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Article

S-allyl Cysteine and Taurine revert peripheral metabolic and lipid profile in non-insulin-dependent diabetes mellitus animals: Combination vs Monotherapy

Nadeem Rais[1], Kehkashan Parveen[2], Rizwan Ahmad[3], Waseem Ahmad Siddiqui[4], Ayasha Nadeem[5], Akash Ved[6*]

[1]Department of Pharmacy, Bhagwant University, Ajmer (Raj.), India, [2,4]Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh, India, [3]Department of Pharmacy, Vivek College of Technical Education, Bijnor (U.P.), India, [5]Department of kulliyat, SUMER, Jamia Hamdard, New Delhi, India, [6]Goel Institute of Pharmaceutical Sciences, Lucknow, (U.P.), India

The present study was designed to evaluate the beneficial synergistic effects of S-allyl Cysteine (SAC) and Taurine (TAU) on hyperglycemia, lipid profile and renal damage markers in type 2 diabetes mellitus (T2DM) in rats. Experimental T2DM was developed by administering an intraperitoneal single dose of nicotinamide (NA; 230 mg/kg) and streptozotocin (STZ; 65 mg/kg) in adult rats. Control and diabetic rats were treated with SAC (150 mg/kg); TAU (200 mg/kg) or SAC and TAU (75+100 mg/kg) combination for four weeks. Measurements of traditional markers of kidney toxicity in serum, such as blood urea nitrogen (BUN), serum creatinine (Scr), and alkaline phosphatase (ALP), together with serum cholesterol/triglyceride such as serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) may yield a snapshot of renal damage and lipid profile in NA/STZ-treated rats. The variation in levels of fasting blood glucose, glycosylated hemoglobin, insulin and lipid profile was significantly augmented in SAC/TAU treatment group. The diabetic group showed elevated renal injury markers in serum, which were decreased significantly by SAC/TAU treatment. Thus the results of the experiment clearly indicate the potential of the SAC/TAU combination in improving diabetic complications.

Keywords: Type 2 diabetes mellitus. Hyperlipidemia. S-Allyl Cysteine. Taurine. Renal damage.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) or non-insulin-dependent diabetes mellitus (NIDDM) is described as metabolic syndrome defined by abnormalities in glucose utilization due to defective insulin secretion or action (Green, Feinglos, 2007). T2DM is often correlated with numbers of metabolic and physiologic changes including hyperglycemia, high blood pressure, insulin resistance, dyslipidemia and renal dysfunction (Maiti, Das, Ghosh, 2005; Clozel *et al*., 2006; Parveen *et al*., 2016). Persistent hyperglycemia and dyslipidemia in diabetic condition may lead to increased atherogenesis and coronary heart disease (Stamler *et al*., 1993; Khan, Sobki, Khan, 2007). Considering that DM is the leading cause of various metabolic derangements and vascular complications, it also imposes an economic burden individually or socially. Hence early interventions are necessary.

Diet composition is an essential target in almost all therapeutic strategies to limit the progressive metabolic derangement in DM. Thus enhanced proteins biodegradation is featured in diabetes (Dice *et al*., 1978), and patients may get benefit from supplementation with specific amino acids like L-Arginine or Taurine (TAU) or with the containing

***Correspondence:** A. Ved. Goel Institute of Pharmaceutical Sciences. Lucknow, (U.P.), India**.** Phone: +918874205341. E-mail: akashved@gmail.com. Nadeem Rais ORCID: 0000-0002-0430-228X

meals (Ouellet *et al.*, 2017). As an essential amino acid which is not utilized in protein synthesis, TAU is one of the most abundant free amino acids in mammals' tissues (Awapara, 1962). Several studies have suggested the effectiveness of TAU in a wide range of pathologies ranging from hepatic disorders (Rodella *et al.*, 2017), epilepsy (Kumar, Goel, 2017) and Alzheimer's disease (Kim *et al.*, 2014). Recently, the potential role of TAU to prevent diabetes and diabetes-related complications has been reviewed (Ito *et al.*, 2012; Sirdah, 2015; Sarkar *et al.*, 2017).

S-Allylcysteine (SAC), a distinct sufur-containing amino acid, found in medicinal Allium plants such as garlic exerts therapeutic values in various disorders including DM, substantiated with several animals and some human studies (Iliya *et al.*, 2016; Ansari *et al.*, 2017; Ansari *et al.*, 2018). SAC has been reported to possess antioxidant (Asdaq, 2015), antihepatotoxic (Nakagawat, Kasuga, Matsuura, 1989), neuroprotective (Kosuge, 2020) and anti-cancer (Chu *et al.*, 2007) activity. In addition to its above mentioned properties, it also has shown anti-diabetic effects in the diabetic model due to its antioxidant potential (Saravanan *et al.*, 2009; Saravanan, Ponmurugan, 2011; Uddandrao, Brahmanaidu, Saravanan, 2017).

Due to the potential antioxidant properties of both TAU and SAC, this preclinical study aims to evaluate if TAU and SAC co-administration may improve the efficacy of each compound to correct the general markers of metabolic derangements in the diabetic animals. For a precise translation, we used a nicotinamide (NA)/ streptozotocin (STZ)- induced diabetes in which the partial protection of β-cells by NA against the cytotoxic action of STZ contributes to a rat model of NIDDM (Masiello *et al.*, 1998).

MATERIAL AND METHODS

Chemicals and reagents

STZ, NA, ethylene diamine tetraacetic Acid (EDTA), nicotinamide adenine dinucleotide phosphate reduced form (NADPH), 5, 5'-dithiobis-(2-nitrobenzoic acid) (DTNB), 1-chloro-2, 4-dinitrobenzoic acid (CDNB) and trichloroacetic acid (TCA) were purchased from Sigma–Aldrich Chemicals Pvt. Ltd. (India). Sulfosalicylic acid (SSA) and bovine serum albumin (BSA) were purchased from SRL and Merck Chemicals Pvt. Ltd. (India). SAC and TAU were gifted from LGC Prochem, Bangalore, India. All the other chemicals were of analytical reagent grade.

Experimental design

All the experiments were carried out in male Wistar rats (160-200g). They were freely allowed to standard rodent pelleted diet (Hindustan Lever Ltd., Bombay, India) and water *ad libitum*, prior to the dietary manipulation. All procedures for using animals were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) which is accredited by the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), Chennai, INDIA. The ethical clearance number is "1446/PO/Re/S/11/CPCSEA".

Mechanism of NIDDM

Masiello *et al.* (1998) developed a truly valuable NIDDM model of NA/STZ that is based on the ability of NA to assert partial protection against the β-cytotoxic consequences of STZ. It is noted that the genotoxic behavior of STZ in animals is accomplished through a reduction of nicotinamide adenine dinucleotide (NAD^+) in pancreatic β-cells via the GLUT2 (Glucose transporter 2) which can cause cellular damage by DNA strand breaks leading to cell death. Extreme DNA damage contributes to the over-activation of poly-ADP-ribose-polymerase-1 (PARP-1), loss of cellular resources, and necrotic cells death. NA is a biochemical precursor of NAD^+ and it is a PARP-1 inhibitor. NAD^+ is an important redox reaction co-enzyme for the production of adenosine triphosphate (ATP) and for many other metabolic pathways. Therefore, some of the pancreatic β-cells remain unharmed by administering NA and are capable of secreting insulin to induce a model of T2DM.

T2DM induction

Experimental T2DM was developed by administering NA and STZ in adult rats. The animals (fasted overnight)

received an intraperitoneal NA (230 mg/kg in saline), 15 min before the intraperitoneal administration of STZ (65 mg/kg), dissolved in 0.1 M ice-cold citrated buffer (pH 4.5) immediately before use. After administration of NA/STZ the animals were allowed to food and water access *ad libitum*. Fasting blood glucose was evaluated after 2 days and the animals with glucose level ≈ 140±8 mg/dl were considered as diabetic and selected for further studies (Masiello *et al*., 1998).

Following the successful induction of T2DM, animals were randomly divided into five groups with eight animals in each. After this strategic segregation, each group of animals was dosed with a different regimen of treating molecules on daily basis for a period of 30 days. For this, we used oral normal saline; SAC (150 mg/kg, b.w.); TAU (200 mg/kg, b.w.); SAC/TAU combination (75+100 mg/kg, b.w.) and glibenclamide (GL; 10 mg/kg, b.w.) as five treatment regimens given separately to five groups of animals.

For appropriate comparison, two separate non-diabetic groups were designed to receive normal saline or SAC/TAU combination as controls. At the end of the 30 days treatment, blood samples were collected and subjected to biochemical analysis of conventional indices of hyperglycemia, hyperlipidemia and renal function.

Sample Preparation and Biochemical Analysis

At the end of experiment, rats were anesthetized by ether inhalation and the blood was collected from the dorsal aorta. Approximately 0.2 ml of whole blood was taken into EDTA containing microtubes and immediately preserved in the refrigerator for subsequent analysis of glycosylated hemoglobin (HbA1c). For testing conventional markers of renal integrity and hyperlipidemia, serum was separated by centrifugation at 1200 x g for 10 min before analysis and stored at −80°C.

Makers of Hyperglycemia

Fasting blood glucose was estimated by the GOD/POD Method (Trinder, 1969) using a commercial diagnostic kit procured from Crest Biosystems, Goa, India. Glucose is oxidised to gluconic acid and hydrogen peroxide in the presence of glucose oxidase. Hydrogen peroxide further reacts with phenol and 4-aminoantipyrine by the catalytic action of peroxidase to form a red color quinoneimine dye complex. The intensity of the color formed is directly proportional to the amount of glucose present in the sample.

HbA1c was estimated by the Ion Exchange Resin method (Nathan *et al*., 1984) using a commercial diagnostic kit procured from Crest Biosystems, Goa, India. HbA1c has been defined operationally as the fast fraction hemoglobins HbA1 (Hb A1a, A1b, A1c) which elute first during column chromatography. The non - glycosylated hemoglobin, which consists of the bulk of hemoglobin, has been designated HbAo. A hemolysed preparation of the whole blood was mixed continuously for 5 minutes with a weakly binding cation-exchange resin. The labile fraction was eliminated during the hemolysate preparation and during the binding. During this mixing, HbAo bind to the ion exchange resin leaving HbA1c free in the supernatant. After the mixing period, a filter separator was used to remove the resin from the supernatant. The percent glycosylated hemoglobin was determined by measuring absorbances of the ratio of the absorbances of the HbA1c & the total hemoglobin fraction of the Control and the Test.

Determination of serum insulin

Insulin was determined in serum samples using Ultra sensitive rat insulin ELISA kit from Crystal chem inc. (USA). The estimation was done according to the instructions of the manufacturer and expressed as ng/ml.

Markers of Renal Function

Kidney damage during diabetes was evaluated by the following markers in serum: blood urea nitrogen (BUN) level, serum creatinine (Scr) concentration and alkaline phosphatase (ALP) activity using commercial diagnostic kits procured from Span Diagnostics Ltd., Surat, India.

BUN was estimated by the DAM Method (Wybenga, Giorgio, Pileggi, 1971). As per standard protocol urea in an acidic medium condenses with diacetyl monoxime at

100°C to form a red color complex. The intensity of the color formed was directly proportional to the amount of urea present in the sample.

Scr was estimated by the alkaline picrate method (Jaffe, 1886). According to standard protocol, picric acid in an alkaline medium reacts with creatinine to form an orange color complex with the alkaline picrate. The intensity of the color formed was directly proportional to the amount of creatinine present in the sample.

ALP was estimated by the Kind and King's method (1954). According to standard protocol, ALP at an alkaline pH hydrolyses di- sodium-phenylphosphate to form phenol. The phenol formed reacts with 4-aminoantipyrine in the presence of potassium ferricyanide, as an oxidising agent, to form a red color complex. The intensity of the color formed was directly proportional to the activity of ALP present in the sample. The calculations were obtained using the standard formula provided by the manufacturer's instructions. The mixture was incubated for 30 min at 25°C after adding 0.1 ml serum. The absorbance was read at 410 nm. ALP activity was expressed as units/dl in serum.

Assay for lipid profile

Serum Cholesterol [total cholesterol (TC) & HDL cholesterol (HDL-C)] was estimated by the one-step method of Wybenga *et al.* (1970) and serum triglyceride (TG) was estimated by GPO-PAP, End Point Assay (Stein, Myers, 1995) using commercial diagnostic kits procured from Span Diagnostics Ltd., Surat, India. LDL cholesterol (LDL-C) and VLDL cholesterol (VLDL-C) were calculated by using Friedewald's equation.

Statistical analysis

Results were expressed as mean ±SEM. Statistical analysis of the data was done by using SPSS 16 software and applying the analysis of variance (ANOVA) followed by Tukey's post-hoc test. The P-value < 0.05 was considered statistically significant.

RESULTS

Effect of SAC and TAU on T2DM-induced hyperglycemia

As direct evidence, our results showed that the combined dose of SAC and TAU was more effective in lowering the blood glucose level in the diabetic rats in comparison to the separate treatment with SAC and TAU. HbA1c as the consequence of significant hyperglycemic blood was also of interest to compare between the treatment groups. According to data presented in (Table I) consistent with effects on serum glucose level combined SAC/TAU dosing was more effective in lowering HbA1c level in NA/STZ group rats in comparison to the separate treatment with SAC and TAU. The four-week treatment with SAC and TAU in combined form resulted in a significant (P < 0.05) decreased in HbA1c level and was comparable to standard groups receiving GL.

TABLE I - Effect of SAC, TAU and SAC/TAU treatment on FBG, HbA1C and insulin in T2DM animals

	Control	SAC/TAU	NA/STZ	NA/STZ + SAC	NA/STZ + TAU	NA/STZ + SAC/TAU	NA/STZ + GL
FBG (mg/dl)	124.53±0.92	121.52±1.67	256.98±1.28*	169.83±0.84**	164.18±1.38**	131.48±0.76***	126.33±0.89***
HbA1c (%)	06.60±1.68	06.80±1.14	12.65±1.27*	09.50±2.09**	09.60±1.59**	08.50±1.29***	08.20±2.17***
Insulin (ng/ml)	3.20±0.13	3.13±0.14	0.52±0.14*	1.70±0.11**	1.80±0.09**	2.30±0.13***	2.50±0.15***

The data represented as the mean ±SEM. *P<0.05 diabetic (NA/STZ) group vs. control OR SAC/TAU group. **P<0.05, ***P<0.01. NA/STZ+SAC, NA/STZ+TAU and NA/STZ+SAC/TAU group vs. diabetic (NA/STZ) group.

Effect of SAC and TAU on insulin in T2DM animals

Insulin values were significantly ($P < 0.05$) lower in NA/STZ group compared to the control group. Treatment with SAC or TAU or SAC/TAU restored a significant level of insulin when compared to diabetic NA/STZ group.

Effect of SAC and TAU on lipid profile in T2DM animals

Lipid profile (serum TC, TG, HDL-C, LDL-C and VLDL-C) values of different groups of animals during the treatment period of study were recorded in (Table II). Accordingly, the NA/STZ group showed significantly ($P < 0.05$) increased levels of serum TC, TG, LDL-C, VLDL-C and decreased level of serum HDL-C compared with the normal control rats. Supplementation of SAC or TAU or SAC/TAU showed a significant ($P < 0.05$) restoration of these parameters. Administration of GL into diabetic rats also showed a significant reduction in the levels of TG, TC, LDL-C and VLDL-C but less effective as compared to SAC/TAU group.

TABLE II - Effect of SAC, TAU and SAC/TAU treatment on lipid profile in T2DM animals

Groups/ parameters	Control	SAC/TAU	NA/STZ	NA/STZ + SAC	NA/STZ + TAU	NA/STZ + SAC/TAU	NA/STZ + GL
TC (mg/dl)	135.65±1.2	153.65±1.4 (+ 1.31%)	270.74±2.6* (+ 99.58%)	201.21±3.4** (- 25.68%)	198.54±3.3** (- 26.66%)	187.42±3.9*** (- 30.77%)	196.35±3.5*** (- 27.47%)
TG (mg/dl)	121.06±0.37	173.06±0.43 (+ 1.69%)	225.73±0.82* (+ 86.46%)	168.58±3.1** (- 25.31%)	161.80±2.11** (- 28.32%)	158.52±2.9*** (- 29.77%)	162.34±3.2*** (- 28.08%)
HDL (mg/dl)	37.44±1.9	43.21±1.2 (- 2.99%)	17.97±3.5* (-52.00%)	28.32±1.7** (+57.59%)	29.63±.81** (+64.88%)	28.35±2.4*** (+57.76%)	29.56±2.1*** (+64.49%)
LDL (mg/dl)	73.99±0.74	97.45±0.86 (- 3.43%)	207.62±1.1* (+ 180.60%)	144.42±2.8** (- 30.44%)	134.87±2.11** (- 35.04%)	127.36±3.9*** (- 38.65%)	132.66±3.1*** (- 36.10%)
VLDL (mg/dl)	24.21±0.62	31.82±0.38 (- 4.91%)	45.14±0.42* (+86.45%)	33.31±0.90** (- 26.20%)	35.75±1.11** (- 20.80%)	31.70±1.3*** (- 29.77%)	33.76±1.5*** (- 25.21%)

The data represented as the mean ±SEM. *P<0.05 diabetic (NA/STZ) group vs. control OR SAC/TAU group. **P<0.05, ***P<0.01.NA/STZ+SAC, NA/STZ+TAU and NA/STZ+SAC/TAU group vs. diabetic (NA/STZ) group.

Effect of SAC and TAU on Markers of Renal Function in T2DM animals

Renal function markers (BUN, Scr and ALP) were estimated to evaluate the efficacy of different treatments on T2DM induced derangements (Figure 1, a-c). The data conclusively depicted that the supplementation of SAC or TAU or a combination of SAC and TAU showed a significant ($P < 0.05$) restoration of renal function markers (BUN, Scr and ALP) as compared with the diabetic group. Following administration of GL diabetic rats also showed a significant reduction in the renal function markers levels but less effective compared to SAC and TAU combination therapy. However, it was found to have no influence on renal function markers of control + SAC/TAU group compared to the control group.

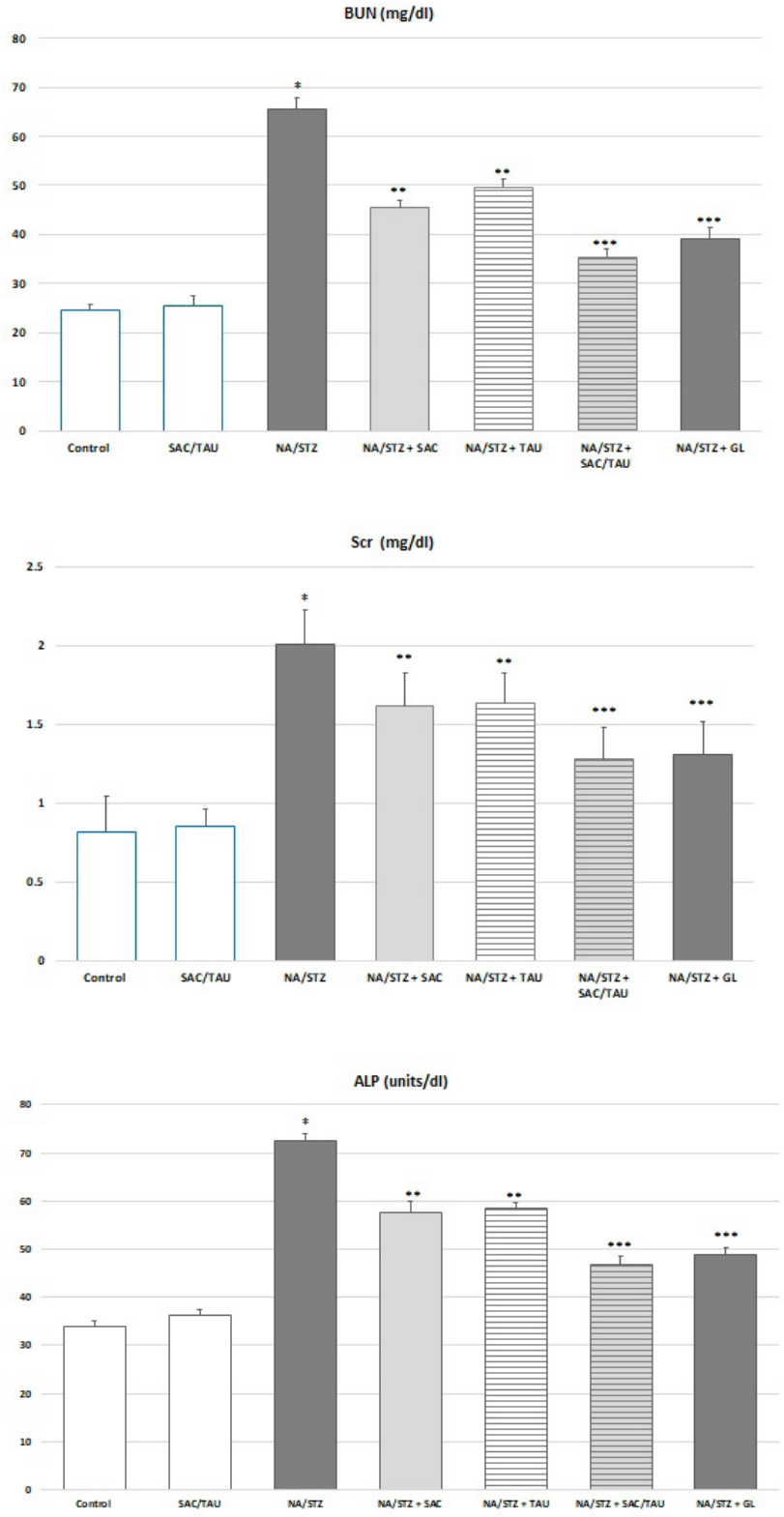

FIGURE 1 - Effect of SAC, TAU and SAC/TAU treatment on conventional markers of renal integrity. NA/STZ group showed a significant increase in (**A**) BUN, **(B)** Scr and (**C)** ALP in serum samples. SAC, TAU and GL treatment preserved the marker levels with the highest effect detected with SAC/TAU combination. Values are expressed as mean ± S.E.M. *P<0.05 diabetic (NA/STZ) group vs. control OR SAC/TAU group. **P<0.05, ***P<0.01.NA/STZ+SAC, NA/STZ+TAU and NA/STZ+SAC/TAU group vs. diabetic (NA/STZ) group.

DISCUSSION

In the present study we determined that NA/STZ-induced T2DM causes hyperglycemia, dyslipidemia followed by renal dysfunction in rats similar to previous research (Clozel *et al*., 2006). Administration of SAC and TAU combination was effective to revert these alterations significantly due to their antioxidant potential. These beneficial effects of SAC and TAU were supported by previous findings indicating either of the amino acids may correct the deranged metabolism in the diabetic subjects (Ito, Schaffer, Azuma, 2012; Sirdah, 2015; Sarkar *et al*., 2017; Ansari *et al*., 2018; Uddandrao *et al*., 2019).

Results showed that diabetic group had a significant increase in the blood glucose level when compared to the control group while supplementation with SAC and TAU improved glucose level. In the present study, NA/STZ induced diabetic rats had much higher HbA1c level and decreased insulin level than of the control group. Oral administration of SAC and TAU decreased the HbA1c level and restore the insulin level in the treatment groups. Studies have suggested a strong relationship between HbA1c and diabetes (Alberti 1982; Parveen *et al*., 2013; Kotha *et al*., 2017). Administration of SAC and TAU restored these metabolic markers by virtue of their potent antioxidant property through inhibiting oxidative reactions consistent with previous findings (Elgawish *et al*., 1996; Haber *et al*., 2003; Harada *et al*., 2004; Nakaya *et al*., 2000). Furthermore we hypothesize that SAC may significantly decreased hyperglycemia in the diabetic animals by improving islet architecture, enhancing glucose utilization and β-cell function or correcting insulin response similar in line with previous studies (Kim *et al*., 2017).

In diabetes, kidneys are unable to filter the blood and produce urine due to altered cell membrane permeability and loss of functional integrity. Consequently, the body showed abnormalities in reabsorption of salt and water along with a buildup of waste materials in the blood than normal. All these result in increased urea and creatinine levels in the blood (Baxmann *et al*., 2008). In the present work, administration of NA/STZ resulted in acute renal function alteration. The data obtained from the present study clearly shows the increased level of renal function markers (viz. BUN, Scr, and ALP) in T2DM. In fact, TAU when administered together with SAC in T2DM animals underlies the remarkable improvement in these markers consistent with previous reports (Mong, Yin, 2012; Sirdah, 2015; Uddandrao *et al*., 2019), thus showing combination therapy more effectively protect against NA/STZ-induced renal damage in T2DM.

Dyslipidemia followed by β-cell dysfunction may lead to moderate changes in insulin signaling along with peripheral utilization of glucose (Mitchell, Veall, Watts, 1972). Earlier studies have demonstrated that high levels of LDL-C in the diabetic patients was associated with an increased risk of cardiovascular diseases (Rachek, 2014). As abnormalities occurred from hypertriglyceridemia and low HDL-C, assessment of lipid profiles is necessary to control diabetes and its related complications. According to our data, SAC and TAU treatment showed approximate reduction in levels of TC, TG, LDL-C and VLDL-C in T2DM as much as that by GL treatment. This might be supported by recent evidences that TAU or SAC supplementation in T2DM animal models is documented to improve circulatory triglyceride and cholesterol level (Nakamura-Yamanaka, Tsuji, Ichikawa, 1987; Yokogoshi *et al*., 1999; Takemura *et al*., 2013; Asdaq, 2015; Ho *et al*., 2016; Ha, Ying, Kim, 2015). Moreover remarkable protective effect of TAU on lipid profile may be due to reduced cholesterol level through CYP7A1 gene upregulation enhancing cholesterol conversion into bile acids (Yokogoshi *et al*., 1999; Chen, Guo, Chang, 2012).

Additionally, studies have suggested that hyperglycemia is linked to nuclear factor kappa-B (NFκB) activation (Schreck, Albermann, Baeuerle, 1992). Furthermore, NFκB is involved in the regulation of COX-2 and iNOS expressions (Mohamed *et al*., 1999), which also play a role in hyperglycemia and correcting secretory defects (Fukuda *et al*., 2001; Gunawardana, Head, Piston, 2008; Surh *et al*., 2001). One possible mechanism of action of SAC to improve hyperglycemia might be that it stimulated the remaining β-cells to secrete insulin by reducing the expression of nitric oxide synthase (Kobuchi, Virgili, Packer, 1999). Furthermore, SAC administration might provide protection against renal damage due to its anti-inflammatory property by counteracting activation

of NFκB consisted with other studies (Fujimoto *et al*., 2005; Mong, Yin, 2012; Uddandrao *et al*., 2019).

In conclusion, our results support the efficacy of combined action of SAC with TAU in improving the hyperglycemia, dyslipidemia along with the severity of renal dysfunction. These beneficial outcomes were supported due to their antioxidant and anti-inflammatory properties, rationally describing its antidiabetic potential. Additionally, we also found the combined therapeutic efficacy of SAC and TAU was comparable with that of GL against NA/STZ induced T2DM. Thus, SAC and TAU when given in combination may provide potent therapeutic efficacy in managing diabetes-related complications.

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