasting blood glucose, serum insulin and insulin C-peptide and lipid profile respectively in rats treated with berberine supplement and Ozempic® injection in the same level of two materials. Berberine supplement may be decrease blood glucose through activation of enzymatic pathway called AMP- activated protein kinase (AMPK), which help body to improving metabolism and increase fat burning (Jeon, 2016), also the AMPK enhance glucose uptake by the cells and reduce liver production of glucose lead to improve insulin sensitivity (Dayarathne *et al.*, 2021). another reason for this result is may be the berberine supplement act on the cell membrane to increase expression and translocation of glucose transporter type 4 receptor (GLUT4) (Lee *et al.*, 2006) which responsible for transport of glucose to the muscle and fat led to decrease level of glucose from blood. Furthermore, berberine supplement act to inhibit enzymes like fatty acid synthase and acetyl-CoA carboxylase (Ming *et al.*, 2023) by this way berberine supplement may be inhibit of hepatocyte for lipid production. Also, berberine supplement increase hepatic lipid clearance through increase Low-Density Lipoprotein Receptor (LDLR) expression and ATP-binding cassette transporter A1(ABCA1) (Cai *et al.*, 2023). However, regarding to the insulin C-peptide the result was indicate a significant down production of both C-peptide and insulin production, this result because the pancreas produces both insulin and C-peptide. When proinsulin is divided, it produces one molecule of insulin C-peptide respectively (Wei *et al.*, 2021). As a result, the level of C-peptide in the blood is proportional to the quantity of insulin generated. By the previous mechanism mechanisms berberine supplement may be lowering blood glucose level and reduce insulin resistance and by the way the body weight also decreased.

Comparing to the berberine supplement, the effect of Ozempic® injection done through a different mechanism which may be help to reduce body weight, fasting blood glucose and insulin sensitivity, Ozempic® is a GLP-1 receptor agonist (Głuszczyk *et al.*, 2024) that enhances insulin release from pancreatic beta cells in a controlled by glucose manner. This implies that it allows the body to create additional insulin when glucose levels are high, but not when they are low or normal. In another way, Ozempic® reduce glucagon secretion from pancreases (Palana *et al.*, 2024) lead to decrease blood sugar. On the other hand, Ozempic® simulates the effect of glucagon-like peptide-1 (GLP-1) (Li, 2024), a hormone related to glucose metabolism and lipid management. This can result in positive alterations in lipid levels. Furthermore, Ozempic® aids weight

reduction by decreasing stomach emptying and boosting sensations of fullness, leading to lower calorie intake and eventual weight loss. Weight loss is frequently related to changes in lipid profiles, including decreases in overall cholesterol levels, LDL cholesterol, and triglycerides.

The result of our study was agreed with Nazari *et al.* (2024) they showed a significant decreased in cholesterol, triglycerides, low-density lipoprotein, fasting blood sugar, insulin, HbA1c, the HOMA-, systolic arterial pressure, and weight, while elevating the amount of high-density lipoprotein (HDL) after treated with Berberine. Also, we agree with Zhang *et al.* (2021) which suggest the berberine may lower intestinal glucose absorption by blocking the IGF-1R-PLC- β 2-GLUT2 signaling pathway after sex week of treatment. And the Wang *et al.* (2021) was concluded that berberine may reduce the development of prediabetes to type 2 diabetes. in ZDF rats by increasing GLP-2 production, permeability of the intestines, and gut microbiota composition.

Our study also agreed with Basha *et al.* (2024) they demonstrate the semaglutide has a significant efficacy in achieving glycemic control and enhancing periodontal health in diabetic rats with induced gingivitis.

Berberine supplements act on the AMPK protein, which causes a decrease in glucose production from the liver, whereas ozempics act on the GLP-1 receptor, which causes an elevation of insulin production. Finally, these two pathways lead to control on glycemic status and ameliorate the dangers of the cardiovascular diseases.

CONCLUSIONS AND RECOMMENDATIONS

From the result of the current study, data reflected the ability of body weight control and improved glycemic status and lipid profile in STZ-induced diabetes rats through reduced glucose levels and improved insulin secretion and lipid profile after treatment with the 100 mg/kg B.W. of berberine supplement and 0.25 mg/kg B.W. of Ozempic® injection. This result suggests the ability of using them to control unintentional weight gain within short treatment times.

We recommended to study the effect of berberine supplement and Ozempic® injection to gather on physiology of cardiovascular and inflammatory states of the body with large papulation and long duration of treatment.

ACKNOWLEDGMENTS

I'd want to thank everyone who helped me accomplish this project.

This study presents a comprehensive analysis of the effect of two materials with two different mechanisms of action on glycemic states and lipid profile in order to investigate whether one of them is more effective than the other. This study concerns an area that has remained relatively under-explored until now. Oure study consider first study compared between berberine supplement and Ozempic® injection in regarding to the glycemic states and lipid profile.

AUTHOR'S CONTRIBUTIONS

Wassan Mhammed Husain: work on methodology, animal design, final formatting of article.

Israa J. Mohammad: Investigation, writing original draft review and discussion and editing.

Dahlia N Al-Saidi: Statistical and formal analysis, data curation.

ETHICAL STATEMENT

Current study with IACUC No. 2589 on August 1st 2024, was conducted in the animal house at the specialized veterinary studies laboratory, Iraq. Followed the ARRIVE criteria (<https://arriveguidelines.org/>) for experiment animals ethic.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

REFERENCES

- Ahmad Nazari, Zahra Rostami Ghotbabadi, Kimia Sadat Kazemi, Yalda Metghalchi, Reza Tavakoli, Razieh Ziaei Rahimabadi MG (2024). The Effect of Berberine Supplementation on Glycemic Control and Inflammatory Biomarkers in Metabolic Disorders: An Umbrella Meta-analysis of Randomized Controlled Trials. Clin. Ther., 46(2): e64-e72. <https://doi.org/10.1016/j.clinthera.2023.10.019>
- Andonova M, Dzhelebov P, Trifonova K, Yonkova P, Kostadinov N, Nancheva K, Ivanov V, Gospodinova K, Nizamov N, Tsachev I (2023). Metabolic Markers Associated with Progression of Type 2 Diabetes Induced by High-Fat Diet and Single Low Dose Streptozotocin in Rats. Vet. Sci., 10(7): 431. <https://doi.org/10.3390/vetsci10070431>
- Basha SM, Essawy MM, Ahmed NM, Shawky HA (2024). Assessment of Semaglutide Therapy on Inflammatory Mediators in Diabetic Rats with Experimental Periodontitis. Egyptian Dental Journal, 70(4): 3367-3377. <https://doi.org/10.21608/edj.2024.309230.3143>
- Cai Y, Yang Q, Yu Y, Yang F, Bai R, Fan X (2023). Efficacy and underlying mechanisms of berberine against lipid metabolic diseases: a review. Front. Pharmacol., 14: 1283784. <https://doi.org/10.3389/fphar.2023.1283784>
- Che CT, George V, Ijnu TP, Pushpangadan P, Andrae-Marobela K (2024). Tradit. Med. Pharmacogn., 11-28. <https://doi.org/10.3389/fphar.2023.1283784>

- org/10.1016/B978-0-443-18657-8.00037-2
- Costes S, Bertrand G, Ravier MA (2021). Mechanisms of beta-cell apoptosis in type 2 diabetes-prone situations and potential protection by GLP-1-based therapies. *Int. J. Mol. Sci.*, 22(10): 5303. <https://doi.org/10.3390/ijms22105303>
- Dakroub A, Dbouk A, Asfour A, Nasser SA, El-Yazbi AF, Sahebkar A, Eid AA, Iratni R, Eid AH (2024). C-peptide in diabetes: A player in a dual hormone disorder? *J. Cell. Physiol.*, <https://doi.org/10.1002/jcp.31212>
- Dayarathne LA, Ranaweera SS, Natraj P, Rajan P, Lee YJ, Han CH (2021). The effects of naringenin and naringin on the glucose uptake and AMPK phosphorylation in high glucose treated HepG2 cells. *J. Vet. Sci.*, 22(6). <https://doi.org/10.4142/jvs.2021.22.e92>
- Domínguez-Oliva A, Hernández-Ávalos I, Martínez-Burnes J, Olmos-Hernández A, Verduzco-Mendoza A, Mota-Rojas D (2023). The importance of animal models in biomedical research: current insights and applications. *Animals*, 13(7): 1223. <https://doi.org/10.3390/ani13071223>
- Farid MM, Aboul Naser AF, Salem MM, Ahmed YR, Emam M, Hamed MA (2022). Chemical compositions of Commiphora opobalsamum stem bark to alleviate liver complications in streptozotocin-induced diabetes in rats: Role of oxidative stress and DNA damage. *Biomarkers*, 27(7): 671–683. <https://doi.org/10.1080/1354750X.2022.2099015>
- Garber AJ (2011). Incretin effects on β -cell function, replication, and mass: the human perspective. *Diabetes Care*, 34(Suppl 2): S258. <https://doi.org/10.2337/dc11-s230>
- Głuszczyk A, Plizga J, Makłowicz A, Kopczyńska E, Szpulak A, Frańczuk A, Grzelka M, Głowska J, Kuleta K, Karkos P (2024). Challenges and risks of using GLP-1 antagonists in treating type 2 diabetes and obesity. *Quality in Sport*, 17: 53683. <https://doi.org/10.12775/QS.2024.17.53683>
- Huo L, Zhang H, Hou S, Li W, Meng Q, Li C, Ma X, Huang L, He J, Zhao B (2025). Low-dose IL-2 restores metabolic dysfunction and immune dysregulation in mice with type 2 diabetes induced by a high-fat, high-sugar diet and streptozotocin. *Int. J. Biol. Macromol.*, 286: 138468. <https://doi.org/10.1016/j.ijbiomac.2024.138468>
- Jeon SM (2016). Regulation and function of AMPK in physiology and diseases. *Exp. Mol. Med.*, 48(7): e245–e245. <https://doi.org/10.1038/emm.2016.81>
- Jiang N, Zhang Y (2022). Antidiabetic effects of nerolidol through promoting insulin receptor signaling in high-fat diet and low dose streptozotocin-induced type 2 diabetic rats. *Hum. Exp. Toxicol.*, 41: 09603271221126487. <https://doi.org/10.1177/09603271221126487>
- Kottaisamy CPD, Raj DS, Prasanth Kumar V, Sankaran U (2021). Experimental animal models for diabetes and its related complications—a review. *Lab. Anim. Res.*, 37(1): 23. <https://doi.org/10.1186/s42826-021-00101-4>
- Kumar A, Sundaram K, Mu J, Dryden GW, Sriwastva MK, Lei C, Zhang L, Qiu X, Xu F, Yan J (2021). High-fat diet-induced upregulation of exosomal phosphatidylcholine contributes to insulin resistance. *Nat. Commun.*, 12(1): 213. <https://doi.org/10.1038/s41467-020-20500-w>
- Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y, Ye JM, Lee CH, Oh WK, Kim CT (2006). Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. *Diabetes*, 55(8): 2256–2264. <https://doi.org/10.2337/db06-0006>
- Li W (2024). Semaglutide Analogues Enhancing GLP-1R Activation: A Dynamic Structural Electrostatic Perspective. *BioRxiv*, 2011–2024. <https://doi.org/10.1101/2024.11.29.625980>
- Mahapatra MK, Karuppasamy M, Sahoo BM (2022). Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. *Rev. Endocr. Metab. Disord.*, 23(3): 521–539. <https://doi.org/10.1007/s11154-021-09699-1>
- Ming JH, Wang T, Wang TH, Ye JY, Zhang YX, Yang X, Shao XP, Ding ZY (2023). Effects of dietary berberine on growth performance, lipid metabolism, antioxidant capacity and lipometabolism-related genes expression of AMPK signaling pathway in juvenile black carp (*Mylopharyngodon piceus*) fed high-fat diets. *Fish Physiol. Biochem.*, 49(5): 769–786. <https://doi.org/10.1007/s10695-022-01143-8>
- Müller TD, Blüher M, Tschöp MH, DiMarchi RD (2022). Anti-obesity drug discovery: advances and challenges. *Nat. Rev. Drug Discov.*, 21(3): 201–223. <https://doi.org/10.1038/s41573-021-00337-8>
- Nazari A, Ghotbabadi ZR, Kazemi KS, Metghalchi Y, Tavakoli R, Rahimabadi RZ, Ghaheri M (2024). The effect of berberine supplementation on glycemic control and inflammatory biomarkers in metabolic disorders: an umbrella meta-analysis of randomized controlled trials. *Clin. Ther.*, 46(2): e64–e72. <https://doi.org/10.1016/j.clinthera.2023.10.019>
- Palana C, Aburumman A, Kachungunu CNK, Hocquard A, Avila G, Pagana A, Chen A, John T (2024). Analyzing The Effects Of Semaglutide (Ozempic/Wegovy) On Metabolism: Investigating Correlations With Weight Reduction. *J. Positive Psychol. Wellbeing*, 8(4): 19–41.
- Rahman MS, Hossain KS, Das S, Kundu S, Adegoke EO, Rahman MA, Hannan MA, Uddin MJ, Pang MG (2021). Role of insulin in health and disease: an update. *Int. J. Mol. Sci.*, 22(12): 6403. <https://doi.org/10.3390/ijms22126403>
- Shehnaz SI, Roy A, Vijayaraghavan R, Sivanesan S, Pazhanivel N (2023). Modulation of PPAR- γ , SREBP-1c and inflammatory mediators by luteolin ameliorates β -cell dysfunction and renal damage in a rat model of type-2 diabetes mellitus. *Mol. Biol. Rep.*, 50(11): 9129–9142. <https://doi.org/10.1007/s11033-023-08804-8>
- Tang LQ, Wei W, Chen LM, Liu S (2006). Effects of berberine on diabetes induced by alloxan and a high-fat/high-cholesterol diet in rats. *J. Ethnopharmacol.*, 108(1): 109–115. <https://doi.org/10.1016/j.jep.2006.04.019>
- Walters SJ, Campbell MJ, Machin D (2021). Medical statistics: a textbook for the health sciences. John Wiley Sons.
- Wang Y, Liu H, Zheng M, Yang Y, Ren H, Kong Y, Wang S, Wang J, Jiang Y, Yang J (2021). Berberine slows the progression of prediabetes to diabetes in Zucker diabetic fatty rats by enhancing intestinal secretion of glucagon-like peptide-2 and improving the gut microbiota. *Front. Endocrinol.*, 12: 609134. <https://doi.org/10.3389/fendo.2021.609134>
- Wei Y, Quan L, Zhou T, Du G, Jiang S (2021). The relationship between different C-peptide level and insulin dose of insulin pump. *Nutr. Diabetes*, 11(1): 7. <https://doi.org/10.1038/s41387-020-00148-7>
- Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingway I, McGowan BM, Rosenstock J, Tran MTD,

- Wadden TA (2021). Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.*, 384(11): 989–1002. <https://doi.org/10.1056/NEJMoa2032183>
- Husain WM, Alli ZS (2022). The Effective Role of Phitofert® Supplement in Male Reproductive Hormones and Epididymal Sperm Quality in Carbon Tetrachloride (CCL4) treated rats. *Adv. Anim. Vet. Sci*, 10(2): 292. <https://doi.org/10.17582/journal.aavs/2022/10.2.292.297>
- Zhang M, Yang H, Yang E, Li J, Dong L (2021). Berberine decreases intestinal GLUT2 translocation and reduces intestinal glucose absorption in mice. *Int. J. Mol. Sci.*, 23(1): 327. <https://doi.org/10.3390/ijms23010327>
- Zhang M, Lv XY, Li J, Xu ZG, Chen L (2008). The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. *Exp. Diabetes Res.*, 2008. <https://doi.org/10.1155/2008/704045>