Protective Effect of Camel Milk and *Ginkgo biloba* Extract Against Alloxan-Induced Diabetes in Rats

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Abstract

Diabetes Mellitus is one of the most important health problems worldwide, indicating high prevalence and mortality. In recent years, *Ginkgo biloba* extract has become a subject of interest because of its beneficial effects on human health, also camel milk has a good nutritive value, in addition to its antigenotoxic and anticytotoxic effects. Therefore the purpose of the present study was to investigate the protective and curative effects of camel milk and *Ginkgo biloba* extract against alloxan-induced diabetes in rats.

Rats were either pre-treated with camel milk, *Ginkgo biloba* extract or both, for 10 days before alloxan administration, or treated with both camel milk and *Ginkgo biloba* extract after induction of diabetes using alloxan.

Pre-treatment of rats with either camel milk or *Ginkgo biloba* extract significantly prevented the alloxan-induced elevation of blood glucose levels. The combination of camel milk and *Ginkgo biloba* extract before and after induction of diabetes prevented and improved blood glucose levels respectively.

Keywords: Diabetes mellitus; Ginkgo biloba; Camel milk; Alloxan; Oxidative stress; Total antioxidant activity

Introduction

Diabetes mellitus is a common disorder associated with marked increase in morbidity and mortality rate. Diabetes mellitus can be defined as a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both, resulting in impaired function in carbohydrate, lipid and protein metabolism [1,2]. There is a reservoir of basic information that suggests the involvement of oxidative stress in the pathogenesis of diabetes mellitus. It is now recognized that sustained hyperglycemia in diabetic patient, causes protein glycation and generates free radicals through auto-oxidation and polyol pathways [3,4].

High levels of free radicals with concurrent decline of antioxidant defense mechanism may lead to damage of cellular organelles and enzymes [5]. This can culminate in increased lipid peroxidation and development of insulin resistance, which may consequently promote the development of complications of diabetes mellitus [6].

In humans, diabetes mellitus is one of the most prevalent conditions with spontaneous manifestation. In animals, it can be induced by partial pancreatectomy or by the administration of diabetogenic drugs such as alloxan, streptozotocin, ditizona and anti-insulin serum [7]. These agents selectively destroy the Langerhans islet β-cells. One of the best known drug-induced diabetes models is the alloxan diabetes. Alloxan (a derivative of uric acid) as well as of other substances of different chemical groups, cases β-cells to degranulate and consequently degenerate. Alloxan induces irreversible diabetes mellitus 24 hours following its administration and the condition proves to be chronic by laboratory tests after seven days [8,9].

Insulin therapy and oral hypoglycaemic agents offer effective glycaemic control, but insulin therapy has shortcomings such as ineffectiveness following oral administration, short shelf life, the need for constant refrigeration, and fatal hypoglycaemia, in the event of excess dosage [10]. As a result, there is a need to search for compounds with effective antidiabetic activity when taken orally. The oral hypoglycemic agents that are capable of reducing blood sugar level belong to two chemical classes; sulfonylures and biguanides [11]. However, the use of oral antidiabetics is limited due to their adverse side effects including hematological, cutaneous and gastrointestinal reactions, hypoglycaemic coma and disturbances of liver and kidney functions. In addition, they are not suitable for use during pregnancy [12].

Plants are well known in traditional herbal medicine for their hypoglycaemic activities, and available literature indicate that there are more than 800 plant species showing hypoglycaemic activity [13]. The World Health Organization has recommended the evaluation of the effectiveness of plants in conditions, where safe orthodox drugs are scarce [14]. Studies have shown that phytochemicals isolated from plant sources have been used for the prevention and treatment of cancer, heart disease, diabetes mellitus, and high blood pressure [15].

Over the past few years, the use of medicinal plants has been rapidly increasing. The therapeutic benefits of these plants are often attributed to their antioxidant properties [16].

The tree *Ginkgo biloba* has long been believed to have medicinal properties, and its extracts are among the most widely-sold herbal supplements in the world. *Ginkgo biloba* extract (GBE), prepared from *Ginkgo biloba* leaves, is defined as a complex mixture containing 24% *Ginkgo* flavoneglycoside (quercetin, kaempferol, and isorhamne) and 6% terpene lactones (ginkgolides and bilobalide). It has been used as a therapeutic agent in some cardiovascular and neurological disorders [17,18].

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The beneficial effects of GbE might be channeled through a combination of one or several mechanisms of action. The combined therapeutic effects are probably greater than that of individual mechanisms and are perhaps the result of the synergistic effects of multiple constituents of the total extract [19]. The chemical structure of GbE 761, both flavonoid and ginkgolide constituents, is responsible for its remarkable antioxidant/reactive oxygen nitrogen species (RONS) scavenging activity. The flavonoids preferentially react with hydroxyl radicals [20] and chelate pro-oxidant transition heavy metal ions [21]. Significant antioxidant activity is consequently one of the most analyzed protective effects of GbE on the central nervous system and the circulatory system. GbE has a number of benefits, including ameliorating hemodynamics, suppressing the platelet-activating factor, scavenging reactive oxygen species (ROS), and relaxing vascular smooth muscles [22]. Nowadays, extract of ginkgo leaves in the form of film-coated tablets, oral liquids or injectable solutions are being used [23]. All of these criteria offered a pharmacological foundation for testing GbE for diabetic therapy.

Camel milk (CM) is an excellent source of well-balanced nutrients and also exhibits a range of biological activities that influence digestion, metabolic responses to absorbed nutrients, growth and development of specific organs and resistance to diseases. These biological activities are mainly due to the presence of peptides and proteins in milk [24,25]. CM is different from other ruminant milk; having low cholesterol, low sugar, high minerals (sodium, potassium, iron, copper, zinc and magnesium) and high vitamin C, B2, A and E. It has no allergic properties and it can be consumed by lactase deficient persons and those with weak immune systems. The milk is considered to have medical properties. A series of metabolic and autoimmune diseases are successfully being treated with CM [26].

Casein is the principal protein component in most of the mammalian milk. Besides casein CM also contains lactoferrin protein. It also contains fat with a relatively large amount of polysaturated fatty acids and linoleic acids, which are essential for human nutrition [27]. The anti-cytotoxic and antigenotoxic effects of most of the CM constituents against the genotoxic effects of chemicals are being investigated (e.g. vitamin C [28-30], selenium [31-33], zinc [34], casein [35,36] and lactoferrin) [37].

In India, CM is used therapeutically against dropy, jaundice, problems of spleen, tuberculosis, asthma, anemia, piles and diabetes [38]. Beneficial role of raw CM in chronic pulmonary tuberculosis patients has been observed [39]. In repeated trials, it was observed that there was 30-35% reduction in daily doses of insulin in patient of type 1 diabetes receiving raw CM [40].

In this study, the effect of oral dietary supplementation of CM and/or GbE in the prevention and/or treatment of alloxan induced diabetes in rat model was investigated. We also investigated the potential role of antioxidant activity of both materials in protecting from diabetes.

Materials and Methods

Animals
Male Wistar rats, weighing 180-220 g, were obtained from the animal house Medical Research Center. Animals were housed in polyplastic cages with steel wire tops in an air conditioned room maintained in a controlled atmosphere of 12 h light/12 h dark cycles with free access to a standard commercial diet and water.

Test compounds

**Camel milk:** Camel milk samples were collected from a Camel farm in Ras Seder, Egypt. All lactating camels consumed the same type of food. The milk was collected in the morning in sterile screw bottles and kept on ice during transportation to the laboratory where milk bottles were stored at 4°C. It was administered in a dose of 33 ml/kg body weight for each rat daily by oral cannula.

**GbE**

GbE (lot No 04002) was provided by Changsha Sunfull Bio-tech company (China) and was dissolved in 30% polyethylene glycol 400 (PEG, pH 7.4). It was used in a dose of 100 mg/kg.b.w. daily by intraperitoneal injection.

Induction of diabetes

Diabetes was induced in fasting rats 12 h by a single intraperitoneal injection of freshly prepared alloxan (120 mg/kg body weight, dissolved in 0.9% saline, Sigma Chemicals, USA). After 48 h of alloxan treatment, rats with marked hyperglycemia (fasting blood glucose >200 mg/dl) were selected for the experiment and considered as diabetic. The experimental animals were divided into 9 groups; each group contained 8 animals. Body weight and fasting blood glucose levels were estimated on 2nd, 4th, 7th and 10th day of the treatment. On the 10th day, blood samples were collected from overnight fasted rats by cardiac puncture under mild ether anesthesia for biochemical estimations.

Experimental design

The various groups used in the experiment:

- **Group N:** Normal control rats did not receive any treatment.
- **Group CM:** Normal rats received CM daily for ten days.
- **Group GbE:** Normal rats received GbE daily for ten days.
- **Group CM + GbE:** Normal rats receive both CM and GbE daily for ten days.
- **Group D:** Diabetic control rats, which received alloxan monohydrate only.
- **Group P CM:** Rats received CM daily for ten days before alloxan treatment.
- **Group P GbE:** Rats received GbE daily for ten days before alloxan treatment.
- **Group P CM+GbE:** Rats received both CM and GbE daily for ten days before alloxan treatment.
- **Group T:** Diabetic rats (alloxan-induced) received both CM and GbE daily for ten days following alloxan injection.

Biochemical investigations

Determination of blood glucose concentration:

Fasting blood glucose concentration was determined by commercially available glucose kit (Egy-Chem) based on Trinder’s [41] glucose oxidase method. The glucose levels were expressed as mg/dl.

**Determination of insulin and C-peptide concentration:** Insulin concentration was determined in serum by radioimmunoassay method using a commercially available DSL-1600 insulin kit (Diagnostic Systems Laboratories, Inc., USA). Insulin values were expressed as μU/ml. Serum c-peptide was estimated by enzyme linked immunosorbent
assay (ELISA) technique by commercial kit and it was expressed as ng/ml.

Biochemical parameters of oxidative stress:

- Determination of the lipid peroxidation (LPO) in serum: Malondialdehyde (MDA) was measured by the method of Ohkawa et al. [42] and read fluorimetrically at excitation wavelength of 532 nm and emission at 533 nm.

- Total antioxidant activity estimation: Total antioxidant activity (TAA) was assessed by the method of Koracevic et al. [43] using bio-diagnostic kit (Egy-Chem).

Determination of liver function tests: Liver function tests, including liver enzymes (Alanine transaminase (ALT), Aspartate transaminase (AST) [44]) and gamma glutamyl transferase (GGT) [45], lipid profile (Total cholesterol (TC) [46], High density lipoprotein cholesterol (HDL) [47] and Triglycerides (TG) [48]) and total proteins [49] were determined using bio-diagnostic kits (Egy-Chem).

Kidney function tests: Kidney function tests, including determination of urea [50] and creatinine [51] in serum were done using bio-diagnostic kits (Egy-Chem).

Pancreatic histopathology

Autopsy samples were taken from Pancreas of rats in different groups and fixed in 10% formalin for twenty four hours. Washing was done in tap water then serial dilutions of alcohol (methyl, ethyl and absolute ethyl) were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56° in hot air oven for twenty four hours. Paraffin bee wax tissue blocks were prepared for sectioning at 4 microns by sliding microtome. The obtained tissue sections were collected on glass slides, deparaffinized and stained by hematoxylin and eosin stains [52] for histopathological examination through the electric light microscope.

Data analysis

Data were statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 17. Hypothesis testing was done by one-way analysis of variance (ANOVA).

Results

In order to evaluate the protective and/or therapeutic potential of individual or combined treatment with CM and GbE, rats were either pretreated for 10 days with CM, GbE, or both, prior to induction of diabetes using a single injection of alloxan, or treated with both compounds for 10 days after the alloxan treatment.

A significant increase in blood glucose levels, at day 2 post alloxan treatment, was observed in the alloxanized diabetic group by 180%, (p<0.001) (Figure 1), compared to the non-diabetic one. Administration of both CM and GbE along with alloxan caused a significant reduction in the blood glucose levels by 46.7%, (p<0.001) as compared to the diabetic control rats.

Treatment of control rats with GbE and CM showed normal levels of insulin and C-peptide as compared with untreated control animal. Notably pre-treatment with GbE, CM or both before alloxan revealed no significant change in results compared to normal control rat. Alloxan-induced diabetic rats showed severe hypoinsulinemia and low level of C-peptide (p<0.001; Table 1) as compared with normal control rats. The administration of GbE and CM to alloxanized diabetic rats partially restored serum insulin level (p<0.05).

Moreover, less weight gain was observed in the diabetic rats as compared to the control. Administering GbE and CM improved the weight gain in the alloxan-induced diabetic rats.

Effect of the different treatments on serum ALT, AST and GGT activities and total proteins is presented in figure 2. Treatment of control rats with GbE and/or CM did not significantly alter the ALT, AST and GGT activities and total protein levels as compared to normal control rats. Meanwhile alloxan-induced diabetes induced a highly significant increase in ALT, AST and GGT activities and decrease in total protein levels (p<0.001) as compared to normal control ones. Importantly, administration of GbE and CM to alloxan-induced diabetic rats significantly improved the enzymes and total protein levels (p<0.001) as compared to diabetic group.

Serum lipid parameters (TC, TG and HDL cholesterol) were not affected by the administration of GbE and/or CM to normal rats as compared to the control group (group N), whereas alloxan-induced diabetic rats showed marked increase in TG and TC (p<0.001). Meanwhile, GbE and CM treatment of diabetic rats, in group T, caused a significant decrease in the previous parameters compared to the diabetic values (p<0.001). The values of HDL were found to be significantly increased in control groups (groups CM, GbE&CM+GbE) when compared with normal control (p<0.05), while alloxan diabetic rats recorded a highly significant decrease when compared to normal control group (p<0.001). Treatment with CM and GbE tested materials (group T) caused a significant increase in HDL cholesterol levels when compared to diabetic control group (p<0.001) as indicated in figure 2.

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Figure 3 shows a marked increase in serum urea and creatinine levels in diabetic control rats compared to normal control ones. Pre-and post-treatment with CM and/or GbE induced a significant improvement of the urea and creatinine levels compared to diabetic control (group D).

Our results indicate that TAA levels were markedly decreased in diabetic group. It was observed that the treatment with GbE and CM caused an increase in TAA compared to diabetic control (Figure 4A). In the control groups (CM, GbE and GbE+CM) there is a significant increase in TAA level compared to normal control group (N). Figure 4B, showed a significant elevation of serum MDA content in diabetic rats compared to normal control. In the treated group (T) there is significant decrease in MDA compared to diabetic rats (group D),while in groups CM and CM+GbE there is a non significant decrease in MDA level compared to normal control group (group N).

**Histopathological findings**

- **Group N:** There was no histopathological finding and the normal histological structure of the islands of Langerhans cells as endocrine structure, the acini as exocrine one and the interlobular blood vessels were recorded in (Figure 5A).
- **Groups CM, GbE and CM+GbE respectively:** There was no histopathological alternation in the islands of Langerhans (Figure 5B-5D).
- **Group D:** Atrophy was noticed in the islands of Langerhans, associated with congestion in the interlobular blood vessels (Figure 5E).
- **Groups P CM, P GbE and P CM+GbE respectively:** There was no histopathological alteration detected in the islands of Langerhans (Figure 5F-5H).
Diabetes mellitus (DM) is possibly the world’s fastest growing metabolic disorder. It is one of the most important health problems worldwide, indicating high prevalence and mortality. Management of diabetes without any side effects is still a challenge to medical communities, therefore herbal and natural products with anti-diabetic activity and fewer side effects are strongly needed [53].

In this study, the pancreatic β cells were destroyed using alloxan, a toxic glucose analogue that accumulate in pancreatic beta cells via GLUT 2 glucose transporter. In the presence of thiols, especially glutathione (GSH), alloxan generates reactive oxygen species (ROS) in cyclic redox reactions. The reduction product of alloxan is dialuric acid. Auto-oxidation of dialuric acid generates ROS, which are responsible for the death of the β cells. Alloxan also inhibits glucose-induced insulin secretion through its ability to inhibit the β cell glucose sensor, glucokinase. Inappropriate activation of NFκB by ROS might start a cascade of events that result in an inflammatory and autoimmune response in pancreas, so the inhibition of NFκB activation by antioxidants could improve the severity of type 1 diabetes [54,55]. In the present study, it can be concluded that pre-treatment with camel milk (CM) and/or *Ginkgo biloba* (*Gb*E) may inhibit alloxan-induced NFκB activation.

Post-treatment with CM and *Gb*E didn’t decrease the blood glucose level back to normal levels where it was still significantly higher than normal. However the pre-administration of CM and *Gb*E before alloxan treatment protected the β-cells from damage and the level of blood glucose was non-significantly different from that of normal rats. It was found that one of the CM proteins presents many characteristics similar to insulin [56] and does not form coagulum in acidic environment. This lack of coagulum formation allows CM to rapidly pass through the stomach, without being destroyed, together with the specific insulin like protein/insulin and remains available for absorption in the intestine. Radioimmunoassay of insulin in CM has revealed high concentration (52 units/liter) [57]. This suggests a very low prevalence of diabetes among subjects that are consuming CM [40].

In addition, administration of *Gb*E and CM caused marked amelioration of serum glucose concentration of alloxan diabetic rats, besides elevating insulin and C-peptide concentrations which were reduced by alloxan administration. Our data are in good agreement with other investigators [58-60] who stated that the positive effects of specific plant extracts on insulin activity suggest a possible role of these plants in improving glucose and insulin metabolism.

The anti-hyperglycemic effects of CM and *Gb*E are possibly linked to their antioxidant properties, which could counteract the toxic and pro-oxidant effects of alloxan. Flavonoids, sterols/triterpenoids, alkaloids and phenolics are known to be bioactive anti-diabetic principles [61-64]. Flavonoids are known to regenerate the damaged β cells in the alloxan diabetic rats [65]. Phenolics were also found to be effective anti-hyperglycemic agents [66,67].

It is evident that increased hepatic glucose output in diabetes mellitus may be derived either from glycogenolysis or from gluconeogenesis or both [68,69]. This was confirmed by our results which showed a marked increase of the detected gluconeogenic serum enzymes; Alanine transaminase (ALT), Aspartate transaminase (AST) and gamma glutamyl transferase (GGT); compared to those of the non-diabetic ones. Our study demonstrated that, the administration of *Gb*E and CM resulted in the attenuation of liver injury induced by alloxan treatment as indicated by the activities of ALT, AST and GGT. These results are in accordance with those of Rawi et al. [69], who found that the decrease of transaminases activities with treatment may be attributed to improved liver function with the return of gluconeogenesis towards its normal rate.

In the present study, alloxan diabetic rats exhibited marked hypertriglyceridemia, hypercholesterolemia with concomitant decrease in HDL cholesterol. Our results are in accordance with the findings of Mathe [70], Ulicna et al. [71] and Wasan et al. [72] who recorded marked increases of serum triglycerides and cholesterol levels and abnormalities in lipoprotein levels in alloxan and streptozotocin diabetic animals. These abnormalities certainly play a role in the increased risk for cardiovascular disease [73].

The abnormally high concentration of plasma lipids in diabetes is mainly due to the increase in the mobilization of free fatty acids from the peripheral depository, since insulin inhibits the hormone sensitive lipase [73]. The marked hyperlipidemia that characterizes the diabetic state may therefore be regarded as a consequence of the unlimited actions of lipolytic hormones on the fat depot [74]. Treatment of alloxan diabetic rats with *Gb*E and CM produced marked decrease of serum triglycerides and total cholesterol concentrations. These observations indicate that the hypcholesterolemic action of the tested materials might be attributed to their ability to suppress cholesterol biosynthesis. Furthermore, correlation between insulin levels, triglycerides and total cholesterol fractions underline the important role of this hormone in the control of blood lipid levels [75].

Oxidative stress may constitute the key and common events in the pathogenesis of different diabetic complications. [76]. Hypoinsulinemia in diabetes increases the activity of the enzyme fatty acyl coenzyme A oxidase which initiates β oxidation of fatty acids, resulting in lipid
The present study showed a significant elevation of plasma malondialdehyde (an indicator of lipid peroxidation) contents in diabetic rats. The GbE and CM significantly reduced the lipid peroxidation product levels in diabetic rats, confirming that GbE and CM are potent antioxidants.

Any compound – natural or synthetic – with antioxidant activity might totally or partly alleviate the oxidative damage [76]. Total antioxidant activity (TAA) reflects the ability to defend against free radical damage more precisely than measurement of individual plasma antioxidants, since TAA is a result of interactions among its various components. Our results indicate that TAA levels were markedly decreased in the diabetic group. It was observed that treatment with GbE and CM caused an increase in TAA.

Alloxan was found to cause a significant reduction in the body weight of rats when compared with the control. Animals receiving GbE and CM, both pre- and post-treatment, with alloxan increased their body weight compared with the diabetic rats. Suresh and Das [79] reported that animals which developed alloxan-induced DM showed a significant decrease in body weight as a result of uncontrolled DM. The ability of GbE and CM to prevent and/or correct body weight loss seems to be due to its hypoglycaemic and hypolipidemic effects.

Plasma urea and creatinine can be used as a rough index of the glomerular filtration rate [80]. High levels of urea and creatinine indicates several disturbances in kidney [81]. In this study, the treatment with GbE and CM (pre and post-treatment) significantly increased serum total proteins and decreased serum urea and creatinine levels, compared to alloxan diabetic rats by enhancing the renal function that is generally impaired in diabetic rats.

The prevention of chemically-induced DM in experimental animals by polyunsaturated fatty acids was studied by Mohan and Das [82]. They observed that oral supplementation with oils rich in ω-3 (EPA, DHA) and ω-6 (linolenic, arachidonic) fatty acids could protect the animals against alloxan induced DM. These oils not only significantly attenuated the chemically-induced DM, but also restored the antioxidant status to a normal range by suppressing production of cytokines [83]. The protective effect of camel milk may be because it also contains fat with a relatively large amount of polyunsaturated fatty acids and linoleic acids.

Finally, it is concluded that the consumption of GbE and CM caused a significant reduction in glucose level of alloxan diabetic rats. In addition, those agents were capable of improving hyperlipidaemia and the impaired kidney functions. Moreover, the pretreatment of rats with GbE and/or CM for 10 days before induced diabetes was effective in controlling the hyperglycaemia, hyperlipidaemia and the oxidative damage.

References


