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Evaluation of anti-obesogenic and anti-diabetic effects of tauroursodeoxycholic acid in Swiss albino rats: possible blockage of CHOP-dependent mitochondrial shuttling of TBP-2 and antagonism of streptozotocin-induced type 2 diabetes

Aitijjo Bhowmick[1], Khokon Kumar Dutta[1], Ratan Hossain[1], Esita Halder[1], Probir Kumar Banjerjee[2], Md. Tofazzal Hossain[3], Mst Muslima Khatun[4], Nigar Sultana[1], Manoj Mandal[1]

[1]Department of Biochemistry and Molecular Biology, Gopalganj Science and Technology University, Gopalganj 8105, Bangladesh | [2]Department of Gastroenterology, Gopalganj Medical College & Hospital, Goplaganj 8100, Bangladesh | [3]Department of Statistics, Gopalganj Science and Technology University, Gopalganj 8105, Bangladesh | [4]Department of Pharmacy, Gopalganj Science and Technology University, Gopalganj 8105, Bangladesh

Correspondence
Khokon Kumar Dutta
Email: kkdutta@gstu.edu.bd

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Muhammad Torequl Islam, PhD
Email: dmt.islam@blrcl.org

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Abstract: Endoplasmic reticulum (ER) stress plays a critical role in the progression of type 2 diabetes mellitus (T2DM) through activation of the pro-apoptotic transcription factor C/EBP homologous protein (CHOP). Accumulation of CHOP in the nucleus promotes thioredoxin-interacting protein (TXNIP) expression and its translocation to mitochondria, thereby contributing to mitochondrial dysfunction and β-cell loss. Tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA) are established inhibitors of ER stress–induced CHOP expression. This study evaluated the combined effects of TUDCA and UDCA on body weight regulation and glycemic control in a rat model of T2DM induced by high-fat diet (HFD) feeding and low-dose streptozotocin (STZ). Swiss albino male rats were divided into four groups: control, HFD control, diabetic (HFD+STZ), and treatment [HFD+STZ+TUDCA (0.02%)/UDCA (0.3%)]. Body weight, fasting blood glucose, and postprandial blood glucose were assessed over 90 days. Supplementation with TUDCA and UDCA significantly reduced weight gain and improved glycemic control in diabetic rats ($p < 0.0001$). The incidence of diabetes was substantially lower in the treatment group compared with untreated diabetic rats, with 0% vs. 50% incidence by day 54 and 34% vs. 75% by day 90. By day 90, PBG levels were significantly lower in treated diabetic rats than in untreated diabetic rats ($p < 0.0001$). These findings indicate that combined TUDCA and UDCA supplementation exerts strong anti-obesogenic and anti-diabetic effects, enhancing glucose homeostasis and delaying diabetes onset. These findings suggest that blockers of TBP-2 mitochondrial shuttling, such as TUDCA and UDCA, may represent promising strategies for the prevention and treatment of T2DM.

Keywords: Bile acids; Blockage mitochondrial shuttling; Obesity; Streptozotocin antagonism; Type 2 diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, glucose intolerance, β-cell dysfunction, and hyperglycemia, affecting millions worldwide (International Diabetes Federation, 2021). The global prevalence of T2DM continues to rise, primarily driven by sedentary lifestyles and high-caloric diets, particularly those rich in saturated fats (Kolb & Martin, 2017). High-fat diet (HFD)-induced obesity has been extensively linked to insulin resistance and pancreatic β-cell stress, which contribute to the pathogenesis of T2DM. In subjects with obesity, particularly central or visceral obesity, elevated levels of free fatty acids, pro-inflammatory cytokines, and adipokines interfere with insulin signaling pathways, leading to decreased glucose uptake in peripheral tissues (Kahn et al., 2000). Numerous epidemiological studies have demonstrated a strong association between body mass index (BMI) and the risk of T2DM, with obese individuals having up to a tenfold increased risk compared to those with normal weight (Colditz et al., 1990; Hu et al., 2001). Various pharmacological and dietary interventions have been explored to prevent or mitigate the progression of diabetes, with bile acids emerging as potential therapeutic agents due to their metabolic regulatory properties (Samuel & Shulman, 2016).

The interplay between endoplasmic reticulum (ER) stress, mitochondrial stress, and the devement of diabetes is a complex

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and increasingly understood area of research. Both ER and mitochondrial dysfunction contribute significantly to the pathogenesis of diabetes, particularly type 2 diabetes. ER stress, triggered by the accumulation of misfolded proteins, activates the unfolded protein response (UPR), which, if prolonged, can lead to beta-cell dysfunction and apoptosis, critical factors in diabetes development. Key markers of ER stress include C/EBP homologous protein (CHOP), which contributes to apoptosis, alongside increased levels of BiP (binding immunoglobulin protein), and the activation of IRE1α, PERK, and ATF6 (Cnop et al., 2012; Ozcan et al., 2004). Deletion of the UPR-induced gene CHOP (Chop−/−) preserves ER function and reduces oxidative stress. The improved ER function prevents β cell failure and the development of diabetes caused by insulin resistance and obesity (Song et al., 2008).

Crucially, the ER and mitochondria are not isolated; they communicate via mitochondria-associated membranes (MAMs), meaning that stress in one organelle can directly impact the other. Proteins like Mitofusin 2 (Mfn2), Inositol 1,4,5-trisphosphate receptors (IP3Rs), Voltage-dependent anion channel (VDAC), and Glucose-regulated protein 75 (Grp75) are key molecules that connect the ER and mitochondrial stress (Rowland & Voeltz, 2012; Hayashi et al., 2009). Disrupted MAM function is strongly implicated in the pathology of type 2 diabetes, through it's effects on calcium signaling, and lipid trafficking (Arruda et al., 2014). Therefore, the combined impact of ER and mitochondrial stress creates a detrimental cycle that promotes beta-cell failure and insulin resistance, key hallmarks of diabetes. ER stress marker CHOP regulates the translocation of TBP-2 (TXNIP) from nucleus to the mitochondria. The presence of TBP-2 in the mitochondria leads to excessive accumulation of ROS, activates inflammasome signaling and inflammation and causes mitochondria dependent cell death (Saxena G et al., 2010; Choi EH et al., 2023; Park SJ et al., 2022). In a condition of excessive oxidative stress, TBP-2 inhibits glucose transporters and cellular glucose uptake. TBP-2 causes glucose transporters to be localized in the lysosomes for degradation (Qualls-Histed SJ et al., 2023). The cells suffer from glucose transporters on their membrane and a condition “insulin resistance” develops. TBP-2 inhibits pancreatic insulin transcription and production via microRNA-204 inhibiting STAT 3 and transcription factor MAFA (Xu G et al., 2013). TBP-2 also increases glucagon production by the alpha cells in the pancreas and increases gluconeogenesis and glucose production in the liver (Lu B et al., 2022). TBP-2 causes insulin producing beta cells to dedifferentiate and to lose their identity (Amo-Shiinoki K et al., 2025). Dedifferentiated beta cells do not produce any pancreatic insulin hormones (Talchai C et al., 2012).

Bile acids, beyond their classical role in lipid digestion, have gained attention for their role in glucose and energy homeostasis through activation of signaling pathways such as the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) (Chiang, 2017; Lefebvre et al., 2009; Pols et al., 2011). Tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA), two bile acid derivatives, have been investigated for their cytoprotective, anti-inflammatory and metabolic benefits (Ozcan et al., 2006). TUDCA, a taurine-conjugated bile acid, has been shown to reduce endoplasmic reticulum (ER) stress and improve insulin sensitivity, making it a promising candidate for diabetes management (Ozcan et al., 2006; Yoon et al., 2016; Malo et al., 2010). Orally administered unconjugated UDCA rapidly conjugates in the liver with taurine and glycine to form tauroursodeoxycholic acid (TUDCA) and glycoursodeoxycholic acid (GUDCA). Both TUDCA and UDCA have shown potential in lowering C/EBP homologous protein (CHOP) levels (Park et al., 2022; Yoon et al., 2016; Malo et al., 2010; Paridaens et al., 2017; Chung et al., 2015; Cao et al., 2016; Mueller et al., 2018; Morales et al., 2023; Habib et al., 2025). CHOP acts as a promoter of TBP-2 (TXNIP) mitochondrial translocation (Park et al., 2022). Blocking TBP-2 translocation to mitochondria may represent a novel therapeutic approach. TBP-2's mitochondrial presence elevates reactive oxygen species (ROS) and triggers inflammasome activation, leading to inflammation and cell death. Similarly, UDCA has been reported to exert anti-inflammatory and hepatoprotective effects, which may indirectly benefit glucose metabolism (Habib et al., 2025).

The low-carbohydrate ketogenic diet (KD) has long been used for weight loss. KD feeding reduces the activity of bile salt hydrolase (BSH), an enzyme produced by the gut bacterium *Lactobacillus murinus*, leading to increased circulating levels of taurodeoxycholic acid (TDCA) and tauroursodeoxycholic acid (TUDCA). TDCA and TUDCA treatments have been shown to protect against obesity and related complications in multiple mouse models (Li et al., 2024).

In type 2 diabetes, qualitative and quantitative alterations in the endogenous lipid environment direct monocytes toward a proinflammatory state, inducing endoplasmic reticulum (ER) stress, TXNIP expression, and inflammasome activation (Szpigel et al., 2018). DNA hypomethylation at the *TXNIP* gene is associated with elevated expression levels. Furthermore, DNA methylation at *TXNIP* has been found to be significantly associated with changes in fasting plasma glucose levels in midlife, with this association being modified by body mass index (BMI) trends during childhood and adolescence (Ma et al., 2023). The interaction of DNA hypomethylation at *TXNIP* with obesity and hypertriglyceridemia has also been linked to increased type 2 diabetes risk (Zhang et al., 2020). In the POUNDS Lost Trial, hypomethylation at *TXNIP* was observed following a weight-loss dietary intervention (Li et al., 2022).

Taken together, supplementation with TUDCA and UDCA may exert anti-obesogenic effects and help prevent the development and progression of diabetes.Previous studies have suggested that TUDCA and UDCA can protect pancreatic β-cells from dysfunction and apoptosis, thereby preserving insulin secretion and preventing hyperglycemia (Habib et al., 2025). However, their combined effects on diabetes prevention, particularly in a diet-induced model of insulin resistance, remain inadequately explored. In this study, we investigated the TUDCA- and UDCA-mediated blocking of TBP-2 (TXNIP) translocation to mitochondria through downregulation of CHOP expression in high-fat diet-fed male rats with streptozotocin (STZ)-induced diabetes. We hypothesized that the combination of TUDCA and UDCA would confer protective effects against diabetes development by exerting anti-obesogenic effects, improving glycemic control, reducing ER and mitochondrial stress, and enhancing insulin sensitivity and β-cell survival.

By elucidating the molecular interplay underlying the potential therapeutic role of these bile acids, our findings may offer novel insights into diabetes prevention and treatment strategies that block TBP-2 (TXNIP) translocation to the mitochondria, thereby paving the way for future clinical investigations.

2. Materials and methods

2.1 Chemicals and reagents

Tauroursodeoxycholic acid (TUDCA; CAS: 14605-22-2; purity: >98%) was obtained from TCI America (Tokyo, Japan). Ursodeoxycholic acid (UDCA; tablet formulation; Biopharma Ltd., Bangladesh) was purchased from a local pharmacy. Streptozotocin (STZ; CAS: 18883-66-4; purity: 98%) was purchased from SRL India. Citrate Buffer (0.1 M, pH 4.5) was freshly prepared in the laboratory using citric acid monohydrate (Smart Lab, Indonesia) and trisodium citrate (Merck Life Science Private Limited, India). All other chemicals and reagents were of analytical grade and obtained from standard commercial sources.

2.2 Experimental animals

A total of 19 male Swiss albino rats (Mice House, Katakhali, Rajshahi, Bangladesh) were used for this study. Male rats were selected because, in the high-fat diet (HFD) and streptozotocin (STZ)-induced type 2 diabetes (T2D) model, they develop insulin resistance and hyperglycemia more consistently than females. This is primarily due to the absence of estrogen-mediated metabolic protection, as well as their faster weight gain and lower hormonal variability, which contribute to greater model reproducibility and efficiency. All animals were screened for non-diabetic status based on baseline blood glucose levels before the experiment. The rats were housed in standard polypropylene cages (430 X 270 X 150 mm) under controlled conditions with a 12-hour light/dark cycle and an ambient temperature of 22-25 °C, with 4-5 rats per cage. This study was approved by the Department of BMB, Goplaganj Science and Technology University, Gopalganj (gstu/bmb/17BMB056).

2.3 High-fat diet

A standard chow diet (4.06% fat, 51.2% carbohydrate, 22.83% protein) was purchased from Jamuna Traders, Dhaka, Bangladesh. The high-fat diet was prepared by thoroughly mixing the standard chow with 25%(w/w) beef tallow resulting in a diet containing approximately 28.05% fat, 38.4% carbohydrate and 17.13% protein. The HFD was further modified by supplementing it with 0.02% tauroursodeoxycholic acid (TUDCA) and 0.3% ursodeoxycholic acid (UDCA) (both w/w).

2.4 Experimental design

Rats were randomly divided into the following groups: (I) Control (normal diet: without treatment), (II) HFD control (high fat containing food), (III) diabetic (HFD (as per/*ad libitum*) + STZ (40 mg/kg)), and (IV) treatment [HFD (as per/*ad libitum*) + STZ (40 mg/kg) + test sample (TUDCA (0.02%) + UDCA (0.3%)). Each groups contained 3-6 animals. The animals were treated for a total of 90 days. TUDCA and UDCA supplementation for the treatment group began on day 1. Throughout the 90-day study period, body weight and FBG levels were monitored every four days, both before and after the STZ injections. On day 90, all rats were sacrificed after a 12-hour overnight fast. Blood samples and relevant tissues were collected and stored at −80 °C for subsequent molecular and histological assays.

2.5 Diabetes induction

On day 28 of the study, the diabetic and treatment groups received a single intraperitoneal injection of streptozotocin (STZ). STZ was dissolved in 0.1 M sodium citrate buffer (pH 4.5) to a concentration of 40 mg/kg body weight. An equivalent volume of the citrate buffer (0.25 mL/kg) was administered intraperitoneally to the HFD control group as a placebo. Following STZ administration, all rats were provided with a glucose supplement in their drinking water for 24 hours to prevent severe hypoglycemia. One month after the initial STZ injection, rats were evaluated for their diabetic status. Fasting blood glucose (FBG) levels were measured using a calibrated digital glucometer (Zhang et al., 2008). Rats with FBG levels ≥11.1 mmol/L and PBG levels ≥12.0 mmol/L were considered diabetic, while FBG levels between 6.1-8.3 mmol/L and PBG level between 8.0–11.0 mmol/L were classified as pre-diabetic. Non-diabetic rats within the diabetic and treatment groups received a second intraperitoneal injection of STZ (40 mg/kg) on day 56 to ensure consistent diabetes induction.

2.6 Statistical analysis

All data are presented as the mean ± standard error of mean (SEM). Statistical significance was assessed using GraphPad Prism software (version 10.5.0; GraphPad Software, San Diego, CA, USA). Comparisons between two groups were performed using an unpaired two-sample Student's t-test. For comparisons involving more than two groups, a one-way analysis of variance (ANOVA) was used, followed by Tukey's post-hoc test to identify specific group differences. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1 Anti-obesogenic test

3.1.1 Variations of body weight

To evaluate the anti-obesogenic potential of TUDCA and UDCA supplementation, body weight was measured every fourth day for 90 days. As detailed in **Table 1**, rats in the high-fat diet control group (HFD fed group) exhibited a continuous and significant increase in body weight in comparison to the control group (normal diet), reaching 201.83 ± 8.67 g by Day 90. In contrast, the treatment group, which received TUDCA+UDCA supplementation from day 1, showed a more controlled weight gain, concluding the study at a significantly lower final body weight of 146.33 ± 8.72 g.

A comparative analysis of the obesity phenotype, captured through representative photographs on Day 90 (**Fig. 1.**), further supports these findings, with the HFD control group displaying a more globular, obese body appearance compared to the leaner body shape of the treatment group. Statistical analysis of the body weight progression from day 19 to day 90, a period where the groups had comparable starting weights, revealed a highly significant difference in weight gain between the groups ($p < 0.0001$). These results collectively suggest a strong anti-obesogenic effect of TUDCA and UDCA supplementation.

3.2 Anti-diabetic test

3.2.1 Fasting blood glucose (FBG) levels

Fasting blood glucose (FBG) levels were monitored every fourth day to assess the baseline glycemic status. The control group consistently exhibited a normal range of FBG level throughout the entire experiment. While the diabetic group consistently exhibited FBG levels in the diabetic range (12.40 ± 3.74 mmol/L on day 54 and 13.03 ± 3.49 mmol/L on day 90). In contrast, the treatment group's FBG levels were normalized on Day 54 (4.95 ± 0.24 mmol/L) and had shifted to the pre-diabetic range by day 90 (9.20±2.24 mmol/L) (**Table 2**) indicating partial but significant ($p<0.0001$) glycemic improvement.

3.2.2 Postprandial blood glucose (PBG) levels

Postprandial blood glucose (PBG) levels were also observed every fourth day to assess the glycemic improvement. The control group consistently exhibited the normal range of PBG levels throughout the entire experimental period. While the diabetic group consistently remained in the diabetic range, with PBG levels of 14.83±3.63 mmol/L on Day 54 and 19.98±4.83 mmol/L on Day 90. The treatment group, however, showed normalized PBG levels on Day 54 (5.90 ± 0.46 mmol/L) and a lower, pre-diabetic level on Day 90 (10.17 ± 2.25 mmol/L) (**Table 3**), indicating partial but significant ($p<0.001$) glycemic improvement.

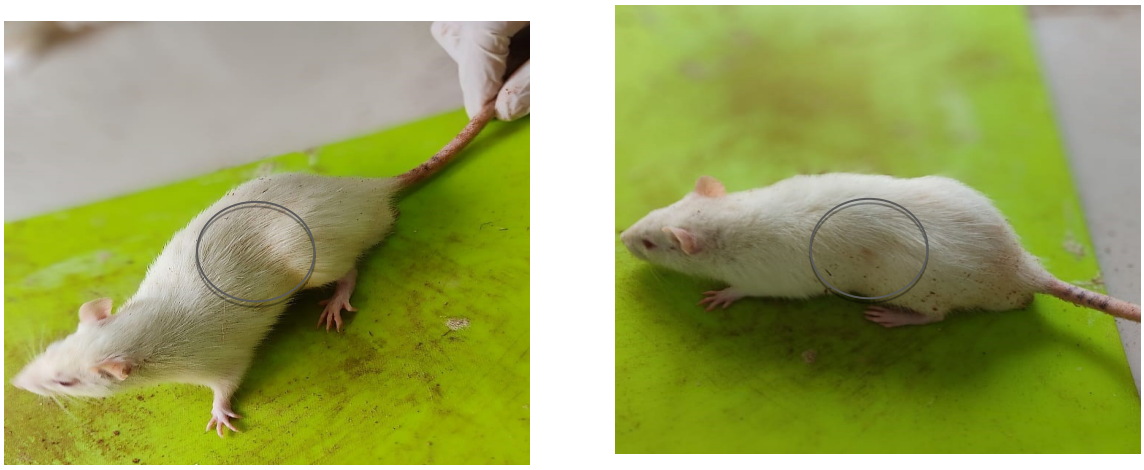
3.2.3 Incidence of diabetes in diabetic and treatment groups

The incidence of diabetes was observed throughout the study. By Day 54, 50% of the rats in the diabetic group had become diabetic, whereas none (0%) of the rats in the treatment group showed symptoms of diabetes based on the blood glucose levels measured after 6.0 hours of fasting and 2.0 hours following oral glucose loading (**Table 3**). Following a second streptozotocin (STZ) dose on Day 56, the incidence of diabetes in the diabetic group increased to

Table 1. Body weight variations in HFD control and treatment groups up to 90 days.

Treatment groups	Body weight variations (g)				
	Day 3	Day 19	Day 27	Day 54	Day 90
HFD control	85.33 ± 9.43	132 ± 12.79	137.00 ± 12.39	172.50 ± 9.50	201.83 ± 8.67
Treatment (HFD+TUDCA+UDCA+STZ)	113.42 ± 9.27	134.58 ± 7.96	133.33 ± 9.46	152.75 ± 5.18*	146.33 ± 8.72*

Values are the mean ± SEM (standard error of mean) (n = 3/6); One-way ANOVA followed by t-Student Tukey *post-hoc* test; $p < 0.05$ indicates a significant difference compared to the *HFD control within the same observation day; Welch-corrected: t = 4.899, df = 20.22; HFD: High fat diet; TUDCA: Tauroursodeoxycholic acid; UDCA: Ursodeoxycholic acid; STZ: Streptozotocin



(a) **(b)**

Fig. 1. Day-78 represents images (a), Leaner phenotype in TUDCA+UDCA supplemented group compared to (b), Obese HFD controls

75% by Day 90. In contrast, only 33.33% of the rats in the treatment group developed diabetes during this period, highlighting a protective effect of the supplementation. Furthermore, a comparison of postprandial blood glucose in the rats that became diabetic in both groups after the second STZ dose until Day 90 revealed a significant reduction in PBG in the supplemented diabetic rats compared to the unsupplemented diabetic rats ($p<0.0001$).

4. Discussion

This study investigated the efficacy of tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA) supplement in mitigating type 2 diabetes mellitus (T2DM) in male rats induced with diabetes was via a high fat diet (HFD) and streptozotocin (STZ). The combined bile acid treatment demonstrated pronounced anti-obesogenic and anti-diabetic effects as evidenced by reduced weight gain, improved fasting and postprandial glycemic control, and attenuated disease onset and severity.

Body weight gain was significantly lower in the treatment group (HFD+STZ+TUDCA+UDCA) compared to the HFD control group, with a steady, restrained weight increase over 90-days. These effects align with previous studies linking bile acids to reduced adiposity, improved insulin sensitivity, and mitigation of ER stress–induced metabolic dysfunction (Kars et al., 2010). Mechanistically, TUDCA mitigates ER stress by acting as a chemical chaperone, enhancing protein folding and restoring cellular homeostasis, thereby attenuating the unfolded protein response (UPR) that impairs insulin signaling. In parallel, UDCA exerts hepatoprotective and lipid-lowering effects, partly through modulation of bile acid signaling via FXR and TGR5 receptors (Beuers et al., 1998; Beuers et al., 2015; Chávez-Talavera et al., 2017). These properties are believed to contribute to the observed improvements in weight and glucose regulation. Visual inspection confirmed that treated rats appeared leaner with less abdominal fat, reflecting enhanced insulin sensitivity, fat oxidation, and energy expenditure.

Glycemic control was markedly improved in the treatment group (HFD+STZ+TUDCA+UDCA). Fasting blood glucose (FBG) remained near-normal, with only 33.33% of rats developing diabetes in the treatment group (HFD+STZ+TUDCA+UDCA), compared to 75% in the diabetic group (HFD+STZ). Postprandial glucose (PBG) was also significantly lower in treatment group, suggesting improved first-phase insulin secretion and peripheral glucose uptake. In contrast, rats in the diabetic group displayed persistently high PBG levels throughout the study. These observations are in line with previous studies demonstrating that TUDCA improves insulin sensitivity in insulin-resistant models (Kars et al., 2010). Likewise, UDCA has been shown to enhance hepatic insulin clearance and reduce gluconeogenesis (Staels et al., 2010), contributing to better fasting glucose control. These results underscore the capacity of TUDCA and UDCA to attenuate postprandial hyperglycemia, a known marker of metabolic dysfunction and cardiovascular risk (Ceriello, 2005). This may be attributed to enhanced first-phase insulin secretion or improved peripheral glucose uptake mechanisms that warrant further investigation.

Furthermore, the combined treatment reduced both the incidence

Table 2. Fasting blood glucose (FBG) levels observed in controls and treatment groups on day 54 and 90 along with their diabetic conditions.

Treatment groups	Fasting blood glucose levels (mmol/L)			
	Day 54	Condition	Day 90	Condition
Control (normal feed)	5.48 ± 0.09	Normal	5.2 ± 0.19	Normal
Diabetic (HFD+STZ)	12.40 ± 3.74*[b]	Diabetic	13.03 ± 3.49*[b]	Diabetic
Treatment (HFD+STZ+TUDA+UDCA)	4.95 ± 0.24[a]	Normal	9.20 ± 2.24*[a]	Pre-diabetic

Values are the mean ± SEM (standard error of mean) (n = 6/4/6); One-way ANOVA followed by t-Student Tukey *post-hoc* test with multiple comparison; $p < 0.05$ when compared to the *Control (normal feed), [a]Diabetic (HFD+STZ), and [b]Treatment (HFD+TUDCA+UDCA+STZ) inspect of observation day; Welch-corrected: t = 3.313, df = 40.00; HFD: High fat diet; TUDCA: Tauroursodeoxycholic acid; UDCA: Ursodeoxycholic acid; STZ: Streptozotocin

Table 3. Postprandial Blood Glucose (PBG) levels observed in controls and treatment groups on day 54 and 90 along with their diabetic conditions.

Treatment groups	Postprandial blood glucose (mmol/L)			
	Day 54	Condition	Day 90	Condition
Control (normal feed)	6.18 ± 0.15	Normal	5.97 ± 0.27	Normal
Diabetic Group (HFD+STZ)	14.83 ± 3.63*[b]	Diabetic	19.98 ± 4.83*[b]	Diabetic
Treatment Group (HFD+STZ+TUDCA+UDCA)	5.90 ± 0.46[a]	Normal	10.17 ± 2.25*[a]	Pre-diabetic

Values are the mean ± SEM (standard error of mean) (n = 6/4/6); One-way ANOVA followed by t-Student Tukey *post-hoc* test with multiple comparison; $p < 0.05$ when compared to the *Control (normal feed), [a]Diabetic (HFD+STZ), and [b]Treatment (HFD+TUDCA+UDCA+STZ) inspect of observation day; Welch-corrected: t = 3.271, df = 37.50; HFD: High fat diet; TUDCA: Tauroursodeoxycholic acid; UDCA: Ursodeoxycholic acid; STZ: Streptozotocin;

and severity of diabetes. By day 90, only 33.33 % of rats in the treatment group had developed diabetes, compared to 75% in the diabetic group. A comparison of postprandial blood glucose in the rats that became diabetic in both groups after the second STZ dose until Day 90 revealed a significant reduction in PBG in the supplemented diabetic rats compared to the unsupplemented diabetic rats ($p<0.0001$). These outcomes suggest that bile acid supplementation not only delays diabetes onset but also attenuates its severity in affected individuals.

At the molecular level, the observed improvements may be attributed to TUDCA's role in enhancing AKT signaling and restoring insulin receptor substrate (IRS) phosphorylation in insulin-sensitive tissues. Additionally, both TUDCA and UDCA possess anti-inflammatory and antioxidant properties that may protect pancreatic β-cells against STZ-induced oxidative damage. UDCA's ability to activate TGR5 in intestinal cells may further stimulate GLP-1 release, promote insulin secretion and improve postprandial glycemic control (Thomas et al., 2009).

A key mechanistic insight highlighted in this study is the role of CHOP-dependent mitochondrial shuttling of thioredoxin-interacting protein (TBP-2/TXNIP). ER stress is a central contributor to T2DM pathology, and chronic UPR activation leads to CHOP upregulation, β-cell dysfunction, and apoptosis. Our findings support existing evidence that TUDCA and UDCA downregulate CHOP expression (Choi & Park, 2023; Kupsal et al., 2015), thereby reducing TBP-2 mitochondrial translocation. This, in turn, limits ROS accumulation, inflammasome activation, and insulin resistance.

TBP-2 is a multifaceted pathological mediator; it impairs glucose transporters, inhibits insulin gene transcription by targeting STAT3 and MAFA via miR-204, increases glucagon production, enhances hepatic gluconeogenesis, and promotes β-cell dedifferentiation (Park et al., 2022). By inhibiting the mitochondrial translocation of TBP-2 through CHOP suppression, TUDCA and UDCA appear to break a critical pathological feedback loop that drives hyperglycemia and β-cell failure.

The anti-obesogenic effects observed in this study further reinforce the metabolic benefits of bile acid supplementation. TUDCA's capacity to reduce weight gain in HFD-fed rats may be related to bile acid-mediated modulation of lipid metabolism and nutrient absorption, as suggested by recent studies linking bile acids to ketogenic diet responses (Staels et al., 2010). Moreover, the interplay between lipid overload, ER stress, and TXNIP expression (Chen et al., 2010), along with TXNIP hypomethylation's association with diabetes risk (Xiang et al., 2021; Zhang et al., 2020), underscores the complex and central role of TBP-2 in metabolic disease. Interrupting this cycle through CHOP suppression and TBP-2 regulation may explain the broad therapeutic effects observed.

These findings highlight the potential of bile acid modulation as a promising therapeutic strategy for obesity-linked insulin resistance and type 2 diabetes. By targeting ER stress and bile acid receptor signaling, TUDCA and UDCA may complement existing interventions aimed at improving metabolic homeostasis.

This study has several limitations that should be acknowledged. First, the relatively small sample size may have reduced the statistical power and the ability to generalize findings. Second, although the results suggest beneficial effects of TUDCA and UDCA

supplementation on glycemic control and body weight, key mechanistic parameters such as circulating insulin levels, HOMA-IR, lipid profiles, inflammatory cytokines, and histological analyses of pancreatic and hepatic tissues were not assessed in the present work. These measurements, which are planned using preserved tissue and serum samples, will be essential to provide deeper mechanistic insights. Finally, the study design did not include groups treated with TUDCA or UDCA alone, which limits our ability to distinguish between the individual and combined effects of these bile acids. Future investigations with larger cohorts and expanded experimental endpoints will be necessary to validate and extend these findings.

5. Conclusion

In conclusion, supplementation with tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic acid (UDCA) in a high-fat diet and streptozotocin-induced rat model of type 2 diabetes resulted in reduced body weight gain, improved fasting and postprandial glucose regulation, and a lower incidence of diabetes. These results suggest that bile acids targeting CHOP-dependent mitochondrial shuttling of TXNIP may offer a promising strategy for the prevention and management of type 2 diabetes. Our findings highlight the therapeutic relevance and potential of TUDCA and UDCA as metabolic modulators, though further mechanistic and translational studies are warranted.

Conflict of interest

The authors declare no conflict of interest.

Declaration by authors

Aitijjo Bhowmick conducted this research work (thesis) as a partial requirement for the completion of her M.Sc. degree in Biochemistry and Molecular Biology from Gopalganj Science and Technology University, under the guidance and supervision of Dr. Khokon Kumar Dutta from the same department. The project also received significant contributions from all other co-authors, including project design, facilities, data analysis, and guidance. The authors used ChatGPT (OpenAI, San Francisco, CA, USA) solely to improve grammar, language clarity, and formatting of the manuscript. All study design, data collection, analysis, interpretation, and intellectual content were conducted by the authors.

Disclosure of ethical statements

Not applicable

Approval of the research protocol

Not applicable

Informed consent

Not applicable

Animal studies

This study complies with the ARRIVE guidelines

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