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Original Article

Berberine Suppresses Gestational Diabetes in Streptozotocin-induced Diabetes Mellitus Rats by Suppression of Inflammatory Mediators

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a serious health condition witnessed among females who experience insulin resistance and glucose intolerance with the onset of pregnancy. Multiple risk factors prevail both to the gestating mother and the growing fetus at the time of pregnancy which may prolong even postpartum. **Aim:** Berberine, a natural plant extract known for its anti-inflammatory and potent antidiabetic activity was used to clinically suppress the risk factors involved in Gestational diabetes mellitus. **Materials and Methods:** Female Wistar rats were used as the models for this study. Streptozotocin was administered to induce diabetes in the female rat model. Berberine was administered to the test animals and monitored with regular analysis of body weight, fetal-placental weight and index, Foetal Blood Glucose (FBG), Serum advanced glycation end products (AGEs), and antioxidant enzyme concentrations. Biochemical parameters, lipids, and pro-inflammatory cytokine levels were assayed to study the influence of Berberine. **Results:** Upon investigating, it was observed that Berberine produced remarkable activity in suppressing glucose intolerance and insulin resistance by targeting multiple criteria, including inflammatory mediators enlisted above. **Conclusion:** From this study, it is evident that Berberine can be used as a therapeutic agent to treat gestational diabetes.

Keywords: Gestational diabetes mellitus, Inflammation, Berberine, Antioxidant, Antidiabetic.

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INTRODUCTION

Glucose intolerance within females, detected either simultaneously, or within 28 weeks from the onset of pregnancy, is termed Gestational Diabetes Mellitus (GDM). The term is independent of the time of diagnosis, method of treatment, or its persistence post-pregnancy.[1] Diabetes mellitus (DM) is an intensively growing health issue that was reported to be 135 million in 1995 and is expected to increase to 300 million by 2025.[2] This chronic disorder disarranges the normal metabolic activity which results in increased blood glucose level, defective insulin activity or production or both. This hyperglycaemic condition induces the production of glycated proteins and reactive oxygen species (ROS), which triggers the manifestation of various pathophysiological events beginning from the occurrence of atherosclerosis.[3]

GDM affects both mother and the fetus. It may result in various short and long-term clinical conditions that may range from placental lesions to type 2 diabetes in the off spring. IR and β-cell dysfunction are among the critical events that may have pre-existed due to type 2 DM or as a manifestation of GDM.[4] With the continuance of pregnancy, a GDM diagnosed mother experience an increase in glycemia. This increase in the hyperglycaemic condition in a continuous fashion increases the risks to the fetus. Thus, a threshold glycaemic condition does not exist, that may help to discriminate between low-risk and high-risk pregnancy.[5]

With the advancement in diabetes research, suggestions arise that intrauterine metabolic disorders induced by GDM may increase the risk to the fetus for obesity and diabetes upon birth. The risks to offspring of GDM mothers have also been associated with the weight at birth and maternal obesity. Children that were observed to be large for gestational age, at birth, were more prone to obesity than the normal weight ones. Of late, it has been studied that low to high-risk mothers can be identified by a technique of measuring the fetal abdominal circumference growth.[6]

Dysregulation of inflammatory mediators has been reported in GDM mothers. Increased TNF-α concentration in the serum with

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the onset of gestation and rise in Interleukin-6 (IL-6) levels during delivery. Furthermore, decreased levels of anti-inflammatory mediators have also been reported, which identified reduced levels of adiponectin, and Interleukin-10 (IL-10) in those who have been diagnosed with GDM independent of obesity. These findings are persistent to establish that a state of inflammatory imbalance is revealed that causes lower sensitization towards insulin.[7] The study is also reliable to establish its association with GDM according to the previous studies conducted on the aged population with type 2 DM.[8]

Expression profiling techniques brought to light that, genes involved in inflammatory responses and those that are responsible for the endothelial reorganization of the fetus are altered as a result of GDM. Out of 110 genes, 1/3rd is modified to induce a state of chronic inflammation in the placental environment leading to various abnormalities in the growing fetus.[9] Accumulation of advanced glycation end products has been reported in recent studies, that are associated with the hyperglycaemic state of the body, where excessive glucose binds to free amino acids of proteins, independently (i.e. non-enzymatically). The conjugating activity has also been observed in lipids and nucleic acids. This results in the formation of advanced glycation end products (AGEs) that are observed to accumulate in the tissues. This induces various pathological effects such as crosslinking of collagen and matrix proteins, increase in vascular permeability, mononuclear cell infiltration, and other complications.[10] Further studies on AGEs reveal, that the receptor for AGEs (RAGE) combine to activate the signaling pathway to induce oxidative stress through an excessive accumulation of ROS in tissues leading to inflammation, hyperglycemia and birth defects.[11]

Drug groups such as salicylates and thiazolidinediones have been used to increase the anti-inflammatory response against the cytokines, thereby improving the glucose metabolism in diabetic individuals.[12,13] Salicylates such as aspirin inhibit the cyclooxygenase pathway of producing prostaglandins and also inhibit the nuclear factor-kappa B to suppress the inflammatory signaling pathways.[14] Thiazolidinediones are agents that aid to upregulate the expression of proteins required for adipocyte differentiation, fatty acid, and glucose metabolism. It also increases adiponectin levels in the plasma and also decreases the concentration of C-reactive proteins, which are a general marker of inflammation.[15]

Phytochemicals including terpenoids, phenols, alkaloids, and other sulfur-containing compounds have been investigated to possess antioxidant and antidiabetic effects. Due to their vast availability, effectiveness, and safe nature, the demand for these compounds has risen for their therapeutic effects.[16] Among such compounds is Berberine, extracted from the plant Coptis Chinensis French, antidiabetic and Pharmacological activities of alkaloids.[17] The antidiabetic activity of Berberine in type 2 DM has been well established by various researchers and its potent activity has been investigated against a placebo in 3 months.[18] Present study intends to investigate the *in vivo* antioxidative and antidiabetic activity of Berberine in gestating rats induced with GDM using Streptozotocin (STN) and simultaneously observes the basic mechanism of its therapeutic action.

MATERIALS AND METHODS

Chemicals

All chemicals used in the current investigation were purchased from a standard local vendor. Streptozotocin and Berberine were purchased exclusively from Sigma Aldrich.

Gestational Rats

30 female and 6 male Wistar rats of 8-10 weeks old, were maintained in laboratory conditions as 12hr day-night cycle, with about 300 Lx illumination at 20-23°C and approximately 70% relative humidity. The rodents were fed saline as 20 ml/kg with the help of oral gavage during the acclimatization period. After 1 week the rats were placed on hanging shelves with litter trays.

Post acclimatization, the male and female rats were housed in 1:1 in individual cages to induce copulation. After 12 hr, the female rats were analyzed for successful fertilization. Vaginal smears were taken with the help of pessaries and taken for microscopic examination for confirmation. The identified gestating female rats were marked as Day 0. Thirty Six female rats including unfertilized individuals were selected for further study.

Conceived rats were maintained further with a high sugar-fat diet whereas, a basic diet was given to the unfertilized female rats.

Induction of gestational diabetes

To induce GDM, the conceived rats were made to fast overnight on the first day of pregnancy. Intraperitoneal injection with 40mg/kg of Streptozotocin was administered. The blood glucose level was tested using commercially available kits following the manufacturer's instructions.[11]

Experimental Protocol

The rodents were divided into five groups containing six rats in each group. The groups were treated as mentioned below:

Group I - Negative control with basic diet;

Group II - Positive control GDM induced rats;

Group III - GDM rats treated with Berberine (25mg/kg) by weight;

Group IV - GDM rats treated with Berberine (50mg/kg) by weight;

Group V - GDM rats treated with Berberine (100mg/kg) by weight;

Oral administration of Berberine was given to the rats as prescribed above, once daily till the completion of the experiments. Blood was collected in serum-free tubes for further tests through retro-orbital sinus bleeding. The animal experiments were conducted following the approval from their Institutional Animal Ethical Committee (JYPH2022A03).

Biochemical Estimation

Parameters such as Foetal Blood Glucose (FBG) level, serum AGEs, serum C-peptide, hepatic glycogen, glycosylated hemoglobin A1c (HbA_{1c}), and free fatty acid (FFA) were assessed through the standard protocols with minor amendments.[11,20,21]

Antioxidant Parameters

Parameters including glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) were analyzed using commercially available kits following the manufacturer's protocol (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Lipid Parameters

For Lipid profile analysis total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), Low-density lipoprotein (LDL), and very-low-density lipoprotein were analysed. LDL and VLDL alone were calculated manually using the below-mentioned formulae,[21] while the rest of the parameters were tested using commercial kits following the kit-insert protocol. (Nanjing Jiancheng Bioengineering Institute, Nanjing, China)

$$LDL = \frac{TC - HDL - TG}{5.0}$$

$$VLDL = \frac{TG}{5.0}$$

Pro-inflammatory cytokines

TNF-α, IL-1β, IL-6, IL-10 were the pro-inflammatory cytokines evaluated through ELISA following the protocol provided by the manufacturer of the commercial kit used to examine. (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Statistical Analysis

Data were studied by using the GraphPad prism software (GraphPad, San Diego, CA). Data were depicted as mean ± standard deviation of triplicate values. One-way ANOVA afterward DMRT analysis was done to assess the disparities between groups. The significance level was fixed at $p < 0.05$.

RESULTS

Body Weight

Among the 5 groups of rats, it was observed that rats treated with Streptozotocin alone (Group II) experienced a significant loss of body weight (Figure 1). The phenomenon was observed both before and after the onset of pregnancy. The negative control group that only received a high sugar-fat diet showed a fair increase in body weight when compared to the rest of the groups, both before and upon gestation. The groups that were treated with Berberine showed a higher body weight in comparison to the positive control group and the increase in body weight was observed to vary in a dose-related trend. Rats that received 100 mg/kg of Berberine were observed to have the highest body weight among the other 2 test groups.

Foetal Weight, Placental Index and Placental Weight

The foetal weight, placental index, and placental weight were observed in all the groups. The furnished results displayed an increase in foetal weight with elevation in the concentration of Berberine from 25mg/kg to 100 mg/kg (Figure 2a). The foetal weight of negative controls was noted to be highest and those that received only Streptozotocin (STN), showed the lowest foetal weight.

The trend in the graph was observed to be different in the case of placental weight and placental index. The placental index was observed to be least for the negative control group. The value was highest for the positive control group that was administered STN alone. Groups III, IV, and V exhibited suppression of placental weight and placental index with an increase in concentration (Figure 2b, 2c).

Foetal Blood Glucose Level

Blood glucose levels were measured at various time intervals after gestation. Upon compilation of the observed results, it was seen that GDM rats had higher blood glucose levels (Figure 3). Negative groups displayed the least blood glucose level. The test groups III, IV, V witnessed suppression in the blood glucose levels significantly, with an increase in the concentration of the drug.

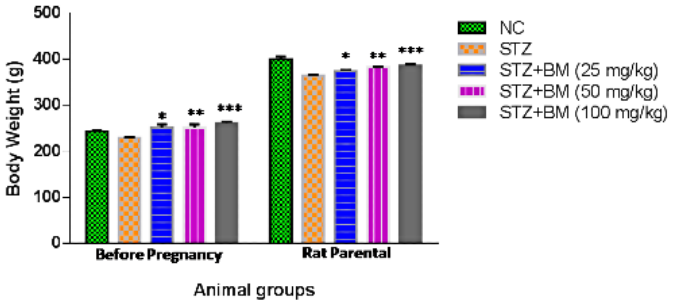

Figure 1: Effect of Berberine on the bodyweight of normal and GDM group of rats. Where *p<0.05, **p<0.01, ***p<0.001 When compared with GDM Group.

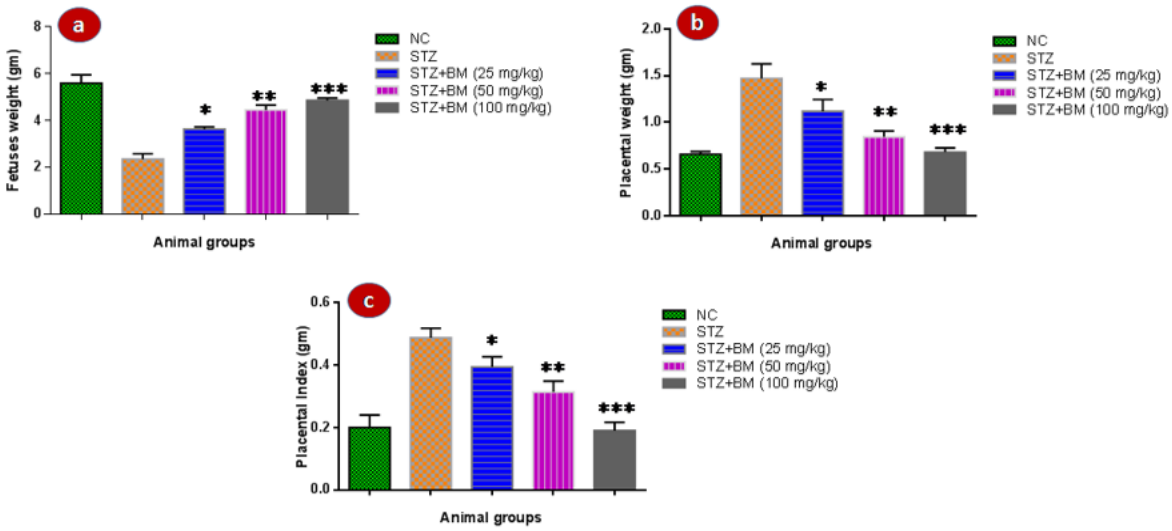

Figure 2: Effect of Berberine on the Faustus weight (a), Placental Weight (b), and Placental Index (c) of normal and GDM group of rats. Where **p*<0.05, ***p*<0.01, ****p*<0.001 When compared with GDM Group.

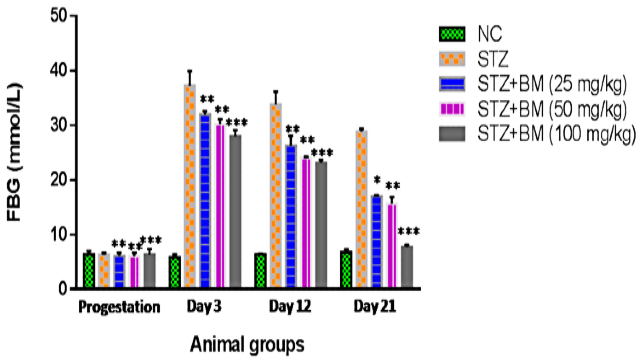

Figure 3: Effect of Berberine on the Blood Glucose level of normal and GDM group of rats. Where **p*<0.05, ***p*<0.01, ****p*<0.001 When compared with GDM Group.

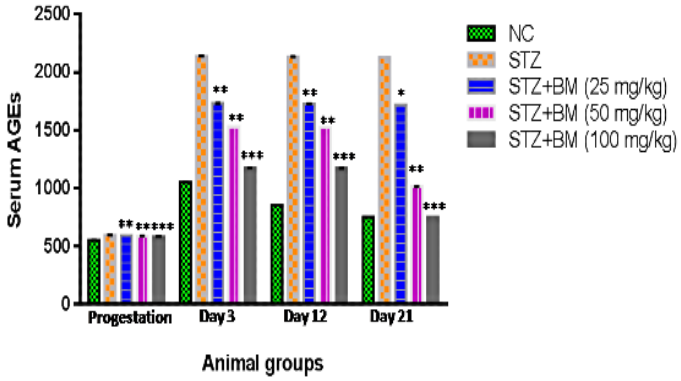

Figure 4: Effect of Berberine on Serum AGEs level of normal and GDM group of rats. Where **p*<0.05, ***p*<0.01, ****p*<0.001 When compared with GDM Group.

Serum AGEs

Serum AGE levels were assessed regularly for all the groups in the protocol. The positive control group was observed to have more serum AGE concentration in the blood, than the test and the negative control groups. The negative controls expressed a minimal amount of serum AGEs followed by the test groups that had GDM and were treated with Berberine. The serum AGE levels were noted to show a decreasing inclination in the graph in a dose-dependent manner (Figure 4). The concentration of serum AGEs was also seen to reduce overall with the prolongation of treatment with Berberine in the GDM induced test groups.

Lipid Profile

Total cholesterol, LDL, VLDL, and Triglycerides were observed to be suppressed in the GDM rats (Figure 5). GDM rodents that did not receive any treatment had significantly elevated TC, LDL, Triglyceride, and VLDL levels. The negative controls indicated the normal lower values of the above-mentioned lipid parameters.

In contrast to the results of the above-mentioned parameters, high-density lipoprotein levels were highest for the negative control groups. The positive controls exhibited the lowest HDL level and the value of this lipid parameter was observed to increase with the concentration of Berberine.

Antioxidant Enzymes

SOD, GPx, CAT, and GSH enzymes were quantified as per the experimental procedures and the levels of these enzymes presented an intriguing style of variation for each group (Figure 6). The antioxidant enzymes were noted to be maximum in Group V that received 100 mg/kg of Berberine. The decrease in trend was observed on moving towards a lower concentration of the same drug and was observed to be least in the positive control group. The negative control rodents presented an explicitly high level of antioxidant enzyme concentrations.

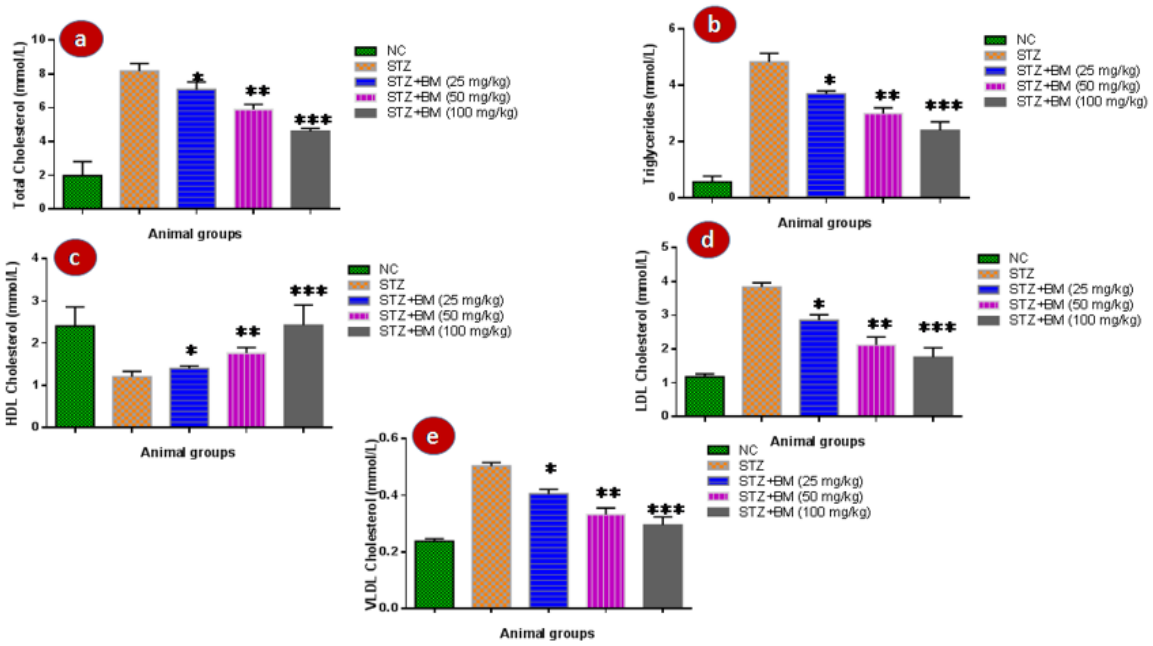

Figure 5: Effect of Berberine on the Lipid profile of normal and GDM group of rats. Total cholesterol (a), triglycerides (b), HDL (c), LDL (d) and VLDL (e) Where *p<0.05, **p<0.01, ***p<0.001 When compared with GDM Group.

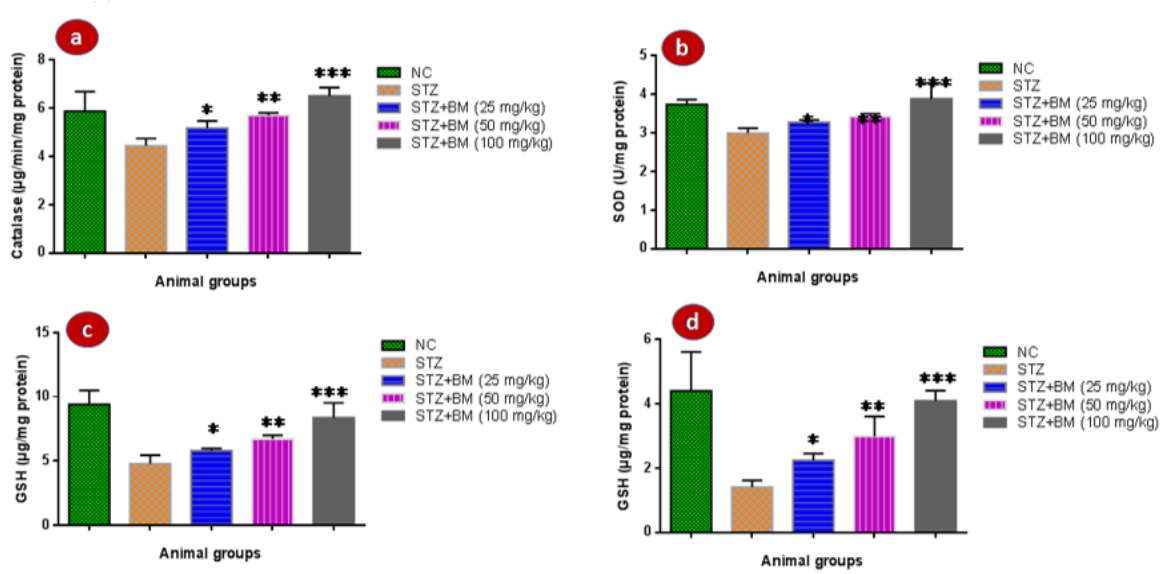

Figure 6: Effect of Berberine on the antioxidant parameter of normal and GDM group of rats. SOD (a), Catalase (b), GPx (c), and GSH (d) Where *p<0.05, **p<0.01, ***p<0.001 When compared with GDM Group.

Biochemical Parameters

The activity of Berberine on HbA_{1c}, Hepatic glycogen, Serum C-peptide and FFA levels was detected using the standard experimental procedures. It was observed values were noted in terms of mean ± standard error (Figure 7).

All parameters were observed to be within the normal range for the negative controls and induction of GDM elevated these levels except for that of free fatty acids (FFA) which observed a sink when compared to the normal group. However, the test groups witnessed a lower elevation in these parameters and suppression can be observed as the concentration of drug increased from Group II to Group V. FFA levels were observed to be raised significantly in the test groups and this rise was also detected to surge depending upon the dosage.

Pro-inflammatory Cytokine Levels

Inflammatory mediators such as TNF-α, IL-6, IL-1β were assayed to detect the presence of inflammation. Along with this IL-10, which is a natural inflammatory suppressor produced by the body, was also quantified to study the effect of Berberine. The concentration of inflammatory mediators was observed to be substantially high in the positive control and test groups when

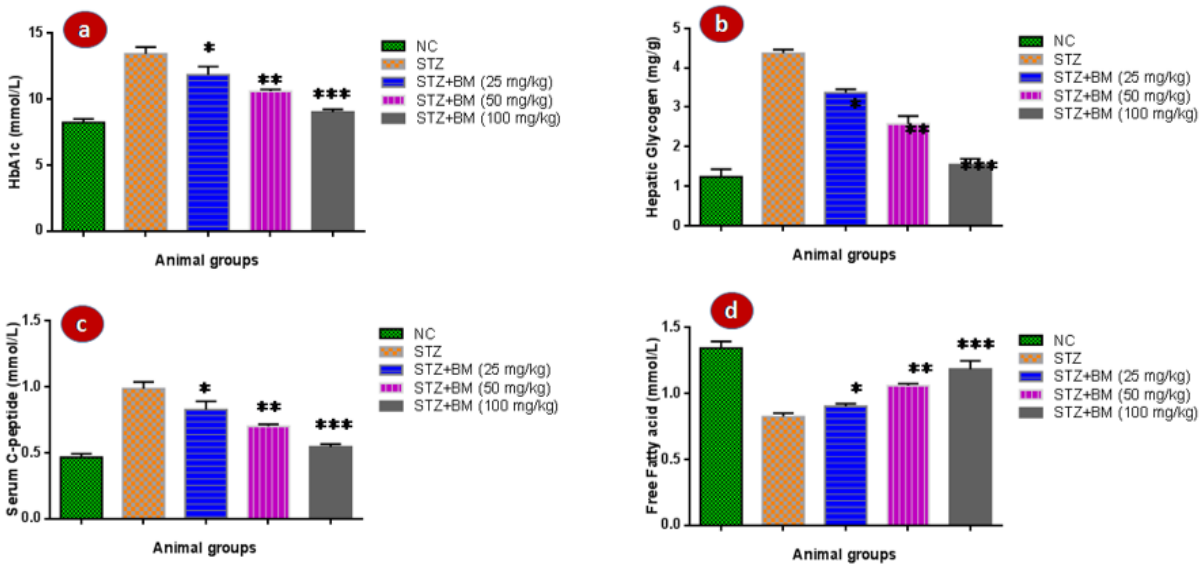

Figure 7: Effect of Berberine on the biochemical parameter of normal and GDM group of rats. HbA1C (a), Hepatic glycogen (b), Serum C-peptide (c), Free fatty acid (d) Where *p<0.05, **p<0.01, ***p<0.001 When compared with GDM Group.

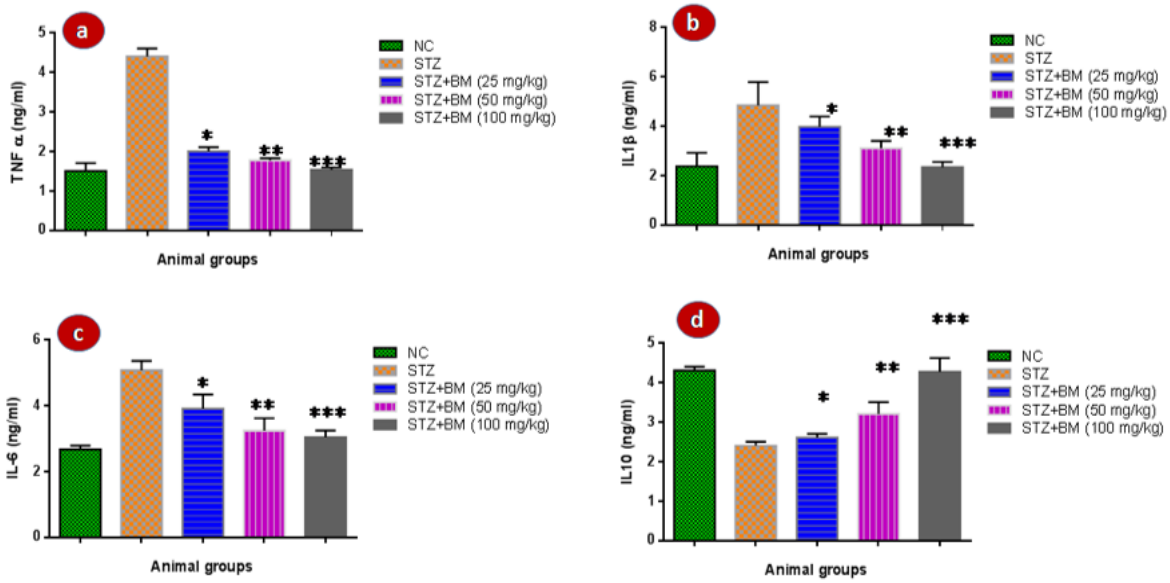

Figure 8: Effect of Berberine on the Pro-inflammatory cytokine parameter of normal and GDM group of rats. TNF α (a), IL-1β (b), IL-6 (c), and IL-10(d) Where *p<0.05, **p<0.01, ***p<0.001 When compared with GDM Group.

compared to the normal rats. The highest levels of these mediators were noted in the positive control group that only received STN. In contrast to this, IL-10 levels were noted to be very low in the test and the positive control groups. Nevertheless, these levels were observed to be regulated towards the normal range (when compared with the negative control group) in Groups III, IV, and V that and the magnitude was seen to change in a dose-dependent manner (Figure 8). IL-10 levels were increased in the test groups notably, with an increase in the concentration of drug dosage from 25mg/kg to 100 mg/kg respectively.

DISCUSSION

14% of the overall population of the United States is affected by Gestational diabetes mellitus every year. Insulin resistance in the body is the major health condition among diabetic individuals, which if not regulated by the body in a compensatory manner with the onset of pregnancy, results in GDM. Women who are obese, in their late twenties, and who have a preceding history of diabetes or those females who belong to such ethnic groups are said to be more prone to this health condition.[22] Risk factors associated with GDM to the growing fetus include- pre-eclampsia, macrosomia, polyhydramnios, operative delivery, shoulder

dystocia, birth canal laceration, neonatal hypoglycemia, and in severe cases even perinatal mortality.[23]

The task of physicians in cases of GDM is to control the glycaemic condition. A specific diet is very essential; however, if this does not result sufficient, then the patient may require insulin therapy. It is still debated as to when to initiate the administration of insulin in such conditions.[24] Hence, in the current scenario researchers have shifted to investigate several other strategies to reduce risk to the infant and the mother.

Inspired by such investigations, this study aims to suppress the pathophysiology of GDM by proposing the use of Berberine. Berberine a natural plant extract has been studied for decades for its anti-diabetic properties and its effectiveness against type2 diabetes is well established.[18]

In the present investigation, GDM was induced in female Wistar rats and made to undergo gestation. The rats were treated with three different concentrations of Berberine ranging from 25 mg/kg to 100 mg/kg, increasing exponentially. Treatment to the test and control groups was initiated before pregnancy and continued till the end of the study. The pregnant female rats were kept under observation and regularly tested for body and fetal weight, placental weight, and index. Biochemical, Lipid, and Antioxidant enzyme profiling were done regularly and the pro-cytokine levels were also monitored on a timely basis.

The observed change in body weight observed among the various groups clearly shows that GDM groups that were treated with Berberine witnessed a healthier increase in body weight in comparison to Group II that witnessed GDM without any other treatment. The increase in body weight was observed to be good when 100 mg/kg of Berberine was administered and quite comparable to the negative control group. This is indicative of the glucose metabolism induced by the activity of Berberine. This effect can be seen in the intriguing variation of fetal and placental weight observed during the study. Placental weight is negatively correlated to the glucose tolerance of the mother. Higher placental weight and index are indicative of insulin resistance during gestation,[25] groups III, IV, and V, that were treated with Berberine exhibited a reduced placental weight and index.

Previous literature reports the anti-diabetic activity of Berberine and its use as a therapeutic agent.[17] This is evident in the present investigation also. The control group administered with STN alone exhibited an elevated FBG level whereas the test groups that received Berberine showed a reducing FBG level as the concentration was increased to 100 mg.

Serum AGEs are a notable factor in individuals diagnosed with GDM. It is one of the major factors that induce inflammation and insulin resistance in the pregnant body.[11] AGE concentration was suppressed in the test groups and was observed to be elevated in the positive control rats. This indicated the activity of Berberine. Furthermore, the suppression was seen to intensify in a dose-dependent manner with time. The highest activity against serum AGE was observed in Group V.

Lipid profile analysis showed suppression in the LDL, VLDL, triglyceride, and TC concentrations, explaining the readjusting metabolic system. HDL levels were significantly higher among the test groups when compared to Group II that received STN alone. HDL levels are good cholesterols that are essential for healthy mother,[26] higher levels of HDL can be observed in the groups treated with Berberine, and suppression of low-density cholesterols and triglycerides indicate the suppression of GDM.

Oxidative stress is induced by the excessive ROS produced and compromised levels of ROS scavengers in the body because of which cell death, tissue damage, and ultimately inflammation are produced.[27] Antioxidant enzymes thus play a significant role suppression of inflammation and other symptoms manifested due to GDM. SOD, GPx, GSH, and CAT were quantified in this study. It was noted that the levels of these enzymes were heavily compromised in the positive control groups that were administered only STN. The negative control groups exhibited a satisfactory level of these enzymes indicating the normal condition in the absence of GDM. The test groups were observed to have a significantly low level of these enzymes; however, the concentrations were distinguishably higher than the positive control. The effect can be associated with the administration of Berberine, correlating it to previous literature. The enzymes were seen to increase quantitatively with a rise in the dosage of Berberine.

All Biochemical parameters were reported to rise significantly upon inducing GDM in the rat models, except for FFA. This rise in levels can be inferred as a consequence of glucose intolerance and insulin resistance. Free fatty acids are produced in the body during regular glucose metabolism. Thus, this clearly explains the reduction in the levels of FFA. The test groups were observed to recover upon receiving Berberine. This can be noted in the distinct elevation in the levels of FFA and suppression of the other parameters quantified throughout this study.

TNF-α, IL-1β, IL-6, and IL-10 are inflammatory cytokines that act as signaling molecules to induce chronic inflammation and interfere with insulin signalling.[28] Berberine-treated test groups exhibited a visible suppression in the levels of these inflammatory mediators (Figure 8) and induced the production of IL-10, an anti-inflammatory mediator in a dose-dependent manner. The highest levels of IL-10 were observed when 100 mg/kg of Berberine was administered. Attenuation in the levels of the anti-inflammatory cytokines and induction of the expression TNF, IL-1β, 6, results in the prolonged inflammation of the gestating patient. It also promotes insulin resistance in the body by inhibiting the insulin signaling pathway.

Berberine thus showed remarkable activity in the suppression of various factors that together are involved in establishing the pathological condition of GDM. This study investigated up to a maximum of 100 mg of Berberine only, for which the results were observed to increase significantly. A recent study on the extensive use of Berberine for its inhibitory effect also causes inhibition of cytochrome P450 in humans.[29] However, further research on factors such as interethnic variability, genotype variability is needed to fully understand the activity of Berberine and standardize its minimum dosage for administration. However, through the summary of the mechanism of action, the molecular mechanism of GDM antidiabetic is still not deep enough. Some pathways are only possibly effective, and no definite proof has been noted. Therefore, more detailed and in-depth studies are needed in the future.

CONCLUSION

GDM was induced in pregnant rat models, to study the antidiabetic activity of the plant extract Berberine. Diabetes was induced in rats with the administration of Streptozotocin. The induction of GDM was confirmed with the change in body weight, fetal weight, and placental index. Elevated Biochemical, lipid parameters, and serum AGEs presented the clinical condition of Gestational diabetes in the rat models. Berberine was administered to assess its antidiabetic property and study its targets in suppressing the pathophysiology of this medical condition.

Berberine was successful in inhibiting multiple signaling pathways. It was able to induce a healthier placental index, and control blood glucose and serum AGE concentrations. It was observed to induce the anti-inflammatory response of IL-10 to suppress the chronic symptoms of GDM by inhibiting pro-inflammatory cytokine accumulation. The potent activity was observed in all the dosages of Berberine employed in this investigation and the effect was noted to increase exponentially with an increase in the concentration of the drug. Thus, Berberine should be used as a therapy against GDM after further standardization of the minimum lethal dosage.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ABBREVIATIONS

GDM: Gestational Diabetes Mellitus; **DM:** Diabetes mellitus; ROS: Reactive oxygen; **IL-6:** Interleukin-6; **IL-10:** Interleukin-10; **AGEs:** Advanced glycation end products; **STN:** Streptozotocin; **FBG:** Foetal Blood Glucose; **TC:** Total cholesterol; **FFA:** Free fatty acids.

SUMMARY

In this study, the increase in body weight was observed to be good when 100 mg/kg of Berberine was administered and quite comparable to the negative control group. This is indicative of the glucose metabolism induced by the activity of Berberine. Berberine showed a reducing FBG level as the concentration was increased to 100 mg. AGE concentration was suppressed in the test groups and was observed to be elevated in the positive control rats. This indicated the activity of Berberine. Higher levels of HDL can be observed in the groups treated with Berberine, and suppression of low-density cholesterols and triglycerides indicate the suppression of GDM. This can be noted in the distinct elevation in the levels of FFA and suppression of the other parameters quantified throughout this study. Attenuation in the levels of the anti-inflammatory cytokines and induction of the expression TNF, IL-1β, 6, results in the prolonged inflammation of the gestating patient. It also promotes insulin resistance in the body by inhibiting the insulin signaling pathway.

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