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Article

Anti-diabetic effects of fullerene C_{60} nanoparticle mediated by its anti-oxidant activity in the pancreas in type 1 diabetic rats

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The present study aims to examine the anti-diabetic effects of fullerene C60 nanoparticle, as an anti-oxidant compound, on serum glucose level, body weight, food and water intake, and pancreatic oxidative stress in the rats with type 1 diabetes. Diabetes mellitus was induced by single intravenous injection of streptozotocine (45 mg/kg) into the tail vein of the rats. Four groups of rats were divided as follow: normal, normal treatment, diabetic, and diabetic treatment groups. Normal treatment and diabetic treatment groups received intra-orally fullerene (1 mg/kg/daily) up to day 60 following streptozotocine injection. Oxidative stress markers in the pancreas were evaluated on day 60 after inducing diabetes mellitus. Injection of streptozotocine significantly increased serum glucose level as well as food and water intake on all experimental days; it decreased body weight on day 60. Streptozotocine increased MDA level and decreased GSH level and SOD activity in the pancreas. Fullerene significantly decreased food and water intake and increased body weight as compared with the diabetic group. Fullerene also could normalize the pancreatic MDA and GSH markers. The present study suggested that fullerene can decrease diabetic symptoms via its anti-oxidant activity in the pancreas in the rats with type 1 diabetes mellitus.

Keywords: Fullerene. Streptozotocine. Diabetes Mellitus. Oxidative Stress. Pancreas. Rat.

INTRODUCTION

Diabetes mellitus (DM) is a common endocrine metabolic disorder with high global prevalence (Yi *et al.*, 2019). It is characterized by sustained extracellular hyperglycemia, chronic inflammation, polyphagia, polydipsia, polyuria, and changes in body weight (Askary-Ashtiani *et al.*, 2016; Barragán-Bonilla *et al.*, 2019). Extensive research has shown that the pathophysiology of DM and its complication has been strongly linked with oxidative stress and damage in the various organs including; liver, heart, kidney, as well as pancreas (Talebanzadeh *et al.*, 2018). Ample evidence has reported that glucose can react with proteins and lipids, leading to high production of reactive oxygen species (ROS), and subsequently, oxidative stress in DM conditions (Mutavdzin *et al.*, 2019). Additionally, chronic hyperglycemia can increase the generation of reactive nitrogen species (RNS), including, nitric oxide radicals and oxidative peroxynitrite radical (Cepas *et al.*, 2020). Hence, the high levels of ROS and RNS in DM conditions can induce protein and DNA damage, and subsequently, multi-organ dysfunction. It is reported that chronic hyperglycemia can induce oxidative stress via several mechanisms including: (1) increasing intracellular formation of advanced glycation end products (AGEs), (2) activating of nuclear factor κB (NFκB), and (3)

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causing over-activity of the hexosamine pathway (Talebanzadeh *et al*., 2018; Cepas *et al*., 2020). First, the increased formation of AGEs and its interaction with the receptor for AGEs (RAGE) can increase ROS generation inside the mitochondria by activating NADPH oxidases and microsomal enzymes, leading to oxidative stress in various tissues (Chen *et al*., 2018). Secondly, the activation of NFκB can induce release of ROS and pro-inflammatory cytokine, and, subsequently, cell apoptosis (Sandireddy *et al*., 2014; Hadipour *et al*., 2018). Additionally, the activation of NFκB can decrease the expression of antioxidant genes by downregulating Nrf-2 pathway (Sandireddy *et al*., 2014). Thirdly, the over-activity of hexosamine pathway in many tissues during DM conditions can induce oxidative stress via suppressing the pentose shunt pathway. Inhibiting the pentose shunt pathway in turn decreases the generation of the cellular antioxidant enzymes, such as glutathione (GSH) (Horal *et al*., 2004). Hence, activation of all the mentioned signaling pathway leads to releaseing of ROS and various pro-inflammatory cytokines, which are associated with inflammation, apoptosis, as well as tissue damage (Oeckinghaus, Hayden, Ghosh, 2011; Wautier, Guillausseau, Wautier, 2017; Ghorbani *et al*., 2018). Taken together, excessive generation of ROS and oxidative stress during chronic hyperglycemia, leads to the oxidation of proteins, lipids and nucleic acids, as well as cell apoptosis in various tissues (Tangvarasittichai, 2015; Sugeçti 2018). Moreover, oxidative stress can induce insulin resistance and glucose intolerance in DM conditions (Tangvarasittichai, 2015; Sugeçti 2018). Hence, targeting oxidative stress via applying of antioxidant agents is widely considered for DM treatment (Sheweita *et al*., 2002). Fullerene C_{60} nanoparticle is a carbonic molecular compound (diameter=0.72 nm), with a hollow cage-like structure. Fullerenes are ellipsoid, tubular or a combination in shape (Tsachouridis, Papaioannidou, 2010). Fullerene C60 is practically soluble in the lipids (Bal *et al*., 2010). However, several chemical derivatization of fullerenes have been found to make fullerene molecules water-soluble and so increase their administration in biological systems (Partha, Conyers, 2009). It is reported that fulleren application has low toxicity. For example, oral administration of fullerene (lethal dose: 2000 mg/kg) in the single group of males and females could not induce toxicity in rats (Mori *et al*., 2006). Additionally, Bal *et al*., (2010) revealed that orally application of C60 fullerene (4 μg/kg daily for 5 weeks) could not induce toxicity in the diabetic rats. Fullerene C_{60} nanoparticle can pass from cell membrane and localized in the mitochondria, the main site of ROS generation (Namdar *et al*., 2019). Several experimental studies have revealed the antioxidant properties of fullerene C_{60} nanoparticle and its benefits in various diseases (Akhtar *et al*., 2017; Galvan *et al*., 2017; Mousavi, Nafisi, Maibach, 2017). For example, it is reported that fullerene C_{60} nanoparticle, based on its solubility in lipids, accumulating in inner membrane of mitochondria provides high radical scavenging activity (Chistyakov *et al*., 2013). Also, it is identified that fullerenol at low concentrations significantly enhanced cultured hippocampal neuron viability due to its effects on reduction-oxidation signaling pathways (Zha *et al*., 2012). Similarly, it is revealed the protective effects of fullerene on ischemia/reperfusion injury (Lin *et al*., 2002). Furthermore, application of polyhydroxylated fullerene suppressed oxidative stress-induced apoptosis by a fortifying Nrf2-regulated cellular antioxidant system (Ye *et al*., 2014). Therefore, the present study was designed to assess the intra-orally effects of fullerene C_{60} nanoparticle on the serum glucose level, body weight, food and water intake, as well as oxidative stress in the pancreas in the rats with type 1 DM. Streptozotocin (STZ)-treated rats developed clinical features and signs, which are similar to those found in type 1 DM (Sheweita *et al*., 2016). To evaluate the inhibitory effects of fullerene on oxidative stress in the pancreas, we assess the contents of MDA and GHS as well as the activity of SOD and CAT enzymes in the pancreas in the rats with type 1 DM.

MATERIAL AND METHODS

Animals

In the present study, adult male Wistar rats (weighing 190–210 g), were used. The animals were acclimatized under standard laboratory conditions for 1

week (temperature: 25 ± 2°C and 12 h dark/light cycle). They were allowed free access to standard diet or water. The present study was conducted in accordance with the Guidelines of National Institute of Health (NIH) for Care and Use of Laboratory Animals. The ethical committee (Baqiyatallah University of Medical Sciences, Tehran, Iran) approved animal experimental procedures. The ethical number, and the date of this approval number are IR.BMSU.REC.1399.332 and 21 May 2020, respectively.

Experimental design

Animals were randomly divided into 4 groups (n=6 per group). These groups were as follows: (Group 1: normal group [intact as a control group]); (Group 2: normal treatment [intact + fullerene]); (Group 3: DM group [STZ]); (Group 4: DM treatment group [STZ + fullerene]). The animals received single intravenous (i.v.) injection of STZ (40 mg/kg) into the tail vein at the start of the experiment for induction of DM (Bayatpoor *et al.*, 2019). The animals with the serum glucose levels of >200 mg/dL were used as the diabetic rats. These animals received fullerene (intra-orally, 1 mg/kg/daily) up to 60 days following STZ injection. Then, serum glucose level, body weight, as well as food and water intake were evaluated on days 1, 30 and 60 after DM induction. Moreover, oxidative stress markers (MDA level, SOD activity, GSH level and CAT activity) in the pancreas were evaluated on day 60 after DM induction.

Chemicals

Fullerene C60 nanoparticle was obtained from Sharif University of Technology (Tehran, Iran). The degree of purity of this compound was more than 85%. Fullerene was dissolved in sesame oil and administered via oral gavage (1 mg/kg/day) according to the previous study (Namdar *et al.*, 2019). STZ (product number: S0130) were purchased from Sigma–Aldrich Inc. (St Louis, MO, USA).

Assessing serum glucose level

Samples were collected from tail vein on days 1, 30, and 60 after STZ injection. Then, samples were centrifuged at 3000× g for 10 min in order for serum separation. The serum samples were stored at −20°C until analysis. Serum glucose level was assessed using glucose enzymatic kit and spectrophotometer based on enzymatic colorimetric method (Zlatkis, Zak, Boyle, 1953).

Assessing body weight as well as food and water intake

The body weight as well as food and water intake of the experimental rats was measured on days 1, 30, and 60 after STZ injection. Pre-determined quantity of food pellets (100 gr) was placed within each cage during 24 h. Also, pre-determined quantity of water (250 ml) was poured into a water bottle for each rat during 24 h. Afterwards, the total amount of water and food was weighed for each rat and the amount of reduction was calculated. Indeed, food and water intake was determined by manually weighing a food dish and water volume before and after a feeding period.

Tissue preparation and evaluation of protein concentrations in the pancreas

On day 60 after STZ injection, the pancreas tissues were quickly removed under deep anesthesia for assessing the oxidative stress markers including, MDA, GSH, SOD, and CAT enzymes. The pancreas tissues were homogenized in ice-cold phosphate buffered saline and then centrifuged at 14000 g for 15 min at 4ºC. Then, the supernatants were separated to analyze the oxidative stress markers and protein levels. The Bradford method was used to quantify the protein levels (Bradford, 1953).

Assessing MDA content of the pancreas

The MDA concentration, as an important oxidative marker, in the pancreas tissues was measured (Rasouli Vani *et al.*, 2019). Briefly, for protein precipitation, 1.5 mL trichloroacetic acid (10%) was added to 0.5 mL of tissue homogenate. The samples were incubated at the room temperature for 10 min. Then, the supernatant (1.5 mL) of samples was isolated and incubated in boiling water for 30 min after adding thiobarbituric acid (2 mL and

0.67%). The sample was cooled at the room temperature and again vortexed after adding n-butanol (1.25 mL). Then, the absorbance of the solution was recorded at 532 nm wavelength using the spectrophotometer. Finally, the standard curve was obtained using 1, 1, 3, 3-Tetraethoxypropane to compute the MDA levels in the pancreas samples as nMol/mg protein.

Assessing GSH content of the pancreas

The GSH level in the pancreas tissues evaluated according to the method of Tietz (1969). Briefly, protein precipitation of the samples was performed using sulfosalicylic acid (5%). After that, the solution was centrifuged at 2000 g for 10 min to separate the supernatant. Then, the GSH content was measured by adding the protein-free supernatant (100 µL) to 800 mL of 0.3 mM Na2HPO4 and 100 mL of 0.04% 5, 50-dithiobis-(2-nitrobenzoic acid) (DTNB) in 0.1% sodium citrate. The absorbance of solution assessed at 412 nm wavelength following 5 minutes. The GSH contents of the pancreas tissues were calculated as nMol/mg protein.

Assessing SOD activity of the pancreas

The SOD activity was evaluated based on the nitroblue tetrazolium (NBT) reduction by SOD. For evaluation of the SOD activity, potassium phosphate buffer (0.067 M and pH 7.8), EDTA (0.1 M) and 0.1 mL of sample, NBT (1.5 mM) and sodium cyanide (0.3 mM) were mixed. After that, riboflavin (0.12 mM) was added to the solution to start the reaction. The solution was incubated for 12 min at room temperature. Then, the absorbance was assessed at 610 nm wavelength after 5 min, using a spectrophotometer. The extent of enzyme that developed 50% inhibition was considered as 1 U, and finally, SOD activity of the samples was calculated as U/mg protein (Rasouli Vani *et al.*, 2019).

Assessing CAT activity of the pancreas

For assessment of CAT activity in the pancreas (Namdar *et al.*, 2019), the reaction mixture was prepared and allowed at room temperature for 10 min. The reaction mixture contained 0.85 ml potassium phosphate buffer (50 mM, pH 7.0) and 0.1 mL homogenate solution. Then, 0.05 ml H2O2 (30 mM prepared in 50 Mm potassium phosphate buffer, pH 7.0) was added to samples. Using a spec-trophotometer (UV 7500, Spectro Lab, England) the reduction absorbance calculated at 240 nm for 3 min. The CAT activity of the samples was calculated as U/mg protein. One unit of catalase was defined as 1 nMol H2O2 decomposed per min.

Statistical analysis

The present data were analyzed in the SPSS software (version 21.0). Data are expressed as mean±SD. Four experimental groups were compared using one-way analysis of variance (ANOVA), followed by Tukey HSD's post hoc test. $p<0.05$ was considered significant.

RESULTS

Effects of fullerene treatment on serum glucose level

Two-way ANOVA analysis confirmed significant effects of groups (F=423.26, df=3, P=0.001), non-significant effects of days (F=1.25, df=2, P=0.29), and the non-significant interaction between both factors (days×groups) (F=1.28, df=6, P=0.27). As shown in Figure 1, injecting STZ significantly increased serum glucose level in the diabetic group [(468±52, day 1), (459±39, day 30), and (431±28, day 60)] as compared with the normal group [(111±11, day 1), (118±11, day 30), and (125±11, day 60)] on all the experimental days (Figure 1, *$p<0.05$). Furthermore, applying fullerene could not significantly reduce serum glucose level in diabetic+fullerene group [(466±77, day 1), (416±84, day 30), and (417±63, day 60)] as compared with the diabetic group on all the experimental days. Aditionally, there was no significant difference between the normal and normal+fullerene groups on none of the experimental days.

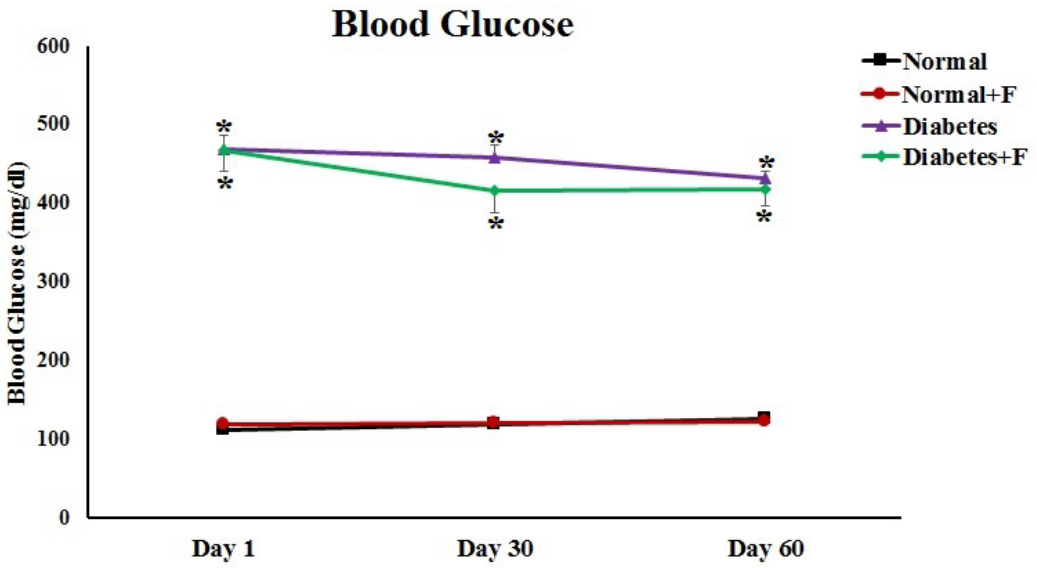

FIGURE 1 - Effects of fullerene on serum glucose level on days 1, 30, and 60 after STZ injection. Differences in measured parameters among 4 groups analyzed by using One-way ANOVA, followed by the Tukey post hoc test. All the data were presented as mean ± standard deviation of the mean. The symbol * denote significant differences with the normal group; *P<0.05. F: fullerene.

Effects of fullerene treatment on body weight

Two-way ANOVA analysis confirmed significant effects of groups (F=12.59, df=3, P=0.001), significant effects of days (F=51.27, df=2, P=0.001), and the significant interaction between both factors (days×groups) (F=7.62, df=6, P=0.018). We reported the effects of fullerene treatment on the body weight on days 1, 30 and 60 after STZ injection in all the experimental groups in Figure 2. Our data analysis revealed that STZ injection significantly decreased body weight in the diabetic group (221±9) on day 60 as compared with the normal group (289±8) (Figure 2, *p<0.05). Application of fullerene significantly increased body weight in the diabetic+fullerene group (257±9) on day 60 as compared with the diabetic group (#p<0.05). Aditionally, there was no significant difference between the normal and normal+fullerene groups on none of the experimental days.

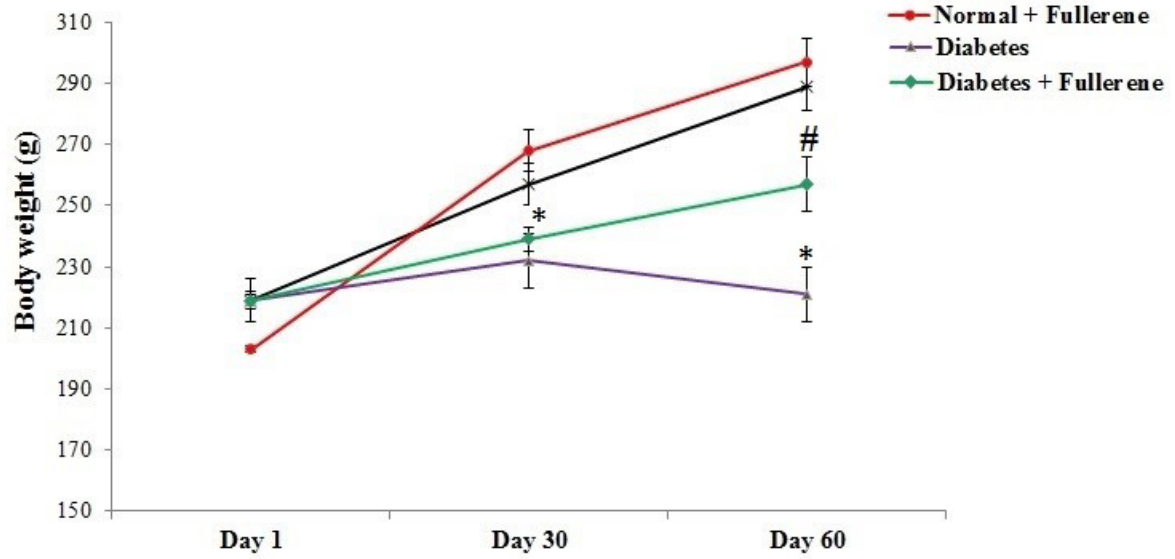

FIGURE 2 - Effects of fullerene on body weight on days 1, 30, and 60 after STZ injection. Differences in measured parameters among 4 groups analyzed by using One-way ANOVA, followed by the Tukey post hoc test. All the data were presented as mean ± standard deviation of the mean. The symbol * and # denote significant differences with the normal and diabetic groups, respectively; *P<0.05 and #P<0.05.

Effects of fullerene treatment on food and water intake

Two-way ANOVA analysis of food intake confirmed significant effects of groups (F=159.77, df=3, P=0.001), significant effects of days (F=6.04, df=2, P=0.003), and the significant interaction between both factors (days×groups) (F=13.07, df=6, P=0.001). As shown in Figure 3A, STZ injection significantly increased food intake on days 30 (54±4) and 60 (60±4) after injection as compared with the normal group (31±4) and (29±2) (Figure 3A; *p<0.05). Similarly, STZ injection significantly increased water intake on all the experimental days [(98±22, day 1), (144±20, day 30), and (150±15, day 60)] as compared with the normal group [(26±4, day 1), (30±3, day 30), and (28±5, day 60)] (Figure 3B; *p<0.05). Fullerene treatment significantly decreased food intake only on day 60 (38±5) after STZ injection as compared with the diabetic group (Figure 3A; #p<0.05). Two-way ANOVA analysis of water intake confirmed significant effects of groups (F=557.22, df=3, P=0.001), significant effects of days (F=16.02, df=2, P=0.001), and the significant interaction between both factors (days×groups) (F=12.72, df=6, P=0.001). Fullerene treatment also significantly decreased water intake on days 30 (99±5) and 60 (103±7) after STZ injection as compared with the diabetic group (Figure 3B; #p<0.05). Aditionally, there was no significant difference between the normal and normal+fullerene groups on none of the experimental days.

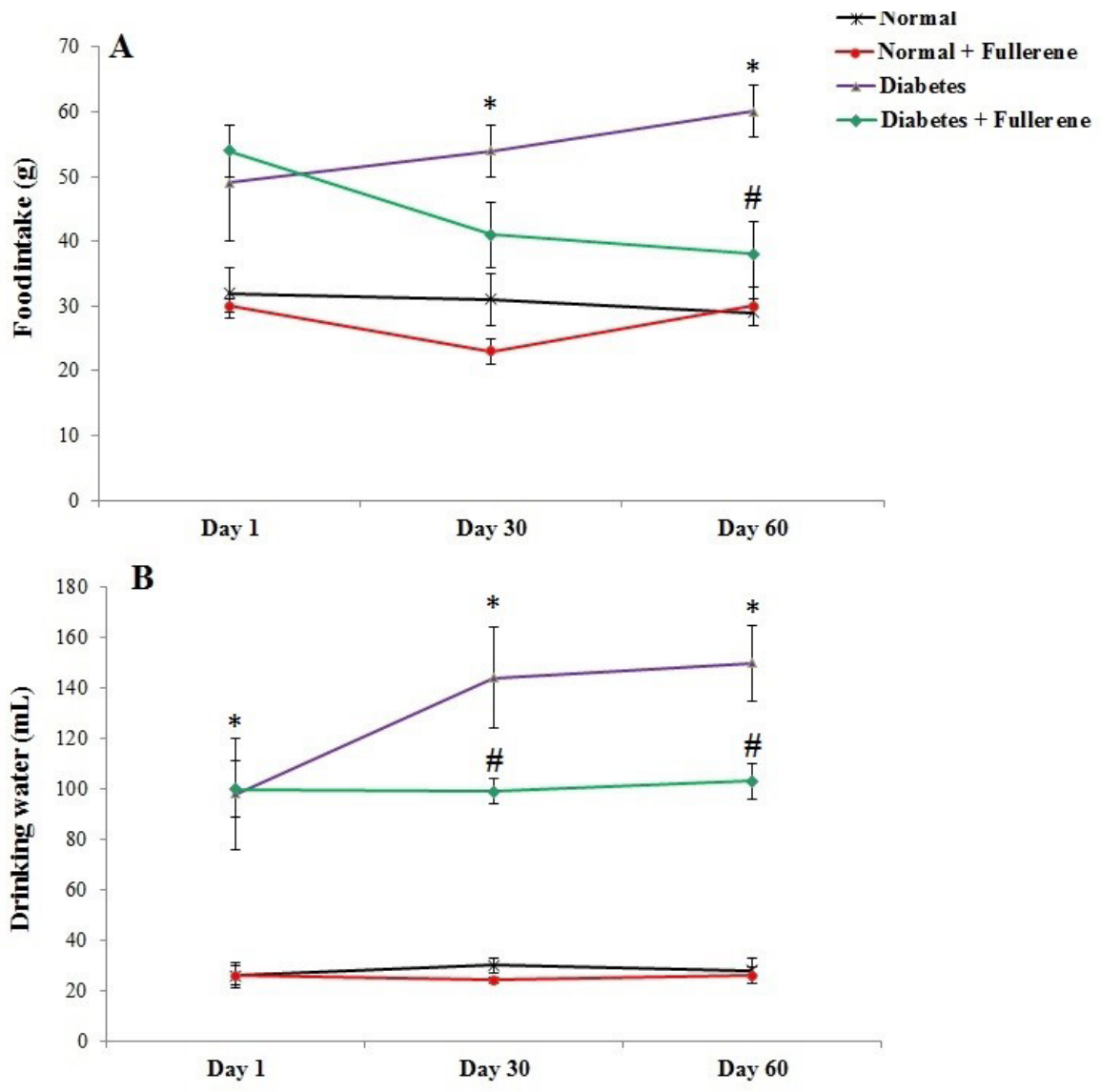

FIGURE 3 - Effects of fullerene on (A) food intake and (B) water intake on days 1, 30, and 60 after STZ injection. Differences in measured parameters among 4 groups analyzed by using One-way ANOVA, followed by the Tukey post hoc test. All the data were presented as mean ± standard deviation of the mean. The symbol * and # denote significant differences with the normal and diabetic groups, respectively; *P<0.05 and #P<0.05.

Effects of fullerene treatment on oxidative stress markers in the pancreas

One-way ANOVA analysis of MDA level confirmed significant difference between groups (F=11.56, df=3, P=0.001). As shown in Figure 4A and B, STZ injection significantly increased MDA level in the pancreas on days 60 (0.47±0.20) after injection as compared with the normal group (0.07±0.07) (Figure 4A; ***p=0.001). Furthermore, one-way ANOVA analysis of GSH level confirmed significant difference between groups (F=9.24, df=3, P=0.001). Our data revealed that STZ injection significantly decreased GSH level in the pancreas on days 60 (31±15) after injection as compared with the normal group (83±17) (Figure 4B; ***p=0.001). The present data revealed that applying fullerene could normalize the MDA and GSH markers in the pancreas. Indeed, application of fullerene in diabetic rats significantly decreased MDA level (0.07±0.09) and increased GSH level (73±19) in the pancreas as compared with diabetic group (Figure 4B; ###p=0.001).

Additionally, one-way ANOVA analysis of SOD level confirmed significant difference between groups (F=21.45, df=3, P=0.001). STZ injection significantly decreased SOD activity in the pancreas on days 60 (1.71±0.38) after injection as compared with the normal group (3.24±0.53) (Figure 4C; *p=0.05). Our one-way ANOVA analysis of CAT level confirmed significant difference between groups (F=7.88, df=3, P=0.002). Injection of STZ could not significantly alter CAT enzyme activity in the pancreas on days 60 (1.35±1.21) as compared with the normal group (0.95±0.3) (Figure 4D). Furthermore, applying fullerene in diabetic rats could not significantly alter both SOD and CAT enzymes activity in the pancreas. However, applying fullerene in normal group significantly increased both SOD (5.69±1.61) and CAT (3.29±1.1) enzymes activity in the pancreas as compared with the normal group (3.24±0.53) and (0.95±0.3), respectively [Figure 4C (***p=0.001), and 4D (**p<0.01)].

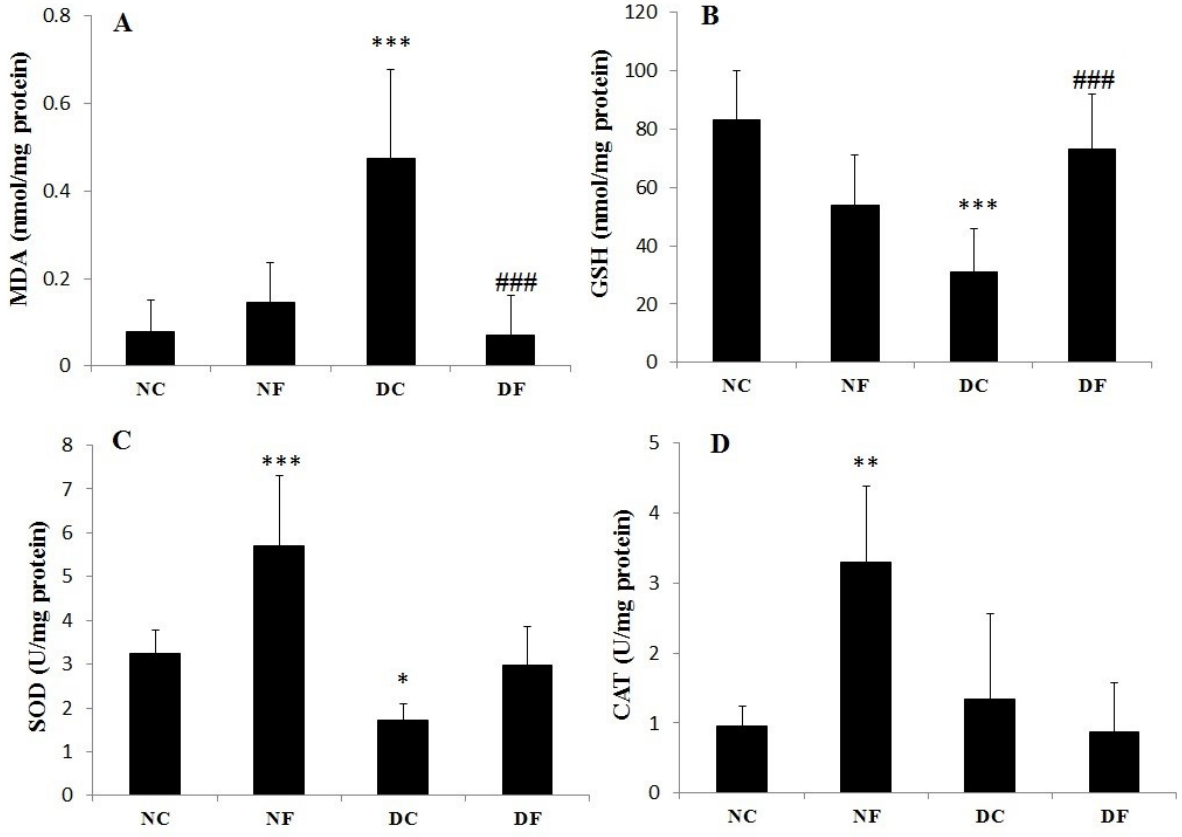

FIGURE 4 - Effects of fullerene on (A) MDA level, (B) GSH level, (C) SOD activity, and (D) CAT activity in the pancreas on day 60 after STZ injection. Differences in measured parameters among 4 groups analyzed by using One-way ANOVA, followed by the Tukey post hoc test. All the data were presented as mean ± standard deviation of the mean. The symbol * and $^{\#}$ denote significant differences with the normal and diabetic groups, respectively; *P<0.05, **P<0.01, ***P=0.001, and $^{\#\#\#}$P=0.001. NC; normal control, NF; normal+fullerene, DC; diabetic control, DF; diabetic+fullerene.

DISCUSSION

In the present study, our data analysis revealed that STZ injection caused weight loss in diabetic rats. Additionally, injection of STZ effectively increased serum glucose levels, and food as well as water intake in diabetic rats. The commonly used chemically-induced models in the rodents for assessing the underlying mechanism of type 1 DM is the STZ-induced model (Kolb, 1987). In line with our study, Montano *et al.*, (2010) reported that

STZ effectively increased feeding behaviors in diabetic rats such as food and water intake. Similarly, Florence *et al.*, (2007) revealed that injection of STZ increased feeding behaviors in diabetic rats. In addition to increased feeding behaviors, we also observed that MDA level (as an oxidative marker) in the pancreas, was markedly increased and GSH level (as an anti-oxidative marker) in the pancreas, was markedly decreased. Additionally, STZ injection effectively decreased activity of SOD enzyme in the pancreas. These results indicated an impairment in oxidant/anti-oxidant balances in the pancreas, leading to oxidative stress. However, STZ injection could not significantly alter CAT enzyme activity in the pancreas. It was reported that excess production of ROS in DM condition is related to hyperglycemia induced-high mitochondrial respiration and down-regulation of the anti-oxidant genes in beta cells of pancreas (Gerber, Rutter, 2017). Furthermore, increased oxidative stress during DM condition can induce damage of β cells because of very low amounts of intrinsic antioxidant enzymes in β cell mass (Jiang *et al.*, 2011). It is reported that the activity of the antioxidant enzymes including; SOD, CAT and GSH can prevent oxidative stress in the body (Jiang *et al.*, 2011; Ebrahimi *et al.*, 2018). It is found that increased MDA level and decreased CAT activity in the testicular tissue of STZ-nicotinamide-induced diabetic rats (Gholizadeh *et al.*, 2018). Moreover, it is revealed that STZ induced-diabetic rats showed a significant increase in the MDA level, and a decrease in the activities of SOD, GHS and CAT in the plasma (Ebaid *et al.*, 2019). Therefore, targeting oxidative stress with new anti-oxidant agents could be a new avenue for DM treatment. We investigated the anti-diabetic effects of nanoparticle fullerene C_{60} in type 1 diabetic rats. The, intra-orally applying fullerene markedly increased body weight in the diabetic+fullerene group on day 60 as compared with the diabetic group. Additionally, fullerene treatment significantly decreased food and water intake in diabetic rats. We also observed that application of nanoparticle fullerene could normalize the MDA and GSH levels in the pancreas. Indeed, fullerene application in the diabetic rats markedly decreased MDA level and increased GSH level in the pancreas. Furthermore, applying fullerene in the diabetic rats could not significantly alter SOD enzymes activity in the pancreas as compared with the diabetic rats. However, there was no significant difference in SOD enzyme activity between the DM treatment and normal groups. Indeed, fullerene treatment normalized the SOD enzyme activity in the pancreas. Bal *et al.*, in 2010 reported that application of hydrated C_{60} fullerene (4μg/kg daily for 5 weeks) suppressed testicular dysfunction and spermatogenic disruption induced by STZ-diabetes in rats via reduces oxidative stress (Gaffari *et al.*, 2010). It is reported that fullerene treatment decreased neuronal damage and diabetic neuropathy (Namdar *et al.*, 2020). Therefore, due to the lack of significant toxicity of these nanoparticles in biological environments, the use of these agents can be considered as new treatment for maintaining the brain health and preventing neuropathy and dementia during diabetes. Results described herein identified novel anti-diabetic activity of fullerene C_{60} and its protective effects on the pancreatic oxidative stress in STZ-induced diabetic rats. To the best of our knowledge currently there are no reports regarding the pancreatic anti-oxidative effects of C_{60} fullerene in type 1 diabetic rats. The limitation of the present study was that assessing food and water intake in animals can create crumbs and cause defecation and urination in the feeding dish. So, it can reduce the accuracy of weight measurements.

CONCLUSION

The present study suggested that injection of STZ caused polyphagia, polypepsia, weight loss, and pancreatic oxidative stress in diabetic rats. Fullerene treatment could decreased feeding behaviors via suppressing of pancreatic oxidative stress.

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REFERENCES

Akhtar MJ, Ahamed M, Alhadlaq HA, Alshamsan A. Mechanism of ROS scavenging and antioxidant signalling by redox metallic and fullerene nanomaterials: Potential

implications in ROS associated degenerative disorders. Biochim Biophys Acta Gen Subj. 2017;1861(4):802-813.

Askary-Ashtiani A, Ghanjal A, Motaqi M, Meftahi GH, Hatef B, Niknam H. The Isokinetic and Electromyographic Assessment of Knee Muscles Strength in the Short- and Long-Term Type 2 Diabetes. Asian J Sports Med. 2016;7(4):e37008.

Bal R, Türk G, Tuzcu M, Yilmaz O, Ozercan I, Kuloglu T, et al. Protective effects of nanostructures of hydrated C60 fullerene on reproductive function in Streptozotocin-diabetic male rats. Toxicology. 2010;282(3):69-81.

Barragán-Bonilla MI, Mendoza-Bello JM, Aguilera P, Parra-Rojas I, Illades-Aguiar B, Ramírez M, et al. Combined administration of streptozotocin and sucrose accelerates the appearance of type 2 diabetes symptoms in rats. J Diabet Res. 2019;2019:3791061.

Bayatpoor ME, Mirzaee S, Abd MK, Mohammadi MT, Shahyad S, Bahari Z, et al. Crocin treatment decreased pancreatic atrophy, LOX-1 and RAGE mRNA expression of pancreas tissue in cholesterol-fed and streptozotocin-induced diabetic rats. J Complement Integr Med. 2019;17(2):DOI: 10.1515/jcim-2019-0117.

Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem. 1976;72:248-254.

Cepas V, Collino M, Mayo JC, Sainz RM. Redox signaling and advanced glycation endproducts (AGEs) in diet-related diseases. Antioxidants. 2020;9(2):142.

Chen YH, Chen ZW, Li HM, Yan XF, Feng B. AGE/RAGE-induced EMP release via the NOX-derived ROS pathway. J Diabet Res. 2018;2018:6823058.

Chistyakov VA, Smirnova YO, Prazdnova EV, Soldatov AV. Possible mechanisms of fullerene C_{60} antioxidant action. Biomed Res Int. 2013;2013:821498.

Ebaid H, Bashandy SA, Alhazza IM, Hassan I, Al-Tamimi J. Efficacy of a methanolic extract of adansonia digitata leaf in alleviating hyperglycemia, hyperlipidemia, and oxidative stress of diabetic rats. Biomed Res Int. 2019;2019:2835152.

Ebrahimi MJ, Aliaghaei A, Boroujeni ME, Khodagholi F, Meftahi G, Abdollahifar MA, et al. Human umbilical cord matrix stem cells reverse oxidative stress-induced cell death and ameliorate motor function and striatal atrophy in rat model of Huntington disease. Neurotox Res. 2018;34(2):273-284.

Florence NT, Théophile D, Désiré DD, Bertin V, Etienne D, Beauwens R, et al. Antidiabetic activities of methanol-derived extract of Dorstenia picta twigs in normal and streptozotocin-induced diabetic rats. Asian J Trad Med. 2007;2(4):140-148.

Galvan YP, Alperovich I, Zolotukhin P, Prazdnova E, Mazanko M, Belanova A, et al. Fullerenes as anti-aging antioxidants. Curr Aging Sci. 2017;10(1):56-67.

Gerber PA, Rutter GA. The Role of oxidative stress and hypoxia in pancreatic beta-cell dysfunction in diabetes mellitus. Antiox Redox Signal. 2017;26(10):501-518.

Gholizadeh F, Mokarram P, Dastgheib S, Rahpeima Z. The effect of the aquatic extract of stevia on the MDA level and catalase activity in the testicular tissue of streptozotocin-nicotinamide-induced diabetic rats. Shiraz E-Med J. 2018;19(9):61044.

Ghorbani Z, Farahani RM, Aliaghaei A, Khodagholi F, Houssein Meftahi G, Danyali S, et al. Resveratrol protects purkinje neurons and restores muscle activity in rat model of cerebellar Ataxia. J Mol Neurosci. 2018;65(1):35-42.

Hadipour M, Kaka G, Bahrami F, Meftahi GH, Pirzad Jahromi G, Mohammadi A, et al. Crocin improved amyloid beta induced long-term potentiation and memory deficits in the hippocampal CA1 neurons in freely moving rats. Synapse. 2018;72(5):22026.

Horal M, Zhang Z, Stanton R, Virkamäki A, Loeken MR. Activation of the hexosamine pathway causes oxidative stress and abnormal embryo gene expression: Involvement in diabetic teratogenesis. Clin Mol Teratol. 2004;70(8):519-527.

Jiang YL, Ning Y, Ma XL, Liu YY, Wang Y, Zhang Z, et al. Alteration of the proteome profile of the pancreas in diabetic rats induced by streptozotocin. Int J Mol Med. 2011;28(2):153-160.

Kolb H. Mouse models of insulin dependent diabetes: low-dose streptozocin-induced diabetes and nonobese diabetic (NOD) mice. Diabetes Metab Rev. 1987;3(3):751-778.

Lin AM, Fang SF, Lin SZ, Chou CK, Luh TY, Ho LT. Local carboxyfullerene protects cortical infarction in rat brain. Neurosci Res. 2002;43(4):317-321.

Montano ME, Molpeceres V, Mauriz JL, Garzo E, Cruz IB, González P, et al. Effect of melatonin supplementation on food and water intake in streptozotocin-diabetic and non-diabetic male Wistar rats. Nutr Hosp. 2010;25(6):931-938.

Mori T, Takada H, Ito S, Matsubayashi K, Miwa N, Sawaguchi T. Preclinical studies on safety of fullerene upon acute oral administration and evaluation for no mutagenesis. Toxicology. 2006;225(1):48-54.

Mousavi SZ, Nafisi S, Maibach HI. Fullerene nanoparticle in dermatological and cosmetic applications. Nanomedicine. 2017;13(3):1071-1087.

Mutavdzin S, Gopcevic K, Stankovic S, Jakovljevic Uzelac J, Labudovic Borovic M, Djuric D. The effects of folic acid administration on cardiac oxidative stress and

cardiovascular biomarkers in diabetic rats. Oxid Med Cell Longev. 2019;2019:1342549.

Namdar F, Bahrami F, Bahari Z, Ghanbari B, Elahi SA, Mohammadi MT. Evaluation of the effects of fullerene C60 nanoparticles on oxidative stress parameters in normal rats liver and brain. J Adv Med Biomed Res. 2019;27(124):8-15.

Namdar F, Shahyad S, Bahrami F, Bahari Z, Mohammadi MT. Application of fullerene nanoparticles to improve brain health and prevent neuronal damages in diabetes mellitus; a review study. Healt Res J. 2020;5(2):110-117.

Oeckinghaus A, Hayden MS, Ghosh S. Crosstalk in NF-κB signaling pathways. Nat Immunol. 2011;12(8):695-708.

Partha R, Conyers JL. Biomedical applications of functionalized fullerenebased nanomaterials. Int J Nanomed. 2009;4:261-275.

Rasouli Vani J, Mohammadi MT, Sarami Foroshani M, Rezazade E. Evaluation of the neuroprotective and antioxidant effects of Dorema aucheri extract on cerebral ischaemia-reperfusion injury in rats. Pharm Biol. 2019;57(1):255-262.

Sandireddy R, Yerra VG, Areti A, Komirishetty P, Kumar A. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int J Endocrin. 2014;2014:674987.

Sheweita SA, Newairy AA, Mansour HA, Yousef MI. Effect of some hypoglycemic herbs on the activity of phase I and II drug-metabolizing enzymes in alloxan-induced diabetic rats. Toxicology. 2002;174(2):131-139.

Sheweita SA, Mashaly S, Newairy AA, Abdou HM, Eweda SM. Changes in oxidative stress and antioxidant enzyme activities in streptozotocin-induced diabetes mellitus in rats: role of alhagi maurorum extracts. Oxid Med Cell Longev. 2016;2016:5264064.

Sugeçti S. Role of protein oxidation, lipid peroxidation and antioxidant defense systems on diabetes mellitus. A J Health Sci. 2018;1(1):47-54.

Talebanzadeh S, Ashrafi M, Kazemipour N, Erjaee H, Nazifi S. Evaluation of the effects of saffron aqueous extract on oxidative stress in the lens of streptozotocin-induced diabetic rats. Biomed Res Ther. 2018;5(4):2133-2141.

Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes. 2015;6(3):456.

Tietz F. Enzymic method for quantitatve determination of nanogram amount of total and oxidized glutathione: applications to mammalian blood and other tissues. Anal Biochem. 1969;27(3):502-522.

Tsachouridis S, Papaioannidou P. Fullerenes: Chemical structure and properties. Front Pharmacol 2010, Conference Abstract: 8th Southeast European Congress on Xenobiotic Metabolism and Toxicity.

Wautier MP, Guillausseau PJ, Wautier JL. Activation of the receptor for advanced glycation end products and consequences on health. Diabetes Metab Syndr. 2017;11(4):305-309.

Ye S, Chen M, Jiang Y, Chen M, Zhou T, Wang Y, et al. Polyhydroxylated fullerene attenuates oxidative stress-induced apoptosis via a fortifying Nrf2-regulated cellular antioxidant defence system. Int J Nanomed. 2014;9:2073-2087.

Yi JK, Ryoo ZY, Ha JJ, Oh DY, Kim MO, Kim SH. Beneficial effects of 6-shogaol on hyperglycemia, islet morphology and apoptosis in some tissues of streptozotocin-induced diabetic mice. Diabetol Metab Syndr. 2019;11(1):1-3.

Zha YY, Yang B, Tang ML, Guo QC, Chen JT, Wen LP, et al. Concentration-dependent effects of fullerenol on cultured hippocampal neuron viability. Int J Nanomedicine. 2012;7:3099-3109.

Zlatkis A, Zak B, Boyle AJ. A new method for the direct determination of serum cholesterol. J Lab Clin Med. 1953;41(3):486-492.

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