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Research Article
Synthetic Zeolite Supplementation as a Potential Candidate for the Therapy of Diabetic Syndrome

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Abstract

Background and Objective: Natural and Synthetic Zeolite (SZ) is potentially useful for biopharmaceuticals and bio tools due to its unique and outstanding physical and chemical properties. Thus, the present study aimed to evaluate the possible effect of synthetic zeolite in (STZ)-induced diabetic rats. **Materials and Methods:** About 4 groups of rats were used, (I) normal control, (II) SZ group, (300 mg/kg/day), (III) STZ group, diabetic rats acted as positive control and (IV) STZ+SZ group, included diabetic rats treated with synthetic zeolite (300 mg/kg/day), statistical analysis comparisons between means were carried out using one-way analysis of variance (ANOVA) followed by a post hock (Tukey) multiple comparisons test at $p \geq 0.05$. **Results:** After six weeks, treatment of diabetic animals with synthetic zeolite markedly exhibited a significant reduction in glucose, lipids, DNA fragmentation, Alanine Aminotransferase (ALAT), Aspartate Aminotransferase (ASAT), urea, creatinine, Malondialdehyde (MDA) and Nitric Oxide (NO) levels concomitant with a significant rise in insulin, Glutathione (GSH), Superoxide Dismutase (SOD) and Catalase (CAT) values close to the corresponding values of healthy ones. **Conclusion:** In conclusion, synthetic zeolite exhibits multi-health benefits with promising potentials against STZ-induced diabetes, this behaviour may be attributed to its antioxidant and free radical scavenging mechanisms.

Key words: Synthetic zeolite, DNA, diabetes, STZ, tetrahedral silicon, clinoptilolite, creatinine

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

INTRODUCTION

Natural products from various sources, including plants, animals and microbes, are frequently used as therapeutic candidates[1]. Nanotechnology may also be useful in the diagnosis and treatment of diabetes[2]. Progressive research has been undertaken into a variety of diabetes-related diseases and fatalities to identify more effective medications to minimize the social burden of diabetes. Various supplements have been used in prior research to enhance some diabetes-related indicators[3]. The petroleum refining industry began using zeolites on a significant scale in catalytic cracking operations in the 1930s when they were first produced[4]. More than 150 zeolites have been produced since then in the quest for more efficient catalysts. The majority of the work was focused on synthetic zeolites but in recent years, natural zeolites have gained in importance, moving from a museum oddity to a valuable commodity. Zeolite is a volcanic inorganic microporous mineral with a highly regular porous and chamber structure[5]. Zeolites are hydrated natural or synthetic microporous crystals with an open 3D framework made up of tetrahedral silicon (SiO_4) and aluminium (AlO_4) linked in various regular patterns to form an open crystal structure. There are around 40 naturally tectosilicate minerals in the zeolite group and the chemical differentiation of zeolites is connected to the silicon/aluminium ratio and water content. These are the most usually mined isometric forms: Chabazite and clinoptilolite, with natrolite being the fibrous form[6,7]. Zeolites have various features due to their chemical structure, including inorganic cation-exchangers, adsorbents and active repositories for metal-catalyzed processes, which have earned them widespread industrial applications and medicinal importance in recent years[8].

Zeolites with varying Si/Al ratios can be made either directly (synthetic zeolites) or indirectly (natural zeolites) by post-synthesis processing. Synthetic zeolites are the most common substitutes for natural zeolites. Synthetic zeolites can be modified in terms of physical and chemical properties to better suit a variety of applications and their quality is more consistent than natural zeolites[5]. Synthetic analogues of natural zeolites are commonly used in a variety of technological processes and the cheap output price conditioned by the world's subterranean location of huge deposits of natural zeolites makes them much more accessible for a wide range of applications[5]. Adsorbents made of zeolites are commonly utilized in agriculture. Zeolite supplementation of feed reduced the number of poultry infections without harming good microorganisms in animals[9]. The use of clinoptilolite, a small particle size clinoptilolite, in the diet can successfully reduce aflatoxins in dairy cow milk[10]. Against buccal mucosa and lung squamous epithelial cell malignancies, a compound made from naturally occurring non-toxic zeolites was patented in the United States[11]. Previous research has shown that zeolite-clinoptilolite has immunostimulatory properties, regulates anti- and pro-inflammatory pathways and could be used as an anticancer adjuvant[12]. Other researches discuss zeolite's potential to adsorb glucose as well as its antidiarrheic and antioxidant properties[13]. Synthetic zeolites are materials with few, if any, drawbacks since they are easily manufactured from readily available raw components and pose no hazardous or environmental risks. Synthetic zeolite's antioxidative properties are based on its ability to reduce free radicals and lipid peroxidation while also increasing Total Antioxidant Capacity (TAC) in blood. As a result, antioxidant enzymes may also be potential targets of SZ action[14]. Given these recent findings, the goal of this investigation was to assess the hypoglycemic effects of synthetic zeolite in diabetic rats produced by Streptozotocin (STZ).

In experimental diabetic rat models, we investigated the effects of zeolite on blood glucose, insulin levels, kidney and liver functioning, serum lipid profile, Insulin and immune-cytokines, DNA damage and antioxidative stress.

MATERIALS AND METHODS

Study area: This study was carried out during the period from September-December, 2020 at the laboratories of the Department of Zoology, Faculty of Science, Al-Azhar University clinical pathology department NRC and Basic Science Center, Misr University for Science and Technology, Egypt.

Chemicals: Streptozotocin (STZ, Sigma 85882), Sodium citrate (Sigma C0909) and Citric acid (Sigma C1909) were acquired by Egyptian Worldwide Center for Consequence, 22 AbuZer El-Ghafary St., Nasr City Cairo, Egypt.

Preparation of synthetic zeolite: Silica extracted from dry rice husk was used as an amorphous silica source for the synthesis of NaY zeolite by the hydrothermal treatment[15]. The stock solutions of 1000 mg L^{-1}. were obtained by dissolving the zeolite in tap water. The specified volume of stock arrangement was included in the respective experimental aquaria to attain the specified concentrations of 1 and 5 mg L^{-1}.

Experimental design: This study was conducted on adult male Wistar albino rats (150-180 g) forty (40) rats obtained from Animal Colony, National Research Centre, Cairo, Egypt. The creatures were housed in reasonable plastic cages for one week for acclimation. Abundance tap water and standard rat pellets [20.3% protein (20% casein and 0.3% DL-Methionine), 5% fat (corn oil), 5% strands, 3.7% salt blend and 1% vitamin, obtained from Meladco Company, El-Obour City, Cairo, Egypt] were always available. All animals received human care in compliance with the standard institutional criteria for the care and use of experimental animals according to the NRC ethical committee (FWA 00014747).

Induction of diabetes in rats: Streptozotocin dissolved in ice-cold sodium citrate-citric acid buffer [20 mL of sodium citrate (0.1 M) with 30 mL of citric acid (0.1M), pH = 4.0). The animals were intraperitoneally injected with (60 mg kg^{-1}) after 16 hrs of fasting, followed by oral administration of 2-3 mL sucrose solution 10% (w/v) for one day next. Then animals fasted overnight and one drop blood sample was obtained by nicking the rat's tail lateral-vein using sterile surgical scissors. Immediately the blood glucose level was determined using Gluco Dr SUPER SENSOR AGM-2200 glucometer (Korea). Animals with blood glucose levels above 240 mg dL^{-1} were considered to be diabetic[16].

Study animal groups: After induction of diabetes, both normal and diabetic rats were rearranged randomly in four groups (8 rats/group), first group normal rats administrated orally with 2 mL distilled water (pH 6.8) and pointed as control, the second group normal rats daily ingested with synthetic zeolite (at a dose of 300 mg kg^{-1}) and pointed as SZ group, third group diabetic rats administrated streptozotocin and pointed as (STZ), fourth group STZ-diabetic rats treated daily ingested synthetic zeolite (at a dose of 300 mg kg^{-1}) and pointed as (STZ+SZ).

Blood and tissue sampling: At the end treatment period (six weeks), rats were weighed then fasted overnight and the blood glucose level of each animal was determined using GlucoDr set through blood specimens from the rat's tails. Following anaesthesia (inhalation with diethyl ether), blood specimens were withdrawn from the retro-orbital plexus using heparinized and sterile glass capillaries, whole blood specimens were cool-centrifuged at 3000 rpm for 10 min using and the sera were separated, divided into aliquots and stored at -80°C till biochemical measurements could be carried out as fast as possible. After blood collection, the animals were sacrificed immediately, then the liver of the animal was dissected out. One of the livers of each animal were washed in saline, dried, rolled in a piece of aluminium foil and stored at -80°C for either biochemical or DNA fragmentation determinations. The pancreas was soaked in formalin-saline (10%) buffer for histological processing and microscopic examination.

Tissue homogenization: A specimen liver was homogenized in ice-cold phosphate buffer (50 mM, pH 7.4) to give 10% homogenate (w/v), the homogenate was centrifuged at 5000 rpm for 20 min to remove the nuclear and mitochondrial fractions, the supernatant was divided into aliquots and stored at -80°C.

Biochemical determinations: Blood glucose and HbA1C level was determined using Gluco Dr. SUPER SENSOR AGM-2200, Korean glucometer through blood sample obtained from the lateral tail vein using sterile surgical scissors. Serum urea creatinine ASAT, ALAT, cholesterol, triglycerides, LDL-cholesterol a nd HDL-cholesterol levels, as well as hepatic GSH, NO, SOD and CAT levels were estimated spectrophotometrically using reagent kits obtained from Biodiagnostic, Dokki, Giza, Egypt. However, Malondialdehyde (MDA) level was determined chemically as described by Ashry *et al.*[17].

DNA fragmentation percentage: The percentage of DNA fragmentation was assayed according to the quantitative method used for grading the DNA damage[17].

Insulin and immune-cytokines: Using the ELISA technique (Dynatech Microplate Reader Model MR 5000), Insulin level, Tumour Necrosis Alpha (TNF-α), Interleukin-1 beta (IL-1β) and CD4 concentrations were measured using rat's reagent ELISA-kits purchased from SinoGeneClon Biotech Co, Hang Zhou, China.

Histopathology: Paraffin sections of 5 µm thick were stained with Hematoxylin and Eosin[18] and investigated by a light microscope.

Statistical analysis: Comparisons between means were carried out using one-way analysis of variance (ANOVA) followed by a post hock (Tukey) multiple comparisons test at $p \geq 0.05$ according to Ashry *et al.*[19].

RESULTS

Effect of synthetic zeolite on glucose, HbA1c and insulin levels: The *in vivo* results exhibited a significant decrease in insulin level coupled with a significant increase in blood glucose and HbA1c in the STZ-induced diabetic group compared with the control group. Interestingly, administration of diabetic rats with synthetic zeolite improved insulin, HbA1c and glucose levels towards normal values as it significantly increased insulin and significantly decreased the glucose and HbA1c levels compared to diabetic rats, (Table 1).

Effect of synthetic zeolite on liver and kidney functions: Oral administration of healthy rats with synthetic zeolite never disturb liver and kidney functions, while a single intraperitoneal injection of STZ resulted in a significant elevation of liver and kidney function biomarkers, this is monitored from the marked elevated serum liver enzymes (ALAT and ASAT) and the raised serum kidney markers (urea and creatinine) compared to their normal rats. Administration of synthetic zeolite to diabetic rats ameliorated significantly the diabetes-induced changes in the measured serum liver function enzymes and kidney function markers (Table 2). As illustrated in Table 3 and compare to the healthy control group, administration of healthy rats with synthetic zeolite didn't deteriorate the lipid profile, while intoxication with STZ led to an atherosclerotic initiation, this was achieved from the significant rise of serum total cholesterol, triglycerides and LDL-cholesterol coupled with the marked reduction in HDL-cholesterol. In contrast, post-treatment of diabetic rats with synthetic zeolite improved all lipid profile parameters.

Effect of synthetic zeolite on hepatic oxidative stress and antioxidant levels: Injection of rats with STZ resulted in sharp damages to their livers as evidenced by the marked depletion in hepatic GSH level, SOD and CAT activities, matched with a significant increase in MDA and NO levels as compared to the normal control group. Fortunately, post-treatment of diabetic rats with synthetic zeolite significantly recharged liver GSH battery and significantly increased the activities of SOD and CAT, moreover, synthetic zeolite succeeded in reducing hepatic NO level whine compare to the corresponding values of diabetic rats (Table 4).

Effect of synthetic zeolite on DNA fragmentation and immune-cytokines: The results showed significant increases in TNF-α, IL1β and DNA damage coupled with significant decreases in CD4 in the STZ group when compared with the control group. Interestingly, the administration of STZ rats with SZ improved inflammatory cytokine and DNA damage within normal values as it significantly decreased TNF-α, IL1β and DNA damage while significantly increased the CD4 level compared to STZ animals Fig. 1(a-d).

Table 1: Glucose, HbA1c and insulin levels of normal, diabetic and diabetic-treated rats

Parameters	Control	SZ	STZ	STZ+SZ
Glucose (mg dL^{-1})	108.0±2.7	100.0±8.4	434.0±25*	269.0±39#
HbA1c (%)	5.6±0.4	6.2±0.11	10.8±0.5*	9.2±0.8#
Insulin (ng mL^{-1})	2.9±0.4	3.5±0.5	0.8±0.12*	2.6±0.15#

Data are presented as Mean±standard error, *Significantly different from the control group, while #Significantly different from the group (STZ) ($p \leq 0.05$) using one-way ANOVA, SZ: Synthetic zeolite and STZ: Streptozotocin

Table 2: Serum liver and kidney functions of normal, diabetic and diabetic-treated rats

Parameters	Control	SZ	STZ	STZ+SZ
ALAT (U L^{-1})	30.6±2.6	35.3±4.2	105.0±8.3*	68.2±10.6#
ASAT (U L^{-1})	33.6±2.7	38.5±4.2	110.5±2.6*	76.7±7.7#
Urea (mg dL^{-1})	40.6±4.0	44.7±3.6	65.9±9.7*	47.5±4.3#
Creatinine (mg dL^{-1})	1.3±0.8	1.42±0.6	2.8±0.3*	1.7±0.31#

Data are presented as Mean±standard error, *Significantly different from the control group, while #Significantly different from the group (STZ) ($p \leq 0.05$) using one-way ANOVA, SZ: Synthetic zeolite and STZ: Streptozotocin

Table 3: Serum lipid profile of normal, diabetic and diabetic-treated rats

Parameters (mg dL^{-1})	Control	SZ	STZ	STZ+SZ
CHO	119±4.9	117.0±3.7	215.0±1.6*	170.0±2.9#
TRG	153±7.3	157.0±12.8	274.0±21*	194.0±27#
LDL-C	62±0.81	64.0±2.01	117.0±1.9*	84.0±1.94#
HDL-C	38±0.39	39.0±0.35	24.0±0.84*	33.0±0.54#

Data are presented as Mean±standard error, *Significantly different from the control group, while #Significantly different from the group (STZ) ($p \leq 0.05$) using one-way ANOVA, SZ: Synthetic zeolite and STZ: Streptozotocin

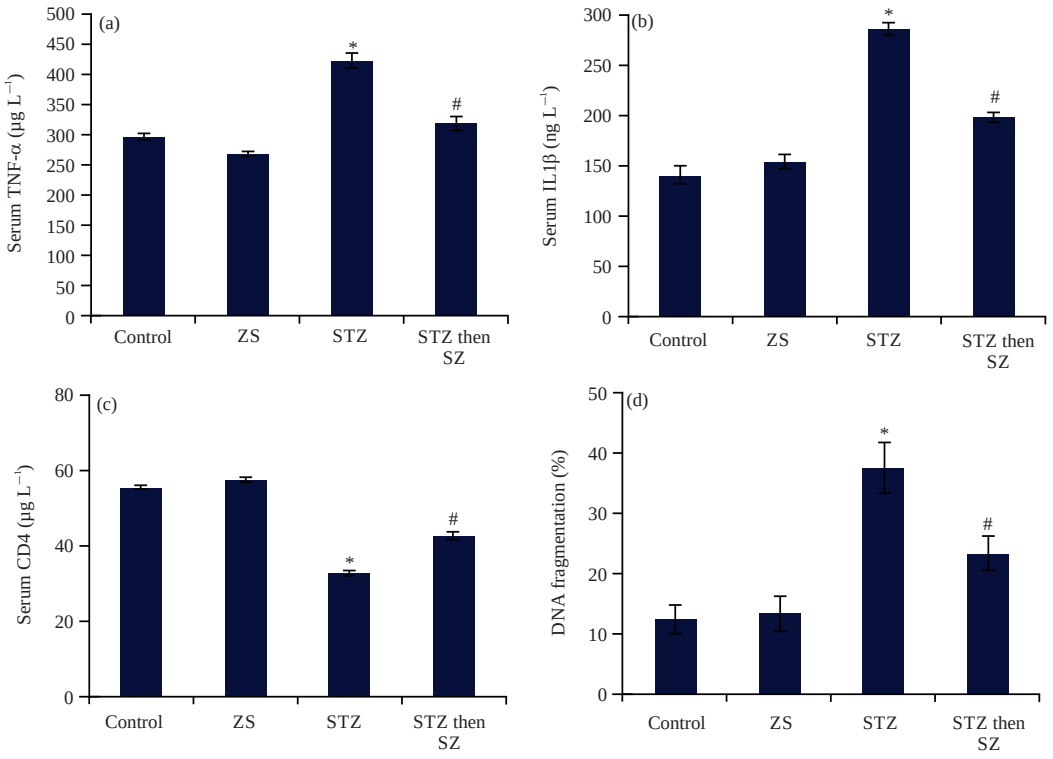

Fig. 1(a-d): Serum TNF-α, IL1β, DNA fragmentation and CD4 levels of control, STZ-intoxicated and SZ-treated male albino rats

*Significantly different from the control group, while #Significantly different from the group (STZ) ($p \leq 0.05$) using one-way ANOVA, SZ: Synthetic zeolite and STZ: Streptozotocin

Table 4: Hepatic oxidant-antioxidant markers of control, diabetic and diabetic-treated rats

Parameters	Control	SZ	STZ	STZ+SZ
MDA (µmol g^{-1} tissue)	18.4±1.08	20.77±0.56	42.0±1.1*	31.2±0.8#
NO (µmol g^{-1} tissue)	401.0±16	368.00±32	817.0±30*	580.0±22#
GSH (nmol g^{-1} tissue)	133.0±13	149.00±11	54.0±4.7*	104.0±22#
SOD (U g^{-1} tissue)	2264.0±67	2346.00±77	1199.0±15*	1871.0±39#
CAT (U g^{-1} tissue)	9.6±0.4	10.20±0.35	4.5±0.30*	7.5±0.25#

Data are presented as Mean±standard error, * Significantly different from the control group, while #Significantly different from the group (STZ) ($p \leq 0.05$) using one-way ANOVA, SZ: Synthetic zeolite and STZ: Streptozotocin

Histopathological examination: Control rats group (I) exhibited normal histological pancreatic tissue architecture, (Fig. 2a).

Group (II) received (SZ) had destructive pancreatic tissue in form of, disrupted islet`s outlines with marked decreased number of cells of the islet, some of these cells showing Karyolysis and vacuolar degeneration, the serous acini) showed flattening of their nuclei (Fig. 2b). Also, group (III) received (STZ) (Fig. 2c), had a similar picture of the previous group.

Group (IV) received STZ+SZ (Fig. 2d), had the similar picture of the previous two groups to an endocrine component in form of disrupted islet`s outlines with mildly decreased number of cells of the islet, noticed increased the connective tissue component of the gland but the exocrine component almost normally appeared (H and E 400x).

DISCUSSION

The present study aimed to evaluate the hypoglycemic and antioxidant effects of synthetic zeolite on STZ-induced experimental diabetes. Zeolites are aluminosilicates whose structure is an open 3D framework built of silicon (SiO_4) and aluminium (AlO_4) tetrahedral[20]. Natural and Synthetic zeolite has a total cation-exchange capacity of about 200 mEq and can adsorb a variety of gases, petrochemicals, moisture, radioactive elements, heavy metals and a variety of other

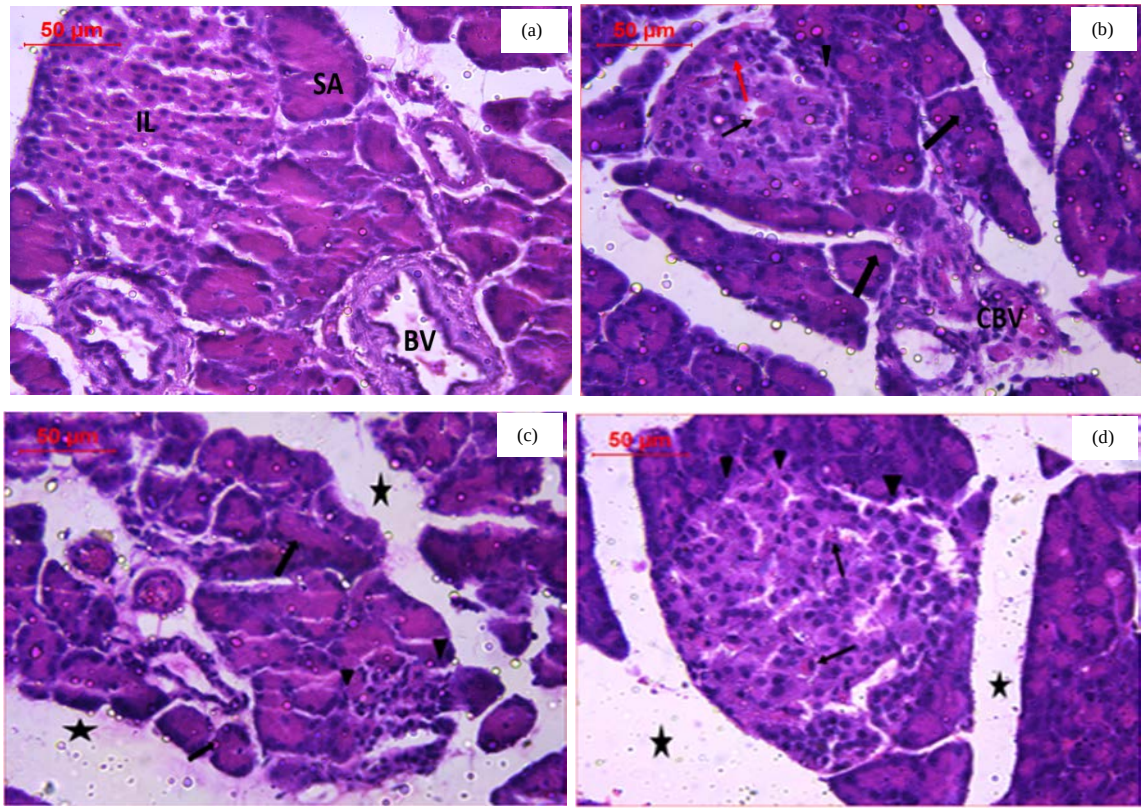

Fig. 2(a-d): Histopathological examination of pancreatic tissue, (a) Control group showing the normal histological pancreatic tissue architecture, (b) A photomicrography of pancreatic tissue for (STZ) showing disrupted islet`s outlines (arrowheads) with decreased number of cells of the islet with increased the connective tissue component of the gland (interlobular and intralobular) (stars), the exocrine component of the gland (serous acini) showed flattening of their nuclei that were pushed to the bottom of the cells (black thick arrows) with dilated congested blood vessels. (H and E 400x), (c) A photomicrography of pancreatic tissue for (SZ) showing mild disrupted islet`s outlines (arrowhead) with marked decreased number of cells of the islet some of these cells showing Karyolysis (black thin arrow) and vacuolar degeneration (red arrow), the exocrine component of the gland (serous acini) showed flattening of their nuclei that were pushed to the bottom of the cells (black thick arrows) with congested blood vessels (CBV). (H and E 400x) and (d) A photomicrography of pancreatic tissue for (diabetic group treated with SZ) showing mild disrupted islet`s outlines (arrowheads) with mildly decreased number of cells of the islet some of these cells showing karyolysis (black thin arrows) with increased the connective tissue component of the gland (interlobular and intralobular) (stars), the exocrine component almost normally appeared. (H and E 400x)

substances. Due to their exchange capacity, it has an important role in therapeutic uses[21]. In the present study, the animals were intraperitoneally injected with (60 mg kg^{-1}), animals with blood glucose levels above 240 mg dL^{-1} were considered to be diabetic. The streptozotocin-induced diabetic rats had considerably higher blood glucose, HbA1c and lower insulin levels compared to normal control rats. These findings are inconsistent with the recent studies[22,23]. Diabetes mellitus is one of the oxidative stress conditions in which free radicals are increased and/or antioxidant mechanisms are inhibited. Free radicals induce oxidative stress and can lead to injury of cellular membrane[24]. The free radical formation has been reported to be a direct consequence of hyperglycemia[25]. Our results showed that the administration of diabetic rats with synthetic zeolite improved insulin, HbA1c and glucose levels towards normal values as it significantly increased insulin and significantly decreased the glucose and HbA1c levels compared to diabetic rats. These hypoglycemic activities may be due to the adsorption properties of zeolites and the presence of silica compound for these reasons the glucose level in the blood is reduced and act as glucose adsorbents[26]. NaX-type zeolites can adsorb fructose, sucrose,

glucose and fructooligosaccharides from aqueous solution[27]. Pavelic and Hadzija[5] reported that synthetic zeolite enhancing insulin production by reducing blood glucose by preventing beta-cell destruction.

Its well-known diabetes mellitus could induce hepatic damage, which could be due to the rise in protein concentrations associated with glucogenesis and urea production. Moreover, liver enzymes as ALAT and ASAT level increasing because they are associated with the conversion of amino acids to keto acids in diabetic condition[28]. In the present study, a single intraperitoneal injection of STZ resulted in a significant elevation of liver and kidney function biomarkers, this is monitored from the marked elevated serum liver enzymes (ALAT and ASAT) and the raised serum kidney markers (urea and creatinine) compared to their normal rats. The increase in ALAT and ASAT activity may be due to the cellular damage in the liver caused by STZ-induced diabetes[27]. In the present study, the administration of synthetic zeolite to diabetic rats ameliorated significantly the diabetes-induced changes in the measured serum liver function enzymes and kidney function markers. Zeolites showed a positive effect on the structural and functional state of the animal's internal organs. In the liver, the hepatocytes showed no signs of granular dystrophy characteristic of the disruption of protein metabolism, which indicated the normalization of metabolism[29]. Several metabolic disorders and complications related to diabetic mellitus, one of which is lipid metabolism, which is influenced by high total triglyceride, total cholesterol, phospholipids and LDL cholesterol levels as well as low HDL cholesterol levels as seen in many cases[30].

Our results showed that, the elevation of total cholesterol, total triglyceride, LDL cholesterol and VLDL cholesterol with decreasing of HDL cholesterol levels in diabetic rats group after administration synthetic zeolite. Organization of manufactured zeolite essentially expanded digestibility values of rough protein and net vitality, conjointly change in all lipid profiles. The mechanisms of how zeolite generally has beneficial effects are attributed to several mechanisms. Zhou *et al.*[31] suggested that dietary of zeolite improve nutrient digestibility, digestion and secretion of digestive enzymes, positive effect on intestinal microflora and binding or removing of compounds derived through the microbial activities, these activities may be attributed to increases in hypertrophied functions of intestinal villi and epithelial cells at the duodenum and ileum after administration of zeolite. Pancreatic islet cells have the lowest expression of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase and catalase than other tissues such as the kidney, liver and adipose tissue[32]. Increased free radicals may lead to degradation of cellular functions and oxidative damage to membranes by consuming antioxidant defence components[33]. Physiological antioxidative defence system as justified in terms of GSH, SOD and CAT. Our results exhibited that, the post-treatment of diabetic rats with synthetic zeolite significantly recharged liver GSH battery and significantly increased the activities of SOD and CAT, moreover, synthetic zeolite succeeded in reducing hepatic NO level whine compare to the corresponding values of diabetic rats. These results are consistent with[27]. According to the previous reports, using STZ causes the production of antibodies, which may lead to the destruction of insulin-producing cells, insulin insufficiency and increase the glucose level which becomes a source of free radical production when autoxidised[32]. The present results showed free radical generation which led to peroxidative damage to the liver tissue and excessive level of malondialdehyde MDA formation this interesting finding coincides with earlier results[34].

The production of free radicals, which reduce the body's defence mechanisms, such as oxidative damage to membranes, cellular dysfunction and increased susceptibility to lipid peroxidation[35]. SOD and GSH are important antioxidants enzymes that may help in the prevention of lipid peroxidation, are involved in cellular defence systems, protecting tissues from oxidative damage, increase MDA content recover the harmed extracellular lattice proteins and cell development[36]. Increased SOD activity has been reported in severe diabetes[37]. Our results showed that treatment with SZ leads to improved antioxidant and detoxification of oxidative stress (Table 4).

The mechanisms of antioxidant effects of zeolites are not well known but they could be due to an indirect interaction with biochemical systems, improved immune system through the mucosal related intestinal lymphoid tissue, removal of waste and toxins from the gut and an increase in the bioavailability of the minerals which are important co-factors for some enzymes[14]. Furthermore, some of the zeolites' antioxidant activities are related to their effect on macrophages' phagocytic function, which is induced by zeolite particle phagocytosis. Phagocytic activity causes the generation of cytokines such as tumour necrosis factor, which activates immune responses while simultaneously increasing SOD expression[38].

The degradation of streptozotocin leads to the production of free radicals which are responsible for the

toxic mechanism of STZ. The other well-known property of STZ is DNA damage through DNA alkylation, which cause double-stranded DNA to become fragmented. STZ inhibits the synthesis of DNA in both bacteria and mammals[39], because of its alkylating properties. In stressed diabetic animals, inflammatory cytokines play a major role in inflammation response and antibody release Inoguchi *et al.*[40]. TNF and IL-1beta are powerful inflammatory cytokine produced by macrophages and T lymphocytes that plays a significant role in the development of insulin resistance as well as the advancement of diabetic microvascular disorders[41-43]. In the present study, the administration of synthetic zeolite improved inflammatory cytokine and DNA damage within normal values as it significantly decreased TNF-α, IL-1beta and DNA damage while significantly increased the CD4 level compared to STZ animals. The reduction of the TNF-α and IL-1beta serum level in the SZ group was reported to be associated with activate biomolecules involved in different pathologies including, kinases MAPK, PKC and SAPK or AP1, NFB proteins and pro-inflammatory cytokines IL-1β and TNF-α[44]. So distant, clinoptilolite is considered the as it were secure zeolite fabric utilized in restorative applications due to its broadly archived advantageous impacts on the creature and human wellbeing and execution. SZ important transcription factors such as activator protein 1 and NFB are also activated and the expression of pro-inflammatory cytokines such as interleukin 1β and TNF-α is enhanced[43]. Moreover, during anticancer therapy using Adriamycin (doxorubicin) zeolites showed a protective effect on hepatocytes. In essential societies of liver cells inferred from rats treated with Adriamycin, consequent treatment with clinoptilolite essentially decreased the generation of fiery cytokines, i.e., tumour rot calculate-(TNF-α), interleukin-1 (IL-1β) by hepatocytes. In addition, this treatment led to reduced apoptosis of hepatocytes. These results were attributed to the antioxidant effects of clinoptilolite[45].

STZ causes diabetes mellitus by selectively destroying pancreatic insulin-secreting cells, leaving less active pancreatic islet cells. Insulin insufficiency is linked to insulin resistance in this well-known model[46]. The histopathological examination in this study proved that STZ causes pancreatic damage observed in the STZ treated rats this agreement with[47].

The administration of synthetic zeolite showed enhancement in the pancreatic tissues and exhibited mild damage compared to the STZ group. Yakimov *et al.*[28] reported that zeolites showed a positive effect on the structural and functional state of the animal's internal organs. Within the liver and pancreas, the hepatocytes and granulocytes of the acini appeared no signs of granular dystrophy characteristic of the disturbance of the protein digestion system, which shown the normalization of the digestion system. Natural and synthetic zeolites have been utilized extensively in animal husbandry to boost productivity. The proposed mechanisms for increasing animal productive performance: ammonia binding, decreasing the harmful effects of ammonia generated by microbial activities in the intestine low digest passage rate through the intestines, resulting in more effective nutrition use, Improved energy and protein retention due to increased pancreatic enzyme activity, which has a favourable influence on feed component hydrolysis over a wider pH range, elimination of mycotoxin growth inhibitory effects[48].

CONCLUSION

The findings of our study revealed that oral treatment with synthetic zeolite could help improve glycemic status in rats with STZ induced diabetic rats. Synthetic zeolite can be used as enhancers of passive immunity and increase health status with a promising perspective in this field. However, further studies are needed to investigate and elucidate the possible mechanism of action of the active ingredients and evaluate the potential value of the synthetic zeolite for the management of diabetes. This may help develop new drugs from synthetic zeolite for the management of diabetes and associated complications.

SIGNIFICANCE STATEMENT

This study discovered the therapeutic effect of synthetic zeolite against diabetes induced by Streptozotocin (STZ), so synthetic zeolite may be a beneficial dietary supplement in the case of diabetic syndrome. This study may help the researchers to uncover the critical areas of using a synthetic zeolite that many researchers were not able to explore.

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