Zeolite intervention counteracts hepato-nephrotoxicity changes and regenerates insulin release in streptozotocin-induced diabetic rats

Hussein A. Sultan, Mahmoud Ashry, Alaa M.H. El-Bitar, Mohsen A. Moustafa

Zoology Department, Faculty of Science, Al-Azhar University, Assiut, Egypt

Correspondence to Mahmoud Ashry, Zoology department, Faculty of Science, Al-Azhar University, Asyut, Egypt. Mobile: +2 01009715015; fax: 0882148093; e-mail: mahmoud_ashry20@yahoo.com

Received: 12 June 2023
Revised: 1 July 2023
Accepted: 4 July 2023
Published: 7 September 2023

Egyptian Pharmaceutical Journal 2024, 23:64–72

Background and objective
Natural products from various sources tend to be potential candidates for drug discovery. Natural and synthetic zeolites are potentially useful biopharmaceuticals and bio-tools due to their unique and outstanding physical and chemical properties; therefore, this study aimed to estimate the hepatorenal preventive and insulin release restoration efficiencies of zeolite (natural and synthetic) in STZ-induced diabetic rats.

Materials and methods
Post inductions of hyperglycemia with a single (ip) dose of STZ (55 mg/kg), the rats were arranged into four groups (8 rats each): (I) normal control group, (II) STZ-diabetic rats, (III) STZ-diabetic rats treated orally with natural zeolite (300 mg/kg/day), and IV) STZ-diabetic rats treated with synthetic zeolite (300 mg/kg/day).

Results and conclusion
After 6 weeks of treatment of diabetic animals, both zeolite types markedly exhibited antidiabetic, anti-inflammatory, hepato-nephroprotective, and antioxidative stress effects that were monitored from the significant reduction in glucose, ALAT, ASAT, urea, creatinine, MDA, and NO values concomitant with a significant rise in insulin, GSH, SOD and CAT values, close to the corresponding values of normal ones. Also, both zeolites succeeded to modulate STZ-induced histological distortion. In conclusion, both zeolites exhibited multi-health benefits with promising potential against STZ-induced diabetes. This effect may be attributed to the antioxidant and free radical scavenging mechanisms of zeolites that were evidenced by hepatorenal protective activities.

Keywords:
antioxidant, diabetes, hepato-nephrotoxicity, rats, streptozotocin, zeolite

Egypt Pharmaceut J 23:64–72

1687-4315

Introduction

Natural products from various sources, such as plants, animals, and microorganisms, tend to be potential candidates for drug development [1]. Nanotechnology might serve as a tool in the diagnosis and treatment of diabetes [2]. Regarding numerous diabetes-related disorders and mortalities, progressive investigations have been conducted to find more effective drugs to reduce the social burden of diabetes. In previous studies, various supplementations have been done for the improvement of some diabetes-related parameters [3]. Zeolites were first synthesized in the 1930s, when the petroleum refining industry started to use them at large scale in catalytic cracking processes [4]. Since then, more than 150 zeolites have been synthesized in an effort to develop more efficient catalysts. Most of the effort was devoted to synthetic zeolites, but in recent years increasing attention has been directed toward natural zeolites, whose status changed from the museum curiosity to an important commodity. Zeolite is an inorganic microporous mineral of volcanic origin with a highly regular structure of pores and chambers [5]. Zeolites are hydrated natural or synthetic microporous crystals, whose structure is an open 3D framework built of silicon (SiO_4) and aluminum (AlO_4) tetrahedral, joined together in various regular arrangements to form an open crystal structure. In the zeolite group, there are about 40 naturally tectosilicate minerals. The chemical differentiation of zeolites is related to the ratio of silicon/aluminum and water content. Chabazite and clinoptilolite, the fibrous forms, are mainly represented by natrolite; these are the most commonly mined isometric forms [6,7]. This chemical structure that gives zeolites many properties such as inorganic cation exchangers, adsorbents, and active reservoirs for metal-catalyzed reactions have earned those extensive industrial applications and medical importance in the last few years [8].

Zeolites of different Si/Al ratios can be obtained either directly by synthesis (synthetic zeolites) or by post-synthesis processing as in the case of natural zeolites. Synthetic zeolites are the major alternate materials to natural zeolites. Synthetic zeolites can be tailored in physical and chemical characteristics to serve many applications more closely, and they are uniform in quality than their natural equivalents [5]. Synthesized analogs of natural zeolites are usually applied in different technological processes, and the low output price conditioned by a subsurface location of massive deposits of natural zeolites throughout the world makes them significantly more available for wide utilization [5]. Zeolites themselves are widely used in agriculture as adsorbents. In animals, zeolite supplementation of the feed resulted in a reduction in the number of poultry pathogens without damaging the beneficial bacteria [9]. Dietary administration of small particle size clinoptilolite can effectively reduce the concentration of aflatoxins in dairy cattle milk [10]. The composition synthesized from naturally occurring nontoxic zeolites was patented in the United States against buccal mucosa and lung squamous epithelial cell cancers [11]. Previous studies have demonstrated that zeolite-clinoptilolite exerts immunostimulatory effects, modulates anti-inflammatory and pro-inflammatory mechanisms, and postulates its use as an adjuvant in anticancer therapy [12]. Other researchers describe zeolite's capability to adsorb glucose, antidiarrheic effects, and its strong antioxidant activity [13]. Synthetic zeolites are materials with few if any problems, as they are readily made from abundant raw materials and present no toxic or environmental problems. The antioxidative roles attributed to synthetic zeolites are based on their ability to diminish free radicals and lipid peroxidation levels as well as to increase total antioxidant capacity (TAC) in serum. Hence, antioxidant enzymes may be potential targets of SZ action as well [14]. Given these recent findings, the present study aimed to evaluate the antidiabetic, anti-inflammatory, and antioxidant potency of zeolite and its counteracting efficiency against hepato-nephrotoxicity changes in streptozotocin-induced diabetic rats.

Materials and methods

Chemicals

Streptozotocin (STZ), sodium citrate, and citric acid were purchased from Sigma, USA. Natural zeolite (NZ) was purchased from Alex Company, Giza, Egypt. Synthetic zeolite (SZ) was prepared using dry rice husk silica by hydrothermal treatment as previously described [15].

Animals

Adult male Wistar albino rats (150–180 g) were obtained from the Animal Colony, National Research Centre, Giza, Egypt. Before starting the experiment, the animals were housed in suitable cages for 1 week for acclimation. Excess tap water and standard rodent pellets were always available. The animals received human care in accordance with the institutional standard criteria as per the methods approved by the Ethics Committee of the Faculty of Science, Al-Azhar University, Assuit. The proposal was approved and registered under AZHAR 13/2022.

Induction of diabetes in rats

After fasting for 16 h, the animals were intraperitoneally injected with (55 mg/kg) streptozotocin dissolved in ice-cold sodium citrate–citric acid buffer [20 ml of sodium citrate (0.1 M) with 30 ml of citric acid (0.1 M), pH=4.0) followed by oral administration of 2–3 ml sucrose solution 10% (w/v) for one day; then the animals were fasted overnight and one drop blood sample was obtained by nicking the rats' lateral tail vein using sterile surgical scissors, and immediately the blood glucose level was determined using Gluco Dr SuperSensor AGM-2200 glucometer (Korea). Animals with blood glucose levels above 240 mg/dl were considered to be diabetic [16].

Study animal groups

After induction of diabetes, the initial weight of both normal and diabetic animals was recorded, then the animals were divided into four groups (8 rats/group): (1) normal rats ingested with distilled water (2 ml/day), (2) untreated STZ-diabetic rats, (3) STZ-diabetic rats treated orally with NZ (300 mg/kg/day) for 6 weeks, and (4) induced diabetic rats treated orally with SZ (300 mg/kg/day) for a similar period.

Blood and tissue sampling

At the end of the treatment period (6 weeks), rats were weighed and then fasted overnight, and the blood glucose level of each animal was determined using the GlucoDr set through blood specimens from the rats' tail. Following anesthesia, 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, 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 killed, and both the liver and kidneys of each animal were dissected out. One kidney and part of the liver of

each animal were washed in saline, dried, rolled in a piece of aluminum foil, and stored at −80°C for oxidative stress determinations. Another portion of the liver and kidney were soaked in formalin-saline (10%) buffer for histological processing and microscopic examination.

Tissue homogenization

A specimen from each organ (liver and kidney) 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 and then the supernatant was divided into aliquots and stored at −80°C till the assessment of oxidative stress markers.

Biochemical determinations

Blood glucose level was determined using GlucoDr Super Sensor AGM-2200, Korean glucometer through a blood sample obtained from the lateral tail vein using sterile surgical scissors. Insulin level was determined in serum using ELISA kits purchased from Immunospec, Canoga Park, USA. Serum urea creatinine, ASAT, and ALAT as well as hepatic and renal GSH, NO, SOD, and CAT were estimated spectrophotometrically using reagent kits obtained from Biodiagnostic, Dokki, Giza, Egypt. Kidney and liver MDA levels were determined chemically as described by Ruiz-Larnea *et al.* [17].

Pro-inflammatory cytokines

Using the ELISA technique (Dynatech Microplate Reader Model MR 5000), tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) concentrations were measured using rats' reagent ELISA kits purchased from SinoGeneClon Biotech Co, Hang Zhou, China.

Histopathology

Paraffin sections of 5μm thickness were stained with hematoxylin and eosin [18] and investigated by a light microscope.

Statistical analysis

The obtained data were subjected to one-way ANOVA followed by Duncan multiple post hoc test at a level of $P \leq 0.05$ according to Steel and Torrie [19] using a statistical analysis system (SAS) program software copyright (c) 1998 by SAS Institute Inc., Cary, NC, USA.

Results

The *in vivo* results performed a significant decrease in insulin level coupled with a significant increase in blood glucose in the STZ-induced diabetic group when compared with the control group. Interestingly, treatment of diabetic rats with either NZ or SZ improved both insulin and glucose levels toward normal values as it significantly increased insulin and significantly decreased glucose levels compared with diabetic rats (Table 1).

Single intraperitoneal injection of STZ resulted in a significant disturbance in liver and kidney function biomarkers; this was monitored from the marked elevation in the activity of serum liver enzymes (ALAT and ASAT) and the raised serum kidney markers (urea and creatinine) compared with their levels of the normal group. Administration of zeolites (natural or synthetic) to diabetic rats significantly ameliorated the deteriorated serum liver and kidney function markers (Table 2).

Injection of rats with STZ resulted in sharp damage in their livers and kidney's oxidative stress status; this was evidenced by the marked depletion in hepatic and renal GSH levels, as well as markedly reduced SOD and CAT activities, matched with a significant increase in hepatorenal MDA and NO levels as compared with the

Table 1 Serum glucose and insulin concentrations of normal, diabetic, and diabetic-treated rats

	Glucose (mg/dl)	Insulin (ng/ml)
Control	98.5 ± 1.6^{A}	3.3 ± 0.94^{A}
Diabetic	395 ± 12.5^{C}	1.01 ± 0.52^{C}
Diabetic ~NZ	245 ± 11.3^{B}	2.61 ± 0.74^{B}
Diabetic ~SZ	235 ± 14.3^{B}	2.87 ± 0.95^{B}

Data are presented as mean±standard error; within each column, means with different superscript letters are significantly different at $P \leq 0.05$ using one-way ANOVA followed by Duncan's multiple post hoc test. NZ, natural zeolite; SZ, synthetic zeolite.

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

	ALAT (U/l)	ASAT (U/l)	Urea (mg/dl)	Creatinine (mg/dl)
Control	30.6 ± 2.6^{A}	41.6 ± 4.7^{A}	38.6 ± 4.1^{A}	0.95 ± 0.2^{A}
Diabetic	105 ± 8.3^{B}	119.5 ± 2.6^{B}	65.9 ± 6.7^{B}	1.84 ± 0.3^{B}
Diabetic ~NZ	55.3 ± 4.2^{C}	69.7 ± 4.7^{C}	42.5 ± 4.2^{C}	1.2 ± 0.31^{C}
Diabetic ~SZ	66.8 ± 10.6^{C}	71.4 ± 6.7^{C}	43.5 ± 3.4^{C}	1.3 ± 0.31^{C}

Data are presented as mean±standard error; within each column, means with different superscript letters are significantly different at $P \leq 0.05$ using one-way ANOVA followed by Duncan's multiple post hoc test. NZ, natural zeolite; SZ, synthetic zeolite.

Table 3 Hepatorenal malondialdehyde (MDA), nitric oxide (NO), and reduced glutathione (GSH) concentrations of normal, diabetic, and diabetic-treated rats

	MDA (nmol/g tissue)		NO (μmol/g tissue)		GSH (mg/g Tissue)	
	Liver	Kidney	Liver	Kidney	Liver	Kidney
Control	15 ± 1.8^{A}	8.1 ± 0.5^{A}	426 ± 26^{A}	254 ± 14.2^{A}	122 ± 13^{A}	85 ± 4.1^{A}
Diabetic	41 ± 1.1^{C}	16.5 ± 1.5^{C}	871 ± 30^{C}	501 ± 16.8^{C}	52 ± 4.7^{C}	22.3 ± 2.7^{C}
Diabetic ~NZ	25 ± 0.8^{B}	12.4 ± 0.5^{B}	542 ± 35^{B}	310 ± 15.4^{B}	101 ± 22^{E}	66 ± 4.1^{B}
Diabetic ~SZ	29 ± 0.8^{B}	13.4 ± 1.0^{B}	580 ± 41^{B}	326 ± 19.1^{B}	107 ± 22^{E}	71.5 ± 8.1^{B}

Data are presented as mean±standard error; within each column, means with different superscript letters are significantly different at $P\leq0.05$ using one-way ANOVA followed by Duncan's multiple post hoc tests. NZ, natural zeolite; SZ, synthetic zeolite.

Table 4 Shows hepatic and renal superoxide dismutase (SOD) and catalase (CAT) concentrations of normal, diabetic, and diabetic-treated rats

	SOD (U/g Tissue)		CAT (U/g Tissue)	
	Liver	Kidney	Liver	Kidney
Control	2295 ± 55^{A}	1204 ± 61.4^{A}	8.5 ± 0.4^{A}	4.1 ± 0.2^{A}
Diabetic	1184 ± 51^{C}	658 ± 41.2^{C}	4.1 ± 0.30^{D}	2.01 ± 0.11^{C}
Diabetic ~NZ	1901 ± 49^{B}	925 ± 31.4^{B}	6.8 ± 0.25^{B}	3.2 ± 0.23^{B}
Diabetic ~SZ	1855 ± 51^{B}	859 ± 27.5^{B}	7.1 ± 0.25^{B}	3.4 ± 0.27^{B}

Data are presented as mean±standard error; within each column, means with superscript different letters are significantly different at $P\leq0.05$ using one way ANOVA followed by Duncan multiple post hoc test. NZ, Natural Zeolite; SZ, Synthetic Zeolite.

normal control group. Fortunately, posttreatment of diabetic rats with both zeolites significantly recharged liver and kidney GSH battery and significantly increased the activities of hepatorenal SOD and CAT (Tables 3 and 4).

When the untreated diabetic group was compared with the control group, the results revealed significantly higher levels of TNF-α and IL-1β. It is interesting to note that administration of NZ and SZ to diabetic rats improved serum pro-inflammatory cytokine levels relative to the control ranges by dramatically lowering TNF-α and IL1β levels, in comparison to untreated diabetic animals (Fig. 1).

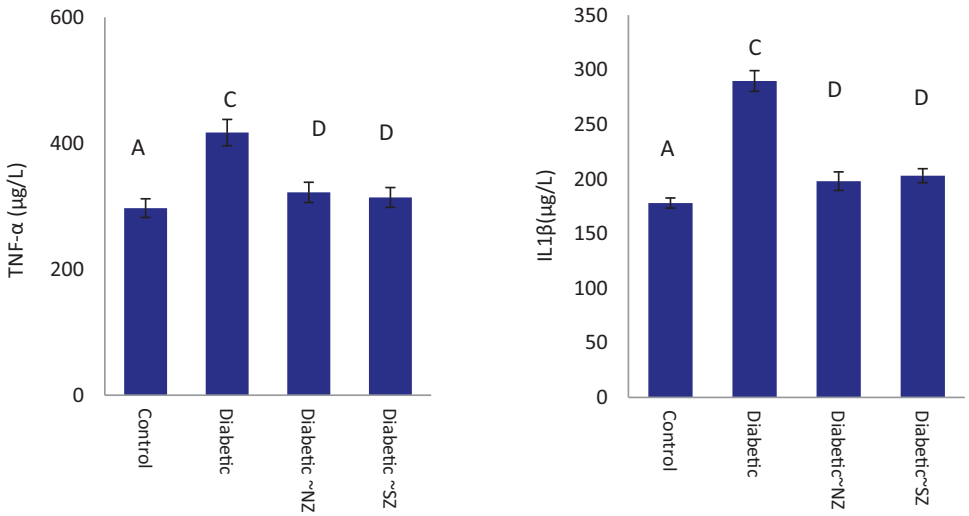
Liver and kidney histopathological examination

Results of histological examination of liver & kidney sections of the study groups are described and illustrated in (Figures 2–9).

Discussion

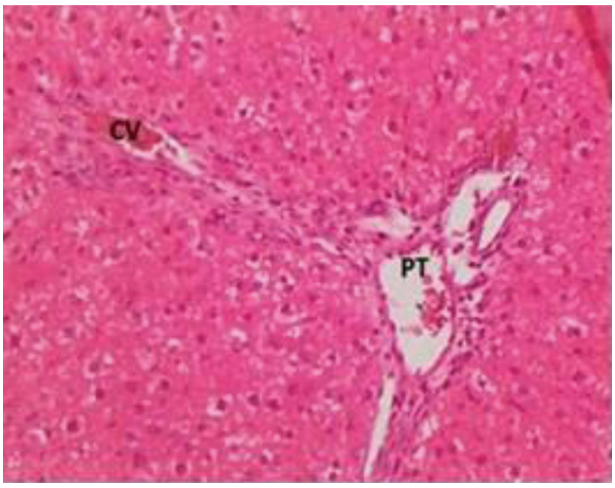
Diabetes mellitus is one of the oxidative stress conditions in which free radicals are increased and/or antioxidant mechanisms are inhibited. Free radicals induce oxidative stress and can lead to injury of the cellular membrane [20]. Free radical formation has been reported to be a direct consequence of hyperglycemia [21]. Our results showed that treatment of diabetic rats with zeolite (either natural or synthetic) improved insulin and glucose levels toward normal values as it significantly increased

Figure 1



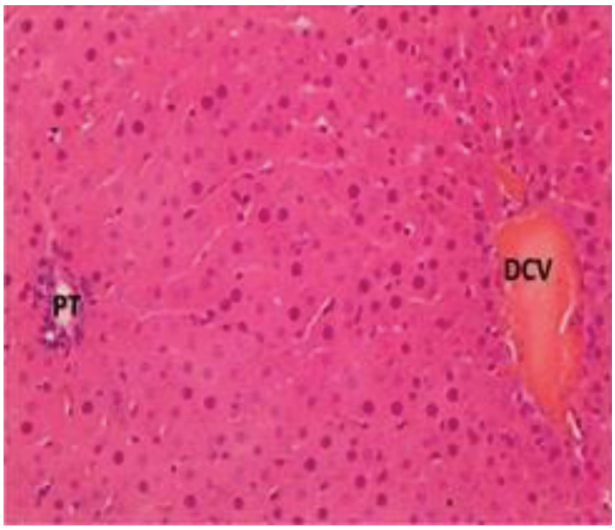
Serum TNF-α and IL1β, levels of control, untreated diabetic, NZ-, and SZ-treated diabetic animals. Data are presented as mean ±standard error; within each column, means with different superscript letters are significantly different at $P\leq0.05$ using one-way ANOVA followed by Duncan's multiple post hoc test; NZ: natural zeolite; SZ: synthetic zeolite.

Figure 2



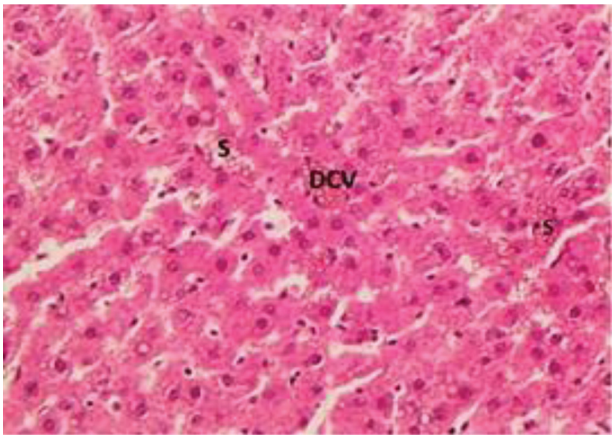
Photomicrograph for hepatic tissue of the normal control group showing normal appearance of hepatic architecture, which consists of hexagonal plates of hepatocytes arranged into strips of average thickness; the hepatocytes are well demarcated. Within each plate, the hepatocytes radiate outward from a central vein (CV) to the portal tract (PT), as they extend toward the periphery, hepatic sinusoids travel between the strips of hepatocytes (H&E 200x).

Figure 3



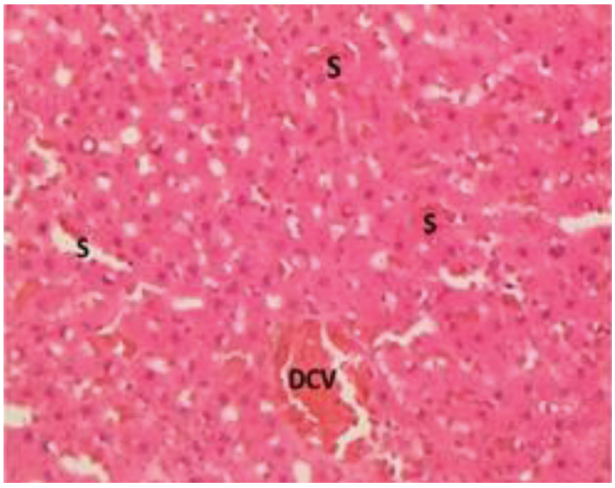
Photomicrograph of the hepatic tissue of the diabetic group showing normal appearance of hepatic architecture;are however, the hepatocytes not well demarcated. Dilated congested central vein (DCV) and portal tract (PT) are normally looking (H&E 200x).

Figure 4



Photomicrograph of the hepatic tissue of the diabetic group treated with natural zeolite showing normal appearance of the hepatic architecture; the hepatocytes are well demarcated. Dilated congested central vein (DCV) with dilated hepatic sinusoids (S) travel between the strips of hepatocytes (H&E 200x).

Figure 5

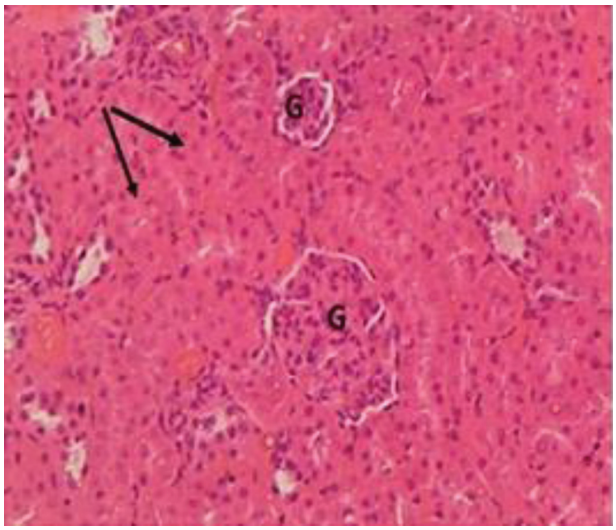


Photomicrograph of the hepatic tissue of the diabetic group treated with synthetic zeolite showing normal hepatic architecture; the hepatocyte walls are not well demarcated. The central vein is dilated and congested (DCV) with dilated hepatic sinusoids (S). (H&E 200x).

insulin and significantly decreased the glucose level compared with diabetic rats. In our study, hypoglycemic activity exhibited by zeolite may be attributed to the presence of the compound silica. Because of the well-known adsorption properties of zeolites, they can reduce the glucose level in blood [22]. Current evidence suggests that zeolites may reduce blood glucose in diabetic animal models [23]. They may act as glucose adsorbents, so individuals with diabetes mellitus could benefit from them [24]. Zeolite might reduce blood glucose by preventing beta cell destruction and thus enhancing insulin production [5]. Previous studies have stated component adsorption of fructose, glucose, sucrose, and fructooligosaccharides by NaX-type zeolites and also adsorption of glucose into zeolite beta from aqueous solution [25].

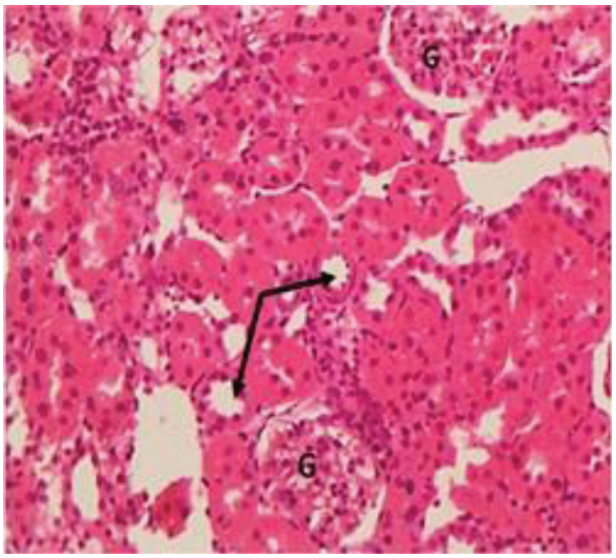
The significant increase in values of ALAT and ASAT activities in the diabetic group rats confirms that diabetes mellitus could induce hepatic injury, which might be owing to the decrease in protein

Figure 6



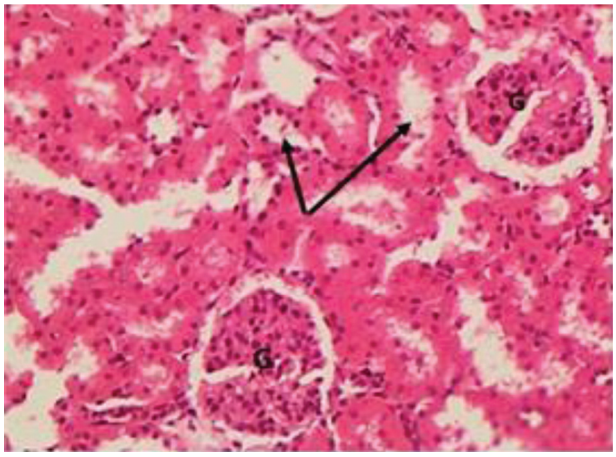
Photomicrograph of the renal tissue of the normal control group, showing normal renal tissue architecture with normal appearance of glomeruli (G), and average thickness of tubules lined by basally placed endothelial cells (black arrows). (H&E200x).

Figure 7



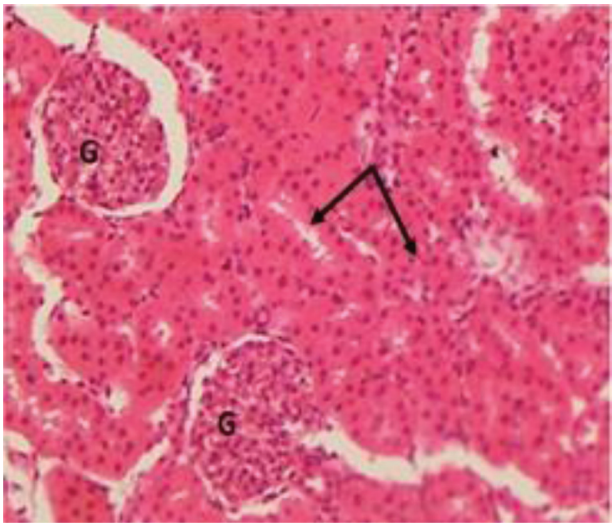
Photomicrograph of renal tissue of the diabetic group showing normal renal tissue architecture with normal appearance of glomeruli (G), and average thickness of tubules lined by basally placed endothelial cells (black arrows). (H&E200x)

Figure 8



Photomicrography of renal tissue of the diabetic group treated with natural zeolite showing normal renal tissue architecture as normal appearance of glomeruli (G) sand average thickness of tubules lined by basally placed endothelial cells (black arrows). (H&E200x).

Figure 9



Photomicrograph of renal tissue of the diabetic group treated with synthetic zeolite showing normal renal tissue architecture with normal appearance of glomeruli (G), and average thickness of tubules lined by basally placed endothelial cells (black arrows). (H&E200x).

concentrations accompanying glucogenesis and urea formation observed in the diabetic state. ALAT and ASAT are directly associated with the conversion of amino acids to keto acids and are reported to increase in diabetic conditions [26]. 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 activity of serum liver enzymes (ALAT and ASAT) and the observable raised levels of serum kidney markers (urea and creatinine) compared with 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, administration of zeolites (natural and synthetic) to diabetic rats significantly ameliorated diabetes-induced hepatorenal changes, reflecting those zeolites showed a positive effect on the structural and functional state of the animal's internal organs, as the hepatocytes showed no signs of granular dystrophy characteristic of the disruption of protein

metabolism, which indicated the normalization of metabolism [28].

Expression of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase are known to be in the lowest level in pancreatic islet cells compared with other tissues such as the liver, kidney, and adipose tissue [29]. Increased free radicals may lead to degradation of cellular functions and oxidative damage to membranes by consuming antioxidant defense components [30]. Physiological antioxidative defense system as justified here in terms of GSH, SOD and CAT; our results exhibited that posttreatment of diabetic rats with zeolites (natural or synthetic) significantly recharged liver GSH battery and significantly increased the activities of SOD and CAT; moreover, zeolites succeeded in reducing hepatic NO level when compared with the corresponding values of diabetic rats. These results are in accordance with the previous study [26], and with a report that suggested that STZ use resulted in the formation of antibodies [31], which may in turn starts the destruction of insulin-producing β-cells and finally leads to deficiency of insulin [32], consequently leading to the excess glucose level in the body. The surplus glucose gets auto-oxidized and becomes the origin of free radical production. Diabetes-induced free radical generation could have led to peroxidative damage to the liver tissue, which further might have caused the excessive level of MDA formation; the interesting finding coincides with earlier results [33]. MDA is an aldehydic product of lipid peroxidation that combines quickly with biomolecules and contributes to cellular disturbance, including β-pancreatic cell, thus, deregulating the glucose metabolism [34].

In diabetes, hyperglycemia results in the generation of free radicals, this weakens the body's defense mechanisms, thus leading to the disruption of cellular functions, oxidative damage to membranes, and an enhanced susceptibility to lipid peroxidation [35]. Decreased SOD activity has been reported in severe diabetes [36]. SOD and GSH are important antioxidants that could be helpful in preventing lipid peroxidation, and is involved in cellular defense mechanisms, thus protecting tissues against oxidative damage [37]. Under hyperglycemic conditions, antioxidants are thought to regenerate the damaged extracellular matrix proteins and cell growth [38]. In addition, increased MDA content has been reported previously in hyperglycemic rats [39]. Treatment with zeolite in this study showed improvement in antioxidant and detoxification of oxidative stress; these data are inconsistent with the recent study [40]; the detoxification effect of zeolites could be attributed to their ability to reduce lipid peroxidation through scavenging free radicals [41]. As they eliminate superoxide, hydrogen peroxide and hydroxyl radicals, antioxidant enzymes (SOD, GSH and CAT) play an important role in defense mechanisms against free radicals [42]. The mechanisms of zeolites or the antioxidant effects are not well known, as zeolite is not absorbed into the blood from the gut; however, the effects may be due to an indirect interaction with biochemical systems, removal of waste and toxins from the gut, improvement of the immune system through the mucosal-related intestinal lymphoid tissue, and an increase in the bioavailability of minerals that are important cofactors for some enzymes [14]. Moreover, some of the antioxidant properties of zeolites are attributed to their effect on macrophages' phagocytic function triggered after phagocytosis of zeolite particles. Phagocytic action subsequently leads to the production of cytokines such as tumor necrosis factor-α, which stimulates immunologic responses and also increases the expression of SOD [43].

In the present study, STZ administration induced a significant increase in the level of TNF-α and IL- 1β compared with that of the control group. These findings are similar to those observed in previous studies [44–46]. TNF-α is a potent inflammatory cytokine, released from macrophages and T-lymphocytes, with important functions on diabetes mellitus (DM), as it not only plays an important role in the development of insulin resistance but also in progression to microvascular complications of DM [47]. IL-1β, which plays a major role in a wide array of auto-inflammatory diseases, was observed to act as the key promoter of tissue and systemic inflammation in DM [48]. It is considered to play an important role in the development of cardiovascular complications of DM, especially diabetic vasculopathy, as its release from adipokines can have an impact on distant organs, including the heart or the vessels, due to increased systemic and vascular inflammation [49]. The reduction of the serum TNF-α and IL-1β level, post zeolite treatment, was reported to be associated with activation of biomolecules involved in different pathologies, including kinases MAPK, PKC and SAPK or AP1, NFκB proteins and pro-inflammatory cytokines IL-1β, and TNF- α [50]. So far, clinoptilolite is considered as the only safe zeolite material used in medical applications due to its widely documented beneficial effects on animal and human

health and performance. Zeolite important transcription factors, such as activator protein 1 and NFκB, are also activated and the expression of pro-inflammatory cytokines such as interleukin 1β and TNF-α is enhanced [51]. Zeolites have a protective effect on hepatocytes during anticancer therapy using Adriamycin (doxorubicin). In primary cultures of liver cells derived from rats treated with adriamycin, subsequent treatment with clinoptilolite significantly reduced the production of inflammatory cytokines, such as TNF-α and IL-1β, by hepatocytes. In addition, this zeolites treatment led to reduced apoptosis of hepatocytes; these results could be attributed to the antioxidant effects of clinoptilolite [52].

Conclusion

In conclusion, the findings of the present study revealed that zeolite could improve the liver and kidney oxidative damage and dysfunction in the STZ-treated diabetic rats. However, our results demonstrated that administration of diabetic rats with zeolites recorded a high degree of protection against hepatorenal injury induced by diabetes. Further investigations are required to elucidate mechanisms for beneficial actions of zeolite during diabetes.

Acknowledgements

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Alam F, Islam MA, Kamal MA, Gan SH. Updates on managing Type 2 diabetes mellitus with natural products: towards antidiabetic drug development. Curr Med Chem 2018; 25:5395–5431.

2 Alam Q, ZubairAlam M, Karim S, Gan SH, Kamal MA, Jiman-Fatani A, *et al.* A nanotechnological approach to the management of Alzheimer disease and type 2 diabetes. CNS Neurol Disord Drug Targets 2014; 13:478–486.

3 Roshanravan N, Alizadeh M, Hedayati M, Asghari-Jafarabadi M, Mesri Alamdari N, Anari F, Tarighat-Esfanjani A. Effect of zinc supplementation on insulin resistance, energy and macronutrients intakes in pregnant women with impaired glucose tolerance. Iran J Public Health 2015 44:211–217.

4 R V. Minerals Year book, Zeolite (Advanxed Release); 2011.

5 Pavelic K, Hadzija M. Medical applications of zeolites. In: Handbook of zeolite science and technology. New York: Dekker, 2003; pg. 1143–74.

6 Khojaewa V, Lopatin O, Zelenikhin P, Ilinskaya O. Zeolites as carriers of antitumor Ribonuclease Binase. Front Pharmacol 2019; 10:442.

7 Zarrintaj P, Mahmodi G, Manouchehri S, Mashhadzadeh AH, Khodadadi M, Servatan M, *et al.* Zeolite in tissue engineering: Opportunities and challenges. MedComm (2020) 2020; 1:5–34.

8 Lamprecht M, Bogner S, Steinbauer K, Schuetz B, Greilberger JF, Leber B, *et al.* Effects of zeolite supplementation on parameters of intestinal barrier integrity, inflammation, redoxbiology and performance in aerobically trained subjects. J Int Soc Sports Nutr 2015; 12:40.

9 Prasai TP, Walsh KB, Bhattarai SP, Midmore DJ, Van TT, Moore RJ, Stanley D. Biochar, Bentonite and Zeolite supplemented feeding of layer chickens alters intestinal microbiota and reduces campylobacter load. PLoS ONE 2016; 11:e0154061.

10 Katsoulos PD, Karatzia MA, Boscos C, Wolf P, Karatzias H. In-field evaluation of clinoptilolite feeding efficacy on the reduction of milk aflatoxin M1 concentration in dairy cattle. J Anim Sci Technol 2016; 58:24.

11 Kaufman H. Epithelial cell cancer drug. In.: Google Patents; 2001

12 Muck-Seler D, Pivac N. The effect of natural clinoptilolite on the serotonergic receptors in the brain of mice with mammary carcinoma. Life Sci 2003; 73:2059–2069.

13 Montinaro M, Uberti D, Maccarinelli G, Bonini SA, Ferrari-Toninelli G, Memo M. Dietary zeolite supplementation reduces oxidative damage and plaque generation in the brain of an Alzheimer's disease mouse model. Life Sci 2013; 92:903–910.

14 Dogliotti G, Malavazos AE, Giacometti S, Solimene U, Fanelli M, Corsi MM, Dozio E. Natural zeolites chabazite/phillipsite/analcime increase blood levels of antioxidant enzymes. J Clin Biochem Nutr 2012; 50:195–198.

15 Pang W, Yu J, Xu R, Huo Q, Chen J. Chemistry of zeolites and related porous materials: synthesis and structure. Singapore: John Wiley & Sons (Asia) Pte Ltd 2 Clementi Loop; 2009.

16 Kim JD, Kang SM, Seo BI, Choi HY, Choi HS, Ku SK. Anti-diabetic activity of SMK001, a poly herbal formula in streptozotocin induced diabetic rats: therapeutic study. Biol Pharm Bull 2006; 29:477–482.

17 Ruiz-Larrea MB, Leal AM, Liza M, Lacort M, de Groot H. Antioxidant effects of estradiol and 2-hydroxyestradiol on iron-induced lipid peroxidation of rat liver microsomes. Steroids 1994; 59:383–388.

18 Drury RAB, Wallington EA. Preparation and fixation of tissues. In: Drury RAB, Wallington EA, editors. Carleton's Histological Technique. 5. Oxford: Oxford University Press 1980. pp. 41–54.

19 Steele R, Torrey J. Principles and procedures of statistics: a biometrical approach. New York: McGraw & Hill. Inc; 1980. 593.

20 Shinde UA, Goyal RK. Effect of chromium picolinate on histopathological alterations in STZ and neonatal STZ diabetic rats. J Cell Mol Med 2003; 7:322–329.

21 Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. Diabetes Care 1996; 19:257–267.

22 Cisneros V, Ocanto F, Linares CF. Ca2+, Mg2+ OR Fe2+ ion-exchanged cancrinite-type zeolites as possible hypoglycemiant agents. Revista latinoamericana de química 2011; 39:55–61.

23 Januškevicìius A, Januškevicìiene G, Plungyte K. Klinoptilolitas suaugusiu sunu racionuose. Veteriin Zootechnika 2013; 64:1392–2130.

24 Zarkovic N, Zarkovic K, Kralj M, Borovic S, Sabolovic S, Blazi MP, *et al.* Anticancer and antioxidative effects of micronized zeolite clinoptilolite. Anticancer Res 2003; 23(2B):1589–1595.

25 Kuhn RC, Mazutti MA, Maugeri Filho F. Kinetic and mass transfer effects for adsorption of glucose, fructose, sucrose and fructooligosaccharides into X zeolite. LWT-Food Sci Technol 2012; 48:127–133.

26 Makena W, Hamman WO, Buraimoh AA, Dibal NI, Obaje SG. Therapeutic effects of balanitoside in streptozotocin-induced diabetic rats. J Taibah Univ Med Sci 2018; 13:402–406.

27 Garella S. The costs of dialysis in the USA. Nephrol Dial Transplant 1997; 12 (Suppl 1): 10–21.

28 Yakimov OA, Gainullina MK, Gasimova GA, Volostnova AN, Frolov GS, Salyakhov AS, Ezhkova MS. The influence of feed additive of zeolite on micromorphology of certain organs of the digestive system of calves. Research Journal of Pharmaceutical. Biol Chem Sci 2018; 9:1122–1129.

29 Tiedge M, Lortz S, Munday R, Lenzen S. Protection against the co-operative toxicity of nitric oxide and oxygen free radicals by overexpression of antioxidant enzymes in bioengineered insulin-producing RINm5F cells. Diabetologia 1999; 42:849–855.

30 Baynes JW. Role of oxidative stress in development of complications in diabetes. Diabetes 1991; 40:405–412.

31 Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi S, Farhangi A, Verdi AA, *et al.* Induction of diabetes by Streptozotocin in rats. Indian J Clin Biochem 2007; 22:60–64.

32 Szkudelski T, Michalski W, Szkudelska K. The effect of thyroid hormones on blood insulin level and metabolic parameters in diabetic rats. J Physiol Biochem 2003; 59:71–76.

33 Kapoor R, Srivastava S, Kakkar P. Bacopa monnieri modulates antioxidant responses in brain and kidney of diabetic rats. Environ Toxicol Pharmacol 2009; 27:62–69.

34 Belce A, Uslu E, Kucur M, Umut M, Ipbuker A, Seymen HO. Evaluation of salivary sialic acid level and Cu-Zn superoxide dismutase activity in type 1 diabetes mellitus. Tohoku J Exp Med 2000; 192:219–225.

35 Prasad K, Mantha SV, Muir AD, Westcott ND. Protective effect of secoisolariciresinol diglucoside against streptozotocin-induced diabetes and its mechanism. Mol Cell Biochem 2000; 206:141–149.

36 Greene MW, Chen TT. Characterization of teleost insulin receptor family members. II. Developmental expression of insulin-like growth factor type I receptor messenger RNAs in rainbow trout. Gen Comp Endocrinol 1999; 115:270–281.

37 Li L-Y., Li L-Q., Guo C-H. Evaluation of in vitro antioxidant and antibacterial activities of Laminaria japonica polysaccharides. J Med Plant Res 2010; 4:2194–2198.

38 Superchi P, Saleri R, Ossiprandi MC, Riccardi E, Passaglia E, Cavalli V, *et al.* Natural zeolite (chabazite/phillipsite) dietary supplementation influences faecal microbiota and oxidant status of working dogs. Ital J Anim Sci 2017; 16:115–121.

39 Atitlan-Gil A, Breton-de la Loza MM, Jimenez-Ortega JC, Belefant-Miller H, Betanzos-Cabrera G. Activated and micronized zeolite in the modulation of cellular oxidative stress in mexican smokers: a randomized clinical trial. Rev Invest Clin 2017; 69:146–151.

40 Samarghandian S, Borji A, Delkhosh MB, Samini F. Safranal treatment improves hyperglycemia, hyperlipidemia and oxidative stress in streptozotocin-induced diabetic rats. J Pharm Pharm Sci 2013; 16:352–362.

41 Zarkovic N. 4-hydroxynonenal as a bioactive marker of pathophysiological processes. Mol Aspects Med 2003; 24:281–291.

42 Ibrahim H, Elshaarawy F, Haggag E. Investigation of Livistona decipiens leaf methanol extract and evaluation of antioxidant, antimicrobial and cytotoxic activities. J Adv Pharm Res 2018; 2:256–268.

43 Yu X, Zhang L, Lu H, Chen H, Yu L, Cao X, Shen D. Rapamycin protects against hepatic injury in streptozotocin-induced diabetic rats by enhancing autophagy. Int J Clin Exp Med 2019; 12:11383–11393.

44 Inoguchi T, Sonta T, Tsubouchi H, Etoh T, Kakimoto M, Sonoda N, *et al.* Protein kinase C-dependent increase in reactive oxygen species (ROS) production in vascular tissues of diabetes: role of vascular NAD(P)H oxidase. J Am Soc Nephrol 2003; 14 (8 Suppl 3):S227–232.

45 Tan DX, Manchester LC, Reiter RJ, Plummer BF, Limson J, Weintraub ST, Qi W. Melatonin directly scavenges hydrogen peroxide: a potentially new metabolic pathway of melatonin biotransformation. Free Radic Biol Med 2000; 29:1177–1185.

46 Ying L, Chaudhry MT, Xiao F, Mao Y, Wang M, Wang B, *et al.* The effects and mechanism of quercetin dietary supplementation in streptozotocin-induced hyperglycemic arbor acre broilers. Oxid Med Cell Longev 2020; 2020:9585047.

47 Dokumacioglu E, Iskender H, Sen TM, Ince I, Dokumacioglu A, Kanbay Y, *et al.* The Effects of Hesperidin and Quercetin on serum tumor necrosis factor-Alpha and Interleukin-6 levels in streptozotocin-induced diabetes model. Pharmacogn Mag 2018; 14:167–173.

48 Borra SK, Mahendra J, Gurumurthy P, Jayamathi P, Iqbal SS, Mahendra L. Effect of curcumin against oxidation of biomolecules by hydroxyl radicals. J Clin Diagn Res 2014; 8:CC01–05.

49 Peiro C, Lorenzo O, Carraro R, Sanchez-Ferrer CF. IL-1beta inhibition in cardiovascular complications associated to Diabetes Mellitus. Front Pharmacol 2017; 8:363.

50 Lim YSKH, Kim HA, Oh MW, Lee KH. Health Prosp 105 (Supll 5) Environ 1997, 1325e1327

51 Pavelić SK, Micek V, Filošević A, Gumbarević D, Žurga P, Bulog A, *et al.* Novel, oxygenated clinoptilolite material efficiently removes aluminium from aluminium chloride-intoxicated rats in vivo. Microporous Mesoporous Mater 2017; 249:146–156.

52 Yapislar H, Taskin E, Ozdas S, Akin D, Sonmez E. Counteraction of apoptotic and inflammatory effects of adriamycin in the liver cell culture by Clinopitolite. Biol Trace Elem Res 2016; 170:373–381.