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STEVIA IMPROVES THE ANTIHYPERGLYCEMIC EFFECT OF METFORMIN IN STREPTOZOTOCIN-INDUCED DIABETIC RATS: A NOVEL STRATEGY IN TYPE 2 DIABETES MELLITUS

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Diabetes mellitus is a major health problem that threatens the whole world. According to WHO reports, the prevalence of diabetic patients in egyptis expected to increase from 2,623,000 in 2000 to be 6,726,000 in 2030. Metformin is the first line drug for type 2 diabetes mellitus, which can be used alone or in combination with other drugs. However, the concomitant use of metformin with stevia needs more investigation to clarify the role of this combination as a new strategy in type 2 diabetes mellitus.

Type 2 diabetes mellitus was induced in rats by i.p. injection of STZ and NA. Animals were divided into five groups, each contains 8 rats. Group I: negative control, group II: diabetic control received saline, group III: diabetic rats received 400 mg/kg/day stevia aqueous extract, group IV: diabetic rats received metformin 250 mg/kg/day, group V: diabetic rats received stevia 400 mg/kg/day + metformin 250 mg/kg/day. After 3 weeks blood samples were collected, animals were sacrificed and tissue samples were collected. Biochemical parameters including FBG, serum insulin, serum DPP-4, TC, TG, LDL, HDL, GSH and MDA were measured by colorimetric and ELISA methods.

Both stevia and metformin significantly reduced FBG level. While serum insulin significantly increased. Serum DPP-4 was significantly reduced in all treated groups, concerning lipid profile, stevia and metformin significantly lowered TC, TG, LDLand increased HDL. Both stevia and metformin significantly decreased MDA and increased GSH compared to diabetic rats. In addition, stevia significantly improved the antidiabetic effects of metformin.

Stevia has an antihyperglycemic effect and could increase the antidiabetic activity of metformin. DPP-4 attenuation, antioxidant and insulin-sensitizing effects may be involved in the antidiabetic action of stevia. Regarding lipid profile stevia showed hypolipidemic effect.

INTRODUCTION

Diabetic patients are increasing in number all over the world due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. Therefore, the number of people with diabetes in the world is expected to approximately double between 2000 and 2030[1]. According to WHO reports, the prevalence of diabetic patients in egypt is expected to increase from 2,623,000 in 2000 to be 6,726,000 in 2030[2].

Metformine is the most commonly prescribed drug for type 2 diabetes mellitus[3]. In recent years, in addition to glucose lowering, several studies have presented evidence suggesting some potential role of metformin, such as antitumor effect, antiaging effect, cardiovascular protective effect, neuro-protective effect or an optional treatment for polycystic ovary syndrome[4].

Stevia rebaudiana Bertoni is a perennial herb belonging to the Asteraceae family. It is a natural sweetener plant known as “Sweet Weed”, “Sweet Leaf”, “Sweet Herbs” and “Honey Leaf”, which is estimated to be 300 times more sweeting than sugar can[5]. The leaves of Stevia contain a natural complex

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mixture of eight sweet diterpene glycosides, including isosteviol, stevioside, rebaudiosides (A, B, C, D, E, F), steviolbioside and dulcoside A[6&7]. Stevia leaf extracts have been used traditionally by folks in the treatment of diabetes mellitus[8]. Their ingestion causes a slight decrease in plasma glucose levels and significantly increase glucose tolerance in normal adult humans[9]. However, the beneficial effects from using combination of stevia and metformin so far not well documented. Therefore, this study was planned to clarify the role of stevia-metformin combination in type 2 diabetes in diabetic rats.

MATERIALS AND METHODS

Chemicals

Streptozotocin (STZ), nicotinamide (NA) obtained from cornal lab company, metformin gifted by said factory, stevia aqueous extract supplied by pharmacognosy department faculty of pharmacy assiut university.

Animals

Male albino rats were used in this study. They weighed 200 to 250g and were maintained in 12- hrs light/dark cycle. The animals had free access to food and water was given through drinking bottles.

Induction of diabetes

Diabetes was induced in the overnight-fasted rats by a single intraperitoneal injection of STZ (60 mg/kg), fifteen minutes after the I.P. administration of nicotinamide (120 mg/kg). Their blood glucose levels were measured 3 days after the STZ injection. Only rats with fasting blood glucose levels greater than 220 mg/dL were considered to be diabetic and were used in the experiment[10].

Preparation of plant extract

5 kg of the air-dried powdered leaves of Stevia rebaudiana Bertoni were extracted by maceration in 70% EtOH (10 L x 3). The alcoholic extract was concentrated and the solvent free residue (835 g). Part of the alcoholic extract (425 g) was mixed with 500 mL of distilled H_2O, and subjected to successive solvent fractionation with dichloromethane till complete exhaustion. The Dichloromethane fraction was concentrated and the solvent free residue was (87 g). The aqueous fraction was concentrated and the solvent free residue was (336 g)[11].

Experimental design

Animals were divided into 5 groups each group contained 8 rats as follow:

1- Negative control group included non-diabetic rats.
2- Diabetic control group included 3-diabetic rats received normal saline
3- Diabetic rats received stevia extract 400mg/kg.
4- Diabetic rats received metformin 250 mg /kg.
5- Diabetic rats received stevia extract 400mg/kg + metformin 250 mg /kg.

All drugs administered orally by stomach tube.

After 21 days blood samples were collected from retro orbital sinus[12], animals were sacrificed under light ether anesthesia and parts of liver and kidney collected for biochemical measurement.

Preparation of tissue homogenate

Liver and kidney were excised immediately after sacrificed, cleaned in saline, homogenized in 10% (w/v) ice cold 100 mM phosphate buffer (pH 7.4) and centrifuged at 10,000 rpm for 15 min at 4°C, and then the supernatant was obtained and used for oxidative stress biomarkers studies[13].

Measurements

The serum glucose was estimated by enzymatic colorimetric method[14]. Both serum insulin and DPP-4 were estimated by using (ELISA) technique.

Serum total cholesterol is estimated by enzymatic colorimetric method[15]. Serum high density lipoprotein cholesterol was estimated by enzymatic colorimetric method precipitating reagent[16]. The serum low density lipoprotein cholesterol was estimated by enzymatic colorimetric method precipitating reagent[17]. The serum triglycerides was estimated by enzymatic colorimetric method[18]. The level of reduced glutathione in liver and kidney tissues was estimated by colorimetric method[19]. The level of malodialdehyde in liver and kidney tissues was estimated by colorimetric method[20].

In order to detect insulin resistance we evaluated HOMA-IR (homeostatic model assessment of insulin resistance) using the following formula: (fasting plasma insulin in mU/l x FPG in mmol/l) / 22.5[21]. For evaluation of insulin sensitivity used the formula, IS = 1/ HOMA-IR[22].

RESULTS AND DISCUSSION

Results

Effect of stevia, metformin, and their combination on fasting blood glucose level (FBG)

Treatment of diabetic rats with stevia aqueous extract or metformin showed a significant decrease in FBG (p< 0.001) compared to positive control rats. Combined administration of stevia aqueous extract plus metformin produced a significant decrease in FBG (p< 0.001) compared to the positive control, stevia and metformin treated rats (Fig. 1).

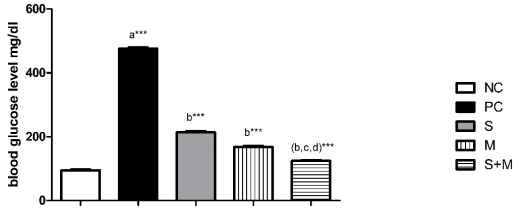

Fig. 1: Effect of 400 mg/ kg stevia aqueous extract, metformin 250 mg/ kg and their combination on FBG mg / dl.

NC: negative control, **PC**: positive control, **S**: stevia and **M**: metformin.
a: significantly different from the mean value of the negative control rats, **b**: significantly different from the mean value of the positive control rats, **c**: significantly different from the mean value of the stevia-treated rats, **d**: significantly different from the mean value of the metformin-treated rats.
P (*< 0.05, **< 0.01, ***< 0.001). N=8. Values are mean ± standard error of the mean (SEM)

Effect of stevia, metformin, and their combination onserum insulin level

Both stevia aqueous extract and metformin produced a significant increase in serum insulin level (p< 0.001) compared to positive control rats. Additionally, co-administration stevia aqueous extract plus metformin produced a significant increase in serum insulin level (p< 0.001) compared to the positive control, stevia and metformin-treated rats (Fig. 2).

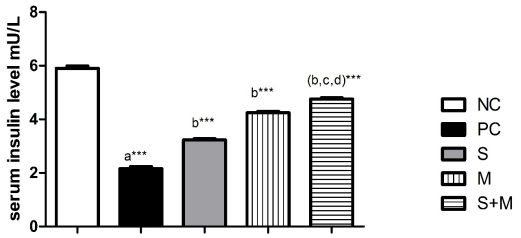

Fig. 2: Effect of 400 mg/kg/day stevia aqueous extract, metformin 250 mg/kg and their combination on serum insulin level mU/L.

NC: negative control, **PC**: positive control, **S**: stevia and **M**: metformin, **a**: significantly different from the mean value of the negative control rats, **b**: significantly different from the mean value of the positive control rats, **c**: significantly different from the mean value of the stevia treated rats, **d**: significantly different from the mean value of the metformin treated rats.
P (*< 0.05, **< 0.01, ***< 0.001). N=8. Values are mean ± SEM.

Effect of stevia, metformin, and their combination on HOMA-IR and insulin sensitivity

Stevia aqueous extract or metformin produced a significant decrease in HOMA-IR (p< 0.001) compared to the positive control rats. The same finding was noticed following daily oral treatment of animals with combinations of stevia aqueous extract plus metformin produced a significant decrease in HOMA-IR (p< 0.001) compared to positive control, a significant decrease in HOMA-IR (P< 0.05) compared to stevia, and a significant decrease in HOMA-IR (P< 0.01) compared to metformin-treated rats.

Stevia aqueous extract or metformin produced a significant increase in insulin sensitivity (p< 0.001) compared to positive control rats. Similarly, stevia aqueous extract combined with metformin showed a significant increase in insulin sensitivity (p< 0.001) compared to positive control, stevia and metformin-treated rats (Table 1).

Table 1: Effect of stevia, metformin and their combination on HOMA-IR, and Insulin sensitivity (IS).

	Negative control	Diabetic control	Stevia	Metformin	Stevia + Metformin
HOMA-IR	1.37± 0.04	2.54 ± 0.09^{a***}	1.72 ± 0.03^{b***}	1.78 ± 0.05^{b***}	1.46 ± 0.04^{b***,c*,d**}
IS	0.73± 0.02	0.40 ± 0.01^{a***}	0.58 ± 0.01^{b***}	0.57± 0.01^{b***}	0.69± 0.02 $^{(b,c,d)***}$

Values are mean ± SEM., N=8. **a**: significantly different from the mean value of the negative control rats. **b**: significantly different from the mean value of the diabetic control rats **c**: significantly different from the mean value of the stevia treated rats **d**: significantly different from the mean value of the metformin treated rats. **P** (*< 0.05, **< 0.01, ***< 0.001).

Effect of stevia, metformin and their combination on DPP 4 level

Stevia aqueous extract or metformin produced a significant decrease in DPP 4 level (p< 0.001) compared to positive control rats. It can be seen in the same figure combined administration of stevia aqueous extract orally with metformin produced a significant decrease in DPP 4 level (p< 0.001) compared to positive control, stevia and metformin treated rats (Fig. 3).

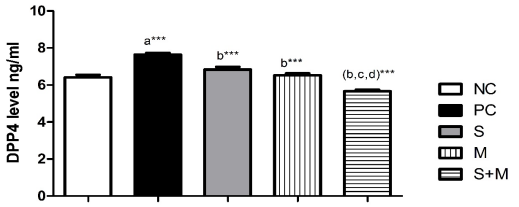

Fig. 3: Effect of 400 mg/kg stevia aqueous extract, metformin 250 mg/kg and their combination on DPP 4 level ng/ml.

NC: negative control, **PC**: positive control, **S**: stevia and **M**: metformin.

a: significantly different from the mean value of the negative control rats, **b**: significantly different from the mean value of the positive control rats, **c**: significantly different from the mean value of the stevia treated rats, **d**: significantly different from the mean value of the metformin treated rats. **P** (*< 0.05, **< 0.01, ***< 0.001). N=8**.**

Values are mean ± SEM.

Effect of stevia, metformin and their combination on lipid profile

Both stevia aqueous extract and metformin produced a significant decrease in total cholesterol level (p< 0.001) compared to positive control rats. The same table showed that combined administration of stevia aqueous extract with metformin produced a significant decrease in total cholesterol level (p< 0.001) compared to positive control, stevia and metformin treated rats.

Similarly, stevia aqueous extract or metformin produced a significant decrease in triglycerides level (p< 0.001) compared to positive control rats. Also, combined daily administration of stevia aqueous extract with metformin produced a significant decrease in triglycerides level (p< 0.001) compared to positive control, stevia and metformin treated rats.

Stevia aqueous extract or metformin produced a significant increase in HDL level (p< 0.001) compared to positive control rats. The same table showed that combined administration of stevia aqueous extract with metformin produced a significant increase in HDL level (p< 0.001) compared to positive control, stevia and a significant increase (p< 0.01) compared to metformin treated rats.

As expected both stevia aqueous extract and metformin produced a significant decrease in LDL level (p< 0.001) compared to positive control rats. The same table showed that combined administration stevia aqueous extract with metformin produced a significant decrease in LDL level (p< 0.001) compared to positive control, stevia and metformin treated rats (Table 2).

Antioxidant effect of stevia, metformin and their combination

1- Effect of stevia, metformin and their combination on reduced glutathione (GSH) level in liver and kidney tissues

Stevia aqueous extract or metformin produced a significant increase in GSH in liver and kidney tissues (p< 0.001) compared to positive control rats. The same finding when stevia aqueous extract combined with metformin produced a significant increase in GSH in liver and kidney tissues (p< 0.001) compared to positive control, stevia and metformin treated rats (Table 3).

Table 2: Effect of stevia, metformin and their combination onserum lipid profile**.**

	Negative control	Diabetic control	Stevia	Metformin	Stevia + Metformin
TC (mg/dl)	105.7 ± 1.53	199.9 ± 2.97^{a***}	155.7 ± 1.45^{b***}	139.3 ± 1.56^{b***}	125.9 ± 1.14$^{(b,c,d)***}$
TGs (mg/dl)	98.53 ± 3.41	252.6 ± 2.35^{a***}	158.6 ± 1.99^{b***}	157.5 ± 2.00^{b***}	138.0 ± 1.35$^{(b,c,d)***}$
HDL (mg/dl)	57.21 ± 1.08	24.52 ± 1.13^{a***}	36.61 ± 0.93^{b***}	39.64 ± 1.55^{b***}	45.87 ± 0.83$^{(b,c)***,d**}$
LDL (mg/dl)	28.75 ± 1.89	124.8 ± 3.64^{a***}	87.38 ± 2.08^{b***}	68.12 ± 2.32^{b***}	52.42 ± 1.53$^{(b,c,d)***}$

Values are mean ± SEM., N=8. **a**: significantly different from the mean value of the negative control rats. **b**: significantly different from the mean value of the diabetic control rats. **c**: significantly different from the mean value of the stevia treated rats. **d**: significantly different from the mean value of the metformin treated rats. **P** (*< 0.05, **< 0.01, ***< 0.001).

Table 3: Effect of stevia, metformin and their combination on GSH and MDA levels in liver and kidney tissues.

	Negative control	Diabetic control	Stevia	Metformin	Stevia + Metformin
GSH liver (mg / g)	21.93 ± 1.03	3.17 ± 0.46^{a***}	12.33 ± 0.43^{b***}	12.32 ± 0.55^{b***}	17.20± 0.79$^{(b,c,d)***}$
GSH kidney (mg/g)	21.63 ± 0.57	6.35 ± 0.36^{a***}	17.28 ± 0.54^{b***}	15.98 ± 0.74^{b***}	21.60± 0.66$^{(b,c,d)***}$
MDA liver (n mol /g)	207.8 ± 3.49	580.5 ± 12.24^{a***}	248.8 ± 4.40^{b***}	242.7 ± 2.00^{b***}	207.8 ± 1.67$^{(b,c,)***,d**}$
MDA kidney (n mol /g)	209.9 ± 2.47	455.0 ± 11.34^{a***}	240.8 ± 3.64^{b***}	264.3 ± 3.87^{b***}	226.4 ± 3.33$^{(b,d)***}$

Values are mean ± SEM., N=8. **a**: significantly different from the mean value of the negative control rats. **b**: significantly different from the mean value of the diabetic control rats. **c**: significantly different from the mean value of the stevia treated rats. **d**: significantly different from the mean value of the metformin treated rats. **P** (*< 0.05, **< 0.01, ***< 0.001).

2- Effect of stevia, metformin and their combination on malodialdehyde (MDA) level in liver and kidney tissues

Stevia aqueous extract or metformin produced a significant decrease in MDA level in liver and kidney tissues (p< 0.001) compared to positive control rats. Combined administration of stevia aqueous extract with metformin produced a significant decrease in MDA level in both liver tissues (p< 0.001) compared to positive control, stevia and a significant decrease (p< 0.01) compared to metformin treated rats. While, combined administration of stevia aqueous extract with metformin produced a significant decrease in MDA level in kidney tissue (p< 0.001) compared to positive control and metformin. But, produced no significant change compared to stevia treated rats (Table 3).

Discussion

Present study showed that aqueous extract of stevia (400 mg/kg) significantly decreased the blood glucose levels of diabetic rats. These findingis in agreement with those obtained by Misra *et al.*,[23] who reported that stevia can decrease the blood glucose level of diabetic rats. Similarly, but more recent study reported that the aqueous extract of stevia lowered the blood glucose levels in streptozotocin- induced

diabetes in rats[24]. However, these studies didn't clarify the exact mechanism of action of stevia in diabetes.On the other side, the mechanism of antihyperglycemic effect of steviosides, the active constituent of stevia, was attributed to the inhibition of phsphoenol pyruvate carboxykinase (PEPCK) gene expression in liver which is responsible for blood glucose level regulation through inhibition of gluconeogenesis[25]. More recently (in 2016), the hypoglycemic activity of the aqueous extract of stevia was explained by PPARγ-dependent mechanism and antioxidant properties[11]. The antioxidant property of stevia will be discussed later in this study.

As expected metformin 500 mg/kg significantly lowered the FBG of diabetic rats. These findings are in agreement with results obtained by Zhou *et al.*, who reported that antihyperglycemic effect of metformin may be mediated by inhibition of AMPK in rat liver and muscles with consequent inhibition of gluconeogenesis in liver and increased glucose uptake in muscles[26]. Whether metformin could activate AMPK in human muscles or not, type 2 diabetic patients received metformin for 10 weeks and then biopsies were taken before treatment began and after 4 and 10 weeks of treatment and AMPK activity was measured in muscle. They found that AMPK 2 activity increased by 52% after 4 weeks and by 80% after 10 weeks of treatment with metformin[27]. Very recently, in a differential study Rada *et al*., (2019) reported that metformin could activate AMPK, inhibit glucose production and increase insulin sensitivity[28]. This study also documented increased insulin sensitivity by metformin but in diabetic rats.

Stevia aqueous extract significantly increased the fasting serum insulin leveland this finding is in the same side with jeppesen *et al*., (2002)[29] they stated that Steviosides could increase insulin secretion by direct action on beta cells. Recently, Piovan *et al*., (2018) found thatethyl acetate fraction of stevia increased insulin secretion in presence of high glucose concentration. This insulinotropic effect may be attributed to an enhancement of cholinergic and attenuation of adrenergic inhibitory effects on glucose stimulated insulin secretion with a result of an increase in insulin levels in the blood[30].

In this study, type 2 model of diabetes showed hypoinsulinemia which coincided with[31] study compared between four different models of type 2 diabetes and concluded that STZ and nicotinamide manifested by hyperglycemia along with hypoinsulinemia. Metformin 250 mg/kg significantly increased the serum insulin level of hypoinsulinemic diabetic rats this finding in the same side with[32&33] suggested direct effect of metformin on beta cells or indirect effect[34] concluded that metformin upregulates incretin receptors on beta cells. Furthermore, this increase in serum insulin may be attributed to the antioxidant properties of metformin[35]. Additionally, this increase could be related to the anti-inflammatory activities of metformin[36] investigated the effect of metformin on experimental insulitis in mice and found that metformin reduced the severity of insulitis further more elevated the serum insulin level. This finding contradicts with[37-39] as metformin reduces hepatic glucose production, increases peripheral glucose utilization and can reduce insulin resistance without affecting the level of circulating insulin. Our results may document the increase in insulin levels in hypo-insulinemic model of diabetes by metformin.

Concerning insulin sensitivity, in an investigation of the effect of stevia on insulin sensitivity in insulin resistant rats[40] induced insulin resistance in rats using high fructose diet. Chang *et al*., found that administration of Steviosides improved insulin sensitivity. Also[41] reported that stevia could enhance insulin sensitivity and increase serum insulin. The present study in the same side with this as 400 mg/kg stevia aqueous extract significantly improved insulin sensitivity while insulin resistance (HOMA-IR) significantly decreased.

Metformin can improve insulin sensitivity by more than one mechanism as it can increase insulin receptor tyrosine kinase activity, enhance glycogen synthesis, and an increase the recruitment and activity of GLUT4 glucose transporters. Concerning adipose tissue, metformin promotes the re-esterification of free fatty acids and inhibits lipolysis, which may indirectly improve insulin sensitivity through reduced lipotoxicity[38]. Recently, in a two years trial the effect of metformin on beta cell function in type 2 diabetic patients of early stage who received initial short-term intensive

insulin induction is compared with the intermittent insulin therapy (IIT)[42] showed that metformin is better than IIT since the beta cell functions,insulin sensitivity andglycemic control were maintained in metformin treated group over the 2 years. In this study metformin improved insulin sensitivity and decreased insulin resistance (HOMA-IR).

Dipeptidyl peptidase-4 (DPP-4) plays an important role in degradation of several hormones implicated in glucose hemostasis this opened the window for thinking about the role of DPP-4 in type 2 diabetes pathogenesis, The breakdown of peptides as GLP-1and GIP by DPP-4 catalytic activity[43], this peptides are important for glucose hemostasis and insulin secretion[44]. Another way is there is a relationship between increased DPP–4 plasma level activity and insulin resistance and impaired insulin signaling[45]. There is a negative correlation between DPP-4 level and active GLP-1 levels in T2DM patients. High DPP-4 levels were associated with increased BMI, cholesterol, and LDL[46].

In this study stevia aqueous extract significantly reduced the serum DPP-4 level this finding is in the same way as reported by[47] who used molecular modeling to study the interaction between compounds extracted from stevia and DPP-4 and found that both stevioside and rebaudioside A inhibited DPP-4 and stevioside produced more optimized inhibition. Steviosides also reported to have the ability to reduce DPP-4 level in diabetic rats[48].

In an attempt for elucidation of DPP-4 inhibition as a possible mechanism of metformin action, metformin produced a dose dependent inhibition of DPP-4 activity in plasma in type 2 diabetic patients[49]. Similar results obtained in 2006 when metformin decreased the plasma DPP-4 activity in *(genetically modified obese) ob/ob* mice, increased the circulating level of intact GLP-1 and improved the glucose-lowering and insulin-releasing effects of exogenous GLP-1 administration[50]. Metformin may modulates the incretin axis by PPAR-α dependent mechanism[34]. In accordance with those in the present study daily administration of metformin showed a significant decrease in DPP- 4 level.

The primary genetic, environmental, and metabolic factors responsible for causing insulin resistance and pancreatic β-cell failure and the precise sequence of events leading to the development of type 2 diabetes are not yet fully understood. Elevated cholesterol and triglycerides lead to dyslipidemia one causatives of insulin resistance[51]. Stevia extract improved the lipid profile of 20 hypercholestremic women, total cholesterol, triglycerides and low density lipoprotein significantly decreased while the high density lipoprotein significantly increased[52]. Recent studies also reported the antihyperlipdemic effect of stevia[53] investigated the effect of aqueous extract of stevia on hyperglycemia and hyperlipidemia induced by stress in rabbits. Similar results obtained in diabetic rats[54&55]. The present study in the same way with this as daily administration of 400 mg/kg significantly reduced TC, TGs and LDL while serum HDL significantly increased.

In this study metformin significantly decreased TC, TG, LDL and significantly increased HDLthis finding agreed with previous studies reported the antihyperlipdemic activity of metformin. Metformin improved dyslipidemia in children with metabolic syndrome and suggested as a cardioprotective in risk patients[56]. Recently[57] concluded that metformin can improve dyslipidemia and reduce cardiac events in type 2 diabetic patients.

Recently, Steviosides showed antioxidant activity and prevented the oxidative damage of DNA in liver and kidney in diabetic rats and significantly elevated the GSH levelcompared to diabeticrats[48]. This study is agree with the previous researches as the daily administration of stevia aqueous extract produced a significant increase in the antioxidant GSH level in liver and kidney tissues furthermore the level of MDA significantly reduced.

In a comparative study the antioxidant activities of metformin, repaglinide and glibenclimide were studied in diabetic rats, metformin significantly increased the antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD). The level of GSH significantly improved while the level of MDA significantly reduced[35]. The renoprotective effect of metformin was investigated in a rat model of type 2 diabetic nephropathy, metformin administered orally for 13 weeks thus produced a significant increment of SOD activity and significantly decreased levels

MDA, as compared with the model group and attenuated the morphological changes associated with type 2 diabetes in rats. Which suggesting that metformin may has a renoprotection activity[58]. In agreement with this the present study showed that metformin could has a renoprotective and hepato-protective effect in type 2 diabetes since treatment of diabetic rats produced a significant increase in GSH level in both liver and kidney tissues while the MDA level significantly decreased.

Conclusion

In conclusion, all the previous parameters shows that stevia has antihyperglycemic effect and significantly improves the effect of metformin in diabetic rats. The antihyper-glycemic effect of stevia and its improvement to metformin may be mediated by its antioxidant activity (reduction of MDA and increasing GSH), DPP-4 attenuation, and improvement of lipid profile and improvement of insulin sensitivity.

Abbreviations: DPP-4: dipeptidylpeptidase 4, TC: total cholesterol, TG: triglycerides, LDL: low density lipoprotein, HDL: high density lipoprotein, GSH: reduced glutathione, MDA: malondialdehyde, STZ: streptozotocin, NA: nicotinamide, FBG: fasting blood glucose.

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نشرة العلوم الصيدلية
جامعة أسيوط

ستيفيا تحسن تأثيرالميتفورمين المضاد للسكرى فى الجرذان المصابة بالسكرى تم احداثه بالستربتوزتوسن استيراتيجية جديدة لعلاج مرض السكرى الثانى

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مرض السكري هو مشكلة صحية كبيرة تهدد العالم بأسره ووفقًا لتقارير منظمة الصحة العالمية فإنه من المتوقع أن يرتفع معدل انتشار مرضى السكري في مصر من ٢،٦٢٣،٠٠٠ في عـــام ٢٠٠٠ إلى ٦,٦٢٧,٠٠٠ في عام ٢٠٣٠. ويعد ميتفورمين افضل دواء لبدء علاج السكري من النوع الثـــاني المنتشر بين مرضي السكري والذي يمكن استخدامه كدواء منفردا أو مع أدوية أخرى. ومع ذلك فإن ما يصاحب ذلك من استخدام ميتفورمين مع ستيفيا يحتاج الى دراسة واستكشاف أعمق. لذلك تم إجراء هذه الدراسة لمعرفة مدى تأثير ستيفيا على نشاط ميتفورمين كعلاج مضاد لمرض السكرى.

تم إحداث داء السكري الثاني في الجرذان عن طريق حقن ستربتوزوتوسن ونيكوتينمايـــد وتـــم تقسيم الحيوانات إلى خمس مجموعات ، كل منها يحتوي على ثمانية جـــرذان. المجموعـــة الأولـــى: مجموعة الجرذان الضابطة ، المجموعة الثانية: جرذان مصابة بداء السكرى وتلقـــت محلـــول ملـــح ، المجموعة الثالثة: جرذان مصابة بالسكرى تتلقى ٤٠٠ ملجم/كجم/يوم المـــستخلص المـــائى لـــستيفيا ، المجموعة الرابعة: جرذان مصابة بالسكري تلقت ميتفورمين ٢٥٠ مجم/كجم/يوم ، المجموعة الخامسة: جرذان مصابة بالسكري تلقت ستيفيا ٤٠٠ ملجم/كجم بالاضافة الى الميتفورمين ٢٥٠ مجم/كجم. وبعد ٢١ يومًا تم جمع عينات الدم وعينات الأنسجة من الحيوانات. وتم قياس المعايير الأتيه (بعضها في الدم وبعضها في الأنسجة) مستوى السكر الصايم ، الأنسولين ، داى بيبتيديل بيبتيديز، الكوليستيرول الكلى ، الجليسريدات الثلاثية، البروتين الدهنى منخفض الكثافة ، البروتين الدهنى مرتفع الكثافة ، والجلوتاثيون المختزل والمالون داى الدهايد باستخدام سبكتروفوتومتر والاليزا..

كل من ستيفيا وميتفورمين خفض بشكل ذو دلالة احصائية مستوى السكر الصايم في حين أن مـــستوى الأنسولين زاد بدرجة ملحوظة. انخفض مستوى داى بيبتيديل بيبتيديز بشكل كبير في جميع المجموعات المعالجة ، فيما يتعلق بالدهون ، كل من ستيفيا وميتفورمين خفض بشكل كبيرالكوليـــستيرول الكلـــى ، الجليسريدات الثلاثية ، كوليسترول البروتين الـــدهنى المـــنخفض الكثافـــة ومـــن ناحيـــة أخـــري زاد كوليستيرول البروتين الدهنى عالى الكثافة كل من ستيفيا والميتفورمين خفض بشكل كبير مـــالون داى الدهايد وزودت الجلوتاثيون المختزل مقارنة مع الجرذان المصابة السكري. بالإضافة إلى ذلك ، وقـــد ازدادت بشكل ملحوظ تأثيرات الميتفورمين المضادة لمرض السكرى عنـــد اضـــافة خلاصـــة ســـتيفيا للمتفورمين.

من هذه الدراسة نستنتج ان: تمتلك ستيفيا تأثير مضاد للسكرى ويمكن أن تزيد من القدرة العلاجية للميتفورمين عن طريق تقليل مستوى الداى بيبتيديل بيبتيديز والدهون في الدم وكذلك زيادة حساسية مستقبلات الأنسولين للانسولين وزيادة الجلوتاثيون المختزل وتقليل المالون داى الدهايد.