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Research Article

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Hypoglycemic and Hypolipidemic Properties of Ethanolic Extract of Brassica oleracea in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Diabetes mellitus has become the most prevalent metabolic disease worldwide. The edible leaves of Red cabbage (Brassica oleracea L.) is one of the most regularly consumed vegetables in Arabic countries. Thus, it was of interest to assess the hypoglycemic and hypolipidemic impacts of ethanolic (50 %) extract of the leaves of red cabbage on blood glucose, glycated hemoglobin (HbA1c) and lipid profile in streptozotocin (STZ)-induced diabetic rats. Diabetes was induced in male Wistar rats by injecting rats with 60 mg/Kg bodyweight of streptozotocin. Diabetic rats demonstrated a significant increase in serum glucose, glycated hemoglobin (HbA1c) total cholesterol (TC), and triacylglycerol (TG). Daily oral supplementation (250 mg/Kg body weight) of extract of red cabbage leaves for 40 days to STZ-induced diabetic rats significantly ameliorated HbA1c ($p < 0.01$), TG ($p < 0.01$), serum glucose ($p < 0.01$), and TC ($p < 0.01$). By comparison, a standard anti-hyperglycemic drug, Glibenclamide, when administered at a dose of 10 mg/kg body weight, decreased TC, blood glucose, HbA1c, and TGs levels. It is concluded that the ethanolic extract of red cabbage decreased the blood levels of HbA1c, glucose, and lipids and it was more efficient than Glibenclamide in reducing blood glucose.

Key words: *Diabetes mellitus, Hyperlipidemia, Hyperglycemia, Metabolic diseases.*

INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine metabolic disorders [1-3] characterized by hyperglycemia due to deficiency of insulin secretion and peripheral insulin resistance [4], which is expanded around the world [5, 6]. Diabetes mellitus (DM) is considered as a major public health challenge with tremendously rising prevalence and long-lasting impairments [4]. Diabetes mellitus (DM) and its complications have a tremendous burden on public health due to its microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, and peripheral vascular disease) complications which are associated with significant mortality and morbidity [7]. It's well established that tight control of blood glucose within the normal range can prevent complications of diabetes mellitus [8]. Today, pharmacological therapies available for diabetes are comprised of insulin and different oral antidiabetic agents like Metformin, Sulfonylureas, Biguanides, and Glinides. Unfortunately, many of them have several profound adverse effects, like lactic acidosis, hypoglycemia, and weight gain [9]. Thus, searching for more efficient and safer hypoglycemic agents is one of the vital areas of research.

Some medicinal plants have been reported to be beneficial in controlling diabetes worldwide and have been utilized empirically in antidiabetic and antihyperlipidemic remedies. The ethnobotanical data suggests that about 800 plants may have anti-diabetic activity, among all of them *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum greacum* is beneficial for the treatment of type 2 diabetes [10, 11]. Around the world, many experimental investigations have confirmed the antidiabetic potential of different medicinal plants. For instance, the aqueous leaf extract of *Aegle marmelos* indicated antihyperglycemic activity in Streptozotocin-induced diabetic rats after 14 days of treatment either by naturally enhancing utilization of glucose or by direct stimulation of glucose uptake through enhanced insulin secretion [12]. In one interesting investigation, the aqueous extract of *Agrimony eupatoria* evoked stimulation of insulin secretion from the BRIN-BD11 pancreatic beta-cell line in vitro, and the impact of the extract was revealed to be glucose-independent [13]. The hypoglycemic influence of Aloe vera in the rats is mediated through stimulation of synthesis or release of insulin from the beta-cells of Langerhans [14].

Cruciferous vegetables such as red cabbages (*Brassica oleracea*) are among the most important dietary vegetables consumed in most Arabic countries including Saudi Arabia owing to their availability in local markets, cheapness, and consumer preference. The red cabbage is characterized by its purple leaves but otherwise looks similar to the more ordinary white cabbage [15]. Cabbage is consumed for lowering the risks of developing breast cancer, lung, stomach, colon, and other types of cancer because of its chemical features which are thought to lower the levels of estrogen in the body [16]. Red cabbage additionally has antimicrobial, and anticancer activities and has become established as an important human food crop plant used because of its large food reserves [17]. Little is known about the hypoglycemic and hypolipidemic effect of red cabbage.

Searching for new antidiabetic drugs from natural plants is still attractive because they have substances that indicate an alternative for synthetic antidiabetic agents with safer side effects profile. In addition, the hypoglycemic action of red cabbage is still not adequately clarified. Therefore, the aim of the present study was to investigate the hypoglycemic and hypolipidemic effects of ethanolic extract of red cabbage.

MATERIALS AND METHOD

Materials

Chemical materials

Streptozotocin (STZ) and Glibenclamide were obtained merely from Sigma (USA). All chemicals in the current investigation are of analytical grade, products of Sigma, Merck, and Aldrich. All kits were provided from Biosystems (Alcobendas, Madrid, Spain), Sigma Chemical Company (St. Louis, MO, USA), Biodiagnostic Company (Cairo, Egypt). Red Cabbage was provided from the local market in Al-Hssa.

Animals

A total of 20 albino rats weighting 166 ± 19 g were provided from the animal house, College of Medicine, King Faisal University, Al-Hssa. Animals were properly housed in cages under conditions of controlled temperature (22 - 28ºC) with a fixed light/dark cycle for 2 weeks as an adaptation period to acclimatize under normal circumstances in combination with free access to water and food ad libitum. The present study is approved by the Ethical Committee of King Faisal University, Kingdom of Saudi Arabia, provided that the animals will not suffer at any stage of the experiment.

Methods

Preparation of red cabbage crude extract

The outer layer of red cabbage was removed, but the inner layer was cut into small pieces, dried at 40-45°C in a hot oven, and crushed to a fine powder. The cabbage powdered leaf (100 g) was soaked in 200 ml of 50% ethanol with a constant stirring by a magnetic stirrer for 24 hours. The mixture was filtered followed by the removal of the solvent by the rotatory evaporator to give a dark brown paste extract [17].

Experimental design

20 albino rats were selected for this study and divided into four groups (5 rats in each group) as follows; Group A: normal healthy control rats; Group B: diabetic control rats; Group C: diabetic control rats treated with oral administration of 150 mg/kg red cabbage extract for 40 days; Group D: diabetic antidiabetic reference drug (e.g. glibenclamide) 5 mg/kg body weight rats administered orally daily for 40 days [18].

Induction of diabetic rats

Diabetes was induced by STZ. Each rat was injected intraperitoneally with STZ (60 mg/kg body weight dissolved in 0.01 M citrate buffer immediately before utilization) [19]. After injection, animals had unrestricted access for food and water and were given a 5% glucose solution to drink overnight to encounter hypoglycemic shock. After 3 days of STZ injection, animals were checked daily for the random blood glucose level [19].

Sample preparations
After 40 days of treatments with RCE, rats were fasted overnight (12-14 hours), anesthetized by diethyl ether, and blood was collected by a cardiac puncture. Blood was maintained in a clean and dry test tube, left 10 minutes to clot, and centrifuged at 3,000 rpm for serum separation.

Biochemical examination
Blood Glucose level was determined by the glucose oxidase technique [20]. Glycosylated hemoglobin (HbA1c) was measured by the method of Mallya and Pattabiraman [21]. Serum TC concentration was determined based on the technique of Allain et al. [22]. Serum triacylglycerol (TGs) concentration was determined based on the method of Fassati and Prencipe [23].

Statistical Analysis
The findings are depicted as means ± SD. The statistical methods used to analyze the data in this study were unpaired Student's t-test (two-tailed) by using SPSS version 25.0. P values < 0.05 were considered statistically significant.

RESULT

Blood Glucose & HbA1c level:
Diabetic rats showed significant elevation in random blood glucose and HbA1c levels as compared to the control rat group (Table 1, 2). Oral supplementation of red cabbage crude extract to diabetic rats resulted in a significant decrease in the levels of random blood glucose as compared to the diabetic control rat group and diabetic rats treated with Glibenclamide. Oral supplementation of red cabbage crude extract to diabetic rats resulted in a significant decrease in the levels of glycated hemoglobin (HbA1c) as compared to untreated diabetic control rat group, but no significant difference as compared to diabetic rats treated with Glibenclamide group (Table 1, 2).

Table 1: Serum HbA1c in studied groups.

	A. Healthy Control Rats.	B. Untreated Diabetic Control Rats.	C. Diabetic Rats treated with Glibenclamide.	D. Diabetic Rats treated with RCE.
Mean ± SD P value	0.29 ± 0.01	0.98 ± 0.03 > 0.0001 [a]	0.42 ± 0.02 > 0.001a > 0.0001 [b]	0.43 ± 0.03 > 0.001 [a] > 0.0001 [b] NS [c]

Table 2: Serum random blood glucose in studied groups.

	A. Healthy Control Rats.	B. Untreated Diabetic Control Rats.	C. Diabetic Rats treated with Glibenclamide.	D. Diabetic Rats treated with RCE.
Mean ± SD P value	98.9 ± 12.8	465.8 ± 34.8 > 0.0001 [a]	308.9 ± 45.8 > 0.0001 [a] > 0.0001 [b]	285.4 ± 54.8 > 0.0001 [a] > 0.0001 [b] > 0.001 [c]

Lipid profile
Diabetic rats showed significant elevation in serum TC and TGs as compared to the control rat group (Tables 3 & 4; Figures 3 & 4). Oral supplementation of red cabbage crude extract to diabetic rats resulted in a significant decrease in the levels of both TC and TGs as compared to the untreated diabetic control rats group (Tables 3 & 4;

Figures 3 & 4). On the other hand, diabetic rats treated with Glibenclamide revealed a significant modification in blood glucose, HbA1c, TC & TGs concentrations as compared to normal control rats (Tables 3 & 4; Figures 3 & 4).

Table 3: serum total cholesterol (TC) in the studied groups.

	A. Health Control Rats	**B. Diabetic Control Rats**	**C. Diabetic Rats treated with Glibenclamide**	**D. Diabetic Rats treated with RCE**
Mean ± S P value	98.7 ± 8.9	235.8 ± 13.8 > 0.0001a	113 ± 15.3 > 0.01a > 0.0001b	102.5 ± 12.8 > 0.01a > 0.0001b > 0.01c

Table 4: serum triglyceride (TGs) in the studied groups.

	A. Health Control Rats	**B. Diabetic Control Rats**	**C. Diabetic Rats treated with Glibenclamide**	**D. Diabetic Rats treated with RCE**
Mean ± SD P value	123 ± 15.9	254 ± 23.9 > 0.0001 [a]	129.6 ± 32.8 > 0.01 [a] > 0.0001 [b]	121.9 ± 22.7 > 0.01 [a] > 0.0001 [b] > 0.01 [c]

DISCUSSION

Diabetes mellitus (DM) is increasing sharply and consider as one of the leading causes of death in the world. Moreover, in the clinic, Metformin, Sulfonylurea, Rosiglitazone, and α-glucosidase inhibitors all poses severe side-effects after prolonged treatment [9]. The present investigation revealed abnormal glucose and lipid metabolism which is considered as an extra metabolic disorder in diabetic complications (Tables 3 & 4). Comparable results were achieved by Rodríguez-Méndez AJ et al., who reported there is dyslipidemia related to hyperglycemia in STZ-induced diabetic rats [24]. In an exact agreement with the current data, Jurgonski et al. demonstrated that hyperglycemia produced a marked in elevation in the serum level of TC & TGs. It was stated that hepatic fat accumulation is a well-recognized complication of DM [25]. This hyperlipidemia related to DM may be attributed to insulin deficiency and increased cortisol levels, which plays a substantial role in the process of fat accumulation [26]. Under normal conditions, insulin activates lipoprotein lipase which hydrolyzes triglycerides. Insulin deficiency fails to activate the enzyme, thereby leading to hypertriglyceridemia [27]. Furthermore, it is reported by the International Diabetes Federation (IDF) that, about 75–80% of people with diabetes die because of cardiovascular complications due to hyperlipidemia related to hyperglycemia [28].

It is approved that tight control of blood glucose can decrease clinical symptoms in diabetic patients [29]. The present research stated that the ethanol extract of red cabbage possesses definite hypoglycemic and hypolipidemic properties in STZ-diabetic rats after 40 days of treatment. The hypolipidemic effect of red cabbage extract may be due to the presence of saponin, which lowers blood cholesterol and increases rejecting of bile acids and neutral lipids out of the body [30], or maybe due to inhibiting hydroxyl methyl glutaryl (HMG)-CoA reductase enzyme which is responsible for the biosynthesis of cholesterol [31]. The hypolipidemic effect of red cabbage leaves may be attributed to their high content of anthocyanins. The leaves of red cabbage have been reported to contain biologically potent anthocyanins which are reportedly ameliorated dyslipidemia in numerous studies. In a good agreement with Wallace TC et al., in their systematic review of RCTs, they reported that anthocyanins and anthocyanin-rich extracts may have the potential to influence markers of cardiovascular diseases [32].

The hypoglycemic effect of red cabbage can be explained by the presence of glucosinolates. Our results are agreed with the study of Verkerk and Dekker [33] which reported that red cabbage contains glucosinolates that have antidiabetic activities. In addition, the variants of *Brassica oleracea* species are also known to contain sulforaphane and glucoraphin, which can also be responsible for the antihyperglycemic effects [34].

The plenty amount of Anthocyanins in red cabbage may play a role in the hypoglycemic effect of red cabbage. Anthocyanins also have an inhibitory effect on α-glucosidase enzymatic activity, so it can prevent the increase of postprandial blood sugar [35]. Anthocyanins may also increase the phosphorylation of the insulin receptor, thereby increasing the entry of glucose into the tissues and lowering blood glucose levels [15].

CONCLUSION

In conclusion, the ethanolic extract of red cabbage in STZ-induced diabetic rats at a dose of 250 mg/kg has definite antihyperglycemic and antihyperlipidemic properties after 40 days of treatment. In addition, red cabbage leaves extract was found to be more effective for reducing blood glucose than glibenclamide. The hypoglycemic and hypolipidemic mechanisms of Red Cabbage extract remains unclear. We suggest further studies to elucidate cellular and molecular mechanisms. Red Cabbage can further be analyzed using modern liquid chromatographic techniques coupled with mass spectrometry (LC-MS), nuclear magnetic resonance spectroscopy (LC-NMR), ultra-violet spectroscopy (LC-UV) identification and isolation of the novel anti-diabetic component(s) and can be analyzed on pancreatic insulin content in STZ-induced diabetic rats, infrared spectroscopy (LC-IR) for the identification and isolation of the novel anti-diabetic component(s) and can be analyzed on pancreatic insulin content in STZ-induced diabetic rats.

Conflicts of interest
The authors declare that they have no conflicts of interest.

Author's contributions
Experimental design: Ali Al-Saeed. Performed the experiments: Ali Al-Saeed, Mohamed Al-Ameer, and Bander Al-Anyzi. Analyzed the data: Ali AL-SAEED. Paper writing: Ali Al-Saeed. Manuscript review: Prof. Mussad Saif. Interpreted the data: Ali Al-Saeed. Data acquisition: Mohamed Al-Ameer, and Bander Al-Onyzy. Overall supervision and critical comments: Prof. Mussad Saif. All authors read and approved the final manuscript.

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