RESEARCH ARTICLE

MoS_2 Improves the Function of Pancreatic β-cells in Type 2 Diabetes Mellitus

Fatemeh Ghafari[1], Tahereh Foroutan[1*], Marzieh Salimi[2], Rambod Norouzi[3]

[1] Department of Animal Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran

[2] Institute for Nanoscience and Nanotechnology, Sharif University of Technology, Tehran, Iran

[3] Department of Molecular Biosciences, Autonomous University of Madrid, Madrid, Spain

ARTICLE INFO

Article History:
Received 09 Apr 2024
Accepted 16 May 2024
Published 01 Aug 2024

Keywords:
MoS_2
Diabetes
Glucose metabolism genes
BCL_2
Nanomaterial

ABSTRACT

In recent years, anti-cancer and stem cell differentiation properties have been reported for some molybdenum derivatives such as molybdenum disulfide (MoS_2). Diabetes mellitus as a chronic metabolic disorder has symptoms such as insufficient insulin secretion or insulin dysfunction due to β cell destruction. Each of the current diabetes treatment methods has limitations. In the present research the effects of MoS_2–PEG on survival rate, expression of genes involved in glucose metabolism, and insulin secretion in diabetic RIN-5F β cell was studied. Synthesized MoS_2-PEG nanosheets was used for possible effects of MoS_2 on RIN-5F cells induced by STZ (40 mM). MTT assay, RT-PCR, and hormonal analyses were used to investigate the anti-toxicity effect of MoS_2 and its role in improving the function of diabetic RIN-5F cells. The results showed that MoS_2 is biocompatible and non-toxic at the dose used in the present study and significantly increased the expression of GLUT4, GCK, and INS genes involved in glucose metabolism as well as anti- apoptotic gene BCL_2 in the diabetic RIN-5F cells. Also, treatment with MoS_2 increased insulin secretion in diabetic RIN-5F cells. It could be concluded that MoS_2 –PEG represents a protective role in the diabetic cells and significantly improve the treatment of diabetic cells mouse model. These results demonstrate the increased expression genes involved in glucose metabolism in pancreatic damaged cells.

How to cite this article
Ghafari F., Foroutan T., Salimi M., Norouzi R. MoS_2 Improves the Function of Pancreatic β-cells in Type 2 Diabetes Mellitus. Nanomed Res J, 2024; 9(3): 243-250. DOI: 10.22034/nmrj.2024.03.002

INTRODUCTION

Diabetes mellitus (DM), insulin-dependent diabetes (Type1), with symptoms of hyperglycemia, mainly occurs due to a decrease in the efficiency of pancreatic cells, which results in insufficient insulin secretion or insulin dysfunction in the body [1, 2] In type 2 diabetes the body does not use insulin effectively, resulting in abnormal blood glucose levels.

Diabetes as 7th cause of death in the world is one of the most important causes of diseases such as Alzheimer's and cardiovascular diseases in aging with symptoms of hyperglycemia and hyperlipidemia [3, 4]. Since the main feature of diabetes (both type 1 and type 2) is the decrease in the number of healthy insulin-secreting cells, therefore, one of the main ways to treat it can be a method to proliferation and differentiation of beta cell mass[5]. People with diabetes 1 and 2 need to take insulin daily and continuously use blood glucose-lowering drugs respectively, both of which have side effects [6, 7]. Today, the use of nanomaterials has helped to treat some diseases [8-10]. Recently, molybdenum disulfide (Mos2) and the other two-dimensional materials have attracted a lot of attention in regenerative medicine due to high efficiency to convert light to heat[11-16]. They have properties such as biocompatibility, high surface ratio, chemical and mechanical performance with medical and pharmacological applications. Their potential has

* Corresponding Author Email: *foroutan@khu.ac.ir*

also been shown in the treatment of Alzheimer's and Corona [17].The mentioned properties are largely dependent on their synthesis method [18]. There are conflicting studies about the toxicity and biocompatibility of MoS_2, some have reported it as non-toxic and others as toxic [19-21]. In order to increase the stability of MoS_2, PEG is added to it. In the present study, the effects of MoS_2 covered by PEG was used to improve glucose metabolism in RIN-5F pancreatic β cells induced by STZ, a diabetes inducing compound.

MATERIALS AND METHODS

$H_{24}Mo_7N_6O_{24}.4H_2O$, 99%, C_2H_5NS, 99%, and PEG, M_w=400 kDa were obtained from Sigma- Aldrich. MoS_2-PEG were synthesized by hydrothermal method based on our previous protocol [22]. XRD, FT-IR using an ABB Bomem MB-100 FT-IR, and scanning electron microscopy (FE-SEM, TE-SCAN, MIRA3) was used to characterize the synthesized MoS_2. The absorbtion of nanosheets was measured with Perkin Elmer (lambda 950) (UV-VIS-NIR-spectrophotometer).

Cell line and reagents

The cells used in this study was obtained from the national cell bank of Iran. STZ and MTT were obtained from Sigma-Aldrich Chemical Co. RPMI and FBS medium cell culture were obtained as a gift. The present study was approved by Ethical Committee of Kharazmi University (Code: IR.KHU.REC.1401.84.

Cell culture conditions

RIN-5F cell line (5 $\times 10^4$ cells/well) cultured in RPMI containing FBS in a humidified environment of 5% CO 2 at 37 °C. STZ was dissolved in cell culture medium. After 48 h the cells received STZ (40 mM) dissolved in medium. The samples divided to 3 groups; (1) control group no received any treatment, (2) STZ group, and (3) MoS_2 group treated with STZ and 60 µg/ml MoS_2 [22].

Insulin secretion assay

Rat RIN-5F cells were cultured at 5 × 10^4 cells/well. The cell culture medium contained low glucose supplemented with MoS_2-PEG. After 12 h, insulin concentration was analyzed by ELISA assay [23].

The effect of MoS_2 on STZ-induced cytotoxicity

Three types of experiments were performed as: RIN-5F cells without any treatment (control group) (a), induced by STZ (b) and STZ incubated with MoS_2 (c). Finally, cell viability was evaluated with MTT assay.

The effect of MoS_2 on apoptosis of RIN-5F cells induced by STZ

MoS_2 ability to prevent apoptosis of diabetic RIN-5F cells was investigated in the next step. Apoptosis of RIN-5F cells induced by STZ and treated cells with MoS_2 was investigated by real time RT-PCR. Also, the expression of Bcl_2 gene was investigated in different groups.

The effects of intraperitoneal injection of MoS_2 on glucose and insulin concentration in model rats induced STZ

A number of 18 male Wistar Albino rats (180-220 g) were kept at 12 h of light-dark cycles with controlled temperature (24 ± 3 °C). The study groups were as follows: 1) control group (n=6) that did not receive any treatment, 2) STZ group (n=6) that treated with STZ at a dosage of 40 mg/kg intraperitoneally, 3) STZ + MoS_2 group that received 1.5 mg/kg MoS_2 after STZ injection [24].

RNA extraction, cDNA synthesis, and real-time polymerase chain reaction

The expression of glucose transporter (GLUT4), *Insulin* (Ins), glucokinase, and BCL2 was analyzed according to our previous study [25].

Statistical analysis

Statistical evaluation was done using one-way analysis of variance with SPSS version 16.0 software. Significant differences were considered as $P < 0.05$.

RESULTS

The XRD pattern of MoS_2-PEG nanosheets is

Table 1. Primer sequences used in real-time PCR

Gene	Forward (5′→3′)	Reverse (5′→3′)
GCK	TCTAGTCAACCTGATTGCCAT	CATTTCAACCGACTCCGCTA
GLUT4	TTTCCTCGCAGCACTTTAGCC	CTCCAGCTTCCCAGTTCCC
Ins	ATCTTCAGACCTTGGCACTGG	GTAGAGGGAGCAGATACTGGT
BCL2	CCCCACAGACGCTCAACATC	TCGGAGGTCTCGGTATGTACT

shown in Figure 1A. Diffraction peaks at 14.0°, 35.5°, and 58.3° are related to (002), (100), and (110) crystal planes of MoS_2 (JPDCF No.37-1492) which confirms the successful synthesis of MoS_2 with a hexagonal crystal structure [22].

FT-IR spectrum of MoS_2 -PEG is shown in Figure 1B. Absorption peaks at 1100, 1630, 2900, and 3400 Cm^{-1} corresponded to C-O, C-O-C, C-H, and O-H stretching vibrations which confirm the successful modification of MoS_2 nanosheets surface with polyethylene glycol molecules as described in or previous report [24]. Moreover, the absorption peak at 480 and 900 Cm^{-1} are related to S-S and Mo-S bonds which confirm the synthesis of MoS_2. As shown in the UV-Vis-NIR spectrum of MoS_2-PEG (Figure1C), the absorption of nanosheets increases by decreasing wavelength which can be due to the existence of the trigonal phase of MoS_2 in the structure [16]. Figure 1C Shows that MoS_2-nanosheets can highly absorb ultraviolet, visible, and near-infrared light. As it is obvious from the FE-SEM image of synthesized MoS_2-PEG (Figure1D), the nanostructure consists of nanosheets which are randomly distributed in the sample. Figure 2 shows schematic illustration of synthesis mechanism of MoS_2-nanosheets and MoS_2-nanoflower.

Effect of MoS_2 on viability, BCL2, INS, GLUT4, and GCK genes expression in RIN-5F induced by STZ

Diabetic RIN-5F were treated with 60 µg/ml MoS_2 and their viability was measured by MTT assay (Figure 3). Control group were cultured in equivalent amount of culture medium alone. RIN-5F induced by STZ treated with MoS_2 showed higher viability compared to STZ group ($P < 0.01$). Analysis of glucose metabolism genes including insulin, glucose transporter GLUT4, and GCK of RIN-5F cells induced by STZ treated with MoS_2showed significant increase compared to STZ group (Figure 4). MoS_2 increased BCL2 gene expression, an anti-apoptosis gene, in RIN-5F induced by STZ significantly ($P<0.001$) (Figure 4D).

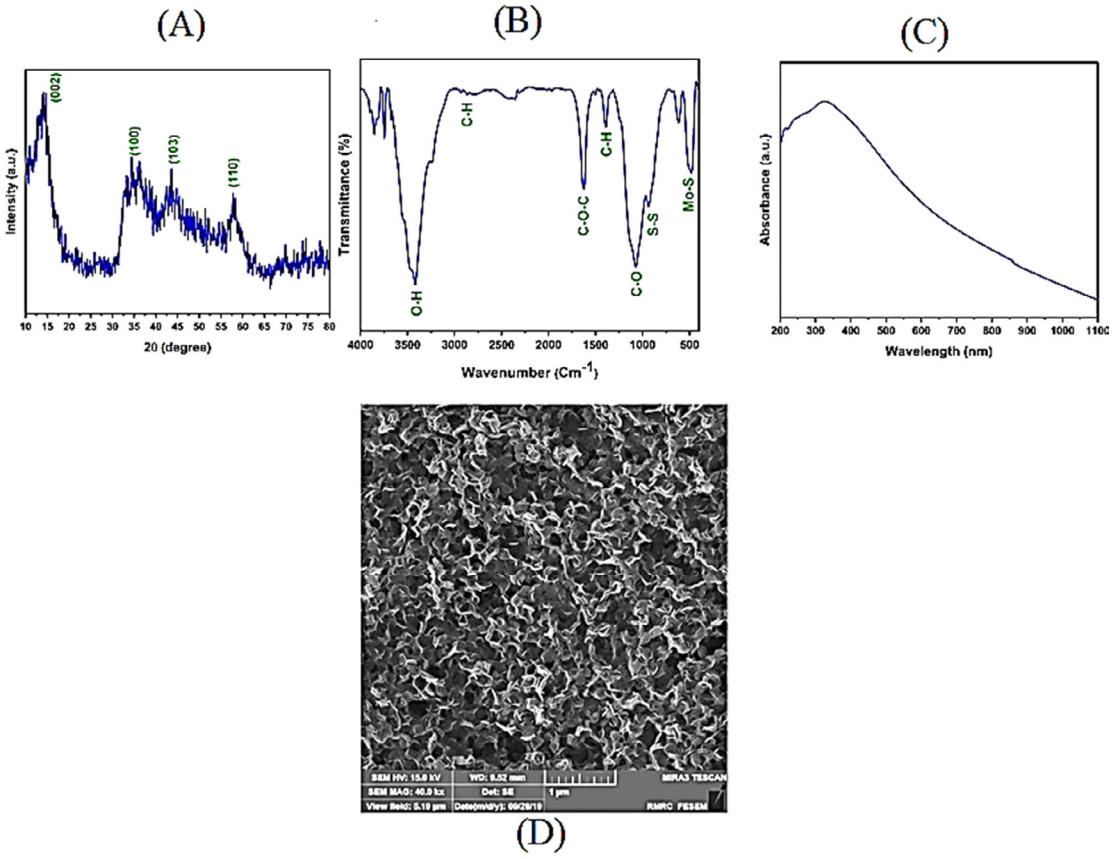

Fig. 1.A: XRD pattern of MoS_2- nanosheet. B: FT-IR spectra. C: UV-VIS-NIR spectrum of MoS2-PEG of MoS_2-nanosheet. D: Field-emission scanning electron microscopy of MoS_2-nanosheet.

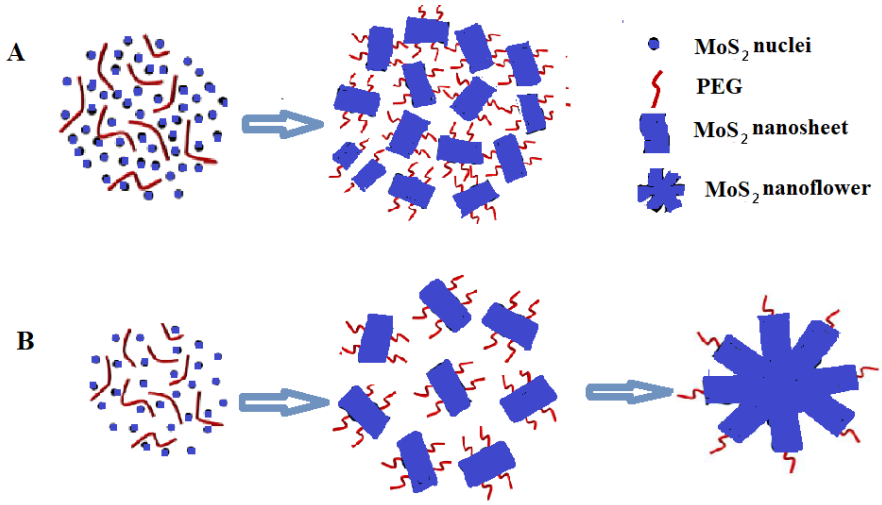

Fig. 2. Synthesis mechanism of (A) MoS_2-nanosheets and (B) MoS_2-nanoflower.

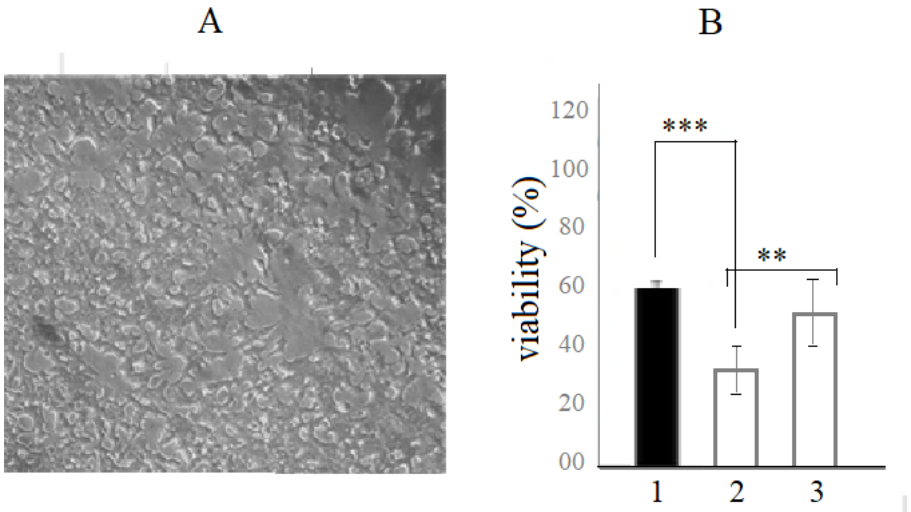

Fig. 3. A: Light microscopy image from RIN-5F cells (100 ×). B: The effect of MoS_2 on viability of RIN-5F induced by STZ. Diabetic RIN-5F were treated with 60 µg/ml MoS_2 and their viability was measured by MTT assay. Control group were cultured in equivalent amount of culture medium alone. The results show the mean ± SD from triplicated experiments. MoS_2 group shows a higher viability compared with STZ group (**P < 0.01).

Glucose and insulin secretory assay

The amount of insulin secreted by RIN-5F induced by STZ in culture medium and *in vivo* was increased markedly after treatment with MoS_2 in examined doses (Figure 5).

DISCUSSION

The results of the present research showed the non-toxic effect of PEG-MoS2 on RIF-5 cells, which can be concluded that adding PEG to MoS2 reduces its toxicity. Various applications of MoS_2 in biological and medical fields have been reported. In confirmation of this result, other studies have also reported the non-toxicity of MoS_2 in low concentrations [11, 12]. Another study reported that although MoS_2 has good biocompatibility, cancer killing, and anti-bacterial effect, it is highly toxic [13]. The MoS_2 used in this study was covered by PEG that reduces MoS2 toxicity [12]. Another study showed hepatocyte toxicity when treated with uncapped MoS_2 even at doses less than 30 µg/ml [26]. In addition to toxicity, increased ROS and

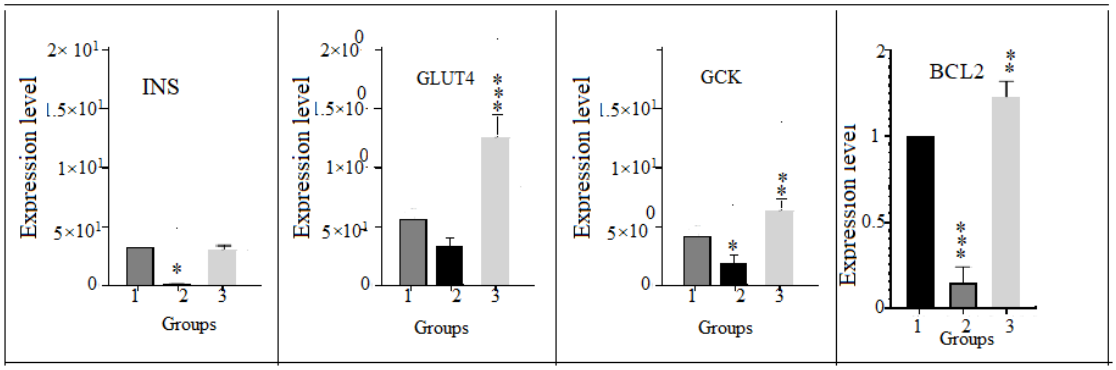

Fig. 4. The effect of MoS_2 on INS, BCL2, GLUT4, GCK, and BCL2 genes expression in RIN-5F induced by STZ. An increase in all genes expression is evident in MoS_2 group compared to STZ group. Increased expression of Glut4 and BCL2 genes is observed in MoS_2 group compared to control and STZ groups. Increased expression of GCK and INS genes is observed in MoS_2 group compared to STZ group 1: control, 2: STZ, and MoS_2 groups. *P < 0.05; **P < 0.01, ***P < 0.001 compared with STZ group.

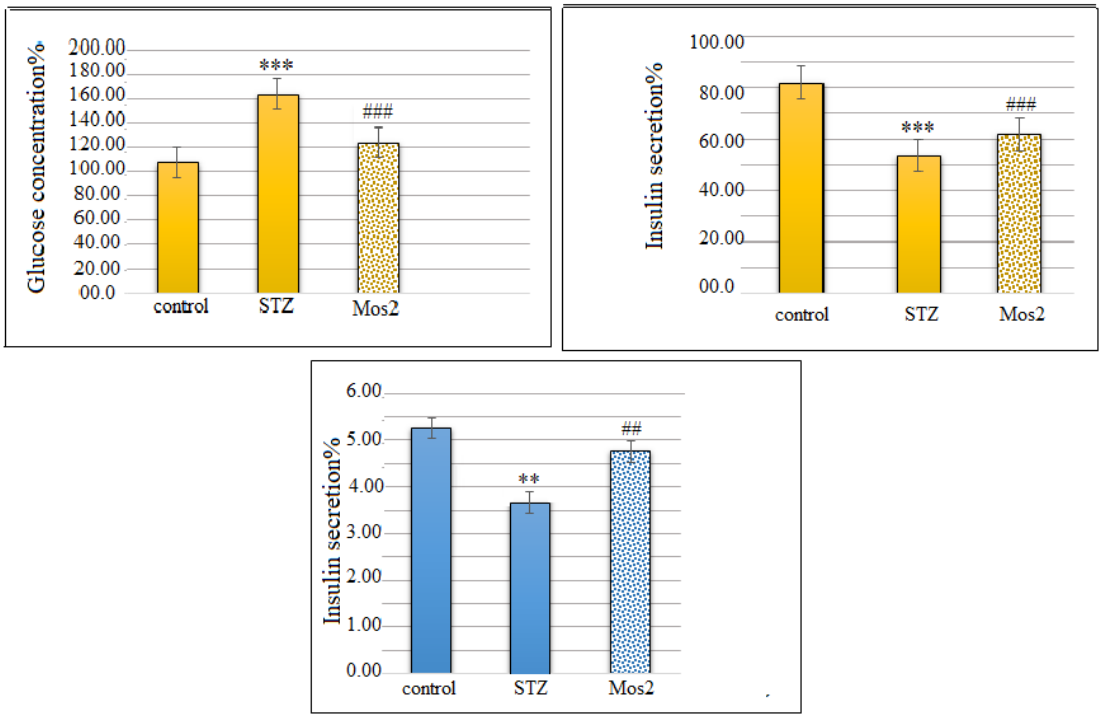

Fig. 5. Intraperitoneal injection of MoS_2 increased glucose (left) and insulin secretion (right) in model rats induced by STZ significantly. MoS_2 increased glucose stimulated insulin release in RIN-5F cells induced by STZ (below). *P < 0.05, **P < 0.01, and ***P < 0.001 show difference between STZ and control group. #P < 0.05, ##P < 0.01, and ###P < 0.001 show difference between MoS_2 and STZ group.

increased cellular inflammation were also reported in hepatocytes cells [14]. It may be concluded that adding PEG to MoS_2 reduces its toxicity [22].

Our data showed that MoS_2 increases the expression of insulin and GLUT4. ROS causes a decrease in insulin secretion response in β-cells depending on glucose concentration [20,21,27,28]. Some reports indicate the role of some MoS_2 nanomaterials in the production or removal of ROS [29]. For example, Chen et al. reported that MoS_2 nano sheet acts as an antioxidant at dose of 30–350 µg/ml and accelerate the electron transfer and thus remove and scavenge reactive oxygen species [30]. Other researcher showed antioxidant role of fullerene-like MoS_2 dose of (10–200 µg/ml) in facilitating electron transfer and subsequently

cleaning ROS.[31]

Considering the harmful role of ROS in the regulation of gene expression, it seems that the increased expression of genes involved in glucose metabolism after using MoS2-PEG is due to its effect in reducing the amount of cellular reactive oxygen species. Since the removal of ROS can be one of the solutions for the treatment of diabetes, the use of MoS_2 -PEG compounds can be a good solution for reducing the harms of diabetes. Insulin resistance can have some reasons such as oxidative stress, which can cause the death of pancreatic cells and disrupt insulin secretion [18, 22].

For example, the presence of oxidative stress biomarker H2O2, has been introduced as one of the symptoms of diabetes [33]. Since β cells have a very low antioxidant capacity, adding MoS_2–PEG increases the antioxidant properties of these cells, thus they show more resistance to apoptosis [32]. Therefore, the increase in the expression of BCL2 and also insulin can be caused by the increase in the antioxidant activity of beta cells after the adding of MoS_2. It has been demonstrated that MoS_2 acts as a nanozyme with functions similar to catalase and superoxide dismutase [30]. Further, MoS_2 has shown activity similar to peroxidase through electron transfer, thus preventing ROS production. In fact, MoS_2 nano-enzymes act as a cascade for efficient intracellular antioxidation and prevent the production of ROS [34]. Molybdenum-based biomaterials have been introduced as one of the promising candidates for healing wounds such as diabetic wounds, and considering their effective role in the overexpression of some genes [35]. perhaps the results of present study in increasing gene expression can be attributed to these properties.

Chen and colleagues designed a nanozyme antioxidant system using MoS_2 to reduce cellular threats such as oxidative stress, etc [30]. These results indicate the ability of MoS_2 to protect cells against possible damages. They concluded that MoS_2 as an antioxidant play a role in the pathological processes and it can have applications in biocatalysis and nano-biomedicine [30].

Recently, a decrease in butyrate-producing bacterial species has been shown people with type 2 diabetes [35]. Cui and colleagues reported that one type of bacteria found in the gut may be involved in the development of Type 2 diabetes, while another may protect from the disease [35].

Although our results revealed that under MoS2 induction the expression of genes involved in insulin metabolism (such as Glut4, GCK, Ins) in diabetic β cells are increase, but there is still no report on the cause of this issue. GLUT4 is an insulin-dependent glucose transporter. GCK in pancreatic β-cells is known to maintain glucose homeostasis by acting as a glucose sensor in the glucose metabolism pathway [36]. The increase in its expression after treatment with MoS_2 can indicate the increase in insulin expression, which our results also confirmed it. Perhaps one of the reasons is the ability MoS_2 to enter cells efficiently to deliver the therapeutic cargo owing to their nanosize [37]. The cargo can be the growth factors in the medium containing the β cells, which facilitate their entry into the cells by MoS_2 can help the treatment. Another reason can be high surface-area-to-volume ratio of MoS_2 that provides high cargo or drug loading capacity.

CONCLUSION

The present study demonstrated that MoS_2-PEG protected RIN-5F cell line from STZ cytotoxicity and significantly potentiated the insulin secretion and expression of glucose metabolism genes. Also it could increase BCL_2 expression as an anti-apoptotic factor for proliferation of β pancreatic cells. These results could translate into beneficial effects of MoS_2 in the management of diabetes. In future, clinical studies are suggested.

AUTHOR CONTRIBUTIONS

F.G. carried out the investigation and formal analysis. T.F. designed and directed this study and wrote the original draft. R.N. and M.S. carried out the investigation and formal analysis.

CONFLICT OF INTEREST

The authors declare no competing financial interest.

REFERENCES

1. Classification and diagnosis of diabetes: standards of medical care in diabetes. Diabetes Care 2019, 42 (Spp 1): S13-S28. https://doi.org/10.2337/dc19-S002
2. Salsali, A.; Nathan, M. A review of types 1 and 2 diabetes mellitus and their treatment with insulin. American journal of therapeutics 2006;13(4):349-61. https://doi.org/10.1097/00045391-200607000-00012
3. Ebrahimpour, S.; Zakeri, M.; Esmaeili, A. Crosstalk between obesity, diabetes, and alzheimer's disease: Introducing quercetin as an effective triple herbal medicine. Ageing research reviews 2020, 62:101095. https://doi.org/10.1016/j.arr.2020.101095

4. Li, S.; Wang, J.; Zhang, B.; Li, X.; Liu,Y. Diabetes mellitus and cause-specific mortality: a population-based study. Diabetes & metabolism journal 2019, 43(3):319-41. https://doi.org/10.4093/dmj.2018.0060
5. Arumugam, G.; Manjula, P.; Paari, N. A review: Anti diabetic medicinal plants used for diabetes mellitus. Journal of Acute Disease 2013,2 (3):196-200. https://doi.org/10.1016/S2221-6189(13)60126-2
6. Salehi, B.; Ata, A.; Kumar, N.; Sharopov, F.; Ramirez-Alarcon, K.; Ruiz-Ortega, A.; et al. Antidiabetic potential of medicinal plants and their active components. Biomolecules 2019, 9(10):551. https://doi.org/10.3390/biom9100551
7. Vavilova N. Homeopathic pharmacodynamics (in Russian), in 2 parts. Homeopathic Center. Smolensk, Everest, Moscow 1994,2:208-11.
8. Karimzadeh, P.; Foroutan, T.; Nafar, M.; Khalvati, S.Impact of Nanographene Oxide on Cisplatin Induced Acute Kidney Injury Managed by Stem Cells Therapy. Iranian Journal of Kidney Disease 2023, 17,5, 271-278.
9. Rahimi, M.; Foroutan, T.; Eini, F.The Effects of Nano Magnetic Graphene Oxide on In Vivo Maturation of Oocyte. Nano Biomedicine & Engineering 15 (4). https://doi.org/10.26599/NBE.2023.9290036
10. Foroutan,T.; Kassaee, MZ.; Salari, M.; Ahmady, F.; Molavi, F.; Moayer, F.Magnetic Fe3O4@graphene oxide improves the therapeutic effects of embryonic stem cells on acute liver damage. Cell Proliferation 2021, 54 (11), e13126. https://doi.org/10.1111/cpr.13126
11. Appel, JH.; Li, DO.; Podlevsky, JD.; Debnath, A.; Green, AA.; Wang, QH.; et al. Low cytotoxicity and genotoxicity of two-dimensional MoS2 and WS2. ACS Biomaterials Science & Engineering 2016,2(3):361-7. https://doi.org/10.1021/acsbiomaterials.5b00467
12. Wang, S.; Chen, Y.; Li, X.; Gao, W.; Zhang, L.; Liu, J.; et al. Injectable 2D MoS2-integrated drug delivering implant for highly efficient NIR-triggered synergistic tumor hyperthermia. Advanced materials 2015, 27(44):7117-22. https://doi.org/10.1002/adma.201503869
13. Kaur, J.; Singh, M.; Dell'Aversana, C.; Benedetti, R.; Giardina, P.; Rossi, M.; et al. Biological interactions of biocompatible and water-dispersed MoS2 nanosheets with bacteria and human cells. Sci. Rep. 2018, 8, 16386. https://doi.org/10.1038/s41598-018-34679-y
14. Liu, S.; Shen, Z.; Wu, B.; Yu, Y.; Hou, H.; Zhang, X-X.; et al. Cytotoxicity and efflux pump inhibition induced by molybdenum disulfide and boron nitride nanomaterials with sheetlike structure. Environmental science & technology 2017,51(18):10834-42. https://doi.org/10.1021/acs.est.7b02463
15. Livak, K.J.; Schmittgen, T.D. Analysis of relative gene expression data using real-time quantitative PCR and the 2− ΔΔCT method. Methods 2001, 25, 402-408. https://doi.org/10.1006/meth.2001.1262
16. Sun, P. Synthesis of hierarchical MoS2 and its electrochemical performance as an anode material for lithium-ion batteries, J. Mater. Chem. A 2. 2014,10, 3498-3504. https://doi.org/10.1039/C3TA13994H
17. Li, A.; Tyson, A.; Patel, S.;Patel, M.; Katakam, S.;Mao, X.; et al. Emerging nanotechnology for treatment of alzheimer's and parkinson's disease. Front. Bioeng. Biotechnol., 2021, 9. https://doi.org/10.3389/fbioe.2021.672594
18. Vaidya, HB.; Ahmed, AA.; Goyal, RK.; Cheema, SK. Glycogen phosphorylase-a is a common target for anti-diabetic effect of iridoid and secoiridoid glycosides. Journal of Pharmacy & Pharmaceutical Sciences 2013,16(4):530-40. https://doi.org/10.18433/J3FS4F
19. Ma, B.; Dang, W.; Yang, Z.; Chang , J.; Wu, C.; MoS2 Nanoclusters-based biomaterials for disease- impaired wound therapy. Applied Materials Today. 2020, 20. https://doi.org/10.1016/j.apmt.2020.100735
20. Tian, J.; Peng, Q.; Shen, Y.; Liu, X.; Li , D.; Li, J.; et al .Chondroitin sulphate modified MoS2 nanoenzyme with multifunctional activities for treatment of Alzheimer's disease. Int J Biol Macromol. 2024, 266:131425. https://doi.org/10.1016/j.ijbiomac.2024.131425
21. Arefi-Oskoui, S.; Khataee, A.; Koba Ucun, O.; Kobya, M.; Ölmez Hanci, T.; Arslan-Alaton, I. Toxicity evaluation of bulk and nanosheet MoS2 catalysts using battery bioassays. Chemosphere 2022, 268. https://doi.org/10.1016/j.chemosphere.2020.128822
22. Salimi, M.; Shokrgozar, MA.; Delavari, HH.; Vossoughi, M. Photothermal properties of two-dimensional molybdenum disulfide (MoS2) with nanoflower and nanosheet morphology. Materials Research Bulletin, 2022, 15,111837. https://doi.org/10.1016/j.materresbull.2022.111837
23. Subash-Babu, P.; Abdulaziz AlSedairy, S.; Abdulaziz Binobead, M.; Alshatwi Metabolites, AA. Luteolin-7-O-rutinoside Protects RIN-5F Cells from High-Glucose-Induced Toxicity, Improves Glucose Homeostasis in L6 Myotubes, and Prevents Onset of Type 2 Diabetes. Metabolites 2023, 13, 269. https://doi.org/10.3390/metabo13020269
24. Kamli-Salino, SEJ.; Brown, PAJ.; Haschler, TN.; Liang, L.; Feliers, D.; Wilson, HM. Induction of experimental diabetes and diabetic nephropathy using anomer-equilibrated streptozotocin in male C57Bl/6J mice. Biochemical and Biophysical Research Communications 2023, 650, 109-116. https://doi.org/10.1016/j.bbrc.2023.01.089
25. Abedi, A.; Foroutan, T.; Shamani, M.; Dargahi, L. Sex-specific effects of high-fat diet on rat brain glucose metabolism and early-onset dementia symptoms. Mechanisms of Ageing and Development, 2023, 211:111795. https://doi.org/10.1016/j.mad.2023.111795
26. Roy S, Deo KA, Singh KA, Lee HP, Jaiswal A, Gahawar AK. Nano-bio interactions of 2D molybdenum disulfide. Advanced Drug Delivery Review, 2022, Advanced drug delivery review.187, 114361. https://doi.org/10.1016/j.addr.2022.114361
27. Lukic M, Stosic-Grujicic S, Ostojic N, Chan W, Liew F. Inhibition of nitric oxide generation affects the induction of diabetes by streptozocin in mice. Biochemical and biophysical research communications 1991,178(3):913-20. https://doi.org/10.1016/0006-291X(91)90978-G
28. Thomas HE, McKenzie MD, Angstetra E, Campbell PD, Kay TW. Beta cell apoptosis in diabetes. Apoptosis 2009, 14:1389-404. https://doi.org/10.1007/s10495-009-0339-5
29. Yu, Y.; Lu, L.; Yang, Q.; Zupanic, A.; Xu, Q.; Jiang, L. Using MoS2 Nanomaterials to Generate or Remove Reactive Oxygen Species: A Review. 2021, ACS Appl. Nano Mater. https://doi.org/10.1021/acsanm.1c00751
30. Chen, T. M.; Zou, H.; Wu, X. J.; Liu, C. C.; Situ, B.; Zheng, L.;Yang, G. W. Nanozymatic antioxidant system based on MoS2 nanosheets. ACS Appl. Mater. Interfaces 2018, 10 (15), 12453−12462. https://doi.org/10.1021/acsami.8b01245
31. Chen, T.; Zou, H.; Wu, X.; Chen, Y.; Situ, B.; Zheng, L.; Yang, G. Fullerene-like MoS2 Nanoparticles as Cascade Catalysts Improving Lubricant and Antioxidant

Abilities of Artificial Synovial Fluid. ACS Biomater. Sci. Eng. 2019, 5 (6), 3079–3088. https://doi.org/10.1021/acsbiomaterials.9b00372

32. Rosa, C.; Gimenes, R.; Campos, D.; Guirado, G.; Gimenes, C.; Fernandes, A.; et al. Apocynin influence on oxidative stress and cardiac remodeling of spontaneously hypertensive rats with diabetes mellitus. Cardiovascular Diabetology 2016, 15:1-12. https://doi.org/10.1186/s12933-016-0442-1
33. Wang, WX.; Jiang, WL.; Mao, GJ.; Tan, M.; Fei, J.; Li, Y.; et al. Monitoring the fluctuation of hydrogen peroxide in diabetes and its complications with a novel near-infrared fluorescent probe. Anal. Chem. 2021, 93, 6, 3301-3307. https://doi.org/10.1021/acs.analchem.0c05364
34. Donath, MY.; Böni-Schnetzler, M.; Ellingsgaard, H.; Ehses, JA. Islet inflammation impairs the pancreatic β-cell in type 2 diabetes. 2009'Physiology. https://doi.org/10.1152/physiol.00032.2009
35. Cui, J.; Ramesh, G.; Wu, M.; Jensen, MT.; Crago O, Bertoni AG, et al. Butyrate-producing bacteria and insulin homeostasis: The microbiome and insulin longitudinal evaluation study (MILES). Diabetes 2022; 71:2438-24461. https://doi.org/10.2337/db22-0168
36. Abu Aqel, Y.; Alnesf, A.; Aigha, II.; Islam, Z.; Kolatkar, PR.; Teo, A.; et al. Glucokinase (GCK) in diabetes: from molecular mechanisms to disease pathogenesis. Cellular & Molecular Biology Letters 2024, 29, 120. https://doi.org/10.1186/s11658-024-00640-3
37. Yadav, V.; Roy, S.; Singh, P.; Khan, Z.; Jaiswal, A. (2D MoS2-based nanomaterials for therapeutic, bioimaging, and biosensing applications. Small 2019, 15, 1803706. https://doi.org/10.1002/smll.201803706