# Natural Diabetes Treatment with Litchi Seeds Extract *In Vivo*

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## Abstract

Background: Diabetes mellitus imposes a substantial health and economic cost on societies. Novel antidiabetic medicines are necessary because the present therapies have impoverished safety and effectiveness. Traditional medicines often make use of medicinal plants, which are considered to be excellent choices. Objective: The aim of the research to investigating the potential anti-diabetic activities of extracts from Litchi chinensis seeds (LCS). Methods: The extract was prepared using an aqueous solvent and 80% ethanol. It was subsequently used in laboratory settings to investigate primary alpha amylase inhibition, with acarbose serving as the reference standard. The extract was then administered in vivo to observe the effects on STZ-mediated diabetes rats. The induction of diabetes in Long-Evans rats was achieved by administering a solitary intraperitoneal injection of streptozotocin at a dosage of 80 mg/kg. the hydroethanolic extract of litchi seed were used at different concentrations (100 and 200 mg/kg BW) to treat rats with diabetes. The finding analyzed various biochemical and histological parameters in diabetic rats over a period of 28 day, using established protocols. Results: The results showed significant improvements in plasma glucose ($p < 0.001$) and considerable increased in body weight ($p < 0.0001$). The LCS extract (200 mg/kg BW) showed significant ameliorative effects on glycemic markers, lipid profile, and renal functioning. Additionally, histopathological studies reveals that LCS can potentially reduce renal inflammation as well as hepatic tissue damage. Conclusions: The findings indicate that hydroethanolic litchi seed extracts may have potential therapeutic benefits in managing diabetes and reducing lipid levels.

**Keywords:** Litchi chinensis, Anti-hyperglycaemic activity, Glibenclamide, Streptozotocin, Hyperlipidemia, Diabetes mellitus.

***Significance*** | This study demonstrated the therapeutic potential of litchi seeds for diabetes as safer, effective alternatives to synthetic drugs.

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## 1. Introduction

In diabetes mellitus (DM), the body's ability to manage blood sugar is impaired. This results in significant complications in nearly all of the body's systems, which depend upon the appropriate breakdown and utilization of carbs, proteins, and lipids. Diabetes mellitus, a medical condition, arises from the meager formulation of insulin by the pancreas. As a result, the insufficient functioning of insulin hinders the usual control mechanisms that keep blood glucose levels stable, resulting in various metabolic irregularities and problems (Association, 2014), (Li et al., 2011). DM is associated with a higher probability of developing many complications, such as cardiovascular illnesses, nephropathy, neuropathy, eyesight

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impairments, weight gain, some types of cancer, and finally, a greater chance of death (Suckling & Gallagher, 2012), (Habib & Rojna, 2013), (Association, 2015). Although many synthetic oral anti-diabetic medications are effective in controlling blood glucose levels, their continued use is linked to a greater probability of cardiovascular diseases (Rados et al., 2016), renal impairments (Hung et al., 2012) and several types of cancers as well. This raises significant concerns about their long-term safety for patients (Thakkar et al., 2013). It appears that discussing the importance of exploring and utilizing various sources of diabetes medicine, which could potentially improve health outcomes for individuals with the condition. Discussing the need to look specifically at the kinds of medicine that come from the natural world, not just the traditional herbs we associate with "alternative medicine," but fruits and vegetables. Recently, litchi seeds have garnered significant attention from medical and biological researchers. Potential treatments for diabetes are under investigation, and scientists are focusing on organic substances. They might offer therapeutic benefits with few negative side effects (Ren et al., 2011). Investigating the litchi seed's potential medicinal properties underscores the current shift toward botanical substitutes for conventional diabetes drugs. It also expresses the work's hope for a truly human-centered, dialed-down medicine.

Litchi fruits are frequently grown in Southeast Asia, with concentrated cultivation in Bangladesh. The litchi fruit has a scientific name, Litchi chinensis Sonnerat. It belongs to the Sapindaceae family, which also holds the litchi and soapberry. A recent study has shown that litchi seeds have very high antioxidant properties due to being rich in polyphenols, while the fruit's flesh possesses a number of natural compounds such as flavonoids, sterols, and saponins—meaning that this fruit has great potential in modern medicine that's still untapped (Wang et al., 2011). Additionally, the seeds of the LC have elements that act against bacteria. These antibacterial elements stop the bad bacteria from growing (Bhat & Al-daihan, 2014). Additionally, they exhibit alpha-amylase potential (Lin et al., 2013) and showed both anti-platelet and alpha-amylase inhibitory properties (Xu et al., 2010), (de Rezende Queiroz et al., 2015). Moreover, several studies have found a correlation between litchi seeds and better non-alcoholic fatty liver performance. What's more, litchi seeds can help to regulate blood glucose levels. Taken together, such studies underscore the diverse and potentially significant health benefits of litchi seeds (Choi et al., 2017). The unusual characteristics of these compounds emphasize their potential as a natural way to treat diabetes and the complications that go along with it.

One category of these medicines includes alpha-amylase inhibitors, which act by competing with a particular enzyme that breaks carbs down into simple sugars. In the alpha-amylase inhibitor mechanism, carbs pass through the small intestine without converting into blood sugar. Thus, the alpha-amylase inhibitors help reduce sudden and sharp blood sugar spikes in the after-meal postprandial range. And this leads us naturally to look at litchi fruit, which, for our kind of medicine, is blessedly free of negative side effects—unlike many convenient lab medications (Gupta et al., 2014). Acarbose and voglibose, which are alpha-glucosidase inhibitors, are commonly used in clinical practice along with dietary modifications or other anti-hypoglycemic drugs to regulate plasma sugar concentrations. These medications inhibit certain enzymes called alpha-glucosidases in the intestines. When the activity of these enzymes is suppressed, the process of converting certain carbs into glucose is decelerated. Reduced rate of carbohydrate conversion into glucose leads to a delayed increase in blood sugar levels following a meal. By employing this method, individuals are provided with an additional chance to effectively tackle the disease in a thorough manner, particularly if they require, like many individuals with diabetes, to integrate dietary modifications and heightened physical activity with other forms of treatment (Van de Laar et al., 2005). These drugs primarily target the colon, leading to side effects such as bloating and diarrhea. Consequently, any factor that hinders the functioning of PTP1B might significantly decrease body fat, enhance the energy equilibrium in our nonfat cells, and elicit a more favorable reaction from our livers in the presence of insulin (Klaman et al., 2000).

Administering streptozotocin (STZ) through fast injection is a well-established method to consistently induce diabetes in animal trials. This disrupts the body's inherent equilibrium of insulin synthesis. This disparity reaches its peak in a reduced production of regular insulin and obstructs the effective utilization of glucose by the human body. Consequently, the blood becomes excessively saturated with sugar, leading to a condition called hyperglycemia. Because of its reproducibility and effectiveness in mimicking diabetic conditions in animal models, STZ remains a commonly used tool in experimental diabetes research (Al-Attar & Zari, 2007), (Shirali et al., 2013).

The study examined the ability of litchi seed hydroethanolic extracts to inhibit alpha-amylase, a key enzyme involved in diabetes, based on the applications of this fruit seeds. Alpha-amylase has a crucial function in controlling the breakdown of starch and lowering blood glucose levels, hence impacting insulin regulation. Specifically, our focus extends to the pancreas, liver and kidney organs intricately involved in metabolic regulation and often profoundly affected by diabetes and litchi seeds extract how improve it willingly. In examine the histopathological organs (pancreas, liver, kidney) and compare to the control group with experimental groups, litchi seeds have the potential to be a cost-effective and effective option for creating pharmaceutical or nutraceutical products.

## 2. Materials and methods

### *2.1. Study Area*

The Department of Applied Nutrition and Food Technology (ANFT) at Islamic University in Bangladesh conducted the investigation and analyzed the samples. The National Medical College in Dhaka, Bangladesh meticulously performed histological examinations of the selected organs, ensuring a comprehensive and precise evaluation of the experimental outcomes.

### *2.2. Chemicals and reagents*

Streptozotocin (STZ) (Sigma Aldrich, Kuri & Company (Pvt.) Limited.), ethanol from Sigma-Aldrich GmbH (Sternheim, Germany); alpha amylase (fungal diastase) from Research-Lab (Mumbai, India), 3,5-Dinitrosalicylic acid 97% from Loba Chemie Pvt. Ltd (Mumbai, India), acarbose from Sisco Research Lab (India), alanine transaminase (ALT), aspartate transaminase (AST), serum creatinine, cholesterol (TC), high-density lipoprotein (HDL), total triglyceride (TG), low-density lipoprotein (LDL), kits were brought from Human GmbH (Germany). All the chemicals, solvents, and reagents used during this present experiment were of analytical grade.

### *2.3. Collecting plant components and preparation of extract*

The litchi (Bombai) seed acquisition and extraction process involved meticulous steps to ensure the quality and potency of the final extract. We sourced fresh fruits from the Ishwardi market in the Pabna area of Bangladesh and carefully dried their seeds at 40°C in an oven before finely powdering them. This powder, weighing 1000 g, underwent three cycles of maceration both with distilled water and 80% hydroethanolic solvent over 24 hours each, yielding a crude distilled water and ethanolic extract. After filtered by using filter paper (What man No 1) the filtrates to remove impurities, it was freeze-dried after being concentrated employing a rotavap (Stuart-RE300) set at 40°C, resulting in 102g of sticky, dark brown or almost black extract. This extract was kept at 28°C for further laboratory investigations, providing a valuable resource for future research into its potential therapeutic applications.

### *2.4. α-amylase inhibition assay*

Acarbose and LCS extract stock solutions were formulated in water and 80% ethanol respectively. The activity of α-amylase was inhibited using (DNSA-3,5-dinitrosalicylic acid) in accordance with previous procedures (KWON et al., 2008). A final concentration (0.5 to 5.0 mg/mL) was achieved by combining 100 µl of Acarbose or LCS extract (concentrated at 2 to 20 mg/mL) with α-amylase (100 µl of 1 U/mL) and sodium phosphate buffer (200 µl of 20 mM, pH 6.9). Starch (200 µl of 1% w/v), which was dissolved in 0.02 M $Na_2HPO_4/NaH_2PO_4$ (pH 6.9), was added to the samples after they had been incubated beforehand for 10 minutes at 25 °C. A 10-minute incubation period at 25 °C was given to the reaction mixtures. After adding 1 ml of DNSA, the reactions were halted by subjecting the mixture to incubation in a scalding water bath for a duration of 5 minutes. After allowing the reaction mixtures to reach ambient temperature and being diluted in a 1:5 ratio with water, the absorbance was quantified at 540 nm via a spectrophotometer manufactured by Hitachi, Japan. The calculation for the % of inhibition of the α-amylase activity was

$$\% \text{ inhibition } = 100 \times \frac{\mathbf{Ac-ALCS}}{\mathbf{Ac}}$$

Where, $\mathbf{A_c}$ is the absorbance of control (without LCS extract) at 540 nm and

$\mathbf{A_{LCS}}$ is the absorbance of the LCS extract at 540 nm.

### *2.5. Development of rat models for type II diabetes*

The present study utilized adult Long-Evans rats that were in good health and weighed between 150 and 210 grams. These rats were grown at the animal house of the Islamic University, Kushtia. A Type 2 diabetic model was created in 16 rats by administering streptozotocin (STZ) intravenously, STZ-a substance that is toxic to β-cells, dissolved in citrate buffer (pH 4.5) at a concentration of 80 mg/kg of BW (Furman, 2015). To ensure that the rats' blood sugar levels were consistent, we had them fast overnight before beginning the study. Then we gave them a single IV injection of STZ and waited for their blood sugars to stabilize before starting the experiments. We used a glucometer to monitor their blood sugars pretty regularly about every three days. And when we saw that their blood sugars were consistently high typically above 8 mmol/L we could confirm that they had developed diabetes. We used this method to study diabetes day in and day out in the lab.

### *2.6. Experimental design*

Throughout our 28-day study, we worked with a total of 20 rats. The group included 4 healthy male Long-Evans rats and 16 rats with Type 2 diabetes, each group have 4 rats. The healthy rats formed the control group (Con). Meanwhile, we separated the diabetic rats into four groups: one with STZ-induced diabetes (STZ), one taking standard diabetes medicine glibenclamide 6mg/kg body weight (GLI), and two groups taking litchi seed extract in either a 100mg/kg dose (STZ+LCSEt1) and a 200mg/kg dose (STZ+LCSEt2). We kept a close eye on each group's blood glucose levels and overall health. And we measured and recorded our group's mean daily body weight, mean daily food consumption, and mean pre-prandial plasma sugar concentration in order to have a full set of data for analysis.

### *2.7. Blood sampling*

After the 28-day study ended, a direct cardiac puncture was conducted on each rat to get its blood samples. Prior to performing a range of biochemical assays, we permitted the blood sample to coagulate spontaneously at ambient temperature. Subsequently, we subjected it to centrifugation at a speed of 3000 RPM/10 min. This facilitated the effortless segregation of the plasma, which was subsequently utilized in conducting various biochemical analyses (Eraslan et al., 2007).

### *2.8. Histopathological examinations*

In a solution containing 10% neutral buffered formalin preservative, kidney, liver, and the pancreas, tissues were minced and inserted. Subsequently, the samples were subjected to a desiccation process to remove any residual moisture. After being dried, they were rendered transparent internally by immersing them in xylene. Subsequently, paraffin wax was poured into them to create compact blocks. We sliced the solid paraffin blocks into extremely thin parts. The thickness of each slice was approximately 5 µm. Later on, we attached these slices to microscope slides composed of glass. Afterwards, applied hematoxylin and eosin, a dye that selectively adheres to the cell nuclei, to the frozen sections. This results in a bluish appearance of the entire tissue (M. S. Ahmed et al., 2020). Analysis on a confocal microscope (Model: Ti2 Nikon )

### *2.9. Statistical analysis*

The trials were conducted in triplicate, both in vitro and in vivo. The results were reported as mean with standard error mean (S.E.M). For statistical analysis, the data were run using GraphPad Prism (version 10) with one-way ANOVA, Student's t-test, as well as Dunnett's post hoc multiple comparison test. Statistical significance was assigned to values less than or equal to 0.05, with $p < 0.0001$ being the most significant.

## 3. Results:

### *3.1. In Vitro Antidiabetic Potential of LCS*

The current experiment's findings revealed a correlation between the dosage and the percentage of the α-amylase inhibition. The aqueous extract and the 80% hydroethanolic extract (2.5-100 µg/mL) of L.chinensis seeds both showed strong α-amylase inhibitory action, which increased with the dose. The aqueous extract exhibited inhibitory efficacy ranging from 0.28 ± 0.04 to 29.42 ± 0.56 %, while the 80% hydroethanolic extract showed activity from 0.54 ± 0.04 to 44.33 ± 1.11 %, with $IC_{50}$ values of 155.04 ± 3.32 µg/mL and 112.8 ± 2.48 µg/mL, respectively. Acarbose, a standard drug for α-amylase inhibition, demonstrated inhibitory activity ranging from 5.4 ± 0.32 to 56.14±1.41 % at concentrations of 2.5-100 µg/mL, with an $IC_{50}$ value of 87.73 ± 1.2 µg/mL. A comparison of the conventional medicines and seed extracts' α-amylase inhibitory action is given in Table 1. The 80% aqueous ethanol extract of LCS showed a higher level of alpha-amylase inhibition compared to the aqueous extract. This validates the selection to go with the ethanol extract for in vivo treatment.

### *3.2. In Vivo Antidiabetic Activity of L.chinensis seed*

#### *3.2.1. Impact of Different Treatments on Plasma Glucose Level*

Table 2, illustrates the impact of LCS in different treatment groups and the diabetic group on the pre-prandial plasma sugar concentrations in rats. Administration of Streptozotocin made a significant rise in pre-prandial plasma sugar concentrations in rats assigned to group STZ on the first day, when comparing the control group (Con) and the groups administered with LCS (groups STZ+LCSEt1 & STZ+LCSEt2). The plasma sugar concentrations of diabetic rats substantially increased ($p < 0.001$) on days 7, 14, 21, and 28 compared to the control rats (group Con). Compared to diabetic control rats, diabetic rats treated with standard glibenclamide (Group STZ+GLI) had significantly lower pre-prandial plasma glucose levels on days 7, 14, 21, and 28 ($p < 0.01$, $p < 0.001$). Although the lowest dosage of 100 mg/kg body weight of LCS had an apparent impact on plasma glucose levels in diabetic rats compared to control rats, the effect was more prominent when the bioactive component was given at a higher dosage of 200 mg/kg body weight. In this case, the pre-prandial plasma glucose levels of the diabetic rats were dramatically decreased ($p < 0.01$, $p < 0.001$). The decline in plasma glucose levels was observed beginning on the $7^{th}$ day and continuing all the way through the $28^{th}$ day, with the patterns being significantly apparent on days 14, 21, and 28 ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively).

#### *3.2.2. Impact of Different Treatments on Body weight in Diabetic Rats*

The investigations involved measuring body weight, and it was shown that the weight of the STZ-mediated diabetic rats was much lower than that of the rats in the control group. ($p < 0.0001$) (Table 3). Conversely, diabetic rats that were administered with two different concentrations of LCS extract (100 and 200 mg/kg BW) exhibited a substantial spike in their body mass ($p<0.0001$) compared to the diabetic control rats in a dose-dependent pattern.

#### *3.2.3. Impact of Different Treatments of LCS on Modifications to the Plasma Lipid Profile in Diabetes Rats.*

Diabetes is linked to lipid abnormalities. Consequently, in order to ascertain whether LCS could rectify the lipid profiles, the blood lipid levels of diabetic rats were examined. The diabetic rats exhibited a substantial increase ($p < 0.0001$) in serum triglycerides (TG), total cholesterol (TC), and LDL cholesterol compared to the control rats, as shown in Table 4, Figures 1(a), 1(b), and 1(c) respectively. In contrast, plasma HDL levels diminished significantly ($p < 0.001$) compared to the control rats (group Con). The plasma levels of TC, TG, and LDL were substantially reduced ($p < 0.001$) in diabetic rats treated with standard glibenclamide compared to the diabetic control group (group STZ). Additionally, administering 100 mg/kg LCS to the diabetic rats resulted in a significant reduction ($p < 0.001$) in serum TG, TC, and LDL cholesterol, along with a significant increase ($p < 0.05$) in HDL cholesterol levels. Furthermore, administering a dose of 200 mg/kg of LCS resulted in an apparent decline in serum TG ($p < 0.0001$), TC ($p < 0.0001$), and LDL cholesterol ($p < 0.0001$), while increasing serum HDL cholesterol levels ($p < 0.001$).

#### *3.2.4. Impact of Different Treatments on Hepatic System Functions in streptozotocin-Induced Diabetes Rats*

Figure 2, illustrates that the diabetic control group had higher levels of hepatic enzyme / hepato enzyme which included ALT and AST, the intervention group, and the control group. Administration of streptozotocin resulted in elevated levels of liver-associated biological indicators, including ALT and AST in comparison to the diabetic control rats ($P<0.001$, $P<0.0001$). However, the administration of standard glibenclamide and LCS at doses of 100 and 200 mg/kg body weight to diabetic rats led to a substantial reduction ($p < 0.001$, $p < 0.0001$) in ALT and AST, as shown in table 4.

***3.2.5. Impact of L.chinensis seed Extract on the Kidney Profile.***

A peripheral blood creatinine examination was conducted to determine the efficacy of the plant extract in reducing or normalizing kidney indicators. Figure 3 demonstrates a substantial and statistically significant elevation ($p<0.0001$) in plasma creatinine levels in the renal systen of animals with diabetes in comparison to those without the condition. The renal system of the animals with diabetes exhibited considerable improvements ($p < 0.0001$) while receiving a dosage of 200 mg/kg of LCS.

**4. Comparative Analysis of Histopathology**

***4.1. Section of Pancreas***

The histopathological analysis of the pancreatic tissues from different treatment groups reveals a clear dose-dependent protective effect of litchi seed hydroethanolic extract in diabetic rats. In the normoglycemic control group (Figer 4A) the pancreatic tissue exhibits normal architecture with well-defined Islets of Langerhans, intact acini, capillaries, and blood vessels. In contrast, the diabetic control group (Figer 4B) shows severe degenerative changes, disorganized islet cells, and dilated interlobular ducts, indicating significant pancreatic damage. Treatment with the standard drug (Figer 4C) results in moderate improvements, with less severe degenerative changes and reduced hemorrhage. The group treated with 100 mg/kg body weight (Figer 4D) of litchi seed extract demonstrates notable improvements, including reduced degenerative changes and better organization of acini. The most significant restoration is observed in the group treated with 200 mg/kg body weight (Figer 4E) of the extract, which shows near-normal pancreatic architecture, minimal degenerative changes, and well-preserved blood vessels. These findings indicate that litchi seed hydroethanolic extract offers significant protective and restorative effects on pancreatic tissue in a dose-responsive pattern, with the higher dose providing the most substantial benefits, suggesting its potential as a complementary therapy for diabetes management.

***4.2 Section of Liver***

The diabetic control group (Fig. 5B) exhibited severe histopathological alterations. There was pronounced centrilobular necrosis and extensive hepatic steatosis, with ballooning of hepatocytes and congested sinusoidal spaces. This disrupted architecture highlights the significant hepatotoxic effects of chronic hyperglycemia, characterized by substantial inflammation and fibrosis. Treatment with the standard antidiabetic drug (Fig. 5C) resulted in moderate improvement. Although there was a noticeable reduction in hepatic steatosis and inflammation, some degree of centrilobular necrosis and sinusoidal congestion persisted. These findings suggest that while the standard drug provides partial protection against diabetic liver damage, it does not completely restore normal liver histology. Notably, liver sections from diabetic rats treated with litchi seed extract at 100 mg/kg body weight and 200 mg/kg body weight (Fig. 5D and 5E) showed remarkable histopathological recovery. The architecture of the liver resembled that of the normal control, with restored central veins and sinusoidal spaces. Hepatocytes appeared normal, and inflammation was significantly reduced. Kupffer cells were active but not excessively proliferated, suggesting an effective immune response with reduced oxidative stress.

***4.3 Section of Kidney***

In the control group (Fig. 6A), the renal tissue maintains normal architecture with intact glomeruli, glomerulus capsule, and well-defined proximal and distal convoluted tubules. Diabetic control rats (Fig. 6B) exhibit significant renal damage, including shrunken glomeruli (G#), interstitial inflammation (I#), and arteriolar hyalinosis (A#), indicative of diabetic nephropathy. The diabetic rats treated with a standard drug (Fig. 6C) show some improvement but still present segmented glomeruli (G*) and interstitial hemorrhage (H#). Remarkably, diabetic rats treated with litchi seed extract at 100 mg/kg (Fig. 6D) and 200 mg/kg (Fig. 6E) demonstrate considerable restoration of renal structures, with reduced glomerular and tubular damage, suggesting a dose-responsive nephroprotective impact of the extracts.

**5. Discussion**

Diabetes is a chronic metabolic disorder with broad spectrum of short-term and long-term consequences, including stroke, heart attack, retinopathy, neuropathy, nephropathy, skin infection, amputations, sexual dysfunction, dental problems, etc. The prevalence of this disease is increasing steadily, surpassing expectations with each passing day. Therefore, it is very crucial period to find out alternatives medicine along with diabetes drugs. Numerous studies have been conducted to see the therapeutic potential of L. chinesis to control diabetes. Hence, our study aims to investigate the therapeutic potential of hydroethanolic extract of LCS seed to control diabetes and its consequences. Streptozotocin (STZ) is a powerful alkylating drug that specifically targets and destroys pancreatic β cells by disrupting glucose transport and glucokinase activity, and by causing DNA strand breaks, ultimately leading to the development of diabetes (Graham et al., 2011; Khandelwal & Khanna, 2020). Furthermore, in order to delay the

**Table .** Invitro alpha amylase inhibition of LCS extracts against reference drug (Acarbose)

| Concentration (µg/mL) | Percent (%) alpha amylase inhibition | | |
|---|---|---|---|
| | Acarbose | LCSAqE | LCSEAqE |
| 0 | 0 | 0 | 0 |
| 2.5 | 5.41±0.32 | 0.28±0.04 | 0.54±0.04 |
| 5 | 12.16±0.11 | 3.30±0.43 | 4.50±0.61 |
| 10 | 18.06±0.32 | 6.43±1.31 | 8.43±0.45 |
| 20 | 21.85±0.25 | 12.37±2.07 | 16.32±1.15 |
| 40 | 29.19±0.2 | 18.01±0.89 | 21.68±1.16 |
| 60 | 36.53±1.17 | 23.79±1.44 | 25.32±0.52 |
| 80 | 43.19±0.60 | 27.34±0.58 | 36.09±0.77 |
| 100 | 56.14±1.41 | 29.42±0.56 | 44.33±1.11 |
| $IC_{50}$ | 87.73±1.2 | 155.04±3.32 | 112.80±2.48 |

The results are reported as mean±SEM, n=3; Where in LCSAqE = Litchi chinesis Seeds Aqueous extract and LCSHAqEE= Litchi chinesis Seeds Hydroethanolic (80% ethanol) extract

**Table 2.** Impacts of LCS extracts on plasma sugar concentrations of Streptozotocin- mediated diabetic rats.

| Group (n=4) | Fasting plasma sugar concentration (mmol) | | | | |
|---|---|---|---|---|---|
| | Day 0 | Day 7 | Day 14 | Day 21 | Day 28 |
| Con | 5.48±0.24 | 5.58±0.27 | 5.45±0.16 | 5.55±0.18 | 5.13±0.21 |
| STZ | 7.63±0.43 | $13±0.75^{a*}$ | $12.38±0.86^{a*}$ | $12.7±0.47^{a*}$ | $12.15±0.7^{a*}$ |
| STZ + GLI | 8.93±0.17 | $9.68±0.7^{ab}$ | $5.1±0.19^{b}$ | $4.7±0.14^{b*}$ | $4.7±0.04^{b*}$ |
| STZ + LCSEt1 | 7.73±0.27 | $12.3±0.29^{a}$ | $10.33±0.21^{ab}$ | $9.45±0.09^{a*b*}$ | $9.13±0.11^{a*b*}$ |
| STZ + LCSEt2 | 7.33±0.13 | $11.85±0.24^{a}$ | $10.13±0.17^{ab}$ | $8.7±0.14^{a*b*}$ | $8.18±0.19^{a*b*}$ |

*The values are represented as mean ± SEM, where, n=4.*

*Diabetic control rats were compared with control rats: a*P < 0.001, a P < 0.01.*

*Drug-treated diabetic rats were compared with diabetic control rats: b* P <0.001, b P < 0.01.*

**Table 3.** Impact of LCS seed extracts on body weight in Streptozotocin- mediated diabetic rats.

| **Group (n=4)** | **Body Weight (g)** | | | | |
|---|---|---|---|---|---|
| | **Day 0** | **Day 7** | **Day 14** | **Day 21** | **Day 28** |
| Con | 170.99±9.25 | 193.55±9.49 | 214.76±8.82 | 231.77±7.6 | 249.19±8.56 |
| STZ | 175.27±6.14 | 168.8±6.04 | 164.31±5.03 | 161.9±9.16 | 156.86±9.31 |
| STZ + GLI | 169.75±9.81 | 165.14±10.27 | 172.37±10.63* | 181.32±10.32* | 191.88±10.75* |
| STZ + LCSEt1 | 205.72±4.69 | 198.44±5.72* | 201.04±8.13** | 214.14±13.41** | 223.3±15.32** |
| STZ + LCSEt2 | 195.49±6.97 | 189.4±5.79* | 193.46±6.03* | 197.5±6.21* | 203.84±8.81** |

*Outcomes are reported as mean±SD, n=4, * p<0.05, **p<0.01, when compared with Diabetic control by using one way ANOVA followed by Dunnette's multiple comparison test.*

**Table 4.** Impact of LCS seed extracts and glibenclamide on various biochemical parameters in Streptozotocin- mediated diabetic rats.

| Groups n=4 | Cholesterol (mg/dl) | HDL (mg/dl) | LDL (mg/dl) | Triglyceride (mg/dl) | Creatinine (mg/dl) | AST (U/L) | ALT (U/L) |
|---|---|---|---|---|---|---|---|
| Control | 95.62±3.39 | 46.11±3.93 | 70.59±5.98 | 61.7±4.06 | 0.68±0.01 | 53.72±2.54 | 43.12±5.88 |
| STZ | 150.75±5.99$^{a*}$ | 18.28±0.62$^{a}$ | 137.39±4.72$^{a}$ | 151.81±7.69$^{a}$ | 0.86±0.01$^{a*}$ | 94.24±1.77$^{a*}$ | 80.53±1.01$^{a*}$ |
| STZ + GLI | 110.3±6.85$^{b*}$ | 27.22±0.55$^{a*b}$ | 80.61±2.73$^{b*}$ | 88.02±4.75$^{b*}$ | 0.71±0.01$^{b*}$ | 58.15±0.97$^{b*}$ | 39.26±0.99$^{b*}$ |
| STZ + LCSEt1 | 109.77±5.07$^{b*}$ | 20.8±0.55$^{a*}$ | 108.25±5$^{abc}$ | 119.81±6.38$^{abc}$ | 0.73±0.01$^{ab*}$ | 66.13±1.21$^{ab*c}$ | 52.42±0.78$^{b*c}$ |
| STZ + LCSEt2 | 112.77±3.84$^{b*}$ | 24.26±1.02$^{a*}$ | 107.49±4.92$^{abc}$ | 101.24±7.24$^{ab}$ | 0.72±0.01$^{b*}$ | 62.11±1.84$^{ab*}$ | 48.17±0.98$^{b*}$ |

*The results are reported as mean ± S.E.M; n=4 in each group. $^{a*}p \leq 0.0001$ vs. control, $^{a}p \leq 0.001$ vs. control, $^{b*}p \leq 0.001$ vs. STZ, $^{b}p \leq 0.01$ vs. STZ and $^{c}p \leq 0.01$ vs STZ + Gli. diabetic rats at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

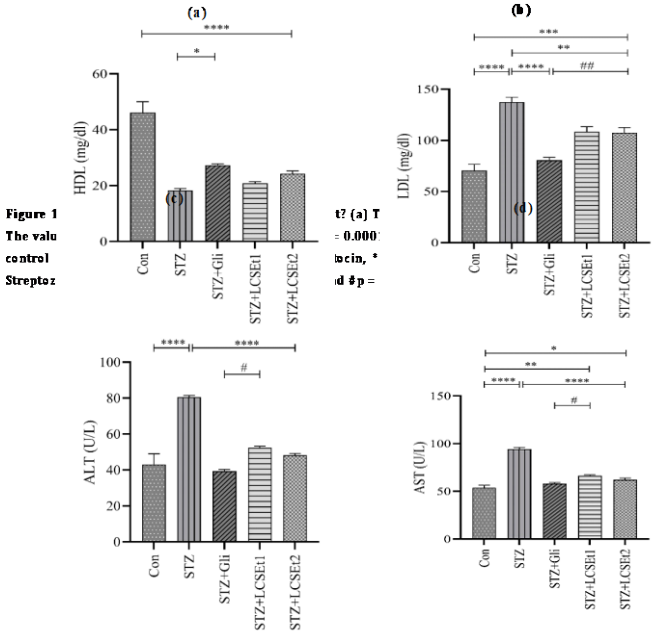


**Figure 1.** The lipid profile and LCS: how did it affect it? (a) TC (b) TG, (c) HDL, and (d) LDL in diabetic rats. The values are shown as mean ± S.E.M. (n =4); ****p ≤ 0.0001 vs. control or Streptozotocin; ***p ≤ 0.001 vs. control or Streptozotocin; **p ≤ 0.01 vs. Streptozotocin, *p ≤ 0.05 vs. Streptozotocin, ##p ≤ 0.001 vs. Streptozotocin + LCSEt1 or Streptozotocin + LCSEt2; and #p ≤ 0.01 vs Streptozotocin + LCSEt1 diabetic rats.

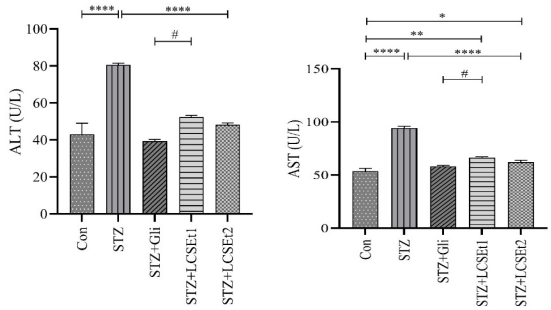


**Figure 2**: The impact of LCS on hepatic functioning. (a) ALT and (b) AST in the Streptozotocin-mediated diabetic rats. The values are presented as means ± S.E.M. (n = 4); ****p ≤ 0.0001 vs. control or streptozotocin; **p ≤ 0.001 vs. control or streptozotocin, *p ≤ 0.01 vs. control or streptozotocin, and #p ≤ 0.01 vs streptozotocin + LCSEt1 diabetic rats

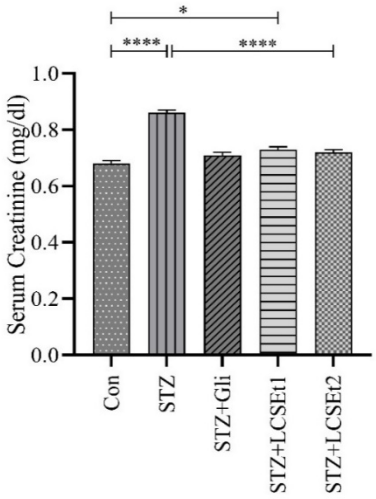


**Figure 3:** The impact of LCS on renal function efficiency. Blood creatinine in streptozotocin-mediated diabetic rats. The outcomes are shown as the means ± S.E.M. (n =4); ****p ≤ 0.0001 vs. control or streptozotocin; and *p ≤ 0.01 vs. control or streptozotocin diabetic rats

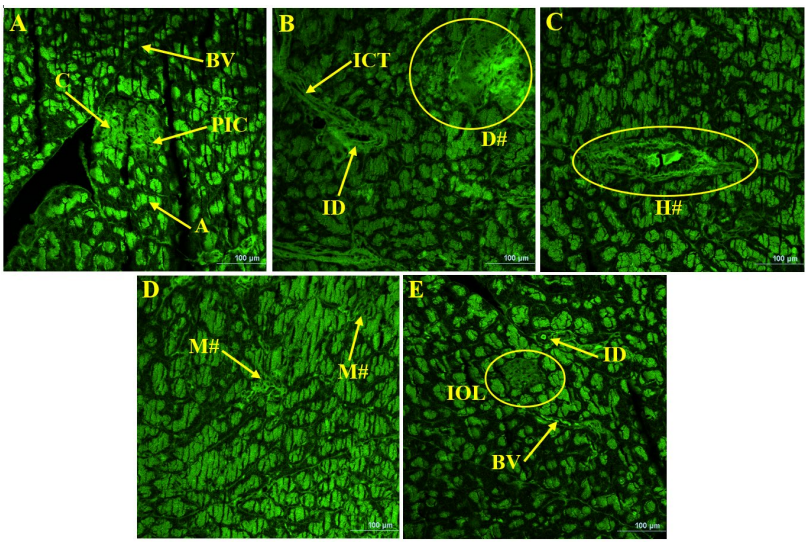


**Figure 4:** Effects of litchi seeds ethanolic extracts on Pancreas Histopathological changes. Photomicrograph by Confocal Microscope object x40 and 100μm scalebar (Mod: Ti2-E Nikon) a section of Pancreas of (A) Control rat (B) Diabetic control rat (C) Diabetic Drug 6mg/kg body weight (D) Diabetic +LCS Extract 100 mg/kg body weight (E) Diabetic +LCS Extract 200 mg/kg body weight. A(Acini), C(Capillaries), D#(Severe Degenerative Changes in Islet of Langerhans), H#(Hemorrhage), ID(Interlobular Duct), IOL(Islet of Langerhans), M#( Immunostaining for insulin reveals fewer β-cells), PIC(Pancreatic Islet Cell).

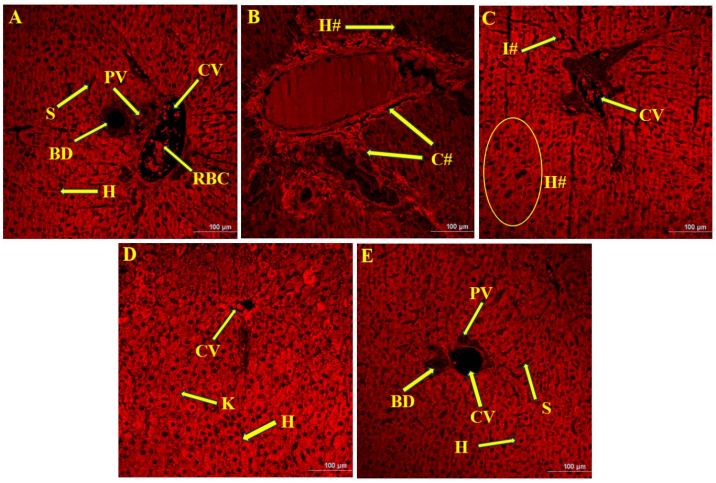


**Figure 5:** Effects of litchi seeds ethanolic extracts on Liver Histopathological changes. Photomicrograph by Confocal Microscope object x40 and 100µm scalebar (Mod: Ti2-E Nikon) a section of the liver of (A) Control rat (B) Diabetic control rat (C) Diabetic Drug 6mg/kg body weight (D) Diabetic +LCS Extract 100 mg/kg body weight (E) Diabetic +LCS Extract 200 mg/kg body weight. BD (Bile Duct), CV (Central Vain), CN (Centrilobular Necrosis), H (Hepatosite), HS (Hepatic Steatosis), In (Inflammation), K (Kuffer Cell), PV (Portal Vain), S (Sinusoid).

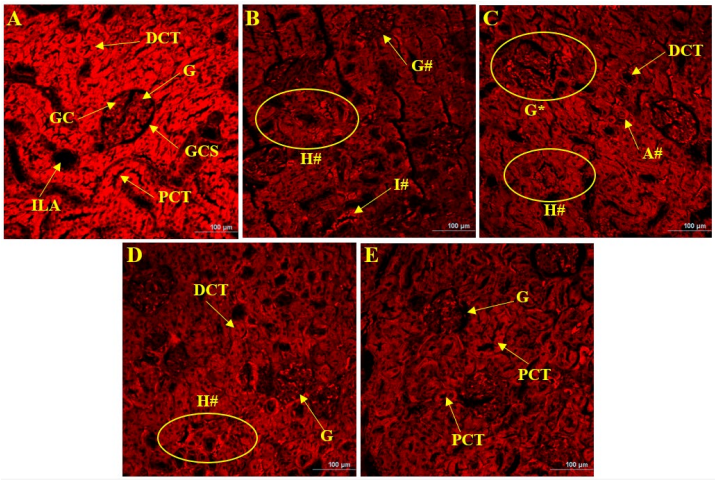


**Figure 6:** Effects of litchi seeds ethanolic extracts on Kidney Histopathological changes. Photomicrograph by Confocal Microscope object x40 and 100µm scalebar (Mod: Ti2-E Nikon) a section of the Kidney of (A) Control rat, (B) Diabetic control rat, (C) Diabetic Drug 6mg/kg body weight, (D) Diabetic +LCS Extract 100 mg/kg body weight, (E) Diabetic +LCS Extract 200 mg/kg body weight. A#(Arteriolar Hyalinosis), DCT(Distal Convoluted Tubule), G(Glomerulus), GC(Glomerulus Capsule), GCS(Glomerulus Capsular Space), (G*)Segmented Glomerulus, (G#)Shrunken glomerulus, (H#)Interstitial Hemorrhage, ILA(Interlobar Arteries), I#(Interstitial Inflammation), PCT(Proximal Convoluted Tubule).

onset of diabetes, it is essential to uphold adequate control over plasma glucose levels. In our investigation, the administration of injections of STZ induced changes in both the regulation of plasma sugar concentrations and the BW of the rats involved in the trial. The plasma sugar concentrations of the STZ-treated rats were higher as opposed to those of the control rats. The hydroethanolic extracts of LCS showed significant antihyperglycemic and antihyperlipidemic effects in streptozotocin-induced diabetes rats. Glycemic markers are reduced significantly in dose dependent manner when administered two LCS doses in different concentration (100 mg/kg body weight and 200 mg/kg body weight). Surprisingly, the body weights of diabetes rats were significantly increased. Additionally, this study reveals that the hydroethanolic extract of LCS significantly protect the hepatic tissue from the adverse effects of diabetic rats. The liver engages several mechanisms to uphold optimal glucose level in the blood. Several enzymes are produced from liver, including AST, ALT, and ALP, which are used as indicator of liver health and an elevated level of these enzyme also indicate the dysfunction of liver are the consequence of diabetes (Rui, 2014; Sharabi et al., 2015). In this study, control group rats are compared with diabetic control to see the significant increase of AST and ALT. Two different treatments of LCS can significantly dropped AST and ALT levels. This indicates that LCS extract could have a protective effect against hepatic tissue damage caused by diabetes induced by STZ. These results are similar to the findings of previous studies (Alexander-Aguilera et al., 2019; Jeon et al., 2013; Jinato et al., 2022; Mahran et al., 2017; Mamun et al., 2020; Y. Zhang et al., 2021). Abnormal lipids are closely associated with diabetes. The liver's ability to synthesize TG is enhanced by elevated levels of free fatty acids. Atherogenic dyslipidemia, defined by increased levels of high TG, reduced levels of HDL cholesterol, and higher levels of LDL or apo lipoprotein-B, is associated with increasing levels of TG (Vergès, 2015).The most common lipid profile pattern has been shown in Type 2 diabetes consist of high triglyceride levels, low high density lipoprotein levels, high level of total cholesterol as well as high level of low density lipoprotein. During our investigation, the hydroethanolic extract of LCS (200 mg/kg) showed significant reduction of TG, TC and LDL, while substantially increased HDL of diabetic's rat. These results align with prior research on the clinical efficacy of LC in treating diabetes, as evidenced by studies (Alexander-Aguilera et al., 2019; Emanuele et al., 2017; Jinato et al., 2022; Noh et al., 2010; Roslan et al., 2017; Y. Zhang et al., 2021). Diabetes has also effects on kidney system, often termed as peripheral nephropathy. Serum creatinine levels are often used as main markers for identifying kidney disease (W. R. Zhang & Parikh, 2019). This investigation revealed that LCS has ameliorative effect of SC level on tested animals, similar to the effects of glibenclamide. Histological examination of pancreatic sections from the groups receiving treatment (LCS treated groups) revealed considerable improvement in comparison to the STZ-induced diabetes group. Vacuolization and alteration in the Langerhans's islet cells were seen in the pancreatic tissue of diabetic rats. When cellular density dropped, the islet of Langerhans shrank in diameter. In addition, pyknotic and shrined nuclei were observable in the central region of the islet. The reduction in β-cell density and islet size became apparent with an unclear border between the pancreas's exocrine and endocrine portions. These results corroborated with the prior investigation (Ramadan et al., 2017). According to our findings, the histological trend of the pancreas wasn't departing from the standard sequence over the study period in groups treated with glibenclamide (6mg/kg/overly) and LCS (100 and 200 mg/kg/BW). In line with prior research, this research showed the drug glib and LCS treatment are beneficial for enhancing the pancreas recuperation, the density or thickness of the islet of Langerhans, as well as the function of β-cells following treatment in STZ-induced diabetic rates (Birgani et al., 2018). Possible alterations in histology caused by STZ's hepatotoxic effects. In diabetic liver some histopathological changes were seen including abnormal hepatocytes, dissolved cytoplasm, infiltration of mononuclear leukocytic cells, beta cell apoptosis, an increase in the number of bile ducts, and worsening conditions in the lining of some bile ducts, inflammation, fibrosis etc. (Abdul-Hamid & Moustafa, 2013; O. M. Ahmed et al., 2023). Numerous hepatic abnormalities, such as steatohepatitis, fibrosis, cirrhosis, and non-alcoholic fatty liver disease (NAFLD), are exacerbated by insulin resistance and chronic hyperglycemia (Asmah Rahmat, 2015). The results of the LCS treatments were quite encouraging. The dose 200mg/kg body weight improved liver histopathology as compared to diabetic control group (STZ). These findings are aligned with the prior (Noh et al., 2010). Nephropathy, or diabetic kidney disease, is a serious consequence of uncontrolled diabetes. Tubule necrosis, glomerulus atrophy, and capillary congestions are the hallmarks of diabetic nephropathy (Jaiswal et al., 2017). Moreover, the process of elimination and excretion processes are greatly aided by kidney systems, while the pancreas plays a role in regulating metabolism (Kolset et al., 2012). The kidneys of the control rats showed no abnormalities upon inspection, including healthy cell structure, thin glomerular basement membranes, healthy glomeruli, and an intact capsular space encircled by acceptable distal and proximal. LCS seems to restore kidney functionality to diabetic rats that is similar to the reference antihyperglycemic medication (Glibenclamide). In summary, the outcomes of our study indicate that LCS has promising therapeutic potential to regulate diabetes related comorbidities. A limitation of the current study is that the acquisition of data is needed for developing a more profound comprehension of the underlying mechanisms responsible for

diabetes consequences. Further investigation could be undertaken in order to solve these issues.

## 6.Conclusion

Our research has yielded quite favorable findings about the impact of litchi seed extract on rats afflicted with diabetes. It is a highly efficient method for reducing blood sugar levels and also appears to have significant positive impacts on the complications in the pancreas, liver, and kidneys that typically occur with the illness. Our investigation has confirmed the efficacy of the hydroethanolic extract of Litchi chinensis seeds in traditional medicine. Further investigation is required to gain a deeper understanding of the impact of the extract derived from Litchi chinensis seeds on the progression of diabetes at the cellular, fundamental, and moderate levels of biological functioning.

## Author contributions

M.A.S., I.A.S., A.K.T., and I.S. conceptualized the study. M.A.S. led data curation, formal analysis, and methodology development, with contributions from T.M.T.I., N.C.M., and M.H.K. I.A.S., I.S., and A.K.T. managed project administration, with I.A.S. supervising and validating. M.A.S. and I.A.S. drafted the manuscript, with I.S. assisting in review and editing. Data from M.A.S.'s PhD research can be accessed upon request.

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## Competing financial interests

The authors have no conflict of interest.

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