The use of natural products from medicinal plants as food and medicine is becoming significantly important in recent years. A significant number of people in both rural and urban areas of the world use some form of medicine from natural sources as part of their primary health care for the prevention or treatment of various diseases. The reason behind this has been attributed to the accessibility, cost, efficacy, and lesser undesirable effect as compared to most of the synthetic drugs.[7,8] Polysaccharides are one of the important naturally occurring bioactive constituents found in plants, algae, micro-organisms, and animals. They display a wide range of structural and biological characteristics, which make them a center of attraction in recent years. Polysaccharides are a group of biological macromolecules which are made up of ten or more monosaccharides.[9,10] Polysaccharides have gained prominent attention as components of functional food and nutraceuticals due to their diverse pharmacological properties, non-toxic nature, and effectiveness.[9,11,12] A growing number of studies have portrayed efficacy of purified and crude form of polysaccharides in diabetic situations. The antidiabetic effects of these reported polysaccharides have been attributed to various mechanisms including improving glucose metabolism, lipid, and metabolism, alleviating pancreatic β-cell dysfunction, and inhibiting α-amylase and α-glucosidase. In addition, some polysaccharide has been reported to inhibit oxidative and inflammatory pathways responsible for complications associated with diabetes.[10,13-16]

The genus *Lycium* belongs to the family *Solanaceae*, comprising mainly edible perennial shrubs with seven identified species. Of these, two varieties (*Lycium chinense* and *Lycium barbarum*) are extensively cultivated and used in China. *L. chinense*, popularly known as Chinese boxthorn or Chinese wolfberry, is an important traditional Chinese medicinal plant due to its application as food and medicine. The leaves of the plant have been pharmacologically explored as a neuroprotective, antimicrobial, antioxidant, anti-angiotensin I-converting enzyme, antiulcer, and antidiabetic agent.[8,17,18] The leave of the plant is a very rich source of a variety of bioactive active compounds, such as polyphenols, diterpene glycosides, with anolides, aliphatic acids, and polysaccharides.[18-20] Numerous studies have portrayed the significant contributions of polysaccharides from medicinal plants and edible fungi as an antidiabetic;[7,16,21] however, polysaccharides from *L. chinense* have not been extensively explored for their pharmacological benefits. Therefore, the crude polysaccharide extract from the leaves of *L. chinense* was extracted and evaluated for this study. Thus, this present study was aimed at revealing the protective effect of *L. chinense* polysaccharide in streptozotocin (STZ)-induced diabetic rats.

MATERIALS AND METHODS

Plant material

The leaves of the plant were collected from Henan Province, China, in 2016. The plant was identified at the School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, Henan. A voucher specimen (No. 2016010 LC) was stored at the herbarium of the university.

Extraction of polysaccharide

The leaves of *L. chinense* was powdered, was depigmented using acetone, and was subjected to distilled water extraction using Soxhlet apparatus at 90°C for 3 h. The water extract was centrifuged at 5000 rpm for 15 min, and the resulting supernatant was concentrated under reduced pressure and further precipitated with 95% ethanol. The precipitate obtained was further deproteinized using Savage method,[22] dialyzed, and lyophilized to obtain the crude polysaccharide (PLC) which was stored at 4°C until further use.

Animals and induction of diabetic rat model

Male Wistar rats (150–200 g) were kept in a room maintained at a temperature of 24°C ± 2°C, relative humidity of 55% ± 5%, and a 12-h light/dark cycle. The rats were allowed 7 days of acclimatization and were fed with a standard rat diet during the experimental period. The animals also had free access to water *ad libitum*. The experimental protocol was approved by the Animals Ethics Committee of Zhengzhou Central Hospital (Ethics number: zxyy20181101). After 7 days of acclimatization, the rats were fasted for 12 h and administered with a single dose of freshly prepared STZ (60 mg/kg, i.p) in sodium citrate buffer solution (pH 4.5) to induce diabetes. Fasting blood glucose (FBG) levels of the rats were measured after 72 h of STZ administration, and rats with Fasting blood glucose (FGB) levels ≥15.0 mmol/L were considered diabetic and included in further experiments.

Experimental design

Rats were randomly allotted into five groups (6 rats per group) as indicated below:

- Normal control group (NCG) received normal saline
- Diabetic control group (DCG) received normal saline
- Glibenclamide-treated group treated with glibenclamide (20 mg/kg)
- PLC 100-treated group (PLC100) treated with PLC (100 mg/kg)
- PLC 400-treated group (PLC400) treated with PLC (400 mg/kg).

The rats were orally treated with PLC and glibenclamide once daily for 4 weeks. Glibenclamide, the standard medication for treating diabetic patients, was used as the positive control drug. The rats were overnight fasted on the last day of the experiment; the body weight and FBG were measured using Accu-Chek active glucometer (Roche Diagnostics, Mannheim, Germany). At the end of the experiments, the animals were anesthetized and sacrificed by cervical dislocation. Blood, kidney, and liver samples were obtained. The blood collected was centrifuged at 5000 rpm for 15 min to obtain the serum. The kidney and liver samples were homogenized in phosphate buffer (0.1 M) and centrifuged at 5000 rpm for 15 min. The supernatant obtained after centrifuging was used for the determination of biochemical parameters.

Biochemical analysis

The serum was used for the determination of liver function enzymes namely alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP); serum lipids namely triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C); and blood urea nitrogen (BUN), urea, and creatinine with the aid of the corresponding commercial ELISA assay kits. The homogenates from the kidney and liver were used for assessing the antioxidant enzyme levels (superoxide dismutase [SOD], glutathione peroxidase [GSH-Px] and catalase [CAT]), lipid peroxidation (malondialdehyde [MDA]) levels, and pro-inflammatory cytokines (tumor necrosis factor alpha [TNF-α], interleukin 1 beta [IL-1β], and interleukin-6 [IL-6]) using commercially available kits.

Statistical analysis

Graphpad Prism Software (Version 7.0, GraphPad Software Inc., San Diego, California, USA) was employed for statistical analysis. All the data are presented as mean ± standard deviation. Statistical analyses were performed by one-way ANOVA followed by Tukey *post hoc* test. $P < 0.05$ was considered statistically significant.

RESULTS

The effect of PLC on the body weight, FBG, and insulin levels in STZ-induced diabetic rats is displayed in Table 1. Comparison of the body weight, insulin, and FBG levels of the DCG with the NCG clearly indicated significant decrease in body weight and insulin levels and a marked increase in the FGB level of the DCG of rats. On treatment with 100 and 400 mg/kg of PLC, the FBG level was apparently decreased, while the body weight and insulin levels were higher than those of the rats in the DCG.

After 4 weeks of treatment with PLC, the serum lipid levels namely LDL-C, TG, and TC were observed to be obviously decreased in PLC100 and PLC400 groups. In addition, HDL-C level was observed to be markedly reduced in the DCG as compared to NCG. After the treatment of diabetic rats with PLC (100 and 400 mg/kg), the serum levels of HDL-C were observed to be evidently higher than those of the untreated DCG [Figure 1].

The effect of PLC on serum level of liver function indexes in the diabetic rats is presented in Table 2. The serum ALP, ALT, and AST levels were significantly higher in the untreated diabetic rats (DCG) when compared to the NCG. However, in the PLC-treated rats, a significant and concentration-dependent decrease in the levels of ALP, ALT, and AST was observed.

The results obtained from this study indicated that serum levels of creatinine, urea, and BUN were remarkably increased in the untreated diabetic rats when compared with the normal control (NC) rats. After 4 weeks of treatment with PLC, the levels of creatinine, urea, and BUN in the serum were significantly decreased in all treated diabetic rat groups [Table 3].

The untreated diabetic rats displayed marked decrease in kidney and liver antioxidant enzyme activities of SOD, GSH-Px, and CAT, while the lipid peroxidation product MDA was apparently increased when compared to the NC rats [Table 4]. Treatment of the diabetic rats with 100 and 400 mg/kg PLC markedly increased the activities of the antioxidant enzymes as well as decreased the level of MDA in the kidney and liver tissues [Table 4].

The anti-inflammatory effect of PLC was further evaluated in the kidney tissues of diabetic rats. As clearly shown in Figure 2, the levels of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 were significantly increased in the kidney of diabetic rats when compared with the NCG. After treatment of the diabetic rats with PLC (100 and 400 mg/kg), the levels of TNF-α, IL-1β, and IL-6 in the kidney were significantly reduced [Figure 2].

Table 1: Effect of PLC on body weight, fasting blood glucose and insulin level in diabetic rats

Groups	Body weight (g)	FBG (mmol/L)	Insulin (μIU/mL)
NCG	280.20±6.11	6.90±0.30	21.20±1.42
DCG	170.19±3.45#	21.40±1.04#	6.80±0.78#
DLG	243.57±7.01**	9.20±0.69**	17.80±1.15**
PLC 100	212.05±5.44**	14.60±1.16**	11.30±1.22**
PLC 400	235.70±5.82**	11.50±0.86**	14.10±0.92**

Values are expressed as mean±SD (n=6). #P<0.05 versus normal control group; **P<0.05 versus diabetic control group. FBG: Fasting blood glucose; NCG: Normal control group; DCG: Diabetic control group; DLG: Diabetic rats treated with glibenclamide; SD: Standard deviation; PLC 100: Diabetic rats treated with *Lycium chinense* polysaccharide (100 mg/kg); PLC 400: Diabetic rats treated with *Lycium chinense* polysaccharide (400 mg/kg)

Table 2: Effect of PLC on aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase level in diabetic rats

Groups	AST (U/L)	ALP (U/L)	ALT (U/L)
NCG	122.73±7.04	11.26±1.69	37.09±2.01
DCG	258.20±11.22#	35.59±3.71#	95.04±2.66#
DLG	148.40±8.26**	19.15±2.04**	48.37±3.68**
PLC 100	190.81±10.61**	28.05±2.84**	70.49±5.08**
PLC 400	159.38±9.19**	23.05±3.03**	56.70±4.40**

Values are expressed as mean±SD (n=6). #P<0.05 versus normal control group; **P<0.05 versus diabetic control group. AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; NCG: Normal control group; DCG: Diabetic control group; DLG: Diabetic rats treated with glibenclamide; SD: Standard deviation; PLC 100: Diabetic rats treated with *Lycium chinense* polysaccharide (100 mg/kg); PLC 400: Diabetic rats treated with *Lycium chinense* polysaccharide (400 mg/kg)

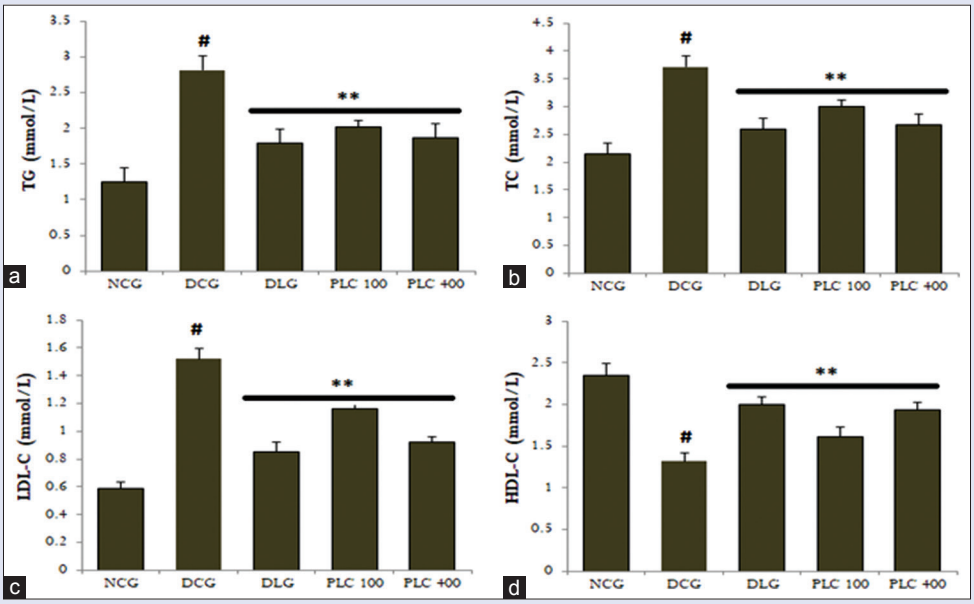

Figure 1: Effect of PLC on serum lipids; (a) TG, (b) TC, (c) LDL-C, and (d) HDL-C in STZ-induced diabetic rats. Values are expressed as mean ± SD (n = 6). #P < 0.05 versus normal control group; **P < 0.05 versus diabetic control group. NCG: Normal control group; DCG: Diabetic control group; DLG: Diabetic rats treated with glibenclamide; PLC 100: Diabetic rats treated with *Lycium chinense* polysaccharide (100 mg/kg); PLC 400: Diabetic rats treated with *Lycium chinense* polysaccharide (400 mg/kg); TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; STZ: Streptozotocin; SD: Standard deviation

DISCUSSION

Bioactive substances from natural origin have been long explored as potential sources of antidiabetic agents. These bioactive natural substances have the ability to function in a multifacet dimension by interacting with various molecular pathways that suppress or attenuate diseases, thus making them prolific alternative to the synthetic drugs, which often act by single mechanism of action and also have undesirable side effects.[23] This study assessed the effects of *L. chinense* polysaccharide extract on blood glucose, lipids, and antioxidant status in STZ-induced diabetic rats. As an alkylating compound, STZ destroys pancreatic β-cells by activating DNA strand breakage as well as instigating the excessive production of ROS, especially superoxide radicals. The resultant toxic effect of STZ leads to hyperglycemia and hypoinsulinemia.[24,25] Hyperglycemia, which is the chief hallmark of diabetes, is mainly responsible for the chronic organ damages experienced by diabetic patients. As such, an effective glycemic control is paramount to mitigate or impede diabetic complications.[26,27] It was observed in this present study that the administration of STZ to the rats significantly increased the blood glucose level and caused a decline in body weight of the rats, which were in consensus with previous reports.[7,28-30] Diabetic rats treated with PLC extract had their blood glucose and declined insulin levels ameliorated. Furthermore, the decline in the body weight of diabetic rats was restored by PLC which indicated improved glycemia, thus suggesting that PLC had excellent antihyperglycemic properties.

One of the key abnormalities experienced in diabetes is dyslipidemia and dyslipoproteinemia, a condition that occurs as a result of impairment in lipid metabolism. Dyslipidemia and dyslipoproteinemia are major risk factors for atherosclerosis and cardiovascular diseases, which are one of the secondary complications of diabetes.[31-33] Hyperglycemic-induced dyslipidemia and dyslipoproteinemia are characterized by elevated levels of TC, TG, and LDL-C and decreased levels of HDL-C. We observed high levels of serum lipids in the untreated STZ-induced diabetic rats in this study, which was similar to results obtained in previous studies.[34-36] However, PLC-treated rats exhibited abated levels of TG, TC, and LDL-C. These results are illustrative of the beneficial actions of PLC as an antihyperlipidemic agent.

Accumulating evidence has continued to implicate ROS and oxidative stress as critical factors in the development and progression of diabetes and its associated complications. The excessive generation of ROS and the incapability of the enzymatic and nonenzymatic antioxidant systems in the cells to scavenge the reactive species generated lead to an imbalance in the oxidant/antioxidant system, resulting in oxidative stress. Persistent hyperglycemia can induce the overproduction of ROS, and STZ-induced diabetes can lead to impairment of the antioxidant defense system through the production of excess intracellular ROS as well as the imposition of oxidative stress.[37,38] Cellular antioxidant enzymes such as GSH-Px, CAT, and SOD primarily act as the foremost defense mechanism against the harmful effect of ROS, thereby affording protection against cellular damages.[7,39,40] On the other hand, lipid peroxidation end product MDA is considered as a suitable index for determining oxidative stress/oxidative damage, as high level of MDA is a reflection of loss or decrease in antioxidant enzymes capacity.[41,42] The results from this study indicated a decrease in the antioxidant enzyme activities (SOD, CAT, and GSH-Px), with a corresponding increase in MDA levels in the kidney and liver tissues of diabetic rats. The data are in agreement with previous report on increased oxidative stress markers in experimental diabetic animals.[8,43] In the diabetic rats that were treated with PLC, stimulation of the antioxidant defense system was notably observed as shown by the increase in the activities of SOD, GSH-Px, and CAT and decrease in the MDA level in the kidney and liver.

Recently, accumulating evidence has indicated the pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 are also critically involved in the onset and progression of diabetes and its complication.[44,45] It is an undeniable fact that oxidative stress and inflammation have been proposed to work synergistically in diabetes. Hyperglycemia-induced oxidative stress can activate a number of stress-induced kinases as well as the formation of advanced glycation end products, which promotes increased expression of pro-inflammatory cytokines. The

Table 3: Effect of PLC on serum creatinine, urea, and blood urea nitrogen in diabetic rats

Groups	Creatinine (mg/L)	Urea (mg/L)	BUN (mg/L)
NCG	0.46±0.03	24.68±0.84	12.65±1.06
DCG	1.81±0.10#	61.03±1.49#	24.96±1.30#
DLG	0.71±0.05**	33.01±0.99**	18.37±0.85**
PLC 100	0.87±0.02**	39.20±0.71**	18.80±0.80**
PLC 400	0.69±0.04**	29.71±0.88**	17.70±1.01**

Values are expressed as mean±SD (n=6). #P<0.05 versus normal control group; **P<0.05 versus diabetic control group. BUN: Blood urea nitrogen; NCG: Normal control group; DCG: Diabetic control group; DLG: Diabetic rats treated with glibenclamide; SD: Standard deviation; PLC 100: Diabetic rats treated with *Lycium chinense* polysaccharide (100 mg/kg); PLC 400: Diabetic rats treated with *Lycium chinense* polysaccharide (400 mg/kg)

Table 4: Effect of PLC on oxidative stress markers in the kidney and liver of diabetic rats

Groups	GSH-Px (U/mg prot)	SOD (U/mg prot)	CAT (U/mg prot)	MDA (nmol/mg prot)
Kidney				
NCG	396.27±12.04	135.70±9.16	34.64±4.08	4.83±0.36
DCG	158.59±12.51#	58.47±11.04#	8.81±3.46#	12.77±0.41#
DLG	281.73±17.13**	83.61±12.20**	15.02±3.07**	8.37±0.24**
PLC 100	270.30±14.08**	90.22±10.07**	17.00±3.50**	8.92±0.17**
PLC 400	315.02±15.00**	117.60±12.88**	22.18±3.90**	6.70±0.20**
Liver				
NCG	582.90±16.81	192.41±8.04	62.18±4.78	5.77±0.51
DCG	304.21±18.51#	67.05±7.39#	20.40±2.50#	17.19±1.04#
DLG	408.73±14.77**	99.10±12.88**	38.01±3.03**	8.92±0.30**
PLC 100	394.05±22.36**	106.63±5.72**	36.91±3.40**	9.04±0.28**
PLC 400	507.78±25.40**	136.87±12.88**	46.09±2.17**	7.03±0.19**

Values are expressed as mean±SD (n=6). #P<0.05 versus normal control group; **P<0.05 versus diabetic control group. GSH-Px: Glutathione Peroxidase; SOD: Superoxide Dismutase; CAT: Catalase; MDA: Malondialdehyde; NCG: Normal control group; DCG: Diabetic control group; DLG: Diabetic rats treated with glibenclamide; SD: Standard deviation; PLC 100: Diabetic rats treated with *Lycium chinense* polysaccharide (100 mg/kg); PLC 400: Diabetic rats treated with *Lycium chinense* polysaccharide (400 mg/kg)

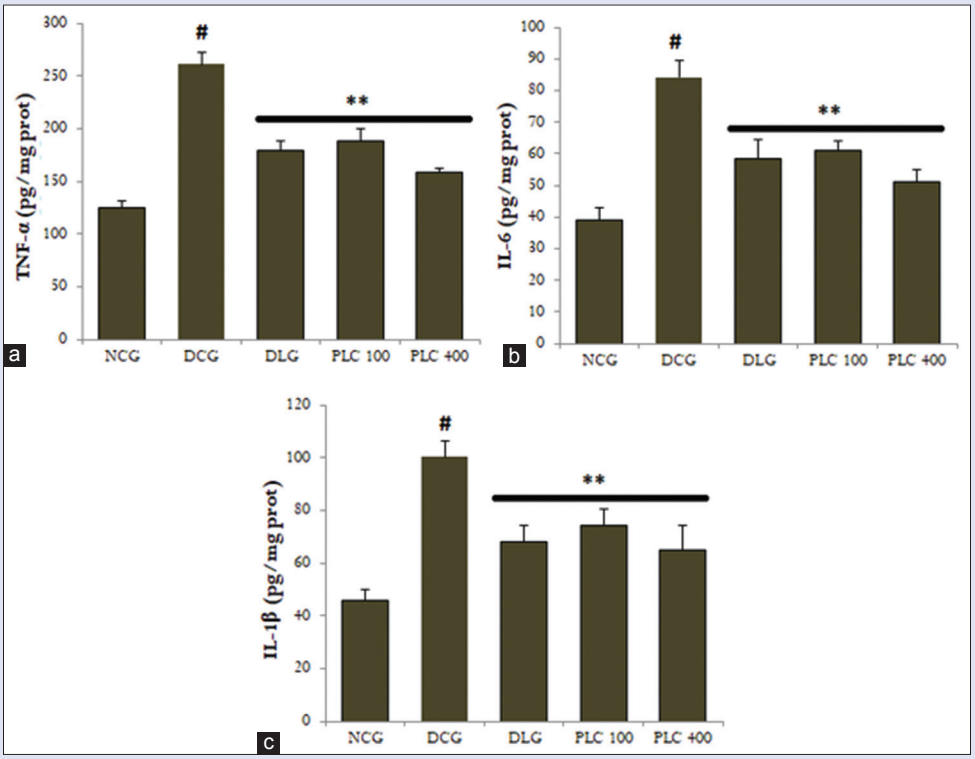

Figure 2: Effect of PLC on proinflammatory cytokines; (a) TNF-α, (b) IL-6, and (c) IL-1 β in the kidney tissues of STZ-induced diabetic rats. Values are expressed as mean ± SD ($n = 6$). #$P < 0.05$ versus normal control group; **$P < 0.05$ versus diabetic control group. NCG: Normal control group; DCG: Diabetic control group; DLG: Diabetic rats treated with glibenclamide; PLC 100: Diabetic rats treated with *Lycium chinense* polysaccharide (100 mg/kg); PLC 400: Diabetic rats treated with *Lycium chinense* polysaccharide (400 mg/kg); TNF-α: Tumor necrosis factor alpha; IL-1β: Interleukin 1 beta; IL-6: Interleukin 6; STZ: Streptozotocin; SD: Standard deviation

pro-inflammatory cytokines produced further instigate the generation of ROS production. In addition, inflammation and oxidative stress play a significant role in the onset and progression of insulin resistance as well as in the macro- and micro-vascular diabetic complications.[46-48] A number of recent studies have reported increased levels and expression of TNF-α, IL-1β, IL-6, and nuclear factor-kappaB in the kidney of diabetic rats.[49-52] In this study, TNF-α, IL-1β, and IL-6 were observed to be increased in the kidney of diabetic rats; interestingly, diabetic rats administered with PLC displayed significantly lowered levels of pro-inflammatory cytokines.

The antidiabetic effect of a number of purified and crude polysaccharide extracts from the genus *Lycium* has been reported, especially from *L. barbarum* and *Lycium ruthenicum*. Luo *et al.* reported the antidiabetic effect of a crude and purified polysaccharide in alloxan-induced diabetic rabbits; the crude polysaccharide extract showed excellent antioxidant, hypoglycemic, and hyperlipidemic effects in the treated animals.[53] Zhou *et al.* also reported that *L. barbarum* polysaccharide (LBP) ameliorated insulin resistance, increased GLUT-4 surface level, as well as improved intracellular insulin signaling in STZ-induced diabetic rats. Furthermore, Al-Fartosy reported that a polysaccharide (LBP3b) obtained from *L. barbarum* significantly reduced serum glucose level, ameliorated decrease in body weight and lipid metabolism, as well as prevented diabetic complications.[54,55] The crude *L. ruthenicum* polysaccharide extract was reported to have hypoglycemic properties in alloxan-induced diabetic mice by significantly reducing blood glucose level and enhancing serum and liver antioxidant enzyme status of diabetic mice.[56] The results obtained in our study is clearly in agreement and correlates well with these previous studies. PLC effectively ameliorated hyperglycemia, hyperlipidemia, oxidative stress, and inflammation in the treated diabetic rats, in addition to improving insulin secretion.

Most of the polysaccharides isolated or characterized from the genus *Lycium* and several other plant species have been shown to comprise majorly of neutral and acidic sugars, such as arabinose, glucose, galactose, mannose, rhamnose, xylose, glucuronic acid, and galacturonic acid.[13,14,56-58] These components play a major role in the bioactivity of these polysaccharides. We envisaged that the antidiabetic properties displayed by PLC may be attributed to some of these constituents, owing to their role as bioactive agents in crude or purified polysaccharides in the previous report. Further studies on the identification and characterization of the substances in the PLC polysaccharide extract are ongoing.

CONCLUSION

The results obtained from this study suggested that *L. chinense* polysaccharide attenuated hyperglycemia-induced oxidative stress, inflammation, and abnormalities in kidney and liver functions indexes in STZ-induced diabetic rats. These findings suggest that *L. chinense* polysaccharide can be useful as a functional food or as a nutraceutical for treating diabetes and diabetic complications.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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