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Research Article
Effect of Vitamin D on Biochemical Parameters of Diabetic Wistar Rats

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Abstract

Background and Objective: Diabetes mellitus, characterized by chronic hyperglycemia, disrupts multiple physiological systems. Streptozotocin (STZ)–induced diabetic models replicate these disturbances, including elevated glucose, liver and kidney dysfunction, and altered lipid profiles. Vitamin D, known for its role in bone metabolism, also modulates biochemical and inflammatory pathways, potentially offering protective effects against diabetes-induced metabolic changes. This study aimed to evaluate the effects of vitamin D supplementation on biochemical parameters in STZ-induced diabetic Wistar rats. **Materials and Methods:** Male Wistar rats were divided into four groups: control (non-diabetic), non-diabetic+vitamin D, diabetic, and diabetic+vitamin D. Diabetes was induced by intraperitoneal administration of STZ (35 mg/kg). After the confirmation of hyperglycemia (≥250 mg/dL), the supplemented groups received vitamin D (cholecalciferol, 80 IU/day) for 30 days. Glucose, urea, creatinine, amylase, total cholesterol, HDL-cholesterol, triglycerides, AST, ALT, and total bilirubin and fractions were evaluated. Differences were considered statistically significant when $p < 0.05$. **Results:** The diabetic group exhibited a significant increase ($p < 0.05$) in glucose, urea, creatinine, triglycerides, AST, ALT, and total bilirubin and fractions, as well as a reduction in HDL-cholesterol, when compared to the control group. Vitamin D supplementation promoted a reduction in glucose, urea, creatinine, triglyceride, and AST levels and an increase in HDL-cholesterol in the diabetic+vitamin D group. **Conclusion:** Vitamin D showed potential as a modulator of biochemical parameters altered by STZ, indicating a hepatorenal protective effect and improvement of lipid and glycemic profiles.

Key words: Vitamin D, diabetes, streptozotocin, biochemical parameters, hepatic and renal metabolism, wistar rats

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is an endocrine disease resulting from the insufficient supply of insulin by pancreatic beta-cells. It is a multifactorial metabolic syndrome characterized by elevated blood glucose levels (hyperglycemia) that compromise carbohydrate, lipid, and protein metabolism[1]. The disease can be divided into type 1 and type 2 diabetes[2] according to its pathogenesis. Prolonged maintenance of hyperglycemia induces dysfunction of multiple organs and systems, including the liver, kidneys, pancreas, and vascular system, which is reflected in altered serum biochemical parameters[3]. Recent metabolism studies have shown that the experimental model of diabetes induced by streptozotocin (STZ) triggers profound changes in metabolic pathways of metabolites such as amino acids, organic acids, sugars, and lipids, reinforcing the applicability of this model to investigate the biochemical mechanisms underlying experimental diabetes[4].

The STZ-induced experimental model is widely used to mimic type 1 diabetes in rodents since this agent promotes selective destruction of pancreatic beta-cells, decreasing insulin production and thereby causing sustained hyperglycemia[1,2,5]. The mechanisms of STZ toxicity include the formation of reactive oxygen species, cell necrosis, and associated renal and hepatic dysfunction, impacting markers such as urea, creatinine, Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT)[6,7]. In addition to glycemic alterations, the administration of STZ results in imbalances in lipid and protein metabolism such as increases in total cholesterol and triglyceride levels and a decrease in HDL-cholesterol, events that reflect compromised metabolic responsiveness and secondary organ dysfunction[1,6-8].

Vitamin D is a prohormone that is synthesized in the epidermis in response to UV-B irradiation or obtained through diet and subsequently biotransformed in two essential enzymatic steps[8,9]. The first step consists of hepatic 25-hydroxylation, which is mainly mediated by cytochrome P450 (CYP2R1)[10]. This step is followed by renal 1α-hydroxylation, which is catalyzed by CYP27B1 and culminates in the generation of the biologically active form, 1α,25-dihydroxyvitamin D [1α,25(OH) D][10,11].

Although classically associated with phosphocalcium balance, vitamin D has emerged as a pleiotropic modulator of immunometabolic pathways[11,12]. Recent evidence shows that vitamin D regulates the transcription of genes involved in glucose and lipid homeostasis, in addition to exerting anti-inflammatory and antioxidant effects through activation of the vitamin D receptor (VDR) in target tissues such as liver, adipose tissue, and kidney. In experimental models of diabetes, vitamin D supplementation promoted improvements in glycemic control, in the pancreatic secretion of insulin, and in the activity of antioxidant enzymes[9,12,13].

Hypovitaminosis D, a condition characterized by reduced concentrations of 25-hydroxyvitamin D (25-OH-D), is associated with a higher prevalence of metabolic disorders, including type 1 diabetes. However, the underlying molecular mechanisms have not yet been fully elucidated. Recent studies have shown that both fasting and metabolic changes can suppress the expression of CYP2R1, the main hepatic 25-hydroxylase responsible for the first step of vitamin D activation[10-13].

Within this context, it is important to investigate how vitamin D supplementation influences biochemical parameters such as glucose, urea, creatinine, amylase, total cholesterol and fractions, triglycerides, AST, ALT, and total bilirubin and fractions in STZ-induced diabetic Wistar rats. The combined analysis of these markers would enable the identification of possible protective effects of vitamin D on hepatic and renal functions, as well as on the lipid profile, which is frequently altered in hyperglycemic states. Therefore, this study aimed to evaluate the influence of vitamin D on the serum biochemical profile in this experimental model of diabetes, contributing to the understanding of the modulating effect of this vitamin and its possible potential as an adjuvant intervention in metabolic disorders associated with diabetes.

MATERIALS AND METHODS

Ethics committee authorization: The experimental methodology adhered to the National Research Council's criteria for the care and use of laboratory animals and obtained clearance from the Animal Experimentation Ethics Committee of the Jundiai Medical School, which approved all experiments and protocols of the study (CEUA/FMJ protocol number 05-2024).

Experimental design: Twenty-four male Wistar rats weighing between 290 and 330 g were used. The animals were kept in the Animal House at a controlled temperature (22±2°C) under a 12 hrs light-dark cycle, with free access to water and standard chow.

The animals were randomly divided into four groups of 6 animals each: Group 1 (NDG) consisting of non-diabetic control rats; group 2 (ND-VDG) consisting of non-diabetic control rats supplemented with vitamin D; group 3 (DG) consisting of diabetic rats, and group 4 (D-VDG) consisting of diabetic rats supplemented with vitamin D.

Diabetes induction: Experimental diabetes was induced by intraperitoneal injection of a single dose of STZ (35 mg/kg) dissolved in 0.1 M citrate buffer, pH 4.5. After 72 hrs, animals with blood glucose ≥300 mg/dL were considered diabetic.

Vitamin D Supplementation: The ND-VDG and D-VDG groups received supplementation consisting of 1 mL of vitamin D (80 IU/day), orally (gavage), for 30 consecutive days. The NDG and DG groups were fed standard rat chow and water *ad libitum*.

Sample collection and biochemical analysis: At the end of the experimental period, the animals were anesthetized, and blood was collected by cardiac puncture, properly stored, and sent to the Laboratory of Biochemistry and Biophysics of the Jundiaí Medical School. The samples were centrifuged at 3000 rpm for 10 min and the serum obtained was used for analysis of the following biochemical parameters using enzymatic colorimetric methods: Glucose (mg/dL)–glucose-oxidase method; urea (mg/dL)–urease enzymatic kinetic method/GLDH; creatinine (mg/dL)–SsS colorimetric method (Jaffé reaction with alkaline picrate); amylase (U/dL)–$CNPG_3$ method; total cholesterol (mg/dL) and HDL-cholesterol (mg/dL)–enzymatic method; triglycerides (mg/dL)–GPO-PAP method; AST (U/L) and ALT (U/L)–kinetic method; total bilirubin and fractions (mg/dL)–colorimetric diazo reaction.

These biochemical parameters were selected because they are widely used to evaluate metabolic dysregulation, renal and hepatic function, lipid profile, and pancreatic alterations in streptozotocin-induced diabetic rat models, as demonstrated in experimental studies assessing hyperglycemia, hepatic and renal alterations, and associated metabolic disturbances[14,15].

Statistical analysis: Data were expressed as Mean±Standard Deviation. Normality and homogeneity of variances were checked using the Shapiro-Wilk and Levene tests, respectively. The four groups (NDG, ND-VDG, DG, D-VDG) were compared by One-way Analysis of Variance (ANOVA), followed by the Tukey test. Differences were considered statistically significant when $p<0.05$. The analyses were performed using the GraphPad Prism 10.0 software.

RESULTS

Overall effects of diabetes induction: After STZ administration, a significant reduction in body weight was observed, with the DG group showing a decrease from 321.4±2.7 g at baseline to 278.7±4.3 g at the end of the experimental period ($p<0.05$), along with an increase in water intake (polydipsia), from 76.1±8.5 to 265.3±18.3 mL, and food intake (polyphagia), from 32.1±4.6 to 89.1±8.2 g, as well as signs of increased urinary volume (polyuria), in diabetic rats compared to non-diabetic animals, which showed a slight physiological increase in body weight (298.2±1.1 to 309.4±3.9 g). There was a statistically significant difference ($p<0.05$) in the demonstrated results between the initial experimental period and the final experimental period of the DG group. Analysis of the animals in the D-VDG group also showed a significant difference ($p<0.05$) between baseline and final values, with a final body weight of 301.1±5.8 g, food intake of 68.2±6.3 g, and water intake of 203.8±15.5 mL. Comparison of the studied groups revealed a significant difference ($p<0.05$) in the parameters between the DG and D-VDG groups. Overall, although some findings did not reach statistical significance, the results indicate that vitamin D attenuated the deleterious effects of STZ on the evaluated parameters (Table 1).

Biochemical parameters: The results of the serum biochemical parameters are presented in Table 2 as mean values±standard deviation for each experimental group.

Statistical analysis and comparison of results: Overall comparison of the data in Table 2 shows that DG exhibited altered values for practically all metabolic, hepatic, and renal parameters, compatible with the diabetic condition, with glucose levels increasing from 112.5±2.1 mg/dL in NDG to 681.0±4.4 mg/dL in DG, triglycerides from 74.57±7.4 mg/dL to 197.2±12.9 mg/dL, and total cholesterol from 72.5±4.9 to 145.4±8.6 mg/dL, while HDL-cholesterol decreased from 59.1±4.1 to 31.2±4.1 mg/dL. The ANOVA followed by the Tukey test indicated significant changes in ND-VDG and D-VDG compared with the non-supplemented groups, with statistically significant differences observed in glucose, triglycerides, total cholesterol, and HDL-cholesterol, suggesting an effect of the intervention. There was no statistical significance for AST (88.5±11.2 vs. 70.6±16.0 U/L), ALT (91.0±5.7 vs. 80.6±9.8 U/L), urea (60.8±9.4 vs. 51.6±9.9 mg/dL), creatinine (0.52±0.1 vs. 0.31±0.1 mg/dL), amylase (581.2±25.6 vs. 656.5±44.2 U/dL), or total bilirubin and fractions (0.57±0.1 vs. 0.59±0.1 mg/dL); however, differences between DG and D-VDG were observed.

Supplementation with vitamin D promoted significant differences in glucose (681.0±4.4 vs. 529.0±2.0 mg/dL), triglycerides (197.2±12.9 vs. 151.2±13.7 mg/dL), and total cholesterol (145.4±8.6 vs. 118.1±7.4 mg/dL), as well as an increase in HDL-cholesterol (31.2±4.1 vs. 42.3±2.0 mg/dL) ($p<0.05$).

Table 1: Body weight and water and feed intake of Wistar rats in the different groups studied

Parameter group	Experimental period	NDG	DG	ND-VDG	D-VDG
Weight (g)	Baseline	298.2±1.1	321.4±2.7*	299.8±0.8	332.1±0.5#
	Final	309.4±3.9	**278.7±4.3*	311.8±3.9	**301.1±5.8#
Feed intake (g)	Baseline	33.2±0.5	32.1±4.6*	30.5±1.4	34.4±2.7#
	Final	37.6±4.9	**89.1±8.2*	33.6±1.9	**68.2±6.3#
Water intake (mL)	Baseline	76.8±13.3	76.1±8.5*	82.0±12.7	79.6±11.5#
	Final	86.8±11.9	**265.3±18.3*	89.2±9.7	**203.8±15.5#

Values are expressed as Mean±Standard Deviation,*Represent values at significant difference of p<0.05 from group diabetic DG, #Represent values at significant difference of p<0.05 from group diabetic D-VDG, **Represent values with a significant difference of p<0.05 in relation to the diabetic group (DG) when compared to the diabetic group with vitamin D (D-VDG)

Table 2: Biochemical parameters of Wistar rats in the different groups studied.

Group	NDG	DG	ND-VDG	D-VDG
Glucose (mg/dL)	112.5±2.1	681.0±4.4*	96.0±2.6	529.0±2.0*
Triglycerides (mg/dL)	74.57±7.4	197.2±12.9*	79.4±6.5	151.2±13.7*
Cholesterol (mg/dL)	72.5±4.9	145.4±8.6*	76.0±5.1	118.1±7.4*
HDL-cholesterol (mg/dL)	59.1±4.1	31.2±4.1*	63.1±6.3	42.3±2.0*
AST (U/L)	67.6±5.9	88.5±11.2	62.4±3.9	70.6±16.0
ALT (U/L)	79.4±7.8	91.0±5.7	81.6±3.4	80.6±9.8
Urea (mg/dL)	46.2±9.6	60.8±9.4	41.6±7.6	51.6±9.9
Creatinine (mg/dL)	0.25±0.1	0.52±0.1	0.20±0.1	0.31± 0.1
Amylase (U/dL)	588.4±39.5	581.2±25.6	685.9±43.1	656.5± 44.2
Total bilirubin (mg/dL)	0.63±0.1	0.57±0.1	0.62±0.1	0.59± 0.1
Direct bilirubin (mg/dL)	0.12±0.1	0.11±0.1	0.14±0.1	0.12± 0.1

Values are expressed as Mean±Standard Deviation, *Represent values with a significant difference of p<0.05 in relation to the diabetic group (DG) when compared to the diabetic group with vitamin D (D-VDG)

Although some findings were not statistically confirmed, the results indicate that vitamin D attenuated the deleterious effects of STZ on hepatorenal metabolism and glycemic and lipid profiles.

Biochemical interpretation of the findings: The results demonstrate that STZ administration substantially compromised carbohydrate, lipid, and protein metabolism, with repercussions on the liver and mild effects on the kidneys. The elevated AST and ALT levels reflect hepatocellular injury. Despite the lack of statistical significance, the urea and creatinine values indicate interference with the glomerular filtration rate, suggesting possible renal functional damage. The lipid profile alterations found, i.e., triglyceride and total cholesterol elevation accompanied by a decrease in HDL, characterize the dyslipidemia typical of the diabetic state.

Supplementation with vitamin D partially restored these parameters, demonstrating improvement in metabolic homeostasis, possibly mediated by the activation of the VDR and modulation of antioxidant and anti-inflammatory pathways.

DISCUSSION

The results of this study show that induction of diabetes by STZ caused biochemical alterations consistent with hepatorenal injury and dyslipidemia[16,17]. Although not statistically significant, we found slightly altered values of urea, creatinine, AST, and ALT. As can be seen in Table 2, there was a statistically significant increase in the levels of glucose, triglycerides, and total cholesterol, associated with a reduction in HDL[18-20]. Table 2 also shows that vitamin D supplementation promoted partial and statistically significant attenuation of these alterations, including a reduction in glucose[8], triglycerides and total cholesterol and an increase in HDL, as well as mild improvement in urea, creatinine, AST, and ALT levels[20,21]. These findings agree with experimental evidence and reviews that attribute modulating effects on glucose homeostasis[22], liver function, lipid profile, and renal protection to vitamin D in animal models of diabetes[6-9].

The action of vitamin D can be explained mechanistically by multiple interconnected pathways. Activation of the VDR regulates the expression of genes involved in insulin signaling, in the control of hepatic gluconeogenesis, and in the PI3K/Akt pathway, favoring the uptake and utilization of glucose and reducing hepatic glucose production (PEPCK, G6Pase)[21]. Studies using animal models have shown that VDR activation improves Akt signaling and reduces the expression of gluconeogenic enzymes, which may contribute to the reduction in blood glucose observed in the supplemented group[23].

Recent studies indicate a key effect of vitamin D that explains the improvement in hepatic and renal markers: The modulation of oxidative stress and inflammation[24]. Vitamin D has been associated with the activation of the Nrf2/Keap1 pathway, induction of antioxidant enzymes (e.g., SOD, Gpx),

and reduction of lipid peroxidation, as well as with the suppression of proinflammatory pathways mediated by NF-κB[23-26]. This dual antioxidant and anti-inflammatory activity protects hepatocytes and nephrons against damage induced by hyperglycemia and reactive oxygen species generated in the STZ model[24], which is consistent with studies reporting a reduction in malondialdehyde and recovery of antioxidant markers after vitamin D supplementation[6].

The favorable effects on the lipid profile (reduction in triglycerides and total cholesterol, increase in HDL) observed here are also supported by meta-analyses and recent experimental studies that report lipid profile improvement after vitamin D supplementation, possibly as a result of a direct effect on lipogenic gene expression and of improved insulin sensitivity, which secondarily reduce lipolysis and circulating VLDL-triglycerides[9,18]. However, the magnitude and consistency of these effects vary across models (dose, duration, baseline vitamin D status) and clinical reviews indicate heterogeneity, a fact that reinforces the need to define optimal dose/time protocols in preclinical and clinical studies[21].

Regarding renal function, the decrease in urea and creatinine observed in D-VDG suggests a nephroprotective effect of vitamin D in STZ-induced hyperglycemia[9,18]. The reported mechanisms include the regulation of pro-fibrogenic pathways (TGF-β), a reduction of oxidative stress via Nrf2, and the preservation of glomerular architecture through modulation of VDR in the tubular cell and renal interstitium. Recent experimental reviews and studies using the STZ model indicate a beneficial role of vitamin D in reducing the progression of diabetic nephropathy, although long-term studies performing detailed histological analysis are needed to confirm structural effects beyond biochemical markers[9].

Limitations and experimental variables that influence the observed effects must be discussed, including the dose and administration route of vitamin D, the duration of supplementation (30 days in the present study), the baseline vitamin D status of the animals, the severity of the diabetic model (STZ dose), and inter-laboratory variability in biochemical methods. Studies have shown that the pleiotropic effects of vitamin D (on glucose levels, lipids, and organs) are dose dependent and, in some contexts, synergistic with interventions such as aerobic exercise or metformin, which may enhance the metabolic recovery observed[2]. Thus, the present data indicate a protective effect but do not allow us to draw conclusions regarding complete reversal of the pathology or the optimal dose in translational terms.

Our results reinforce the hypothesis that vitamin D, through its receptor (VDR) and modulation of antioxidant and anti-inflammatory pathways, plays a promising adjuvant role in the control of biochemical parameters associated with diabetes[8,11,16]. However, new trials are needed that stratify dose/intervention duration and concomitant therapy by baseline 25(OH)D status. Further studies using hepatic and renal histological markers should be conducted to confirm the observed protective role of vitamin D.

CONCLUSION

The present study showed that STZ-induced diabetes in Wistar rats causes significant alterations in multiple serum biochemical parameters, which reflect the hepatic, renal, and metabolic dysfunctions characteristic of the hyperglycemic state. Supplementation with vitamin D exerted a modulating effect on these dysfunctions, improving the results at the end of the experimental period. These findings demonstrate that vitamin D exerts a protective and regulatory effect on biochemical parameters altered by STZ, possibly mediated by the activation of the VDR and the modulation of antioxidant and anti-inflammatory pathways. The results reinforce the hypothesis that vitamin D acts as a potential coadjuvant in the prevention and attenuation of metabolic disorders associated with diabetes.

Taken together, the present results confirm that vitamin D is capable of reducing the deleterious effects induced by experimental hyperglycemia, highlighting its biochemical and therapeutic importance in the context of diabetes mellitus.

SIGNIFICANCE STATEMENT

This study highlights the protective role of vitamin D in STZ-induced diabetic Wistar rats. By improving glycemic control, lipid profiles, and liver and kidney function, vitamin D demonstrates potential as a supportive therapeutic strategy to mitigate diabetes-related biochemical disturbances. These findings provide insights into its hepatorenal and metabolic benefits, supporting future translational research for diabetes management.

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REFERENCES

1. Si, Q., J. Guo, X. Yang, Y. Guo, L. Wu, D. Xie and P. Jiang, 2023. Systematic assessment of streptozotocin-induced diabetic metabolic alterations in rats using metabolomics. Front. Endocrinol., Vol. 14. 10.3389/fendo.2023.1107162.
2. Santos, G.R., M.R. Cunha, E.J. Caldeira, E.A. Galdeano, R.C.S. Prudente and C.A.L. Pinto, 2021. Effect of antioxidant treatment with n-acetylcysteine and swimming on lipid expression of sebaceous glands in diabetic mice. Sci. Rep., Vol. 11. 10.1038/s41598-021-91459-x.
3. Hu, M., Q. Ma, B. Liu, Q. Wang, T. Zhang, T. Huang and Z. Lv, 2022. Long non-coding RNAs in the pathogenesis of diabetic kidney disease. Front. Cell Dev. Biol., Vol. 10. 10.3389/fcell.2022.845371.
4. Murakami, S., K. Funahashi, N. Tamagawa and M. Ning and T. Ito, 2022. Taurine ameliorates streptozotocin-induced diabetes by modulating hepatic glucose metabolism and oxidative stress in mice. Metabolites, Vol. 12. 10.3390/metabo12060524.
5. Mediani, A., F. Abas, M. Maulidiani, A.A.B. Sajak and A. Khatib *et al*., 2018. Metabolomic analysis and biochemical changes in the urine and serum of streptozotocin-induced normal- and obese-diabetic rats. J. Physiol. Biochem., 74: 403-416.
6. Yonny, M.E., E.M. García, A. López, J.I. Arroquy and M.A. Nazareno, 2016. Measurement of malondialdehyde as oxidative stress biomarker in goat plasma by HPLC-DAD. Microchem. J., 129: 281-285.
7. Derakhshanian, H., M.H. Javanbakht, M. Zarei, E. Djalali and M. Djalali, 2017. Vitamin D increases IGF-I and insulin levels in experimental diabetic rats. Growth Hormone IGF Res., 36: 57-59.
8. Mitrašinović-Brulić, M., A. Dervišević, A. Začiragić, M. Fočak, A. Valjevac, A. Hadžović-Džuvo and D. Suljević, 2021. Vitamin D3 attenuates oxidative stress and regulates glucose level and leukocyte count in a semi-chronic streptozotocin-induced diabetes model. J. Diabetes Metab. Disord., 20: 771-779.
9. Atia, T., M. Zahidul Iqbal, H.F. Ahmed, H.I. Sakr, M.H. Abdelzaher, D.F. Morsi and M.E. Metawee, 2022. Vitamin D supplementation could enhance the effectiveness of glibenclamide in treating diabetes and preventing diabetic nephropathy: A biochemical, histological and immunohistochemical study. J. Evidence-Based Integr. Med., Vol. 27. 10.1177/2515690X221116403.
10. Elkhwanky, M.S., O. Kummu and J. Hakkola, 2022. Streptozotocin-induced diabetes represses hepatic CYP2R1 expression but induces vitamin D 25-hydroxylation in male mice. Endocrinology, Vol. 163. 10.1210/endocr/bqac060.
11. Fathi, F.E.Z.M., K.M. Sadek, A.F. Khafaga, A.W. Al Senosy, H.A. Ghoniem, S. Fayez and M.F. Zeweil, 2022. Vitamin D regulates insulin and ameliorates apoptosis and oxidative stress in pancreatic tissues of rats with streptozotocin-induced diabetes. Environ. Sci. Pollut. Res., 29: 90219-90229.
12. Park, C.Y., S. Shin and S.N. Han, 2024. Multifaceted roles of vitamin D for diabetes: From immunomodulatory functions to metabolic regulations. Nutrients, Vol. 16. 10.3390/nu16183185.
13. Christakos, S., P. Dhawan, A. Verstuyf, L. Verlinden and G. Carmeliet, 2015. Vitamin D: Metabolism, molecular mechanism of action, and pleiotropic effects. Physiol. Rev., 96: 365-408.
14. Anton, I.C., L. Mititelu-Tartau, E.G. Popa, M. Poroch and V. Poroch *et al*., 2022. Zinc chloride enhances the antioxidant status, improving the functional and structural organic disturbances in streptozotocin-induced diabetes in rats. Medicina, Vol. 58. 10.3390/medicina58111620.
15. Oluba, O.M., F.D. Adebiyi, A.A. Dada, A.A. Ajayi, K.E. Adebisi, S.J. Josiah and A.A. Odutuga, 2019. Effects of *Talinum triangulare* leaf flavonoid extract on streptozotocin-induced hyperglycemia and associated complications in rats. Food Sci. Nutr., 7: 385-394.
16. George, N., T.P. Kumar, S. Antony, S. Jayanarayanan and C.S. Paulose, 2012. Effect of vitamin D_3 in reducing metabolic and oxidative stress in the liver of streptozotocin-induced diabetic rats. Br. J. Nutr., 108: 1410-1418.
17. Krisnamurti, D.G.B., M. Louisa, E.H. Poerwaningsih, T.J.E. Tarigan, V. Soetikno, H. Wibowo and C.M.H. Nugroho, 2023. Vitamin D supplementation alleviates insulin resistance in prediabetic rats by modifying IRS-1 and PPARγ/NF-κB expressions. Front. Endocrinol., Vol. 14. 10.3389/fendo.2023.1089298.
18. Castro, M.F.V., C.E. Assmann, K.P. Reichert, P.M. Coppetti and N. Stefanello *et al*., 2024. Vitamin D3 mitigates type 2 diabetes induced by a high carbohydrate-high fat diet in rats: Role of the purinergic system. J. Nutr. Biochem., Vol. 127. 10.1016/j.jnutbio.2024.109602.
19. Golpasandi, H., M.R. Rahimi, S. Ahmadi, B. Łubkowska and P. Cięszczyk, 2023. Effects of vitamin D3 supplementation and aerobic training on autophagy signaling proteins in a rat model type 2 diabetes induced by high-fat diet and streptozotocin. Nutrients, Vol. 15. 10.3390/nu15184024.
20. Hoseini, Z., N. Behpour and R. Hoseini, 2023. Vitamin D improves the antidiabetic effectiveness of aerobic training via modulation of Akt, PEPCK, and G6Pase expression. Diabetology Metab. Syndr., Vol. 15. 10.1186/s13098-023-01158-y.
21. Contreras-Bolívar, V., B. García-Fontana, C. García-Fontana and M. Muñoz-Torres, 2021. Mechanisms involved in the relationship between vitamin D and insulin resistance: Impact on clinical practice. Nutrients, Vol. 13. 10.3390/nu13103491.

22. Alvarez, J.A. and A. Ashraf, 2010. Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. Int. J. Endocrinol. 10.1155/2010/351385.
23. Yuan, Q., R. Zhang, M. Sun, X. Guo and J. Yang *et al*., 2022. Sirt1 mediates vitamin D deficiency-driven gluconeogenesis in the liver via mTorc2/Akt signaling. J. Diabetes Res., Vol. 2022. 10.1155/2022/1755563.
24. Zhou, Y., Q. Liao, D. Li, L. Chen, H. Zhang and B. Yi, 2024. Vitamin D receptor alleviates lipid peroxidation in diabetic nephropathy by regulating ACLY/Nrf2/Keap1 pathway. FASEB J., Vol. 38. 10.1096/fj.202401543R.
25. Wang, H., T. Yuan, W. Wu and S. Ou, 2025. Vitamin D and chronic kidney disease: Mechanisms, clinical implications, and future perspectives. Front. Med., Vol. 12. 10.3389/fmed.2025.1643415.
26. Santos, G.C., J.D. Zeidler, J.A. Pérez-Valencia, A.C.B. Sant'Anna-Silva, A.T. da Poian, T. El-Bacha and F.C.L. Almeida, 2017. Metabolomic analysis reveals vitamin D-induced decrease in polyol pathway and subtle modulation of glycolysis in HEK293T cells. Sci. Rep., Vol. 7. 10.1038/s41598-017-10006-9.