ACTA ABP BIOCHIMICA POLONICA

Vol. 70, No 4/2023
985–990
https://doi.org/10.18388/abp.2020_6947

Regular paper

Protective effect of tretinoin derivative and TXNRD1 protein on streptozotocin induced gestational diabetes *via* an age-rage signaling-pathway

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Background: In the present study effect of tretinoin derivative was investigated on the pathogenesis of gestational diabetes mellitus (GDM) in mice model *in vivo*. Materials and Methods: Diabetes was induced in mice by injecting Streptozotocin (STZ) for 5consecutive days at a dose of 65 mg/kg body weight through the intraperitoneal route. Tretinoin derivative was given to the mice at 0.12 and 0.25 mg/kg doses through gavage in normal saline alternately for one week after STZ injection.Results: The results demonstrated that tretinoin derivative administration to the diabetic mice significantly ($P<0.05$) alleviated the blood FBG and FINS levels. Administration of tretinoin derivative to the diabetic mice significantly ($P<0.05$) promoted the blood HDL level and alleviated TC and TG levels. The administration of tretinoin derivative to the diabetic mice significantly ($P<0.05$) alleviated the CRP, IL-6and TNF-α production in pancreatic tissues. Tretinoin derivative administration to the diabetic mice significantly ($P<0.05$) elevated the SOD activity, and CAT level and lowered the MDA level in pancreatic tissues. The TXNRD1 expression in diabetic mice was comparable to that in the normal group after administration of tretinoin derivativeat the dose of 0.25 mg/kg dose. *In silico* data demonstrated that tretinoin derivativeinteracts with TXNRD1 protein with the binding affinity ranging from –10 to 9.4 kcal/ mol. Conclusion: In conclusion, tretinoin derivative administration effectively regulated streptozotocin-induced changes in fasting blood glucose, insulin level, high-density lipid level and triglyceride level in diabetic mice *in vivo*. The streptozotocin-induced excessive production of C-reactive protein and inflammatory cytokines was also down-regulated in diabetic mice on administration of tretinoin derivative. Therefore, tretinoin derivative can be investigated further as a therapeutic agent for the treatment of gestational diabetes mellitus.

Keywords: Streptozotocin, Cytokines, Gestational diabetes, Triazoles, Antioxidant

Received: 26 July, 2023; revised: 21 October, 2023; accepted: 27 October, 2023; available on-line: 07 December, 2023

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Acknowledgements of Financial Support: The research and practice of "Dual-element" cooperative loose-leaf teaching material development in schools and enterprises---taking "Applied Anatomy of Nursing" as an example; The 2022 Henan Province vocational education reform research and practice project (Grant No. Henan Education [2023]03053). Henan Engineering and Technology Research Center of home care products for the mentally incapacitated elderly; 2022 Henan Engineering and Technology Research Center. Document number: Laboratory and Platform Base Construction Office of Henan Science and Technology Agency [2023] No. 1.

Abbreviations: GDM, Gestational diabetes mellitus; STZ, Streptozotocin; FBS, Fasting plasma glucose; FBI, Fasting blood insulin; CRP, c-reactive protein; IL, Interleukin; TNF-α, Tumor necrosis factor-α

INTRODUCTION

Gestational diabetes mellitus (GDM) is a leading medical complication in pregnant females characterized by high glucose level (Metzger *et al*., 1998). It has been observed that the bodies of pregnant females react differently to elevated sugar levels. In most cases high blood glucose level during pregnancy leads to miscarriage or premature birth (Metzger *et al*., 1998). Despite being the leading life threat to pregnant females and their babies the pathogenesis of GDM is yet to be fully known (Johns *et al*., 2018). Studies have revealed that one of the major factors involved in the development and pathogenesis of GDM is insulin resistance (IR) (Hajifaraji *et al*., 2018; Sha *et al*., 2019). Furthermore, the pathogenesis of GDM is complicated by the excessive release of inflammatory factors and induction of oxidative stress pathways during pregnancy (Hajifaraji *et al*., 2018; Sha *et al*., 2019). During type-2 diabetes, the expression of the antioxidant gene, thioredoxin reductase-1 cytoplasmic (TXNRD1) is markedly elevated which complicates the disorder (Baig *et al*., 2020; Nazem *et al*., 2019). The activity of superoxide dismutase (SOD) is also found to be higher in patients suffering from type-2 diabetes (Baig *et al*., 2020; Nazem *et al*., 2019). It is reported that elevated levels of inflammatory factors persistently in pregnant females play a prominent role in the pathogenesis of GDM (Sudharshana *et al*., 2018).

The TrxR1, a member of the thioredoxin system which is encoded by TXNRD1 plays a vital role in regulating the redox system. It also constitutes an important part of the antioxidant defense system and inhibits Trx expression to maintain the reduced state of intracellular proteins (Cebula *et al*., 2015). Up-regulation of TXNRD1 plays a crucial role in increasing the resistance of cells to oxidative stress by neutralizing hydrogen peroxide and inactivation of apoptotic pathway. Thus, increasing the expression of TXNRD1 is believed to be of therapeutic significance for the treatment of diabetes (Kabuyama *et al*., 2008; Chang *et al*., 2018). The TrxR/Trx system has been demonstrated to be associated with inhibition of oxidative stress, inactivation of apoptosis, DNA synthesis and regulation of NF-κB pathway (Park *et al*., 2015; Raninga *et al*., 2016; Matsui *et al*., 1996). It is also reported that inflammatory response in cells is regulated by TXNRD1 expression (Shi *et al*., 2020).

Triazoles are known for various pharmaceutical activities, such as anti-cancer, antioxidant, anti-inflammatory, anti-HIV, anti-diabetic, and anti-protozoal properties. Structural-activity relationship investigations have revealed that the 1,2,3-triazole part is the most active pharmacophoric group in numerous bioactive compounds.

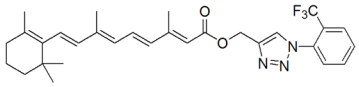

Figure 1. Chemical structure of tretinoin derivative.

The pharmacological activity of 1,2,3-triazoles is mainly attributed to various types of interactions such as hydrogen bonds, van der Waals forces, and dipole–dipole bonds with proteins, enzymesand different receptors in living organisms (Bonandi *et al*., 2017; Bozorov *et al*., 2019). The compounds containing 1,2,3-triazole scaffold have been found to exhibit various pharmaceutical activities like antibacterial (Zhang, 2019; Chu *et al*., 2020), antimalarial (Chu *et al*., 2019; Feng *et al*., 2020), anti-tubercular (Yan *et al*., 2020), anti-viral (Feng *et al*., 2021), and anti-cancer (Slavova *et al*., 2020) properties. The present study was designed to investigate the therapeutic effect of a tretinoin derivative on gestational diabetes mellitus and understand the underlying mechanism.

MATERIALS AND METHODS

Mice model of gestational diabetes

Male C57BL/6 mice eighty in number (body weight 18–30 g and around 10 weeks old) were supplied by the Experimental Animal Center belonging to the Hospital in Shanghai, China [Registration number 09/2020]. The mice were kept in cages in the animal center at a regulated temperature of 24±1°C, humidity of 65%, and exposed to 12/12-hour light/dark cycles. Mice in the normal group were fed a normal diet and those in the model GDM groups were given fat rich and sucrose diet. The animal experimental procedures were conducted in compliance with the guidelines of the institutional laboratory and Guide of the National Institute of Health for Care and Use of Laboratory Animals [Ethical clearance certificate number 102/2020].

The female mice were caged overnight with male mice at the proestrus stage and microscopy was performed to confirm the pregnancy on the following day. Diabetes was induced in mice by injecting STZ (Sigma-Aldrich, St. Louis, MO, USA) for 5 consecutive days at a dose of 65 mg/kg body weight through intraperitoneal route. Induction of diabetes in mice was confirmed by measuring the glucose blood for 8weeks after STZ injection. The mice having elevated level of blood glucose (16.7 mmol/L) and suffering from polyuria, polyphagia and weight loss were considered to be diabetic (John *et al*., 2012). The mice were divided into four groups of 10 each; normal, model diabetes and two tretinoin derivative treatment (administered with 0.12 and 0.25 mg/kg body weight) groups. Tretinoin derivative was given to the mice by gavageat doses of 0.12 and 0.25 mg/kg in normal saline alternately for one week after STZ injection.

Mice were fasted for 10 hours and then injected with 1% pentobarbital sodium (50 mg/kg) anesthesia after completion of the treatment. The blood samples were collected from the abdominal aorta of the mice for biochemical analysis of the various parameters. The collected blood samples were stored overnight in a refrigerator and thencentrifuged at 4°C for 25 minutes at 12000×*g* to collect the serum. Tissue samples were extracted from the pancreatic islets and placental for investigation of pathological changes.

Assay for FBG, FINS, IR, HDL and TG determination

The blood samples collected from the mice abdominal aorta were analyzed for FBG level using the commercially available glucose test strips (Nova Biomedical Corporation) according to the supplier's instructions. The enzyme-linked immunosorbent assay kits (Shanghai Huzhen Biological Technology Co., Ltd.) were used for the measurement of FINS in the mice blood samples as per manufacturer's guidelines. BK-400 automatic biochemical analyzer (BioBase) was used for the measurement of TG and HDL levels in the mice blood samples. The HOMA-IR was calculated using the reported formula [FBG (mmol/l)×FIN S (mU/l)] /22.5.

Measurement of oxidative stress factors in mice pancreatic tissues

The tissue sections from the pancreas of the mice were extracted, sliced into thin sections and then homogenized. The lysate obtained was subjected to centrifugation at 2000×*g* for 15 min at 4°C to separate the supernatant for measurement of various oxidative factors. The commercially available UV-visible spectrophotometer assay kits (Beyotime Institute of Biotechnology) were used for the measurement of CAT, MDA levels, and activity of SOD in mice pancreatic tissues.

Western blot analysis

The pancreatic tissue samples of the mice were lysed on treatment with RIPA lysis buffer (Sigma-Aldrich; Merck KGaA) to obtain the tissue lysate. The protein content in the tissue lysates was estimated using the Bradford method. Protein samples (30 µg) in equal quantities were separated on 10% SDS-PAGE gel and then transferred onto the PVDF membranes. Incubation of the membranes was performed with 5% skimmed milk powder for 2 hours at 4°C to block the non-specific sites. Membranes were incubated overnight with anti-CRP (cat. no. ab207756), anti-TNF-α (cat. no. ab205587), anti-IL-6 (cat. no. ab208113), anti-TXNRD1 (cat. no. ab124954) and anti-GAPDH (cat. no. ab9485; all purchased from Abcam) primary antibodies at 4°C. After washing with PBS the membranes were incubated again at room temperature for 1 hour with HRP-conjugated secondary antibodies (cat. no. ab7090; 1:10,000; Abcam). Expression of protein bands was visualized using the Chemiluminescence enhancement reagent (Thermo Fisher Scientific, Inc.) and analyzed by the ImageJ software (version 1.46r; National Institutes of Health).

Statistical analysis

The presented data are the mean ± S.D. of the three independently conducted experiments. Analysis of the data was performed using the Graph-Pad Prism software (version 8; Graph-Pad Software, Inc.). The difference between the groups was determined using the Student's test and ANOVA followed by Tukey's post hoc test. The values at $P<0.05$ were considered to represent the statistically significant differences.

RESULTS

Tretinoin derivative administration alleviates FBG and FINS levels in diabetic mice

In diabetic mice, the FBG as well as FINS levels were significantly ($P<0.05$) elevated in blood compared to the

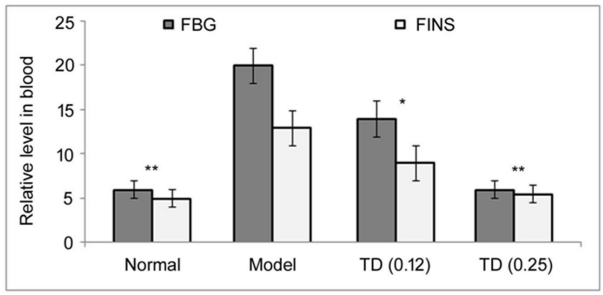

Figure 2. Effect of tretinoin derivative on blood FBG and FINS levels in diabetic mice.
Diabetic mice were administered Tretinoin derivative at 0.12 and 0.25 mg/kg doses or physiological saline (normal and model groups). Commercially available glucose test strips and enzyme-linked immunosorbent assay kits were used for the determination of blood FBG and FINS levels, respectively in mice. **P*<0.05,***P*<0.01 *vs* model group.

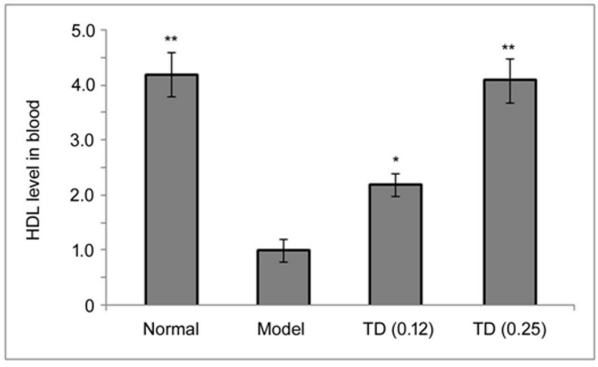

Figure 3. Effect of tretinoin derivative on blood HDL level in diabetic mice.
Diabetic mice were administered tretinoin derivative at 0.12 and 0.25 mg/kg doses or physiological saline (normal and model groups). A commercially available BK-400 automatic biochemical analyzer was used for the determination of blood HDL in mice. **P*<0.05, ***P*<0.01 *vs* model group.

normal group (Fig. 2). Tretinoin derivative administration to the diabetic mice significantly ($P<0.05$) alleviated the blood FBG as well as FINS levels in a dose-dependent manner. The FBG and FINS levels in diabetic mice were reduced more closely to those in the normal group after treatment with 0.25 mg/kg tretinoin derivative compared with the 0.12 mg/kg group.

Tretinoin derivative administration promotedHDL level in diabetic mice

The HDL level showed a significant ($P<0.05$) decrease in blood samples of diabetic mice compared to the normal group (Fig. 3). Administration of tretinoin derivative to the diabetic mice significantly ($P<0.05$) promoted the blood HDL level in a dose-dependent manner. The HDL level in diabetic mice was promoted more comparable to those in the normal group after treatment with tretinoin derivativeat a dose of 0.25 mg/kg compared to the group receiving 0.12 mg/kg.

Tretinoin derivative administration alleviates TC and TG levels in diabetic mice

In diabetic mice, the TC and TG levels were significantly ($P<0.05$) elevated in blood compared to the normal group (Fig. 4). Administration of tretinoin derivative to the diabetic mice significantly ($P<0.05$) alleviated the

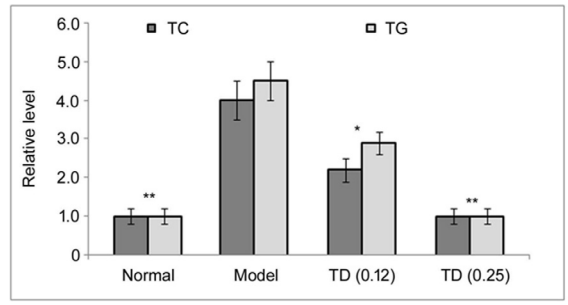

Figure 4. Effect of tretinoin derivative on blood TC and TG levels in diabetic mice.
Diabetic mice were administered tretinoin derivative at 0.12 and 0.25 mg/kg doses or physiological saline (normal and model groups). The BK-400 automatic biochemical analyzer was used for the determination of blood TC and TG levels, respectively in mice. **P*<0.05,***P*<0.01 *vs* model group.

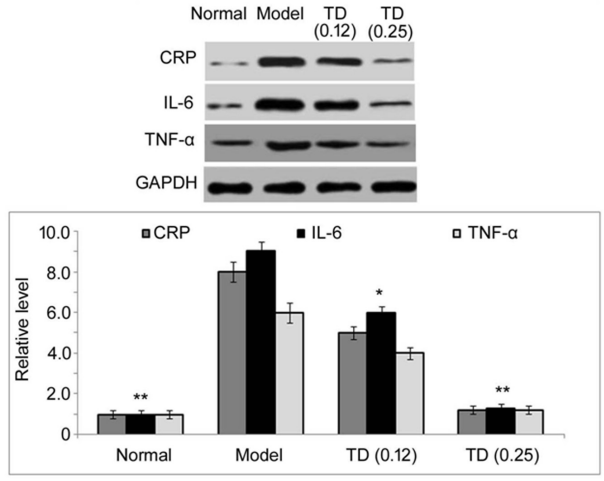

Figure 5. Effect of tretinoin derivative on CRP, IL-6 and TNF-α production in pancreatic tissues of diabetic mice.
Diabetic mice were administered tretinoin derivative at 0.12 and 0.25 mg/kg doses or physiological saline (normal and model groups). Western blotting assay was performed to assess the production of CRP, IL-6 and TNF-α in mice pancreatic tissues. **P*<0.05,***P*<0.01 *vs* model group.

blood TC and TG levels in a dose-dependent manner. The TC and TG levels in diabetic mice were reduced more comparable to the normal group on treatment with 0.25 mg/kg dose tretinoin derivative compared to the 0.12 mg/kg group.

Tretinoin derivative administration alleviates inflammation of pancreatic islets in diabetic mice

In diabetic mice, the CRP and IL-6 production showed a significant ($P<0.05$) increase in pancreatic tissues compared to the normal group (Fig. 5). Additionally, the TNF-α level in diabetic mice pancreatic tissues was also significantly ($P<0.05$) increased compared to the normal group. However, the administration of tretinoin derivative to the diabetic mice significantly ($P<0.05$) alleviated the CRP and IL-6 production in pancreatic tissues in a dose-dependent manner. The tretinoin derivative administration also suppressed the TNF-α level in diabetic mice pancreatic tissues comparable to the normal group.

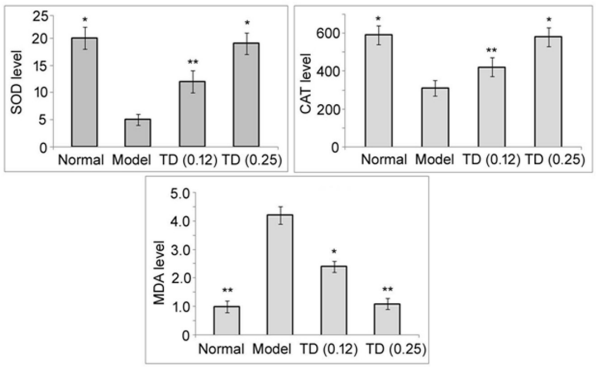

Figure 6. Effect of tretinoin derivative on SOD activity and CAT and MDA levels in pancreatic tissues of diabetic mice.
Diabetic mice were administered tretinoin derivative at 0.12 and 0.25 mg/kg doses or physiological saline (normal and model groups). The UV-visible spectrophotometer was used for the determination of SOD activity and CAT and MDA levels in mice pancreatic tissues. *P<0.05,**P<0.01 *vs* model group.

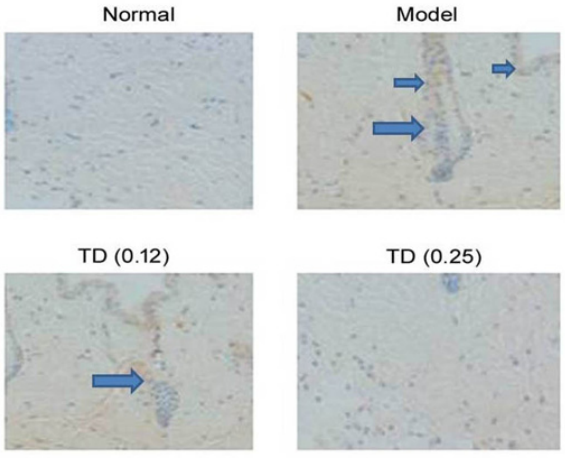

Figure 7. Effect of tretinoin derivative on the expression of AGEsin dermal tissues of diabetic mice.
Diabetic mice were administered tretinoin derivative at 0.12 and 0.25 mg/kg doses or physiological saline (normal and model groups). Immunohistochemical staining was used for the determination of the expression of AGEsin mice.

Tretinoin derivative administration alleviates inflammatory response in diabetic mice

The SOD activity and CAT level showed a significant (P<0.05) decrease in pancreatic tissues of diabetic mice compared to the normal group (Fig. 6). Moreover, the level of MDA showed a significant (P<0.05) increase in diabetic mice pancreatic tissues in comparison to the normal group. Administration of tretinoin derivative to the diabetic mice significantly (P<0.05) elevated the SOD activity and CAT level in pancreatic tissues in a dose-dependent manner. The SOD activity and CAT level in diabetic mice were elevated comparable to the normal group on the administration of 0.25 mg/kg dose of tretinoin derivative. The tretinoin derivative administration lowered the MDA level in diabetic mice pancreatic tissues close to the normal group. The MDA level in diabetic mice pancreatic tissues was lowered to the level of the normal group on administration of tretinoin derivative at 0.25 mg/kg dose.

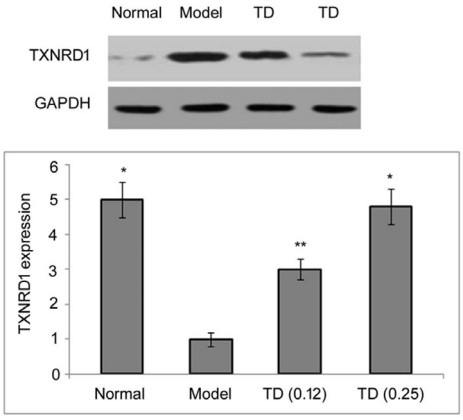

Figure 8. Effect of tretinoin derivative on TXNRD1 expression in serum samples of diabetic mice.
Diabetic mice were administered tretinoin derivative at 0.12 and 0.25 mg/kg doses or physiological saline (normal and model groups). The western blotting assay was used for the determination of TXNRD1 protein in mice serum samples. *P<0.05,**P<0.01 *vs* model group.

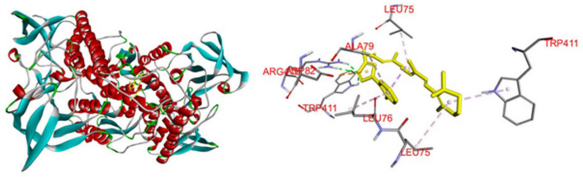

Figure 9. The *in silico* interaction between tretinoin derivative andTXNRD1 protein.
The binding of tretinoin derivative with TXNRD1 protein was investigated using the AutoDock Vina and Discovery Studio software.

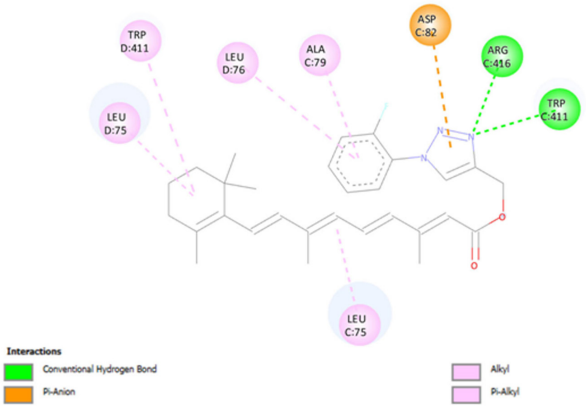

Figure 10. Demonstration of binding between tretinoin derivative and TXNRD1 protein through two-dimensional diagram.
AutoDock Vina and Discovery Studio software were used for understanding the binding of tretinoin derivative with TXNRD1 protein.

Tretinoin derivative targets AGEs in diabetic mice

The expression of AGEs was prominently higher in the dermal tissues of diabetic mice compared to the normal group (Fig. 7). However, the administration of tretinoin derivative effectively alleviated the expression of AGEs in dermal tissues of diabetic mice in a dose-dependent manner. The expression of AGEs in diabetic mice was reduced comparable to the normal group on

administration of 0.25 mg/kg dose tretinoin derivative compared to the 0.12 mg/kg group.

Tretinoin derivative administration elevates TXNRD1 expression in diabetic mice

The TXNRD1 expression showed a remarkable decrease in diabetes mice serum samples compared to the normal group (Fig. 8). However, administration of tretinoin derivative to the diabetic mice led to a prominent increase in TXNRD1 expression in serum samples in a dose-dependent manner. The TXNRD1 expression in diabetic mice was promoted comparable to the normal group on administration of 0.25 mg/kg dose of tretinoin derivative compared to the 0.12 mg/kg group.

Tretinoin derivative interacts with TXNRD1 protein

It was observed from *in silico*data that trizoleinteracts with TXNRD1 protein (3EAN) with the binding affinity ranging from –10 to 9.4 kcal/ mol (Fig. 9). The binding of tretinoin derivative with TXNRD1 protein involves arginine (ARG C:416) andtryptophan (TRP C:411) amino acid residues of TXNRD1 *via* conventional hydrogen bonds (Fig. 10). Moreover, the protein interacts with tretinoin derivative *via* pi-alky and alkyl interactions involving leucine (LEU D:75), tryptophan (TRP D:411), leucine (LEU D:76) and alanine (ALA C:79) amino residues.

DISCUSSION

Expecting mothers have a serious life threat to themselves as well as to their children because of gestational diabetes mellitus (Johns *et al*., 2018). Unfortunately, the incidence of the disorder has been increasing every year over the past decade in Chinese women (Johns *et al*., 2018). High blood glucose levels during pregnancy have been found to be responsible for premature deliveries and increased abortion rate (Poston *et al*., 2016). The present study was designed to understand the effect of tretinoin derivative on gestational diabetes in mice model *in vivo*. Initially, it was observed that streptozotocin administration in the mice caused a significant increase in FBG and FINS levels compared to the normal group. Other specific features of diabetes such as polyuria, polydipsia, polyphagia and weight loss were also observed in the mice administered with streptozotocin. Thus, these features confirmed the induction of diabetes in mice model. However, the administration of tretinoin derivative to the diabetic mice significantly ($P<0.05$) alleviated the blood FBG and FINS levels in a dose-dependent manner. Further, it was observed that FBG and FINS levels in diabetic mice were alleviated comparable to the normal group on treatment with 0.25 mg/kg dose of tretinoin derivative. In diabetic mice, the HDL level showed a significant ($P<0.05$) decrease in blood samples compared to the normal group. On the other hand, tretinoin derivative administration effectively promoted the blood HDL level in diabetic mice in a dose-dependent manner. The TC and TG levels were also elevated significantly in blood samples of the diabetic mice compared to the normal group. However, the administration of tretinoin derivative to the diabetic mice significantly ($P<0.05$) reversed the streptozotocin-induced increase in TC and TG levels in blood samples in a dose-dependent manner. Thus, initial data clearly showed that tretinoin derivative reverses streptozotocin-induced changes in FBG, FINS, lipoprotein and triglyceride levels in the mice and therefore needs to be investigated further for possible role in the treatment of diabetes.

The increased expression of C-reactive protein (CRP) in diabetic patients is an indicator of inflammatory reactions and it is also associated with insulin resistance (Batemanet *al*., 2016). It is reported that CRP promotes activation of various substrates of insulin receptors and inhibits tyrosine kinase activity (Kaushik *et al*., 2009). Thus, insulin synthesis and its secretion are inhibited by CRP thereby leading to the development of resistance to the insulin action. Additionally, excessive secretion of TNF-α has been found to down-regulate the expression of glucose transporter-T4 and consequently increase insulin resistance. Studies have also demonstrated that elevated IL-6 production is associated with a decrease in insulin sensitivityand an increase in secretion of glucocorticoids and growth hormones. Thus, excessive IL-6 level in diabetic patients promotes insulin resistance and increase the level of blood glucose (Skórzyńska-Dziduszko *et al*., 2016; Roca-Rodríguez *et al*., 2017; Khaliq *et al*., 2018; Bhat *et al*., 2018; Dar *et al*., 2016; Ansari *et al*., 2018). In the present study, the CRP and IL-6 production was elevated in diabetic mice pancreatic tissues compared to the normal group. The TNF-α level in diabetic mice pancreatic tissues was also increased remarkably compared to the normal group. On the other hand, tretinoin derivative administration indiabetic mice effectively alleviated the CRP and IL-6 production in pancreatic tissues in a dose-dependent manner. Further, tretinoin derivative administration also led to a prominent reduction in TNF-α level in diabetic mice pancreatic tissues. In diabetic mice, SOD activity and CAT level showed a prominent decrease in pancreatic tissues than those of the normal group. The level of MDA also showed a remarkable increase in diabetic mice pancreatic tissues in comparison to the normal group. Fortunately, administration of tretinoin derivative to diabetic mice effectively elevated the SOD activity and CAT level in pancreatic tissues. It was found that tretinoin derivative administration lowered the MDA level in diabetic mice pancreatic tissues. Administration of tretinoin derivative to the diabetic mice also reversed the streptozotocin-induced increase in TXNRD1 protein expression effectively.

CONCLUSION

In conclusion, tretinoin derivative administration effectively regulated streptozotocin-induced changes in fasting blood glucose, insulin level, high-density lipid level and triglyceride level in diabetic mice *in vivo*. The streptozotocin-induced excessive production of C-reactive protein and inflammatory cytokines was also down-regulated in diabetic mice on administration of tretinoin derivative. Furthermore, the activity of SOD and the level of CAT in diabetic mice were elevated by triazole administration. Tretinoin derivative administration suppressed TXNRD1 protein expression and *in silico* data revealed that it binds to arginine (ARG C:416) and tryptophan (TRP C:411) amino acid residues of the protein *via* conventional hydrogen bonds. Therefore, tretinoin derivative can be investigated further as a therapeutic agent for the treatment of gestational diabetes mellitus.

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