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Safely effective hypoglycemic action of stevia and turmeric extracts on diabetic Albino rats

Abdalla El-Hadary[1] | Mahmoud Sitohy[2]

[1]Biochemistry Department, Faculty of Agriculture, Benha University, Benha, Egypt

[2]Biochemistry Department, Faculty of Agriculture, Zagazig University, Zagazig, Egypt

Correspondence
Mahmoud Sitohy, Biochemistry Department, Faculty of Agriculture, Zagazig University, Zagazig, Egypt.
Email: mzsitohy@hotmail.com

Abstract

The potentiality of Stevia leaves and turmeric roots as remedies against diabetes mellitus type 2 was tested in this study. Stevia leaves and turmeric roots were extracted with ethanol:water (80:20 v/v) and analyzed by HPLC. Turmeric extract (TUE) was rich in; curcumin, gallic acid, and eugenol. Stevia extract (STE) contained 28 known compounds, including glycosides, aromatic organic acids, and catechin. Fifty rats were divided into five groups (10 rats each); the control group were fed with feed and water ad libitum. Forty rats were injected a single dose of alloxan, then treated with either 10 mg/kg glibenclamide (GLI), 300 mg/kg STE, or 200 mg/kg TUE or water (positive control) through daily gastric oral gavages for 56 days. Treating diabetic rats with TUE significantly reduced serum glucose and glycated hemoglobin down to the negative control levels. Both GLI and STE produced similar but less effective actions. Animals treated with either STE or TUE exhibited reduced levels of liver and kidney markers compared to the negative control, while GLI increased them significantly. It could be concluded that turmeric roots and stevia leaves extracts can be used treatment for type 2 diabetes.

Practical applications

Turmeric roots and stevia leaves extracts may be used as a remedy for type 2 diabetic patients as aiding substituting treatments under medical supervision. The two plant sources can be used as raw materials for the extracts, which can be used under medical supervision as a gradual replacement of the synthetic antidiabetic drugs. These extracts can be used after a preliminary clinical study to determine the dose and frequency of administration. Stevia extract can be incorporated in drinks as a sweetener and drug. Turmeric extract has a bitter taste, so it may be incorporated in some foods such as bread, which is a traditional practice in some kinds of bread in Egypt. But its content in the bread and the acceptability of the taste should be adjusted. Alternatively, this food can incorporate both TUE and STE to get the best biological action and to conceal the bitter taste of turmeric.

KEYWORDS

diabetes mellitus, glycated hemoglobin, serum glucose, stevia leaves, turmeric roots

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1 | INTRODUCTION

Diabetes mellitus (DM) is one of the most serious widespread chronic diseases that causes death worldwide. It is characterized by elevated blood glucose, altered metabolism of carbohydrates, lipids, and proteins. Uncontrolled chronic hyperglycemia in diabetic patients turn them more liable to heart attack, stroke, and atherosclerotic disease (Zimmet et al., 2001). Hyperglycemia may also generate resistance to insulin action leading to glucose autoxidation, triggering the formation of reactive oxygen species (ROS), and some other complications such as atherosclerosis, cardiovascular disease, and hepatorenal failure (Leslie et al., 2016). Obesity, a prevailing health problem in Egypt is a major risk factor developing type 2 diabetes has been recently found associated with the level of leptin hormone (Rashad et al., 2019).

Alloxan is one of the essential agents in experimental diabetes. Alloxan selectively kills β-cells that secrete insulin from the pancreatic, leaving fewer active cells, and resulting in diabetic conditions. In a redox cycle reaction, alloxan will produce ROS with its reduction product, dialuric acid with the formation of superoxide radicals, which are dismutated by hydrogen peroxide (Lenzen, 2008). Alloxan dosage also varies across trials, ranging from 90 to 150 mg/kg of body weight, with 120 mg/kg of body weight being the most commonly used dosage (Ighodaro et al., 2017).

Various traditional drugs used in treating diabetes are expensive, inadequate, and may have deleterious side effects. For example, biguanides and sulfonylureas (glibenclamide) diabetic drugs are not only incapable of lowering glucose to normal value but also may have some side effects on cardiovascular, liver, and kidney function (El-Hadary & Ramadan, 2019). A long-term study revealed that using glibenclamide reduces blood glucose levels at doses 10 mg/day (Rambiritch et al., 2014).

Turmeric (Curcuma longa L.), a perennial herb belonging to ginger family *Zingiberaceous*) is well known in Egypt and used safely as a traditional medicine against many diseases, for example, inflammation, hepatotoxicity, hyperlipidemia, and arthritis (Hussein et al., 2014). The ground rhizomes of turmeric contains a yellowish pigment, composed of several chemical constituents, principally; curcumin I, curcumin II (demethoxycurcumin), and curcumin III (bisdemethoxycurcumin), where Curcumin I [1,7-bis(4-hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the main active compound with potent antioxidant, hepatoprotective, and anti-inflammatory activities (Li et al., 2011).

Stevia rebaudiana Bertoni is a shrub plant belonging to the *Asteraceae* family whose leaves are safe non-calorie sugar substitute, with antihyperlipidemic effects (Ahmed et al., 2018). Stevia leaves extract (STE) is 300 times sweeter than sucrose and is currently used as a sweetening food additive agent. STE has several bioactive components; glycosides, phenolic, and flavonoids with antioxidant, antimicrobial, anti-viral activities (Ghosh et al., 2008), hypolipidemic, anti-inflammatory, hepatoprotective (Das & Kathirya, 2012), hypoglycemia, and anticancer properties (Assaei et al., 2016). The main sweet compounds in STE are dulcosides A, rebaudioside A, B, C, D&E, steviolbioside, and stevioside (Bhutia & Sharangi, 2016).

Since both turmeric roots and stevia leaves are reputedly used in traditional medicine and nutrition due to their richness in different antioxidants and bioactive components, it is intriguing to test and understand their potential action against some known specific diseases. This study is primarily targeting the effect of these two natural materials on DM and its associated complications compared with a synthetic-specific drug. Hence, the current work aims at comparatively and comprehensively evaluating the potential antidiabetic effects of TUE and STE on alloxan-induced diabetic albino rats against glibenclamide as a standard. The potential outcome is probably a cheap, simple, and safe approach curbing the spread of type 2 diabetes using well-specified natural products.

2 | MATERIALS AND METHODS

2.1 | Materials

Turmeric (*Curcuma longa* L.) dried roots were purchased from the local market of Benha City, Egypt and *Stevia rebaudiana* Bertoni leaves were purchased from the Farm Agricultural Research Station, Faculty of Agriculture at Moshtohor, Benha University. All reagents and standards were purchased from SIGMA-ALDRICH Co. (Louis, Missouri, USA). Diagnostic kits that is, lipid profile, liver, and kidney function were purchased from Bio Meriêuex Laboratory Reagents and Products, France.

2.2 | Methods

2.2.1 | Preparation of stevia and turmeric hydroethanol extracts

Stevia and turmeric materials were completely dried, pulverized, and soaked in ethanol:water (80:20 v/v) at 1:5 ratio at room temperature for 24 hr. Extracts were concentrated under vacuum at 40°C using a rotary evaporator (IKA-WERKE, Germany) in the dark and then, freeze-dried (LABCONCO Free Zone 2.5 Liter −50C Benchtop, India). Stevia and turmeric extracted were designated as STE and TUE, respectively.

2.2.2 | Determination of total phenolic (TPC) and total flavonoid compounds (TFC)

Phenolics were determined according to (Bobinait et al., 2012). Phenolics were expressed as gallic acid equivalent. Flavonoids were determined using aluminum chloride colorimetric method (Meda et al., 2005). Flavonoid contents were expressed as quercetin equivalents.

2.2.3 | Determination of antioxidant activity

DPPH· radical scavenging activity

The extracts were assayed by 2,2-diphenylpicrylhydrazyl (DPPH·) antiradical test according to the Blois (2002) and 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\cdot+}$) radical scavenging activity was carried out using cation decolorization assay as described by (Thaiponga et al., 2006).

2.2.4 | HPLC analyses

The extracts were dissolved in ethanol (1.0 mg/ml) then filtered and injected (20 μl) into YL 9100 HPLC system (Young YL instruments Co., Ltd, Korea) and separated on stationary phase YL9131 column compartment C18 column (0.46 × 25 cm). The solvent system included acetonitrile:water having 1% acetic acid using linear-gradient program, starting from 18% acetonitrile changing to 32% in 15 min and finally reaching 50% in 40 min (Prakash et al., 2007).

2.2.5 | Experimental animals

Healthy adult Wister Sprague Dawley albino male rats, (160–170 g), obtained from the animal farm (Faculty of Veterinary, Benha University, Egypt) were handled according to WHO guidelines and kept under 25°C, 50% relative humidity, and 12 hr light-dark cycle. Free access to water and a standard diet was allowed (Reeves et al., 1993). The Research Ethics Committee approved the experimental animal design at Benha University numbered (BDFABU/16/06/2017).

Experimental design

After a 2-week acclimatization, 50 rats were randomly divided into five groups, 10 rats each (El-Hadary & Ramadan, 2016). The first group (Normal negative control) was fed on basal diet and injected with normal saline (0.9%) without any treatments. The other four groups received a single intraperitoneal injection of alloxan monohydrate (120 mg/ kg body weight) dissolved in normal saline (0.9% saline) (Ighodaro et al., 2017) and were confirmed diabetic by having blood glucose more than 300 mg/dl after 48 hr of injection. One group did not receive any further treatment and served as diabetic positive control. The three remaining groups received through gastric oral gavages for 56 days, the following treatments in aqueous solutions; 10mg/kg glibenclamide (Group III) (Rambiritch et al., 2014), 300 mg/kg STE (Group IV) (Ahmed et al., 2018), and 200 mg/kg TUE (Group V) (Pari & Murugan, 2007).

Blood analysis

At the experimental end, blood samples were withdrawn from the retro-orbital plexus veins by fine capillary heparinized tubes and divided into three tubes. A mixutre of sodium fluoride and potassium oxalate mixture (1:1) was added to the blood samples at a ratio of 4 mg per ml, in the first tube to determine the fasting blood glucose after 10 min centrifugation at 900 x*g* according to (Trinder, 1969). The second tube received blood sample into Ethylenediaminetetraacetic acid (EDTA) solution to determine the glycated hemoglobin (HbA1c) according to (Nayak & Pattabiraman, 1981). In the third tube, the whole blood was allowed to clot and serum was separated by centrifuging at 2,016 x*g* for 15 min. Serum lipid profile; including total lipids (TL), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) was immediately determined according to Fossati and Precipe (1982), Finely, (1978), Naito and Kaplan (1984). Low-density lipoprotein cholesterol (LDL-C) levels were calculated according to the equation: LDL-C=TC-(HDL + VLDL-C), where VLDL-C was calculated as TG/5 (Friedewald et al., 1972).

Liver enzymatic activities of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and liver total Bilirubin were determined according to (Reitman & Frankel, 1957; Tietz, 1983). Kidney function parameters, that is, urea, uric acid, and creatinine, were assessed according to (Tab acco et al., 1979).

Hepatic oxidative stress,

Liver samples were immediately washed, mixed with 0.1M potassium phosphate saline (pH = 7.4) at 1:9 w/v extraction ratio and centrifuged at 5,600 x*g* for 10 min at 4°C. The supernatant was used for the analysis of antioxidant markers. Glutathione peroxidase (Gpx), was determined according to (Flohe & Gunzler, 1984). Glutathione S-transferase activity was determined according to (Moatamedi Pour et al., 2014). Reduced Glutathione was assayed according to (Shaik & Mehvar, 2006) and superoxide dismutase according to (Weydert & Cullen, 2010). Malondialdehyde, (MDA) was estimated following (Janero, 1990).

Histopathological examination

Small tissue specimens were collected from the pancreas of representative rats from all groups and rapidly fixed in 10% neutral buffered formalin. After proper fixation, thin paraffin sections were examined by H&E staining according to (Drury & Wallington, 1986).

2.2.6 | Statistical analysis

Data were subjected to ANOVA and statistical analyses using the statistical software SPSS 11.0 (SPSS Ltd., Surrey, UK) (SAS, 1996). The findings are shown as mean of ±*SD*. The significance level was set to $p < .05$.

3 | RESULTS AND DISCUSSION

3.1 | Biochemical constituents

The data in Table 1 indicate that the extract yield of the plant material is much higher in stevia (ca. 72%) than in turmeric (ca. 10%).

However, the contents of the extract of TPC, total flavonoids, and antioxidant activity were higher in the case of turmeric than in stevia.

The higher extract yield in stevia than turmeric may probably be due to the fact that the plant material was leaves in the case of stevia while roots in turmeric. High levels of TPC are general characteristics of natural plant material.

Abdel-Shafi et al. (2019). Richer contents of TPC and flavonoids in TUE may be a characteristic property of this plant material and may explain its higher antioxidant activity than STE (Braga et al., 2003).

The hydro-ethanolic extract of turmeric is specifically rich in three components; curcumin, gallic acid, and eugenol amounting to 29%, 8%, and 18% (Figure 1). There were more than 10 other small peaks on the HPLC chromatogram, referring to other unknown compounds.

TABLE 1 Extracts yield, total phenolic content, flavonoid contents, and antioxidant activity of turmeric and stevia leaves extracts

Material parameter	Turmeric roots	Stevia leaves
Extract yield (g/100 g material)	9.93 ± 1.55	72.42 ± 2.02
Total phenolic content (mg GAE/g extract)	43.1 ± 1.68	17.7 ± 0.86
Total flavonoids (mg QE/g extract)	49.3 ± 2.52	3.2 ± 0.75
Antioxidant activity (g/100 g DPPH)	60.28 ± 1.03	44.15 ± 1.11
Antioxidant activity (g/100 g ABTS)	65.20 ± 1.64	42.33 ± 0.96

Abbreviations: GAE, gallic acid equivalent;QE, Quercetin equivalent.

The dominance of the three components; curcumin, gallic acid, and eugenol, forming together more than half of the extract components (55%), in the TUE may refer to a characteristic trait of this plant material and may stay behind different traditionally known medicinal effects of this material (Li et al., 2011).

The data in Table 2 indicate the presence of 28 known compounds in STE, forming the majority of the extract. The predominant compounds in STE are the stevia glycosides, that is, stevioside, rebaudiosides A, B, C, D&E, and dulcoside, forming altogether about 38% of the extract in accordance with Bhutia and Sharang (2016). Other 15 compounds belonging to aromatic organic acids represented about 16% of the total extract, that is; gallic acid, 4-Aminobenzoic acid, protocatechuic acid, *P*-OH-benzoic acid, caffeic acid, vanillic acid, *p*-coumaric acid, ferulic acid, iso-ferulic acid, ellagic acid, alpha-coumaric acid, benzoic acid, salicylic acid, 3,5,5-methoxy-cinnamic acid, and cinnamic acid. Catechin represented more than 14% of the total extract as a major flavonoid, Catechol and pyrogalol; di-and tri-ol derivatives of benzene, represent together about 2.6% while coumarin was only 0.15% of the extract. The aforementioned data are in harmony with (Shivanna et al., 2013 and Gaweł-Bęben et al., 2015) reporting the presence of phenolic acids; ferulic acid (0.86 mg/g), chlorogenic acid (0.3 mg/g), and caffeic acid 0.29 mg/g as well as catechin as the major flavonoids (0.24 mg/g).

3.2 | Serum glucose and glycated hemoglobin

It is evident in the results presented in Table 3 that positive control animals contained significantly much higher levels of serum glucose and glycated hemoglobin, that is, more than double of the normal

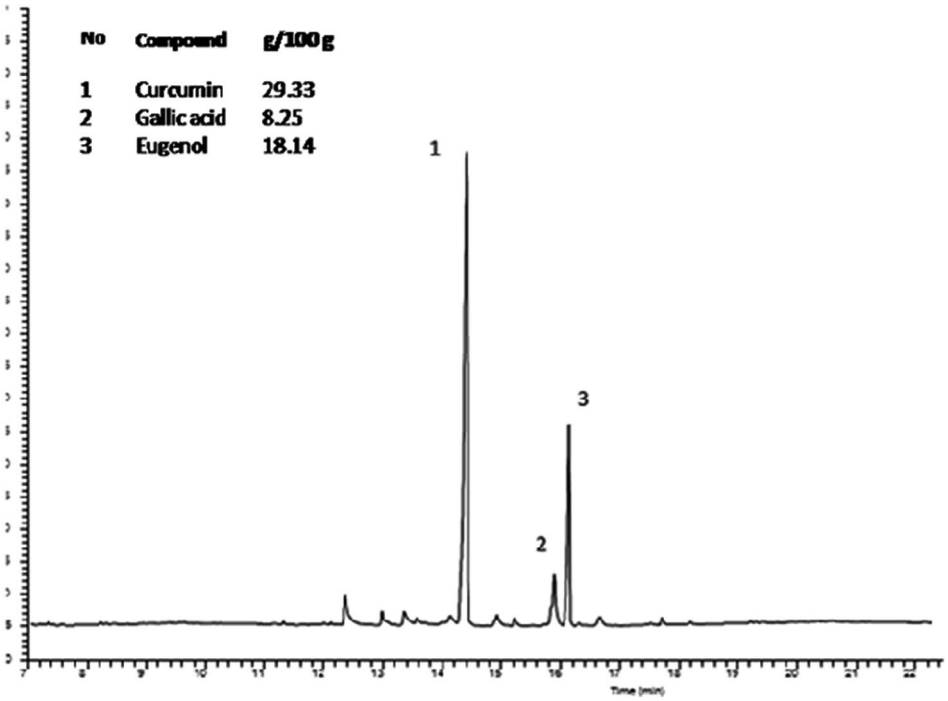

FIGURE 1 Phenolic compounds of hydro-ethanolic fraction of turmeric roots extract analyzed by HPLC

TABLE 2 HPLC compounds of ethanolic extract (80:20 v/v) of Stevia leaves extract (STE) expressed as g/100 g STE

No	Compound	g/100 g	No	Compound	g/100 g	No	Compound	g/100 g
1	Dulcoside	3.542	11	Rebaudioside A	11.39	21	Iso-ferulic	1.3652
2	Rebaudioside B	1.492	12	Catechol	0.5901	22	Ellagic	3.6030
3	Gallic	0.095	13	Caffeine	0.6663	23	Alpha-coumaric	0.0425
4	Pyrogallol	2.0235	14	P-OH-benzoic	0.4969	24	Benzoic	4.0774
5	Stevioside	6.835	15	Caffeic	0.1527	25	Salicylic	2.8787
6	4-Aminobenzoic	0.3556	16	Vanillic	0.1829	26	Methoxy-cin[a]	1.33
7	Rebaudioside C	3.245	17	Rebaudioside E	5.575	27	Coumarin	0.1494
8	Protocatechuic	0.6917	18	p-Coumaric	0.1449	28	Cinnamic	0.0232
9	Catechin	14.3828	19	Ferulic	0.4091	29	Unknown	24.612
10	Chlorogenic	3.8678	20	Rebaudioside D	5.780			

[a]3,4,5-Methoxy-cinnamic.

TABLE 3 Effect of treatment with stevia (STE), turmeric (TUE) ethanolic extracts, and glibenclamide (GLI) on HbA_{1c} and blood glucose in negative control and positive control (diabetic)

Group	Treatment	Glucose mg/dL	HbA_{1c}* g/100 g
1	Negative control	114.33 ± 1.76^{d}	6.09 ± 0.04^{d}
2	Positive control	390.00 ± 5.77^{a}	12.99 ± 0.07^{a}
3	Diabetic + GLI 10 mg/kg	131.00 ± 2.08^{c}	7.35 ± 0.23^{b}
4	Diabetic + STE 300 mg/kg	143.67 ± 3.28^{b}	7.62 ± 0.16^{b}
5	Diabetic + TUE 200 mg/kg	123.67 ± 4.63^{cd}	6.62 ± 0.24^{c}

Note: Different small letters refer to significant differences ($p < .05$) in the same column.

*HbA_{1c} (glycated hemoglobin).

levels (negative control). Treating rats with STE and TUE significantly reduced the levels of these two parameters to be within the level of negative control in the turmeric-treated rats' case but still higher than the negative control in the case of stevia-treated rats.

The significant reduction in serum glucose levels and HbA1c by STE is in line with previous reports (Shivanna et al., 2013) reporting that stevia leaves protect rats against streptozotocin-induced diabetes. Curcumin, the main active component of turmeric, was reported to have anti-inflammatory proprieties being useful in various diseases, including DM (Boarescu et al., 2019).

This action was attributed to the presence of some bioactive constituents such as glycosides (Stevioside), phenolic, flavonoids, and terpenoids. However, the higher effectiveness of TUE than STE in alleviating diabetic symptoms may be due to the synergistic antioxidant effect of curcumin, gallic acid, and eugenol in TUE preventing the destruction of pancreas β-cells and stimulating pancreatic β-cells to release insulin (Pivari et al., 2019). This high antidiabetic efficiency of TUE, which equalizes or excels GLI in reducing serum glucose and glycated hemoglobin, may nominate it as a good natural substitute to synthetic antidiabetic drugs.

3.3 | Liver and kidney functions

The results in Table 4 indicate that the positive control rats were associated with significantly higher liver function markers; AST, ALT, and ALP but not total bilirubin. Treating rats with GLI (10 mg/kg) significantly further increased these levels but both STE and TUE brought them down significantly to the corresponding levels of the negative control.

The increasing side effects of GLI (10 mg/kg) on the levels of the liver markers even higher more than the positive control may be due to the reported adverse effects of active ingredient (sulfonylurease) including inhibition of the metabolic flux via the pyruvate carboxylase reaction and hepatotoxic effects augmenting the liver enzymes activities and leading to leaking them into the bloodstream (El-Hadary & Ramadan, 2019). The reducing action of both TUE and STE on the levels of the liver function markers at the used dosages may refer to the safety of such treatments in accordance with reports on other natural plant sources for example, goldenberry and Cordia dichotoma (Ramadan et al., 2013) and (El-Newary et al., 2016) and can be attributed to the antioxidant capacity of these extracts. This fact may also explain the higher hepatic protective effect of turmeric than STE, as having higher antioxidant capacity (Table 4). The association between the antioxidant action and the hepatic protective effect is well established (Osman et al., 2019); (Abdel-Hamid et al.., 2020) and (Salman et al., 2020). It was also reported that curcumin not only induces the downregulation of oxidative stress but also reduces matrix metalloproteinases in liver injury. (Dogaru et al., 2020). Due to curcumin hydrophobic characteristics and low bioavailability, curcumin nanoparticles were shown to exert ameliorated effects on oxidative stress compared to native one (Bulboacă et al., 2019).

It is also evident in Table 5 that artificial induction of diabetes in Albino rats has caused significantly higher levels in renal function parameters, creatinine, uric acid, and urea. Treating the diabetic rats with GLI (10 mg/kg) reduced creatinine and urea to levels still higher than the negative control and increased uric acid higher than the positive control level. Both stevia and turmeric reduced the levels

TABLE 4 Effect of treatment with stevia (STE), turmeric (TUE) ethanolic extracts, and glibenclamide (GLI) on liver function in diabetic rats as compared to glibenclamide (GLI) as well as negative control and positive control (diabetic)

Group	Treatment	AST (U/L)	ALT (U/L)	ALP (U/L)	Total Bilirubin (mg/dL)
1	Negative control	40.00 ± 1.15^{c}	54.00 ± 1.15^{c}	104.20 ± 2.83^{d}	0.90 ± 0.03^{c}
2	Positive control	76.00 ± 1.15^{b}	83.67 ± 2.73^{b}	165.58 ± 1.76^{b}	1.01 ± 0.01^{b}
3	Diabetic + GLI (10mg/kg)	87.67 ± 1.20^{a}	104.33 ± 1.20^{a}	190.38 ± 2.61^{a}	1.49 ± 0.04^{a}
4	Diabetic + STE 300 mg/kg	43.67 ± 0.88^{c}	59.33 ± 2.40^{c}	118.03 ± 4.03^{c}	0.94 ± 0.03^{bc}
5	Diabetic + TUE 200 mg/kg	41.33 ± 2.73^{c}	56.00 ± 3.06^{c}	97.18 ± 1.50^{d}	0.87 ± 0.04^{c}

Note: Different letters (a, b, c, and d) refer to significant differences ($p < .05$) within the values of each column. Nonsignificant differences are observed between the rats receiving STE and TUE and the negative control ($p < .05$) in AST, ALT, and total bilirubin. Significant increases ($p < .05$) are seen in the group receiving GLI over the negative control in AST, ALT, ALP, and total bilirubin.

TABLE 5 Effect of treatment with stevia (STE), turmeric (TUE) ethanolic extracts on kidney function in diabetic rats as compared to glibenclamide (GLI) as well as negative control and positive control (diabetic)

Group	Treatment	Creatinine (mg/dL)	Uric (mg/dL)	Urea (mg/dL)
1	Negative control	0.84 ± 0.05^{c}	4.04 ± 0.15^{c}	32.02 ± 2.31^{d}
2	Positive control	2.40 ± 0.21^{a}	5.48 ± 0.17^{b}	55.93 ± 0.75^{a}
3	Diabetic + GLI 10 mg/kg	1.46 ± 0.08^{b}	7.13 ± 0.24^{a}	44.68 ± 1.10^{b}
4	Diabetic + STE 300mg/kg	1.07 ± 0.04^{c}	4.09 ± 0.17^{c}	36.38 ± 1.84^{cd}
5	Diabetic + TUE 200mg/kg	0.95 ± 0.08^{c}	3.71 ± 0.09^{c}	36.75 ± 2.10^{cd}

Note: Different letters (a, b, c, and d) refer to significant differences ($p < .05$) within the values of each column. Nonsignificant differences are observed between the rats receiving STE and TUE and the negative control ($p < .05$) in creatinine, uric acid, and urea. Significant increases ($p < .05$) are seen in the group receiving GLI over the negative control in creatinine, uric acid, and urea.

of the three renal parameters down to the significant levels of the negative control.

The destructive action of alloxan on renal function is mainly due its action on the glomerular filtration rate (GFR) and the induction of oxidative stress (Sharma et al., 2006). The impotency of GLI to correct the action of alloxan and even worsening it may be due to its damaging action on the blood vessels in kidneys leading to the abnormal renal function manifested in reduced glomerular filtration (Bamanikar et al., 2016). The remediating action of both stevia and turmeric on the renal function may originate from ROS inhibition and production of vasoactive mediators (Sharma et al., 2006; Shivanna et al., 2013).

3.4 | Lipid profile

It can be observed in Table 6 that alloxan augmented the levels of lipid profile components of albino rats; total lipids, total triglycerides, total cholesterol, LDL cholesterol, and VLDL-cholesterol by about 27%, 27%, 13%, 67%, and 14%, respectively, while reduced HDL-cholesterol by about 30% relative to the negative control. Treating the diabetic rats with GLI (10 mg/kg) significantly reduced the first five items by about 13%, 14%, 9%, 23%, and 9%, respectively, while increased HDL by about 22%, compared to the positive control.

Both stevia (300 mg/kg) and turmeric (200 mg/kg) treatments better corrected the alloxan-induced changes in lipid profiles inducing higher relative reductions in the first five respective lipid component amounting to 21%, 19%, 11%, 37%, and 11%, alongside with a relatively higher increase in HDL level amounting to an average of 38% relative to the positive control, so that the final levels were not significantly different from the negative control.

Alloxan treatments were previously reported to disrupt the lipid profile of experimental animals, increasing the total lipids, total triglycerides, total cholesterols, LDL cholesterol, VLDL-cholesterol, and decreasing HDL. Alloxan-induced insulin deficiency may be responsible for dyslipidemia through promoting 3-hydroxyl-3-methyl-glutaryl-CoA reductase and enhancing immobilization of free fatty acids from peripheral fat depots. The corrective action of glibenclamide was previously attributed to its hypoglycemic effect. The

TABLE 6 Effect of treatment with stevia (STE), turmeric (TUE) ethanolic extracts, and glibenclamide on lipid profile in diabetic rats as compared to glibenclamide (GLI) as well as negative control and positive control (diabetic)

Group	Treatment	Total cholesterol (mg/dL)	Total lipid (mg/dL)	Triglyceride (mg/dL)	HDL-Cho (mg/dL)	LDL-Cho (mg/dL)	VLDL-Cho (mg/dL)
1	Negative control	162 ± 1.1^{b}	470 ± 3.9^{c}	159 ± 0.73^{c}	50.8 ± 0.66^{a}	79.78 ± 0.3^{c}	31.8 ± 0.1^{c}
2	Positive control (diabetic)	205 ± 1.1^{a}	595 ± 2.9^{a}	180 ± 2.83^{a}	35.6 ± 0.35^{c}	133.3 ± 0.4^{a}	36.1 ± 0.6^{a}
3	Diabetic + GLI 10mg/kg	179 ± 2.7^{b}	510 ± 5.7^{b}	164 ± 1.46^{b}	43.5 ± 0.52^{b}	102.0 ± 2.0^{b}	33.0 ± 0.3^{b}
4	Diabetic + STE 300 mg/kg	162 ± 9.9^{b}	489 ± 2.9^{c}	158 ± 1.45^{c}	46.8 ± 2.4^{ab}	83.6 ± 7^{c}	31.6 ± 0.3^{c}
5	Diabetic + TUE 200 mg/kg	165 ± 3.7^{b}	475 ± 11^{c}	162 ± 1.5^{bc}	49.2 ± 1.5^{a}	83.1 ± 2.4^{c}	32.4 ± 0.3^{bc}

Note: Different letters (a, b, and c) refer to significant differences ($p < .05$) within the values of each column. Nonsignificant differences are observed between the rats receiving STE and TUE and the negative control ($p < .05$) in different components of lipid profile.

TABLE 7 Effect of treatment with stevia (STE), turmeric (TUE) ethanolic extracts, and glibenclamide (GLI) on antioxidant marker in diabetic rat's tissue as compared to glibenclamide (GLI) as well as negative control and positive control (diabetic)

Group	Treatment	Glutathione peroxidase (U/g tissue)	Glutathione S-transferase (U/g tissue)	Glutathione reduced (μmol/g tissue)	SOD (U/g tissue)	MDA (mol/mg)
1	Negative control	165.6 ± 0.7^{c}	6.30 ± 0.06^{c}	80.8 ± 0.9^{a}	54.3 ± 2.3^{b}	5.33 ± 0.2^{c}
2	Positive control (diabetic)	137.8 ± 1.4^{d}	4.66 ± 0.04^{e}	57.2 ± 1.7^{c}	47.2 ± 1.2^{c}	11.9 ± 0.5^{a}
3	Diabetic + GLI 10 mg/kg	159.8 ± 1.2^{c}	5.20 ± 0.22^{d}	69.9 ± 2.6^{b}	50.7 ± 0.7^{bc}	6.7 ± 0.3^{b}
4	Diabetic + STE 300 mg/kg	175.8 ± 5.3^{b}	6.99 ± 0.19^{b}	81.6 ± 1.9^{a}	58.8 ± 0.9^{a}	4.9 ± 0.1^{c}
5	Diabetic + TUE 200 mg/kg	191.2 ± 2.1^{a}	7.54 ± 0.10^{a}	83.9 ± 1.4^{a}	60.4 ± 1.3^{a}	4.8 ± 0.8^{c}

Note: Different letters (a, b, c, and d) refer to significant differences within the values of each column ($p < .05$). Significant increases ($p < .05$) are seen in the values of glutathione peroxidase, glutathione S-transferase, and SOD in the rats receiving STE and TUE over both negative and positive controls. Significant decreases ($p < .05$) are noticed in the values of MDA in the rats receiving STE and TUE over the positive control but not the negative one.

corrective actions of both stevia and turmeric agree with previous reports; (Ahmed et al., 2018 and Sudha et al., 2017) and can be attributed to decrease the fat absorption and increase the fat excretion. Stevia extract may be able to increase the bile acid excretion by preventing re-absorption from the small intestine through disrupting micelle formation of bile acid and increasing 3-hydroxyl-3-methylglutaryl-CoA reductase (HMG CoA). Turmeric extract may exert its action by increasing the hepatic cholesterol-7a-hydroxylase and HMG CoA reductase and increasing fat excretion in the feces (Alwi et al., 2008).

3.5 | Oxidation markers

The data in Table 7 indicate that antioxidant enzyme markers in albino rats were negatively affected by alloxan treatment, incurring 17%, 20%, 29%, and 13% reductions in the activities of Gpx, glutathione S-transferase, reduced glutathione, and superoxide dismutase (SOD), respectively. In contrast, the oxidative stress marker MDA (Malondialdehyde) was increased by 123% of the negative control. Treating the animals with GLI (10mg/kg) enhanced the first four markers' levels by about 16%, 12%, 22%, and 7%, respectively, while reducing MDA by 44% relative to the positive control. STE treatment could achieve higher increases in the first four anti-oxidative biomarkers amounting to 28%, 50%, 43%, and 25% coupled with a higher reduction in MDA (59%). TUE achieved the highest increases in the antioxidant biomarkers, that is, 39%, 62%, 47%, and 28%, alongside a 60% reduction in MDA compared to the positive control. However, the antioxidant markers in the stevia- and turmeric-treated animal tissues were not brought up to the corresponding negative control levels.

The negative effect of alloxan on the antioxidant markers and enhancing action on MDA in albino rats are following previous results, ascribing them to enhanced oxidative stress, increased generation of free radical via glucose auto-oxidation, lipid peroxidation, and diminished antioxidant enzyme (Oluwafemi et al., 2017). The ameliorative action of glibenclamide on the aforementioned parameters was previously attributed to reduce diabetes and decrease the free radical

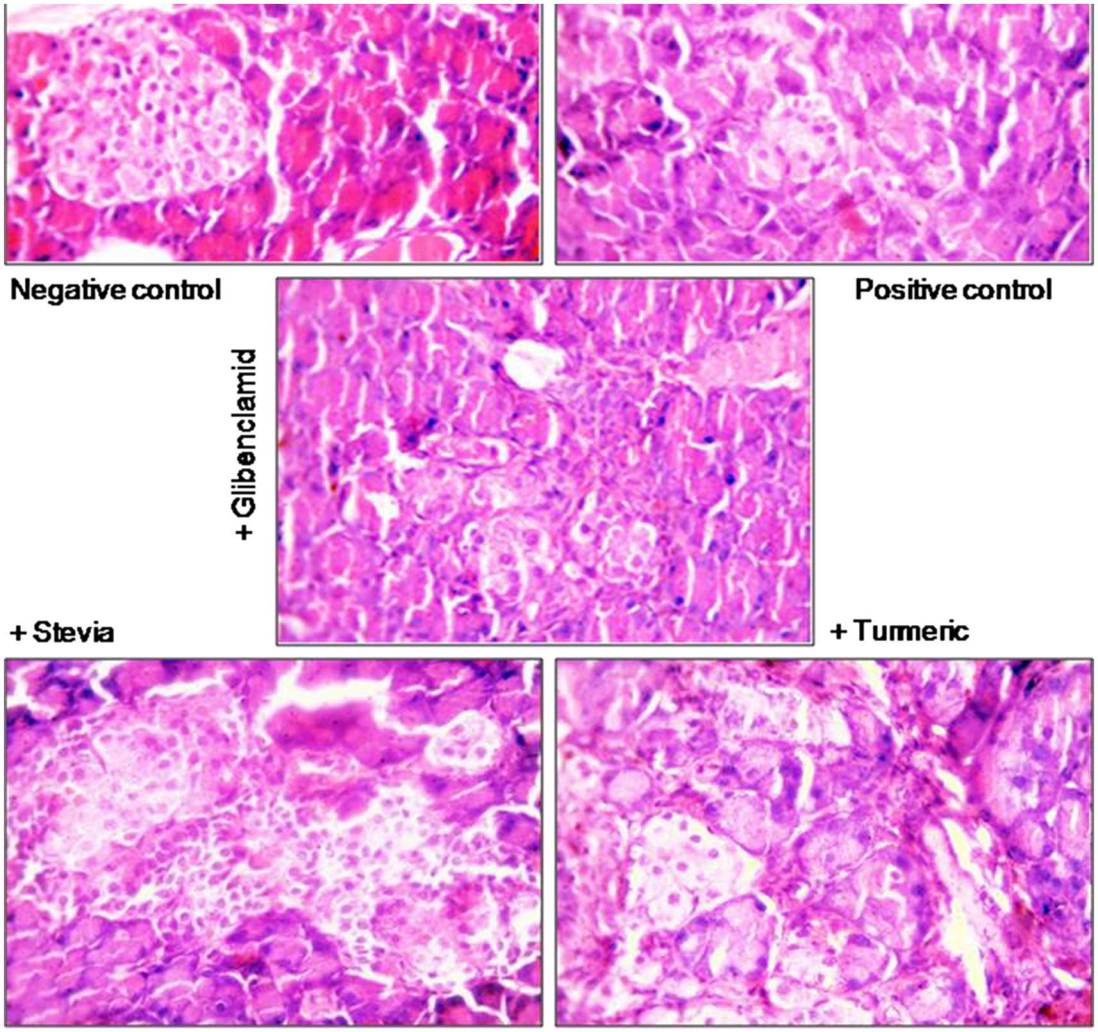

FIGURE 2 Rat pancreas photomicrographs from negative and positive control and as treated with glibenclamide 10 mg/kg, stevia 300 mg/kg, or turmeric 200 mg/kg ethanolic extracts. The pancreas of the positive control shows degeneration changes, acini, and Langerhans islets. Pancreases of Diabetic rats treated with glibenclamide show nearly normal histological structure with focal regeneration of Langerhans islets. Likewise, micrograms of the pancreas of diabetic rats treated with ethanolic turmeric extracts (200 mg/kg) show mild degenerative pancreatic acini changes with clear regenerative signs of Langerhans islets. Pancreas of rats treated with turmeric ethanolic extract shows mild degeneration change in pancreatic acini with clear regeneration of Langerhans islets

generation. The observed pronounced enhancing effect of Stevia treatment on the antioxidant markers are in accordance with Sharma et al., 2012 and that of turmeric is in accordance with (Oluwafemi et al., 2017) and (Ozcelik et al., 2018). The highly enhancing action on the biological antioxidant activities of both STE and TUE are based on their high antioxidant capacity as previously shown.

3.6 | Pancreas histopathology

The photomicrographs of the pancreas of different rat groups are presented in Figure 2. It can be observed that images from positive control rats showed degenerative pancreatic acini and islets of Langerhans. Pancreases of diabetic rats treated with GLI 10mg/kg showed nearly normal histological structure alongside with focal regeneration of Langerhans islets. Micrographs of the pancreas of diabetic rats treated with STE (300 mg/kg) exhibited some regeneration in Langerhans islets coupled with few inter-acinar mononuclear leuhogtic infiltration. Likewise, micrograms of pancreas of diabetic rats treated with ethanolic turmeric extracts (200 mg/kg) show mild degenerative changes in pancreatic acini with clear regenerative signs of Langerhans islets.

The degenerative signs revealed in the pancreas' photomicrographs from rats treated with either STE or TUE may indicate that the pancreas is still suffering the damaging action of the alloxan treatment. However, reducing these degenerative signs by the natural treatment with both stevia and turmeric may formulate a safe approach to diabetes. This palliating action of the natural components in both STE and TUE may agree with Assaei et al. (2016). The protective histopathological action may originate from the antioxidant capacity of the extracts that can protect living tissues from oxidative damages.

4 | CONCLUSION

Ethanolic extracts of both the studied extracts (STE and TUE) can be potential agents against diabetes, particularly TUE, without posing harmful side effects on the liver, kidney functions, or affecting the lipid profile. This action is apparently dependent upon the bio-constituents' antioxidant activity of both extracts (glycosides, phenolics, and flavonoids) as exhibited on the bio-oxidant status in the treated animals.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Abdalla E. El-Hadary: Conceptualization; Data curation; Investigation; Methodology; Resources; Visualization; Writing-original draft. **Mahmoud Sitohy:** Conceptualization; Investigation; Project administration; Supervision; Validation; Writing-original draft; Writing-review & editing.

ORCID

Abdalla El-Hadary https://orcid.org/0000-0002-5784-8606
Mahmoud Sitohy https://orcid.org/0000-0001-6623-4860

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