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Effect of traditional plant medicines (*Cinnamomum zeylanicum* and *Syzygium cumini*) on oxidative stress and insulin resistance in streptozotocin-induced diabetic rats

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Abstract Many traditional plants have been used to fight life-threatening diseases such as diabetes. These plants have been shown to possess antioxidant activities, improving the diabetes inconveniences. Wister albino rats became diabetic by streptozotocin (STZ) induction. The effect of 200 mg/kg ethanolic extracts of either *Cinnamomum zeylanicum* bark (CZ) or *Syzygium cumini* seeds (SC) was investigated on STZ-induced diabetic rats. The impact of CZ or SC administration was observed. Blood glucose, insulin level, hemoglobin content, lipid profile, liver and kidney functions, and antioxidant enzymes in plasma were evaluated. Diabetic rats exhibited an increase in the levels of blood glucose, total cholesterol, triglycerides and low density lipoprotein cholesterol (LDL-cholesterol). In contrast, the levels of insulin and high density lipoprotein cholesterol (HDL-cholesterol) were diminished.

The oral administration of CZ and SC showed a decrease in glucose level, total cholesterol, triglycerides, and LDL-cholesterol, whereas an increase in insulin level and HDL-cholesterol were recorded. What's more, the antioxidant enzymes in diabetic control rats showed significantly abnormal activities of low superoxide dismutase (SOD), catalase (CAT), glutathione peroxide (GPx) activities and reduced glutathione (GSH) compared to treated diabetic rats. Also, in the extent of lipid peroxidation (LPO).

Both CZ and SC possessed antioxidant activity as shown by elevated SOD and GPx activities and reduction in LPO. CZ and SC are functioning to improve the level of insulin, hyperglycemia, hyperlipidemia, oxidative stress and kidney and liver dysfunctions in STZ-induced diabetic rats.

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Introduction

The metabolic disorders such as hyperglycemia, altered lipid profile, carbohydrates and protein metabolisms and increased risk of cardiovascular disease complications are associated with diabetes mellitus (Davis and Granner, 2001). It is influencing upwards of around 200 million throughout the world. Both types 1 and 2 of diabetes offer hyperglycemia, microvascular and macrovascular intricacies. Moreover, the altered lipoprotein metabolism has been involved in both forms of diabetes in the pathogenesis of the cardiovascular ailment (Howard, 1987). Furthermore, expanded free radicals' level is accompanied with diabetes which has been seen as debilitated antioxidant defense. Progression of diabetes and its complications are caused by oxidative anxiety (Berryman et al., 2004). Currently, medications such as oral hypoglycemic agents and insulin control diabetes sickness have their own constrains. It has been found that the antioxidant action of many traditional medicinal plants may play some role in their remedial activities (Tanko et al., 2008). *Cinnamomum zeylanicum* (CZ) and *Syzygium cumini* (SC) are used in the present study as ethanolic extracts. Previous studies specify the active ingredients of both plant extracts. The primary constituents of CZ bark oil are trans cinnamaldehyde (72.0–82.15%), which is assessed by GC–MS analysis (Wang et al., 2009). Minor constituents were estimated in all Cinnamomum species such as trans cinnamyl acetate (3.24–3.65%), eugenol (1.07–13.3%), trans cinnamyl alcohol (0.5–0.6%), o-methoxy benzaldehyde (0.09–0.15%), benzyl benzoate (0.4–1.0%), α-terpineol (0.35–0.62%), β-caryophyllene (1.0–2.0%), linalool (0.7–1.06%), limonene (0.09–0.095%), myrcene (0.07–0.08%), β-pinene (0.02–0.03%), traces of benzaldehyde and trans cinnamic acid have been estimated by GC (Charalambous, 1994; Wang et al., 2011; Kamaliroosta et al., 2012). Gas chromatography of ethanolic extract of SC seeds reveals the presence of gallic acid, ellagic acid, corilagin and related ellagitannins, 3,6-hexahy droxydiphenoyl-glucose and its isomer, 4,6-hexahydroxydip henoyl glucose, 1-galloyl glucose, 3-galloyl glucose and quercetin (Bhatia and Bajaj, 1975). The seed oil consists of 33.2% 1-chlorooctadecane, 9.24% tetratetracontane, 8.02% decahydro-8a-ethyl-1,1,4a,6-tetramethylnapahthalene, 5.29% 4-(2-2-dimethyl-6-6-methylenecyclohexyl) butanol, 5.15% octadecane, 3.97% octacosane, 1.72% heptacosane and 1.71% eicosane (Kumar et al., 2009).

The present study explores the possible action of medicinal plants, *C. zeylanicum* and *S. cumini* that may treat oxidative anxiety in experimental diabetic rats. Additionally to determine whether the ethanolic extracts of CZ and SC have any lipidemic impact or anti-progression of diabetic complications.

Materials and methods

Plant

CZ bark and SC seed samples were collected from the market in Riyadh. Identification of samples was done on record in the herbarium of the research center for Medicinal Aromatic and Poisonous Plants, College of Pharmacy, King Saud University, Riyadh, SA.

Extraction of CZ bark and SC seeds

CZ Barks and SC seeds were both washed separately under running tap water followed by sterile distilled water. These were dried at room temperature (300C) for 2 days and ground to fine powder then stored in air-tight bottles. Ethanolic extraction was done by dissolving 10 g of bark or seed powder in 100 ml ethanol with shaking then kept for 24 h. The suspension was filtered then extract was concentrated under vacuum below 400C using Rotary Evaporator System (Cole-Parmer). UV rays for 24 h were applied on the dried extract that was checked for sterility on nutrient agar plates. The extract was stored in a freezer at 40C, in labeled sterile bottles until use.

Animal

Thirty healthy adult male Wister albino rats weighing 150–200 g, 2–3 months of age were used for the present study. Animals were caged individually under controlled standard conditions of light, temperature and humidity. They were fed with standard pellet diet and provided water ad libitum. All experiments were conducted according to the ethical guidelines of the International Association for the Study of Pain (Zimmermann, 1983) and the standard guidelines for animal use.

Experiment

Twenty-four animals were grouped into four trials as follows:

(1) Normal Control rats (6 rats) administered citrate buffer (0.1, pH 4.5; i.p).
(2) Diabetic Control rats (6 rats) which were Streptozotocin-induced diabetic rats.
(3) *S. cumini* (6 rats). STZ-induced diabetic rats were administered 200 mg SC/kg body weight 14 days after induction of diabetes. Oral administration of SC was given for 4 weeks, once weekly.
(4) *C. zeylanicum* (6 rats). STZ-induced diabetic rats were administered 200 mg CZ/kg body weight 14 days after induction of diabetes. Oral administration of CZ was given for 4 weeks, once weekly.

Diabetes mellitus induction

In the overnight fasted rats, streptozotocin (STZ) (Sigma Chemicals, St. Louis, MO, USA) dissolved in freshly prepared 0.1 M cold citrate buffer, pH 4.5 was injected intraperitoneally (60 mg/kg) (Ramachandran et al., 2011). To avoid fatal hypoglycemia after 6 h of STZ injection, rats received 5% dextrose solution for the next 24 h (Tanko et al., 2008). Blood glucose levels were measured to confirm diabetes after 72 h by using one touch glucometer with glucose oxidase–peroxidase strips. Diabetic rats were kept 14 days under standard laboratory condition for stabilizing blood glucose levels. After 14 days of diabetes induction, blood glucose levels were rechecked. Animals with blood glucose level higher than 250 mg/dl were picked out for the current experiments.

Samples

Rats were anaesthetized with halothane (4%) to collect blood from the cardiac puncture. Also, livers were taken for monitoring antioxidant activity. Glucose was determined directly after collecting blood. The rest of blood was kept frozen as a serum at −20 °C.

Glucose, insulin and hemoglobin estimation

Glucose was determined according to the method of Trinder (1969). Serum insulin was determined by radioimmunoassay method using rat insulin as a standard, according to Adebajo et al. (2007). The hemoglobin (Hb) and glycosylated hemoglobin (HbA1c) were estimated in fresh blood using the cyanomethemoglobin method described by van and Zijlstra (1961).

Kidney & liver functions

The serum creatinine, urea, total protein, serum glutamate-pyruvate transaminase (SGPT) and serum glutamate–oxaloacetate transaminase (SGOT) levels were analyzed by commercial kits (Span Diagnostics Ltd, Surat, India). All biochemical parameters were estimated using semi-autoanalyzer (Photometer, Germany).

Serum lipid profiles

Cholesterol and triglycerides were determined according to Richmond (1973) and Young (1997). Low-density lipoproteins (LDL) and very low density lipoproteins (VLDL) in samples precipitate with phosphotungestate and magnesium ions (Young, 1995). After centrifugation, the cholesterol concentration in the HDL fraction remaining in the supernatant is determined (Lopes-Virella et al., 1977).

Liver antioxidants

Lipid peroxidation (LPO) was assayed according to the method of Ohkawa et al. (1979). Superoxide dismutase (SOD) activity was assayed according to the method of Marklund and Marklund (1974). Catalase activity was measured based on the ability of the enzyme to break down H_2O_2 (Sinha, 1972). Non-enzymatic antioxidant as reduced glutathione (GSH) was determined by the method of Ellman (1959).

Statistical analysis

Results are expressed as mean ± SE. Statistical analysis was performed on SPSS software (version 18) using unpaired Student's *t*-test, to compare results between two groups at different times. Moreover, comparison within each group (before-after test) was conducted using ANOVA and Bonferroni's Multiple Comparison Test. *P* values less than 0.05 were considered statistically significant.

Results

Effect of ethanolic extract of CZ and SC on blood glucose level

The blood glucose levels were significantly increased after the injection of STZ compared to the normal control rats (Table 1). There was a significant decrease in blood glucose level after treatment of 200 mg/kg SC ($p < 0.05$) or CZ however the drop was more significant ($p < 0.001$) (Table 1).

Effect of ethanolic extract of CZ and SC on serum insulin levels

STZ-induced rats of diabetes had decreased level of serum insulin significantly ($p < 0.001$) in comparison with normal control rats, while the treatment of SC and CZ significantly ($p < 0.001$ and $p < 0.05$) increased serum insulin levels, toward normal levels, more than diabetic control rats (Table 2).

Effect of ethanolic extract of CZ and SC on Hb, HbA1c

Induction of diabetes significantly ($p < 0.001$) increased the level of HbA1c, but decreased the level of Hb when compared to normal control rats (Table 2). In diabetic rats, treatment of SC and CZ significantly ($p < 0.001$ and $p < 0.05$) reduced elevated HbA1c levels and increased Hb toward normal levels compared to diabetic control rats (Table 2).

Effect of ethanolic extract of CZ and SC on lipid profiles

There was a significant ($p < 0.05$) increase in total cholesterol (TC), low density lipoprotein (LDL), very low density lipopro-

Table 1 Hypoglycemic activity of *Cinnamomum zeylanicum* (CZ) and *Syzygium cumini* (SC) in STZ-induced diabetic rats (mean ± SE) ($n = 6$).

Treatment	Blood glucose (mg/dL)				
	14 days of STZ injection	1 week	2 weeks	3 weeks	4 weeks
Normal control	71.3 ± 4.6	74.9 ± 5.1	78.4 ± 4.9	75.9 ± 5.1	81.2 ± 6.2
Diabetic control	280.4 ± 16.2[a]	261.5 ± 16.2[a]	284.1 ± 17.3[a]	262.4 ± 15.1[a]	297.0 ± 2[a]
SC treatment	268.8 ± 13.1[b]	168.6 ± 14.1[*]	139.2 ± 15.2[b*]	107.7 ± 9.7[b*]	92.3 ± 8.2[b*]
CZ treatment	257.5 ± 21.2	176.2 ± 12.3[c*]	147.4 ± 11.4[c*]	125.3 ± 0.1[c*]	122.9 ± 11.2[c*]

[a] $p < 0.001$ between the normal control and diabetic control.
[b] $p < 0.001$ between the diabetic control and SC treatment.
[c] $p < 0.05$ between the diabetic control and CZ treatment.
[*] $p < 0.01$ between STZ injection and SC or CZ treatment.

Table 2 Effect of *Cinnamomum zeylanicum* (CZ) and *Syzygium cumini* (SC) on serum insulin, Hb and HbA1c in STZ-induced diabetic rats (mean ± SE) (n = 6).

Treatments	Serum insulin (IU/mL)	Hb (g/dL)	HbA1c (%)
Normal control	2.73 ± 0.09	14.07 ± 0.49	7.02 ± 0.17
Diabetic control	0.87 ± 0.04[a]	8.56 ± 0.52[a]	12.07 ± 0.30[a]
SC treatment	1.35 ± 0.08[b]	12.35 ± 0.64[b]	9.56 ± 0.19[b]
CZ treatment	0.99 ± 0.06[c]	10.27 ± 0.37[c]	10.03 ± 0.13[c]

Hemoglobin (Hb); glycated hemoglobin (HbA1c).
[a] $p < 0.001$ between the normal control and diabetic control.
[b] $p < 0.001$ between the diabetic control and SC treatment.
[c] $p < 0.05$ between the diabetic control and CZ treatment.

tein (VLDL), and triglyceride (TG) levels (Table 3). Oppositely, high density lipoprotein (HDL)-cholesterol levels recorded a significant ($p < 0.05$) decrease in STZ diabetic rats as compared to control rats (Table 3). CZ and SC administration showed significant ($p < 0.001$) reduction in elevated TC, TG, and LDL when compared to diabetic control rats. Also, a significantly ($p < 0.05$) increased level of HDL was observed in diabetic rats after treatment with CZ and SZ compared to diabetic control rats (Table 3). However, treatment with both CZ and SC could not produce any significant change in the levels of VLDL. Finally, treatment with SC showed more significant improvements in the lipid levels compared to CZ treated diabetic rats (Table 3).

Effect of ethanolic extract of CZ and SC on liver and kidney functions

Table 4 represents the efficacy of CZ and SC on SGOT, SGPT, total protein, creatinine and urea levels in diabetic rats. The mentioned biochemical parameters were significantly ($p < 0.001$) altered in STZ-induced diabetic rats compared to normal control rats. In diabetic rats, administration of CZ significantly ($p < 0.05$) lowered the increased levels of SGOT, SGPT, creatinine and urea in diabetic control rats. The SC treatment showed significantly ($p < 0.001$) higher reduction of SGOT, SGPT levels compared to CZ treated diabetic rats (Table 4).

Effect of ethanolic extract of CZ and SC on antioxidant activity

The antioxidant activity of CZ and SC in the liver was studied in diabetic rats. After the induction of diabetes by STZ, significant ($p < 0.001$) decreased levels of SOD, CAT, GPx, reduced GSH and increased the levels of TBARS in liver were observed in comparison to normal control rats (Fig. 1). These altered antioxidant levels were reversed significantly to near normal levels after the administration of SC ($p < 0.001$) and CZ ($p < 0.01$) by comparing to diabetic and normal control rats (Fig. 1).

Discussion

STZ [2-deoxy-2-3(3-methyl-3-nitrosoureido)-D-glucopyranose] is commonly used to instigate experimental diabetes in

Table 3 Hypolipidemic activity of *Cinnamomum zeylanicum* (CZ) and *Syzygium cumini* (SC) in STZ-induced diabetic rats (mean ± SE) (n = 6).

Treatment	Serum lipid profile (mg/dL)				
	TC	TG	HDL	LDL	VLDL
Normal control	56.31 ± 5.19	104.24 ± 4.93	71.04 ± 4.36	38.14 ± 3.27	23.48 ± 3.57
Diabetic control	91.25 ± 6.21[a]	158.24 ± 5.75[a]	37.48 ± 4.20[a]	91.58 ± 5.39[a]	31.28 ± 5.21[a]
SC treatment	62.46 ± 5.32[b]	109.27 ± 4.11[b]	58.32 ± 2.49[b]	61.26 ± 4.48[b]	28.25 ± 2.56
CZ treatment	71.39 ± 3.97[c]	124.32 ± 4.18[c]	61.69 ± 5.04[c]	55.47 ± 3.94[c]	29.03 ± 2.47

Total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL).
[a] $p < 0.05$ between the normal control and diabetic control.
[b] $p < 0.05$ between the diabetic control and SC treatment.
[c] $p < 0.05$ between the diabetic control and CZ treatment.

Table 4 Effect of *Cinnamomum zeylanicum* (CZ) and *Syzygium cumini* (SC) on serum biochemical parameters in STZ-induced diabetic rats (mean ± SE) (n = 6).

Treatment	SGOT (IU/L)	SGPT (IU/L)	Total protein (g/dL)	Creatinine (mg/dL)	Urea (g/dL)
Normal control	102.48 ± 4.8	86.36 ± 3.2	8.52 ± 1.62	0.54 ± 0.31	38.48 ± 2.2
Diabetic control	167.37 ± 7.3[a]	139.05 ± 4.1[a]	5.98 ± 1.3	0.78 ± 0.42	128.29 ± 5.3[a]
SC treatment	136.35 ± 5.6[b]	99.74 ± 4.1[b]	6.71 ± 1.0	0.65 ± 0.34	83.39 ± 2.9[b]
CZ treatment	143.26 ± 3.7[c]	107.37 ± 3.2[c]	7.02 ± 0.9	0.69 ± 0.27	69.24 ± 3.9[c]

Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT).
[a] $p < 0.05$ between the normal control and diabetic control.
[b] $p < 0.05$ between the diabetic control and SC treatment.
[c] $p < 0.05$ between the diabetic control and CZ treatment.

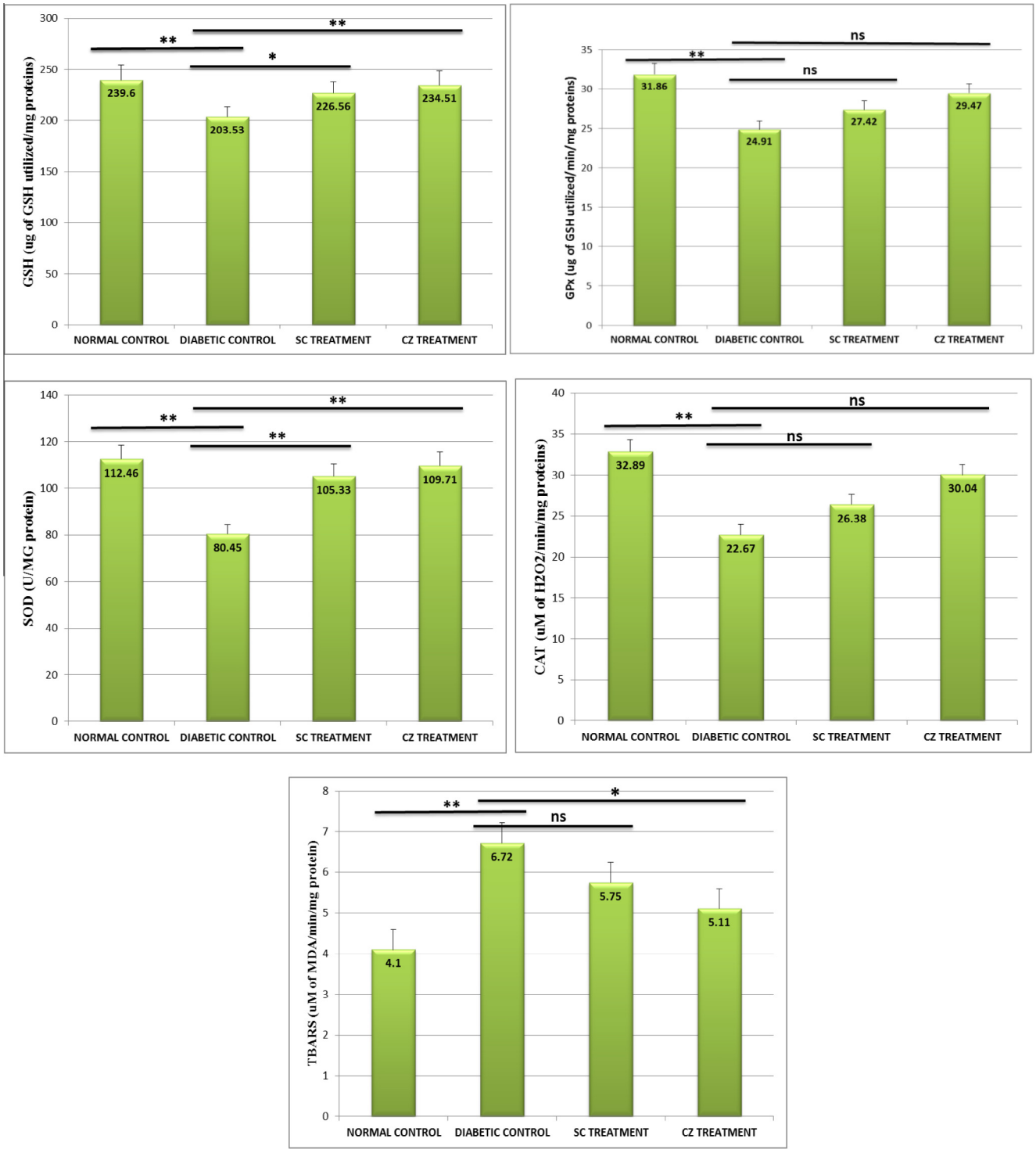

Figure 1 Antioxidant activity of *Cinnamomum zeylanicum* (CZ) and *Syzygium cumini* (SC) on liver in STZ-induced diabetic rats (mean ± SE) ($n = 6$). GSH; reduced glutathione, GPx; glutathione peroxidase, SOD; superoxide dismutase, CAT; catalase, MDA; malondialdehyde. ($^{*}p < 0.05$; $^{**}p < 0.01$, ns = not significant.)

animals (Al-Attar and Zari, 2007). In our study, raised blood glucose level and decreased insulin level were markedly observed in STZ-induced diabetic rats. The toxicity of STZ is due to DNA alkylation of its methyl nitrosourea moiety mainly at the O6 position of guanosine (Szkudelski, 2001). The transfer of the methyl group from STZ to the DNA molecule causes damage which results in fragmentation of DNA and functional imperfections of the beta cells (Szkudelski, 2001). Moreover, STZ has potential to act as an intracellular nitric oxide (NO) donor and generates reactive oxygen species (ROS). The synergistic action of both NO and ROS may also contribute to DNA fragmentation and

other deleterious changes caused by STZ (Lenzen, 2008). CZ and SC ethanolic extracts were administered orally at 200 mg/kg body weight. The oral LD50 of cinnamon bark oil in rats has been determined as 4.16 g/kg body weight. For cinnamaldehyde, the oral LD 50 in rats is 2.22 g/kg body weight (ESCOP, 2003). Evaluation of the safety of the hydroalcoholic extract (HE) of *S. cumini* (L.) is done in rodents. Acute toxicity is evaluated through the determination of an LD50 in mice and rats (up to 14 days). In mice, the oral administration of the HE (0.1 at 6 g/kg) causes no death (Silva et al., 2012). In the present study, the oral dose given (200 mg/kg body weight) has been used in several studies, even more up to 600 mg/kg, as safe and sublethal doses (Rekha et al., 2008; Tanko et al., 2008; Alikatte et al., 2012). Administration of CZ and SC to diabetic rats significantly reduced blood glucose level from the first week to the fourth week contrasted with diabetic control rats. Accompanied to that decline of glucose level, these plant extracts (particularly SC) increased the insulin level compared to diabetic control rats. Consequently, the hypoglycemic activity of CZ and SC may be due to their protective action against STZ-mediated damage to the pancreatic beta cells or regeneration of damaged beta cell. Sharma et al. (2012) suggest that SC improved glucose homeostasis occurred through a mechanism that restored β-cell capacity and insulin activity. Also, Anandharajan et al. (2006) shows that SC augmented glucose uptake by up-regulating the glucose transporter-4, PPARγ, and phosphatidylinositol 3-kinase in L6 myotubes. The hypoglycemic activity of SC in diabetic rats has been indicated as a result of increased hexokinase and decreased glucose-6 phosphatase enzyme activities in the liver, leading to increased glycogenesis and decreased glycogenolysis and gluconeogenesis (Sharma et al., 2008). On the other hand, CZ prevents the development of insulin resistance, at least in part by enhancing insulin signaling and possibly via the NO pathway in skeletal muscle (Qin et al., 2010a). Additionally, other study affirms that CZ increased glucose uptake and GLUT4 (glucose transporter) expression in 3T3-L1 adipose cells. It has been revealed that a water extract of cinnamon (Cinnulin PF®) reduces blood glucose level and soluble cluster of differentiation 36 (CD36), which is reported as a novel marker of insulin resistance (Handberg et al., 2006; Qin et al., 2010b). In other study, reduction of blood glucose by CZ appears by many mechanisms as reducing intestinal glucose absorption, stimulating cellular glucose uptake, glycogen synthesis, insulin release, potentiating insulin receptor activity and inhibiting gluconeogenesis (Ranasinghe et al., 2013). Likewise, cinnamon bark extracts are found potentially useful for the control of uptake glucose in diabetic patients through inhibition of intestinal α-glucosidase and pancreatic α-amylase (Adisakwattana et al., 2011; Kongstad et al., 2015).

Also, the present results demonstrate the increased level of HbA1c and decreased Hb level in diabetic rats compared to normal control rats, which may indicate the occurrence of glycosylation in diabetic rats due to hyperglycemia. HbA1c is the product of non-enzymatic response between glucose and free amino groups of Hb (glycosylation) (Mohammadi and Naik, 2008). Administration of CZ and SC to the diabetic rats significantly reduced HbA1c levels and increased Hb levels compared to diabetic control rats. This indication may due to improved blood glucose level or glycation process inhibition. HbA1c is a marker of evaluation of long-term glycemic control in diabetic patients and predicts risks for the development and/or progression of diabetic complications (Tembhurne and Sakarkar, 2011). Previous studies have reported that 10% steady reduction in HbA1c determined a 35% risk reduction for retinopathy, a 25–44% risk reduction for nephropathy and a 30% risk reduction for neuropathy (Tembhurne and Sakarkar, 2010). Also, cinnamon has found to prevent glycation mediated RBC-IgG cross-links and HbA1c accumulation in diabetes rats (Muthenna et al., 2014). Also, Sartorius et al. (2014) have recorded a decrease of fasting glucose levels in heavily obese and insulin resistant mice by CZ extract supplementation for 6 weeks. The previous model shows a decrease in liver triglyceride content and an increase in glycogen concentration alongside improved insulin sensitivity of the liver and in SC as well (Sartorius et al., 2014; Bitencourt et al., 2015). Same results are observed after SC extract administration (Tripathi and Kohli, 2014).

In STZ-induced diabetic rats, elevated levels of SGPT and SGOT, urea and creatinine were observed. This behavior suggested the occurrence of liver and kidney damages after the administration of STZ to the rats. Others have referred these elevations to STZ mediated liver damages, which may cause leakage of above enzymes into the blood (Calisti and Tognetti, 2005). The persistent hyperglycemia, hemodynamic changes within the kidney tissue and free radical generation mediated renal dysfunction, which results in elevation of urea and creatinine levels in blood (Aurell and Bjorck, 1992; Prabhu et al., 2008; Shokeen et al., 2008). Administration of CZ and SC to the diabetic rats essentially reduced the SGOT, SGPT, creatinine and urea levels, which indicated the preservative action of CZ and SC on liver and kidney damages in diabetic condition. CZ ameliorates diabetes mediated renal malfunction in rats as evidenced by reduced urinary albumin and creatinine (Muthenna et al., 2014). Ethanolic extract of SC fruit causes a reduction in serum ALT and AST levels in male albino rats (Bilal et al., 2011). Also, other study reveals the utilization of CZ as a medicinal plant for kidney and liver diseases (Saganuwan, 2010).

In the diabetic condition, increased levels of TC, TG and reduced level of HDL along with the altered composition of LDL particles have been commonly reported (Howard et al., 2000). The previous study is compatible with our study after administration of STZ which altered the normal lipid profiles. TC, TG, LDL and VLDL levels were increased whereas decreased HDL level was shown when compared to normal control rats. The same findings have been shown in high-fat diet diabetic rats by Sharma et al. (2012). These lipid profiles were turned around to close normal levels after the treatment with both CZ and SC. This lipid lowering action may be due to proper stabilization of glucose level and increase in insulin level after the administration of CZ and SC, which may normalize the disturbed lipid metabolism in diabetic rats. SC and CZ may inhibit HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase) which indicates the decline of TC level (Sartorius et al., 2014). Therefore, the hypolipidemic effect of CZ and SC in diabetic rats supports their ability to prevent the cardiovascular diseases associated with diabetes. The decrease of liver triglyceride content which accompanied with increased glycogen storage by CZ administration has been noticed (Sartorius et al., 2014).

Hyperglycemia increases the generation of free radicals by glucose auto-oxidation and the increment in free radicals thereby depleting the activity of antioxidant defense system

and thus promoting de novo free radical generation that may lead to liver cell damage (Baynes and Thorpe, 1999). That explanation is noticed currently by the elevated GOT and GPT enzymes in STZ treated rats. Endogenous enzymatic antioxidants CAT, SOD and GSH act as reducing agents and detoxified highly reactive oxygen and nitrogen species. The measured GSH, GPx, CAT and SOD are markedly depressed. A marked increase of LPO as TBARS in STZ treated rats was also observed. That increase may lead to tissue injury and failure of the endogenous antioxidant defense mechanisms to prevent over production of free radicals (Maritim et al., 2003). LPO, GSH, GPx, CAT and SOD levels were restored toward normal level in CZ and SC treated diabetic rats in a dose-dependent manner. Same result of SC has been found by Sharma et al. (2012). This antioxidative effect has been done by polyphenols present in SC pulp, which acts as strong singlet oxygen quenchers and superoxide radical (Banerjee et al., 2005). Increased level of SOD by CZ and SC helps to convert superoxide free radicals to hydrogen peroxide which is then decomposed by increased CAT level. GPx and GSH complete the decomposition process of extra hydrogen peroxide produced. Hyperglycemia is an essential reason for the release of free radicals, which develop the diabetic complications including vascular disease, retinopathy and renopathy (Maritim et al., 2003). Currently, antioxidants are suggested as mechanism underlying diabetes and its complications. Food of plant origin as SC is reported to contain anthocyanins cyanidin, tannins, vitamin C, gallic acid, glucoside, malvidin, and petunidin which have the antioxidative potency (van Acker et al., 1996; Rupasinghe et al., 2003; Sroka and Cisowski, 2003). The phenolic constituents of CZ are likely to be responsible for the anti-oxidant and free radical scavenging activity (Ranasinghe et al., 2012; Im et al., 2014).

In conclusion, the present study indicates that treatment with *C. zeylanicum* and *S. cumini* had an ideal impact not only as anti-hyperglycemia but also on lipidic profile, liver and kidney function improvement and as a powerful antioxidant. These findings point out the promising effect of *C. zeylanicum* and *S. cumini* as helpful antidiabetic specialists, preventing any diabetic entanglements, the therapeutic efficacy of which can be only conceivable after clinical trial.

Conflict of interest statement

All authors have no actual or potential conflict of interests including any financial, personal or other relationships with other people or organizations.

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