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# Anti-diabetic, anti-obesity and anti-hypertensive effect of *Cinnamomum burmannii* oil and aqueous extract in experimental diabetic rats

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**Abstract** - This study was designed to examine the effect of the administration of essential oil (CEO) and aqueous extract (CE) of cinnamon on key enzymes related to diabetes, obesity and hypertension and kidney-liver and metabolic disorders indices in diabetic rats. Results of this study showed that the administration of CEO or CE to surviving diabetic rats inhibited α-amylase rate in small intestine by 48 and 42% for diabetic rats. Moreover, CEO or CE protect pancreas β-cells from death and damage and increase insulin sensibility by oral glucose tolerance test (OGTT), which leads to decrease of blood glucose level by 59.9 and 402% respectively as compared to untreated diabetic rats. In addition, this study demonstrated that administration of CEO or CE to diabetic rats ameliorated the glycogen rate in liver and muscle. In addition, the administration of CEO or CE reverted back the activity of angiotensin converting enzyme (ACE) respectively in kidney and plasma. Interestingly, the CEO or CE inhibited lipase activity in small intestine by 48 and 42% which leads to the regulation of lipid profile. Moreover, the CEO or CE protected liver-kidney function evidenced by blood indices toxicity. In conclusion, our finding demonstrates that the administration of CEO or CE to diabetic rats can make it a potential strong candidate for industrial application as a pharmacological agent for the prevention and treatment of hyperglycemia, obesity and hypertension.

**Key words**: Cinnamon, diabetes, obesity, hypertension, essential oil.

## 1. Introduction

Diabetes mellitus is a major public health problem, with an estimated worldwide prevalence in 2008 more than of 347 million people (Hamden *et al.*, 2011). It is reported that diabetes constitutes the 16th leading cause of global mortality. It is generally recognized that patients with diabetes are at risk for numerous severe complications, including, hyperlipidemia, hypertension, liver-kidney toxicity (Beji *et al.*, 2016; Belfeki *et al.*, 2016). One of the therapeutic approaches for decreasing postprandial hyperglycaemia, hyperlipidemia and ACE is to retard absorption of glucose and lipid by the inhibition of lipid and carbohydrate-hydrolyzing enzymes, such as α-amylase and lipase, in the digestive organs and ACE in kidney (Hamden *et al.*, 2011).
In addition, the available drugs (insulin, biguanides, orlistat, fluvastatin etc.) used in the management of diabetes, hyperlipidemia and hypertension has been characterized with side effects (Schattenberg and Schuppan, 2011). Accordingly, recent research seems to have granted special interest for the search of effective natural α-amylase, lipase and ACE inhibitors. Actually, there is a need to search for alternative remedy. Previous studies reported that several plants have been used for the treatment of diabetes with no minimal side effect (Debbabi *et al.*, 2017; Ouerghemmi *et al.*, 2017; Touhami *et al.*, 2017; Medini *et al.*, 2018; NAJAR *et al.*, 2018; Zouaghi *et al.*, 2018; Oueslati *et al.*, 2020). Natural remedies of medicinal plants are considered effective and safe alternative treatment for various human diseases and disorders such as inflammation, hyperglycemia, obesity and hypertension (Mohamed, 2014; Chukwuma *et al.*, 2019; Bais and Patel, 2020; Cam *et al.*, 2020; Ebrahimpour *et al.*, 2020; Kumaraswamy *et al.*, 2020; Li *et al.*, 2020; Amerikanou *et al.*, 2021; Chakraborty and Roy, 2021; Asiimwe *et al.*, 2022; Liu *et al.*, 2022; Maarman and Lecour, 2022; Sharma *et al.*, 2022; Wasana *et al.*, 2022; Lee *et al.*, 2022; Zhang *et al.*, 2023). In fact, the rising interest in herbal remedies because of their effectiveness, minimal side effects in clinical experience, and relatively low cost. Previous studies have reported that cinnamon has been the subject of many ethnopharmacological studies. These reports have pointed out that cinnamon is the source of bioactive compounds with protective properties against inflammation, oxidative stress, diabetes (regulation of insulin,

glucose uptake), obesity, hypercholesterolemia, hypertension, and blood lipid profile (Cheng *et al.*, 2022; Das *et al.*, 2022; Faddladdeen, 2022; Li *et al.*, 2022; Miah *et al.*, 2022; Rasool *et al.*, 2022; Senevirathne *et al.*, 2022; Wu *et al.*, 2022; Milagres de Almeida *et al.*, 2023). Moreover, cinnamon has been used as anticancer agent (Hamidpour *et al.*, 2015; Sadeghi *et al.*, 2019; Rasool *et al.*, 2022) and to treat of the dental problems (Gupta and Jain, 2015; Sethi *et al.*, 2019). Cinnamon extract also ameliorate metabolic disorders, has also been shown, by enhances glucose utilization in animal models and potentiates insulin stimulated tyrosine phosphorylation of IR-β, insulin receptor-1 (IRS-1) and Insulin receptor substrate-1 (IRS-1) (Qin *et al.*, 2003).

This study aimed to evaluate in the first time the effect of the administration of CEO and CE on key enzymes related to diabetes, obesity and hypertension as α-amylase, ACE and lipase activities and liver-kidney function in diabetic rats.

## 2. Materials and Methods

### 2.1. Materials

Cinnamon was purchased from an ayurvedic store in Monastir, Tunisia in January 2015. The plant material was identified as per Auyervada literature, by a local expert in herbal gardens. Cinnamon essential oil purchased from local pharmacy, Monastir.

### 2.2. Extraction methods

Cinnamon powder (50 g) was soaked in 500 mL water for 5hat 40 °C. The extract was centrifuged at 7000 g for 10 min, and the supernatant (cinnamon water extract (CE)) was lyophilized and stored at 20 °C until use (Jiao *et al.*, 2013).

### 2.3. Acute toxicity study

Healthy adult male mice, weighing 25g and aged 45 days were starved overnight and divided into four groups (n=6). the rat were fed with CEO or CE orally in graded doses of 50, 100, 500, 1000 mg/kg bw. The animals were observed continuously for 2 h to know their behavioral, neurological and autonomic profiles. The number of mice that died in each group after 48 h was recorded. Acute toxicity study was performed.

### 2.4. Induction of Diabetes

The assays of the present study were conducted on adult male Wistar rats, weighing 179 ± 10 g, which were obtained from the local Central Pharmacy, Tunisia. All rats were kept in an environmentally controlled breeding room (temperature: 20 ± 2°C, humidity: 60 ± 5%, 12-h dark/light cycle) where they had free access to tap water. The animals fasted overnight before blood and tissue collection. Diabetes was induced in the rats by intraperitoneally administering of alloxan solution (150 mg/kg) (Hamden *et al.*, 2011). Non-diabetic rats were intraperitoneally administered physiological saline and were kept in their cages for the next 24 h on 5% glucose solution bottles to prevent hypoglycemia. Two weeks later, the rats with moderate diabetes having glycosuria and hyperglycemia (*i.e.*, with blood glucose levels of ≥ 2 g/L) were chosen for the subsequent experimental assays. The animals were handled in accordance with the guidelines set forth by the Tunisian Ethical Committee for the care and use of laboratory animals.

### 2.5. Experimental procedure

A total of 30 rats (24 surviving diabetic rats and 6 control animals) were divided into five groups consisting of ten rats each.

Group1 referred to surviving diabetic rats that were scarified and named as diabetic rats at day 0 [$D_0$] (glycemia ≥ 2 g/L).

Group 2 designated the diabetic control rats that were named as diabetic rats after treatment [$D_{30}$].

Group 3 referred to CEO-treated diabetic rats at dose 50mg/kg bw by gastric gavage route named [$D_{30}$ + CEO].

Group 4 referred to CE -treated diabetic rats at dose 50 mg/kg bw by gastric gavage route named [$D_{30}$ + CE] (18).

Group 5 consisted of ten normal rats that were used as controls named [$C_{30}$].

One month after the administration of these fractions to the diabetic rats, the animals were sacrificed by rapid decapitation and their trunk blood was collected. The serum was prepared by centrifugation (1,500 × g, 20 min at 4°C), the small intestine, muscle, liver and kidney were removed, and all samples were stored at –80°C until further use.

For oral glucose tolerance test (OGTT), 6 normal and 18 surviving diabetic rats obtained 3 days after alloxan were used. Rats were subdivided into normal rats administrated glucose 2g/Kg/bw by gastric gavage route. Blood samples were collected at 5, 10, 20, 30, 60 and 90 min subsequent to received glucose (2 g/kg) injection and fasting glucose was measured.

### 2.6. Analytical methods

The liver, muscle and intestine were then homogenized and centrifuged (5,000 × g, 20 min). The α-amylase and lipase activities; and serum lipids level of triglycerides (TG), total-cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) were measured using the corresponding commercial kits (Biolabo, France) on an automatic biochemistry analyzer (BS 300, China). The plasma and kidney ACE activity was measured using Hippuryl-His-Leu (HHL) as a synthetic substrate. Serum lipase activity was measured using the corresponding commercial kits (Biolabo, France). The measurement of glycogen content was performed using methods that were previously described in the literature (Chandrasekaran *et al.*, 2018). The protein level was essayed with commercial kits (Biolabo, France). Creatinine, uric acid and urea rates were measured in frozen aliquots of serum by standardized enzymatic procedures using commercial kits from (Biolabo, France) on an automatic biochemistry analyzer (Vitalab Flexor E, USA). For histological studies, pieces of pancreas were fixed in a Bouin solution for 24 hours, and then embedded in paraffin. Sections of 5-µm thickness were stained with hematoxylin-eosin and examined under an Olympus CX41 light microscope.

### 2.7. Statistical analysis

Data are presented as means ± SD. Determinations were performed from six animals per group. The differences were examined using one-way analysis of variance (ANOVA) and Fisher test (Stat View) and the significance value was accepted at $p < 0.05$.

## 3. Results

### 3.1. Acute toxicity studies

Acute toxicity studies revealed the nontoxic nature of the CEO or CE to rats in grades doses up to 1000 mg/kg bw until 48 h post-administration. No toxic symptoms and mortality were reported at any of the doses selected until the end of the study period.

### 3.2. Effect of essential oil and aqueous extract of cinnamon pancreas architecture and α-amylase activity in small intestine of diabetic rats

The histopathological examination of the pancreatic tissues revealed that the pancreas of the control rats (Con) showed normal islets whereas those of diabetic rats showed a clear atrophy of β cells (Diab). Conversely, a clear ameliorative action was observed in the pancreas of the diabetic rats after essential oil and aqueous extract of cinnamon. Moreover, results indicated that compared to the control, there was a significant increase in the activity of α-amylase in the intestine of diabetic rats. However, after the administration of fenugreek after essential oil and aqueous extract of cinnamon to treated diabetic rats, a considerable reduction in intestinal α-amylase activity was observed, which provides some evidence for the contribution of fenugreek TG in the treatment of diabetes (Fig.1, 2).

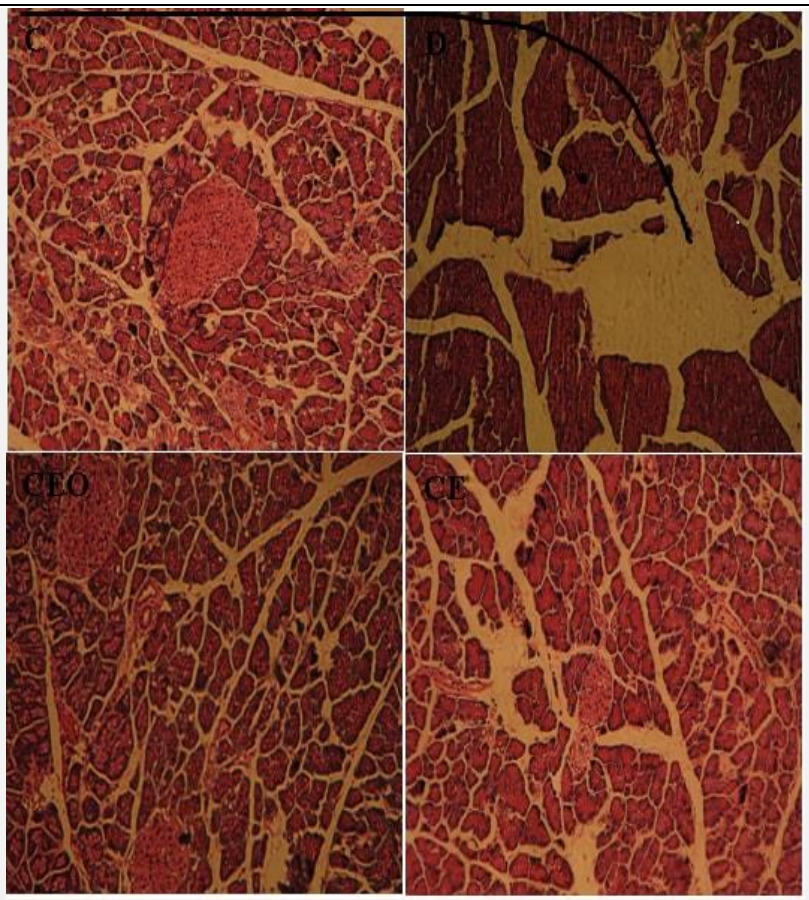


**Fig. 1.** Effect of CEO or CE on the histological changes of the pancreas of the rats evaluated by Haematoxylin and eosin (H&E) staining (100×). Con: Normal control rats showed normal β cells. Diab: Severe injury in the β cells of the pancreas of diabetic male rats. Diabetic rats treated with CEO or CE: a protective action was showed

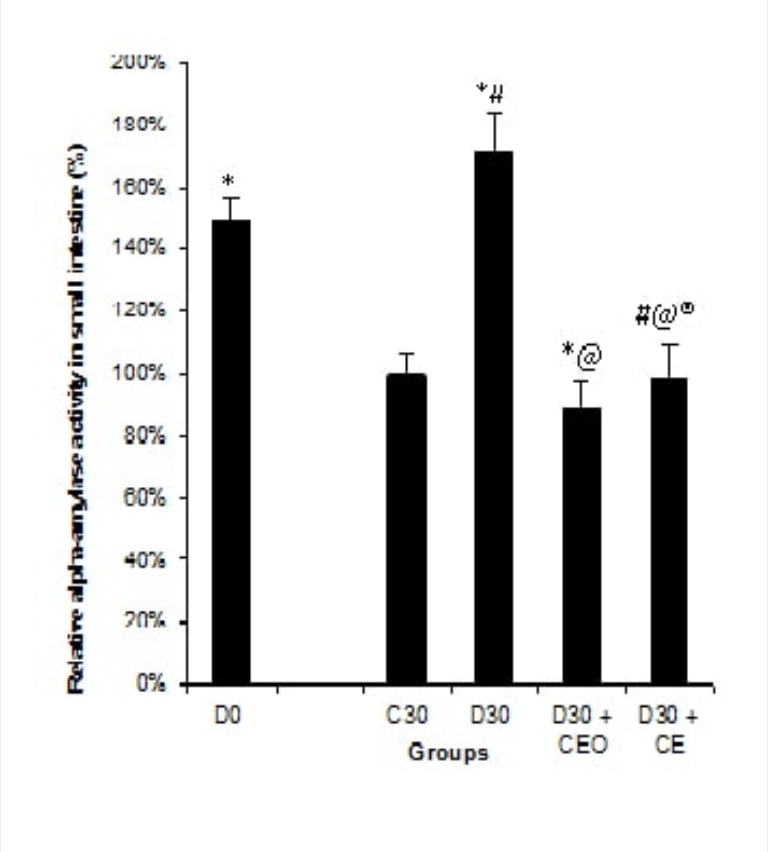


**Fig. 2.** Effect of the administration of CEO or CE on intestinal α-amylase activity of surviving diabetic rat

### 3.3. Effect of essential oil and aqueous extract of cinnamon on oral glucose tolerance test (OGTT) in diabetic rats

The results of the oral glucose tolerance test in experimental animals are depicted in Fig. 3. Results provided in fig.3 show that administration of 2 g/kg of glucose by gastric gavage method to control rats (OGTT) caused a significant (about by 50%) increase in blood glucose in 1 h and gradually decreased to the pre-glucose load level. The administration of 2g/kg of glucose in surviving diabetic rats caused a significant (about by two folds) than that in controls rats during OGTT. Pretreatment with essential oil and aqueous extract of cinnamon significantly decreased blood glucose rate 1 h after initiating OGTT.

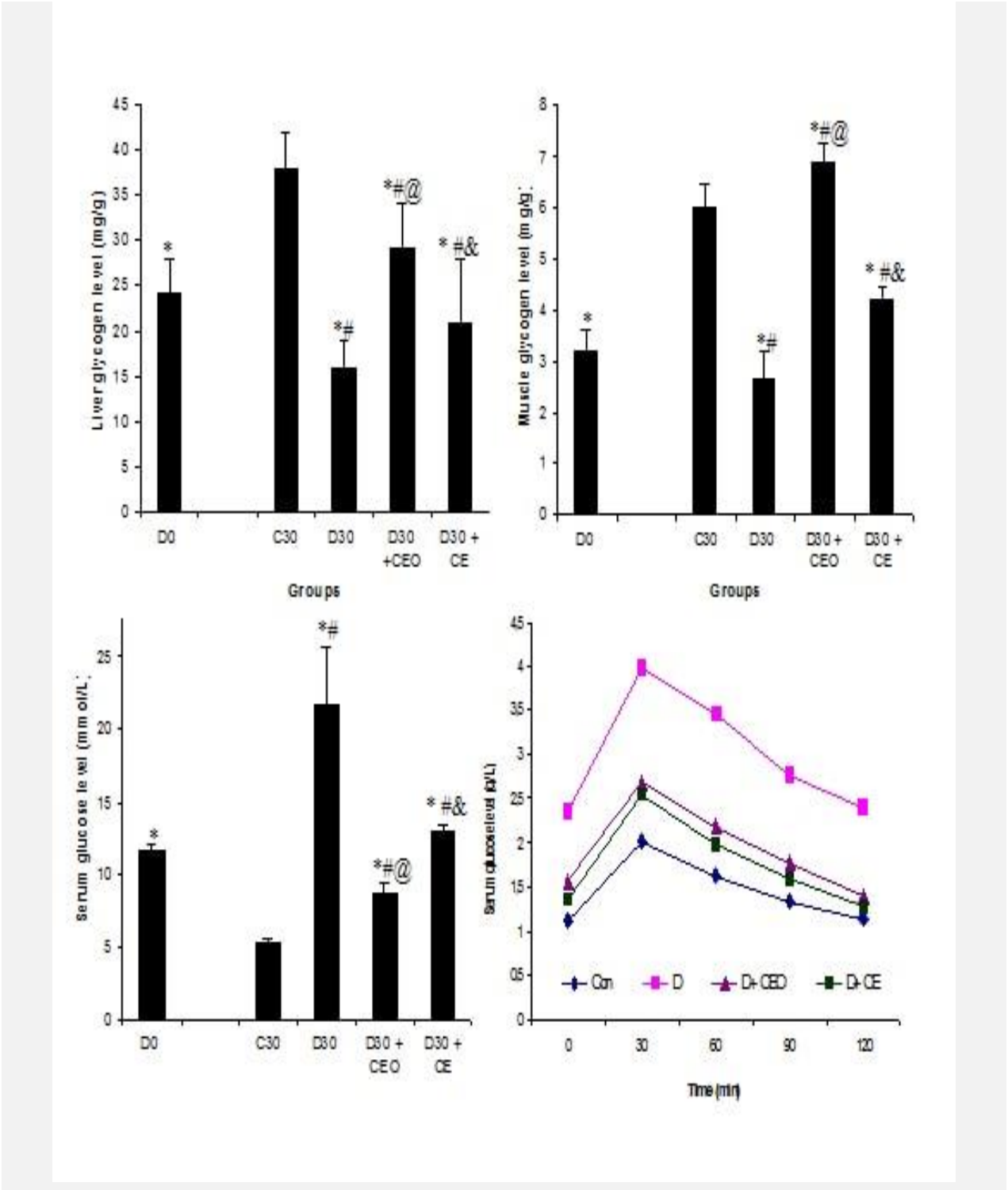


**Fig. 3.** Level of glycogen on liver and muscle, blood glucose rate and oral glucose tolerance test in diabetic rat treated with CEO or CE.

### 3.4. Effect of essential oil and aqueous extract of cinnamon on liver and muscle glycogen content and plasma glucose Level

The quantity of glycogen in liver and skeletal muscle was decreased significantly and this was associated with increase in serum glucose rate by 155% in the diabetic group compared with the control one. Administration of aqueous extract of cinnamon for 30 days resulted in a significant elevation in the levels of glycogen in liver and skeletal muscle by 93 and 144% respectively. In addition, cinnamon *essential oil ingestion* caused an increase in liver and muscle glycogen rate by 44 and 59% as compared to diabetic-untreated rats. and a decrease in serum glucose level towards the control level (Fig.3).

### 3.5. Effect of essential oil and aqueous extract of cinnamon on serum ACE activity in diabetic rats

Fig.4 evidenced that the ACE activity in the kidney and the serum of diabetic rats underwent a potent increase by 56 and 88% respectively as compared to the control rats. However, the administration of the essential oil and aqueous extract of cinnamon to the diabetic rats reverted back the activity of ACE in the kidney by 36 and 18% respectively and by 24 and 9% in serum respectively as compared to untreated diabetic rats.

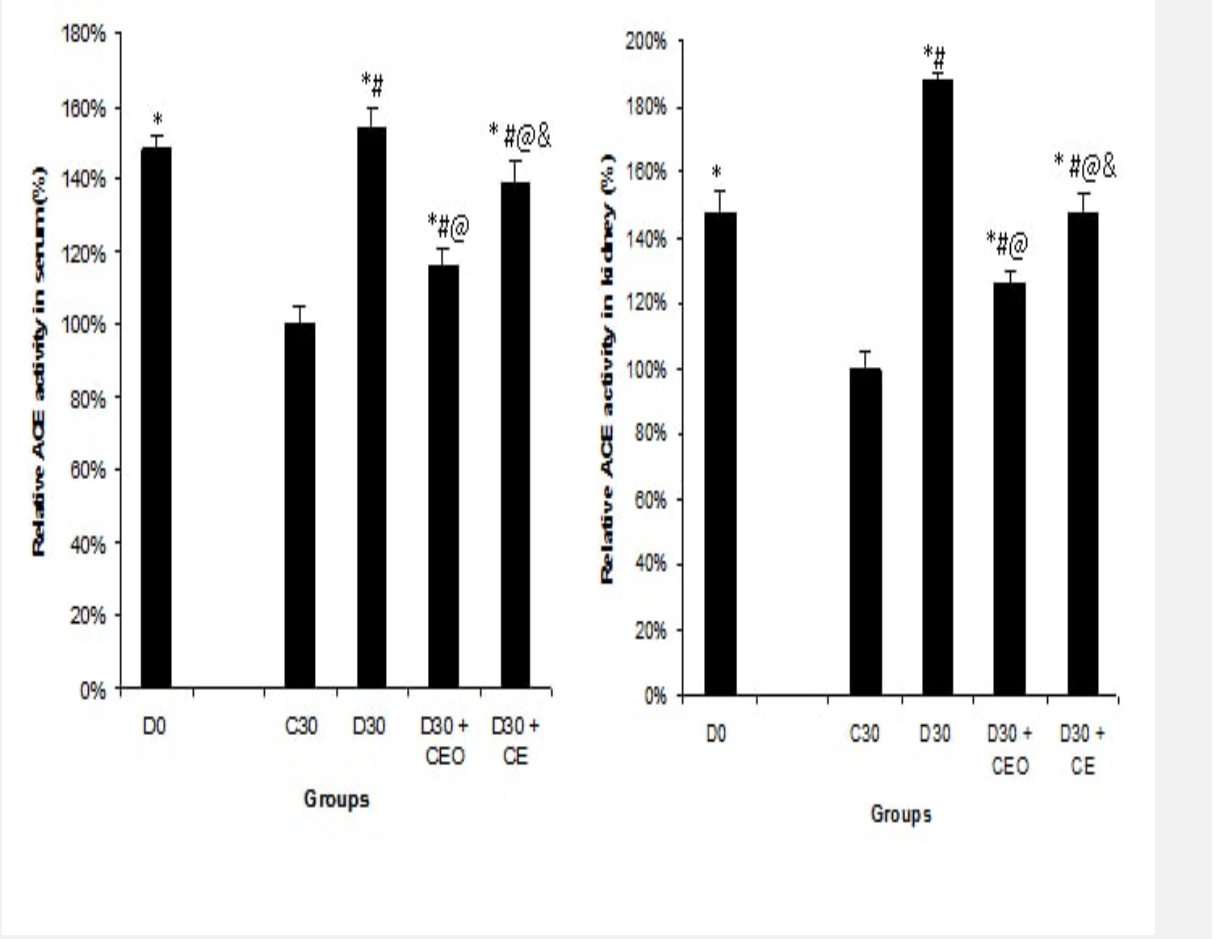


**Fig. 4.** Effect of the administration of CEO or CE on intestinal ACE activity in serum and Kidney of surviving diabetic rat

### 3.6. Effect of essential oil and aqueous extract of cinnamon on lipase activity in diabetic rats

The findings indicated that compared to the control, there was a significant increase in the activity of lipase in the intestine of diabetic rats 73%; which leads to a significant increase in LDL-C, TG and TC and decrease in HDL-C. However, after the administration of the essential oil and aqueous extract of cinnamon to treated diabetic rats, a considerable reduction in intestinal lipase activity was observed, which provides sheer evidence to the regulation in the lipid profile (Fig.5).

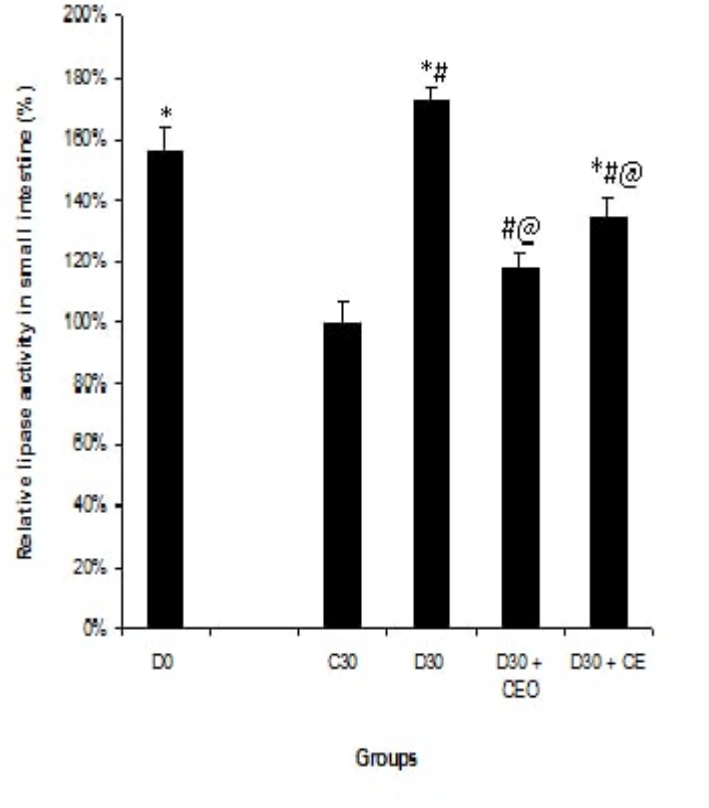


**Fig. 5.** Effect of the administration of CEO or CE on intestinal lipase activity of surviving diabetic rat

### 3.7. Effect of essential oil and aqueous extract of cinnamon on liver-kidney toxicity in diabetic rats

Table 1 illustrates that the activities of AST, ALT and LDH and the level of creat, urea and albumin in the plasma of diabetic rats witnessed a significant increase when compared to non-diabetic rats. In fact, the supplementation of essential oil and aqueous extract of cinnamon was found to bring about a potent decrease in terms of the three indices of liver-kidney toxicities.

**Table 1:** Effect of the essential oil and aqueous extract of cinnamon on liver indices toxicity (AST, ALT and LDH activities), kidney indices dysfunctions (Creatinine, urea and albumin rates) and lipid profile (TC, TG LDL-C and HDL-C levels) in serum of diabetic rats.

| | $D_0$ | $C_{30}$ | $D_{30}$ | $D_{30}$+CEO | $D_{30}$+CE |
|---|---|---|---|---|---|
| AST | 68 ± 5$^{*}$ | 44 ± 8 | 84 ± 11$^{*\#}$ | 56 ± 7$^{\#@}$ | 57 ± 8$^{\#@}$ |
| ALT | 45 ± 9 | 34 ± 4 | 61 ± 6.4$^{*}$ | 38 ± 5.1$^{*\#@}$ | 38 ± 6$^{*\#@}$ |
| LDH | 335 ± 17$^{*}$ | 131 ± 14.9 | 379 ± 12.4$^{*}$ | 166 ± 13.7$^{*@}$ | 183 ± 16$^{*\&}$ |
| Urea (g/L) | 1.71 ± 0.41$^{*}$ | 1.18 ± 0.32 | 1. 89 ± 0.41$^{*\#}$ | 1.08 ± 0.11$^{*\#@}$ | 1.11± 0.2$^{*\#@\&}$ |
| Albumin (g/L) | 33.2 ± 3.8$^{*}$ | 23.4 ± 2.3 | 41.2 ± 3.2$^{*\#}$ | 27.9 ± 3.1$^{*@}$ | 27 ± 2.8$^{*\#@\&}$ |
| Creatinine (mg/L) | 25.3 ± 2.8$^{*}$ | 19.2 ± 2.1 | 31.9 ± 3.1$^{*@}$ | 23.1 ± 1.8$^{*\#@}$ | 24 ± 3$^{*\#@\&}$ |
| TC (g/L) | 1.74 ± 0.26$^{*}$ | 1.32 ± 0.22 | 2.35 ± 0.53$^{*\#}$ | 1.44 ± 0.28$^{\#@}$ | 1.49 ± 0.36$^{@}$ |
| HDL-C (g/L) | 0.59± 0.16$^{*}$ | 0.89 ± 0.10 | 0.39 ± 0.08$^{*\#}$ | 0.71 ± 0.08$^{\#@}$ | 0.68 ± 0.09$^{*@}$ |
| LDL-C (g/L) | 1.16 ± 0.28$^{*}$ | 0.43 ± 0.19 | 1.96 ± 0.33$^{*\#}$ | 0.73 ± 0.23$^{*@}$ | 0.84 ± 0.43$^{*@}$ |
| TG (g/L) | 1.18 ± 0.19$^{*}$ | 0.81 ± 0.22 | 1.59 ± 0.23$^{*\#}$ | 0.89 ± 0.28$^{\#@}$ | 0.94 ± 0.42$^{\#@}$ |

$^{*}P < 0.05$ significant differences compared to controls; $^{\#}P < 0.05$ significant differences compared to $D_0$.; $P < 0.05$ significant differences compared to $D_{30}$: $^{\&}P < 0.05$ significant differences compared to **$D_{30}$+TG**.

## 4. Discussion

Diabetes mellitus, a chronic, progressive metabolic disorder characterized by fasting and postprandial hyperglycemia and relative insulin insufficiency (Tiss *et al.*, 2021; Tiss and Hamden, 2022). One of the therapeutic approaches used for the decrease of postprandial hyperglycemia and hyperlipidemia is the retardation of glucose and lipid absorption through the inhibition of lipid and carbohydrate-hydrolyzing enzymes, such as α-amylase and lipase, in the digestive organs (Tundis *et al.*, 2012; Fujita *et al.*, 2015; Kothari *et al.*, 2018; Aladaileh *et al.*, 2019). In an attempt to contribute to the current body of knowledge,

the present study revealed that administration of essential oil and aqueous extract of cinnamon to surviving diabetic rats restores the structure of pancreas β-cells. This positive action resulted in part in the Immunomodulation, anti-inflammatory and antioxidant action CEO and CE in pancreas (Hong *et al.*, 2012; Goel *et al.*, 2016; Sadeghi *et al.*, 2019). In addition, the findings of the present study showed that, when compared to their non-diabetic counterparts, the diabetic rats demonstrated significant decreases of intestinal α-amylase activity after administration of essential oil and aqueous extract of cinnamon. Both the protection of β-cells and inhibition of digestives enzymes by essential oil and aqueous extract of cinnamon lead to an increase in insulin sensibility and signalling, and consequently a decrease of plasma glucose level and an increase in glycogen rate in muscle and liver.

The positive effect of essential oil and aqueous extract of cinnamon in hyperglycemia was confirmed by glucose loading test. In fact, administration of starch (2.5 g/kg body weight by gastric gavage route) to surviving diabetic rats resulted in a rapid increase in blood glucose concentrations from 2.3 to a maximum of 4.1 g/L after 30 min. Thereafter, blood glucose levels recovered to the pretreatment level at 120 min. A significant suppressive effect of the blood glucose level was achieved with 50 mg/kg body weight of essential oil and aqueous extract of cinnamon after 15 and 30 min.

In fact, previous studies have reported that administration of methanol cinnamon extract to diabetic rats is associated with regulation α-glycosidases activities (Adisakwattana *et al.*, 2011). The antidiabetic action of cinnamon, also, exerted by insulin secretagogue action and insulin resistance amelioration (Qin *et al.*, 2010). Diabetes is the accumulation of excessive glucose, which can cause an increase in metabolic diseases such as fatty liver, hyperlipidemia and hypertension. Lipase is a key enzyme for the absorption of dietary triglycerides. Interference with fat hydrolysis results in the reduced utilization of ingested lipids, therefore inhibition of lipases decreases fat absorption. The findings of the present study also demonstrated that diabetes increased lipase activity in the intestine and that the increased lipid absorption from the intestine consequently amplified the hypercholesterolemia and hyperlipidemia effects (Miah *et al.*, 2022). On the other hand, the administration of CEO or CEto surviving diabetic rats, on the other hand, clearly reverted back the activity of intestinal lipase nearly back to that of the non-diabetic rats. The inhibitory action of lipase in the intestine decreased the TG, TC and LDL-C and increased the HDL-C in plasma of diabetic rats (Miah *et al.*, 2022).

Ping *et al.* (Ping *et al.*, 2010) have observed significant declines in plasma C-peptide, serum triglycerides, total cholesterol and blood urea nitrogen with a significantly increased serum high-density lipoprotein levels, after 35 days of treatment of 'cinnamon' oil to diabetic mice.

Renin produces angiotensin I from angiotensinogen, after which it is cleaved by angiotensin I converting enzyme (ACE) to release angiotensin II, a potent vasoconstrictor. The physiological function of ACE is inactivates bradykinin, which has depressor action. Therefore, a good rationale for treating hypertension would be to administer drugs or natural compounds which selectively inhibit ACE.

This study showed that diabetes was associated with increase in plasma ACE activity and this activity was decreased significantly by addition of essential oil and aqueous extract of cinnamon and this action probably resulted from the hypoglycaemic action of this drug. Previous studies reported that Cinnamon in the diet reduced the systolic blood pressure of spontaneously hypertensive rats (SHR) eating sucrose-containing (Rasool *et al.*, 2022).

The hypoglycemic effect of CEO and CE prevents glucose auto-oxidation reaction and inhibits the formation of advanced glycation endproducts (AGEs). Consequently, low rate in free radicals and more activity in antioxidant capacity consequently preserve liver function as was observed by low rates in AST, ALT, ALP, total and direct bilirubin. In addition, administration of TG to diabetic rats prevented kidney toxicity observed by low rates in creatinine and urea in plasma which increased in diabetic rats.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**Acknowledgments**

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