Reishi Mushroom (*Ganoderma lucidum*) Extract Ameliorate Hyperglycemia and Liver/Kidney Functions in Streptozotocin-induced Type 2 Diabetic Rats

Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

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**ABSTRACT**

Diabetes is a metabolic condition characterized by hyperglycemia and insufficient insulin production or activity. Since ancient times, the reishi mushroom (*Ganoderma lucidum*) has been utilized as a traditional herbal treatment. **Aim of the study:** investigate the effectiveness of *Ganoderma lucidum* extract (GLE) to ameliorate hyperglycemia and liver/kidney functions in streptozotocin-induced type 2 diabetic rats. Six groups of adult male Sprague–Dawley rats were formed at random. Group 1: Normal rats with a normal diet. Group 2: Diabetic rats by injection Streptozotocin (STZ) and fed without intervention as a model control group. Groups 3-6: GLE, diabetic rats with intervention groups receiving GLE at doses of 200, 400, 600, and 800 mg/kg BW via oral gavage for 28 days. After GLE intervention, blood samples were tested for changes in hyperglycemia, glycosylated hemoglobin, insulin, liver, and kidney functioning.

**Results:** Within the first two weeks of GLE intervention, blood glucose levels were reduced, and insulin levels in diabetic rats in the GLE group were considerably higher at four weeks than in the positive control group. Furthermore, it was discovered that GLE intervention significantly improved the liver and kidney functioning of diabetic rats. **Conclusion:** This research suggests that GLE consumption may help reduce blood glucose levels by boosting insulin production. Meanwhile, GLE therapy was linked to a reduction in diabetes problems in type 2 diabetic rats by improving their liver and renal functioning.

**Keywords:** *Ganoderma lucidum*, Weight, blood glucose, glycosylated hemoglobin, insulin.
INTRODUCTION

Fasting and postprandial blood glucose levels rise because of his actions. Hyperglycemia develops if the unbalanced homeostasis does not return to normal and persists for an extended period of time, leading to diabetes mellitus (DM), (WHO, 1999 and Tiwari and Madhusudana, 2002).

Furthermore, people with diabetes have bodies that either do not produce enough insulin or cannot use the insulin they do produce as well as they should. When there is not enough or cells stop responding to it, blood sugar stays too much in your system. This can lead to serious health problems at the end. Such as reviewed by WHO, (1999) and Yang et al., (2016), the primary complications of DM due to damage in small blood vessels include damage to the eyes (Diabetic retinopathy), kidneys (diabetic nephropathy), and nerves (Diabetic neuropathy). DM is also a leading cause of blindness, kidney failure, heart attacks, strokes, and lower limb amputations, according to Konstantinos et al., (2018). This disease is divided into two types. Type 1 diabetes (T1D), also known as insulin-dependent diabetes (IDD), and Type 2 diabetes (T2D), also known as noninsulin-dependent diabetes, are two types of diabetes (NIDDM). T2D is the most common type of diabetes, accounting for more than 90% of all diabetes cases around the world (IDF, 2021). Hyperglycemia in T2D is caused by the body's cells' failure to respond adequately to insulin, a condition known as insulin resistance (Stumvoll et al., 2005). Insulin resistance reduces the hormone's effectiveness, resulting in an increase in insulin production. Because of the pancreatic beta cells' inability to keep up with demand, insufficient insulin production might develop over time. According to the International Diabetes Federation (IDF), 537 million adults (20-79 years) would have diabetes by 2021, accounting for one out of every 10 persons. This number is predicted to rise to 643 million by 2030, and to 783 million by 2045. Diabetes will be the cause of 6.7 million deaths in 2021, or one every five seconds. Low- and middle-income countries have a higher prevalence of diabetes than high-income countries (Tiwari...
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In Egypt, People with diabetes (20-79 y) estimates 10.93 million in 2020 which predicted to rise to 13.74 million by 2030 and 19.98 million by 2045 (IDF, 2021).

Furthermore, the expense of administering contemporary anti-diabetic medications is out of reach for the majority of low-income people and those living in rural areas (Jevas, 2011). In this context, DM caused at least USD 966 billion dollars in health expenditure by 2021 – a 316% increase over the last 15 years. For all of these reasons, numerous traditional medicinal systems take a more holistic approach to healing. Modern techniques are still unable to describe the fundamental mechanics of these medical systems. Traditional remedies are made up of a number of plant components (vegetables, fruits, herbs, spices, algae, and so on) that are said to work on a variety of objectives through a variety of modes and methods (Tiwari and Madhusudana, 2002; Elhassaneen et al., 2016 and Matsui et al., 2006). As a result, there has been a surge in interest in plant-based medicines that can be used by the public but are difficult to maintain over term with the least number of side effects and the best preventive outcomes (Matsui et al., 2006). The reishi mushroom (Ganoderma lucidum) is a wood-decaying fungus that belongs to the Polyporales family Ganodermaceae and has hard fruiting bodies (Leskosek et al., 2010).

According to nutritional research, G. lucidum is primarily composed of protein, fat, carbohydrate, and fibre (Stojkovi et al., 2014). G. lucidum's fruiting body, mycelia, and spores contain roughly 400 distinct bioactive/phytochemical chemicals, primarily triterpenoids, polysaccharides, nucleotides, sterols, steroids, fatty acids, proteins/peptides, and trace elements. G. lucidum has been reported to have immune-modulating, anti-inflammatory, analgesic, chemo-preventive, anti-tumor, radio protective, sleep promoting, antibacterial, antiviral (including anti-HIV), hypolipidemic, anti-fibrotic, hepatoprotective, anti-oxidative and radical-scavenging, anti-aging, hypoglycemic, and anti-ulcer properties due to its unique content of bioactive compounds and their biological roles (reviewed in Liu,
1998; McKenna et al., 2002 and Wasser, 2005). Although there have been few investigations on the association between G. lucidum nutrition and diabetes. As a result, the current work used a streptozotocin (STZ) -induced diabetic rat model to assess the efficiency of in regulating hyperglycemia. GLE’s influence on liver and renal functions, as well as several biomarkers of hyperglycemic consequences were studied.

MATERIAL AND METHODS

Material

Reishi mushroom:
Dried fruits of reishi mushroom (Ganoderma lucidum) were purchased from ElMisryia Company for Trading Herbs and Medical Plants (Haraz), Bab ElKhalk, Cairo, Egypt. Taxonomic confirmation of G. lucidum was carried out by the Agricultural Plant Department, Faculty of Agriculture, Menoufia University, Shebin El-Kom, Egypt.

Chemicals:
Streptozotocin (STZ), which was utilized to induce DM in rats, was purchased from Sigma Chemical Co. in St. Louis, Missouri. Morgan Company for Chemicals provided casein as the primary protein source. Cairo is the capital of Egypt. El - Ghomhorya Company for Trading Drugs, Chemicals and Medical Instruments, Cairo, Egypt, provided analytical quality vitamins and salts mixes, organic solvents, and other chemicals.

Kit's: Kit's assays for serum glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were purchased from BIODIAGNOSTIC, Dokki, Serum creatinine and urea from Biocon Company, Cairo, Egypt.

Machines:
All biochemical analyses were performed with a UV-visible-light spectrophotometer (UV-160A; Shimadzu Corporation, Kyoto, Japan).

Methods
Preparation of Ganoderma lucidum ethanol extract (GLE)
Dried fruits of Ganoderma lucidum samples were ground in high miller speed (Moulinex Egypt, Al-Araby Co., Egypt), reduced to powder (20 mesh), and mixed to obtain homogeneous samples. GLE was prepared such as mentioned in Oludemi et al.,
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

(2017). Five grams of G. lucidum dry powder were extracted in an 80 percent ethanol Soxhlet apparatus (Soxhelt Semiautomatic equipment Velp business, Italy) for 5-6 hours (25-5 minutes per cycle). To obtain the dried solvent extract, the solvent was evaporated under reduced pressure (rotary evaporator Büchi R-210, Switzerland) and stored at 4 0C before use. The total yield of GLE was 1.16% (w/w) in terms of the G. lucidum fruiting body.

Biological experimental Ethical approval
The biological experiments for this study were approved by the Scientific Research Ethics Committee (Animal Care and Use), Faculty of Home Economics, Menoufia University, Shebin El-Kom, Egypt (Approval no. 05- SREC- 11-2020).

Animals
Adult male albino rats (130-140 g) were procured from Helwan Station, Ministry of Health and Population, Helwan, Cairo, Egypt, for this investigation.

Basal Diet
The basic diet for rats was made according to the following formula, as stated by Reeves et al., (1993) with some modified: protein, 10%; corn oil, 10%; vitamin mixture, 1%; mineral combination, 4%; choline chloride 0.2 percent; methionine 0.3 percent; cellulose 5%; and corn starch, 69.5 percent. According to AIN, (1993) the vitamins and salts mixture components were formulated.

Induction of diabetes
In the trials, normal healthy rats were given a single intraperitoneal injection of STZ at a low dose (45 mg/kg body weight, dissolved in 0.05 M citrate buffer, pH 4.5, shortly before usage) to create a diabetic state, as described by Ji et al., (2011). After 72 h injection of STZ, fasting blood glucose (FBG) levels were determined from tail blood using a specific kit (Bio diagnostic, Dokki Cairo, Egypt). The rats with FBG levels were higher than 126 mg/dl demonstrating a successful induction of diabetes. (Wang et al., 2010).

Experimental design
All biological studies were carried out the National Research Council's Institute of Laboratory Animal Resources, Commission on
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Life Sciences rules (NRC, 1996). Rats (n=36 rats), were housed individually in wire cages in a room maintained at 25 ± 2 °C and kept under normal healthy conditions. For acclimation, all rats were fed a basic diet for one week before beginning the experiment. The rats were divided into two groups after a one-week period for acclimation; all rats were fed a basic diet for one week before beginning the experiment. The rats were divided into two groups after a one-week period. The first group, normal control, group 1 (6 rats) still fed on basal/standard diet (SD). The other main group (30 rats) was used for diabetes induction and classified into five sub-groups as follow: group (2), model control, fed on standard diet only as a positive control (rats with diabetes) and groups (3-6) fed on BD and administered by oral gavages, using a feeding needle with 200, 400, 600, and 800 mg/kg BW GLE, respectively. GLE extract concentrations were selected for experiments based on many of the results of our previous studies (Salman, 2016; Elhassaneen et al., 2016, Sayed-Ahmed et al., 2020). For 28 days, each of the above groups was housed in a single cage. Rats were weighed at the start of the trial, then weekly, and finally at the completion of the experiment.

Biological evaluation
The diet consumed was recorded every day; body weight was every week during the experimental period (28 days). The following equations were used to compute the body weight gain (BWG, percent), food intake (FI), and food efficiency ratio (FER) according to Chapman et al., (1959): BWG (%) = (Final weight – Initial weight)/ Initial weight×100, FER = Grams gain in body weight (g/28 day)/ Grams feed intake (g/28 day).

Blood sampling
At the end of the 28-day trial, blood samples were taken from the abdominal aorta after 12 hours of fasting, and rats were sacrificed under ether an anaesthesia. For collecting plasma and serum, blood samples were deposited in clean, dry centrifuge tubes and allowed to clot at room temperature before being spun for 10 minutes at 3000 rpm to separate the serum, according to Drury and Wallington (1980). The serum was gently aspirated, transferred to
clean sterile tubes, and frozen until analysis at -20°C.

**Hematological analysis**

The following procedures were used to determine the various measured parameters in serum: aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities according to Tietz, (1976), and Yound, (1975), respectively. Colorimetric measurement of serum glucose was done using enzymes according to Yound, (1975) and Tietz, (1976). Insulin level was determined according to the method of Held (2009). Serum creatinine and urea concentrations were determined using the modified kinetic methods of Fawcett and Soctt, (1960), Chaney and Marbach (1962), respectively. Glycosylated hemoglobin was determined according to the improved colorimetric assay of Parker et al., (1981).

**Statistical Analysis**

Student $t$-test and MINITAB 12 computer programme statistical software were used to evaluate the data (Minitab Inc., State College, PA). The results were presented as means ± a standard deviation (SD). Differences between treatments at $P \leq 0.05$ were considered significant (Snedecor and Cochran, 1967).

**RESULTS AND DISCUSSION**

**Effect of GLP intervention on body weight gain (BWG), feed intake (FI) and feed efficiency ratio (FER) of diabetic rats**

BWG, FI and FER of diabetic and intervention by *G. lucidum* ethanol extract (GLE) were shown in Table (1) and Figure (1). From such data it could be noticed that the STZ-treated rats exhibited significantly $(p \leq 0.05)$ decreased in percent change of BWG (-38.82), FI (-31.72) and FER (-23.29) compared to the normal group. However, intervention with GLE (200 to 800 mg/kg BW) in feeding rats for 28 days significantly $(p \leq 0.05)$ led to an increase the levels of BWG, FI and FER. The rate in those parameters exhibited a dose-dependent increase with GLE intervention. Such data are in agreement with that observed by many authors whither it is in *G. lucidum* or other genera of algae (Salman, 2016; Elhssaneen et al., 2019; Sayed-Ahmed et al., 2020 and Essa, 2021). Such as reported by Sayed-Ahmed et al., (2020) the
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

The effect of GLE intervention on serum glucose and insulin of diabetic rats

Data in Table (2) and Figures (2-3) were shown the effect of GLE on serum glucose and insulin concentration of STZ-induced diabetic rats. Such data indicated that treatment of rats with STZ caused a significant increase ($P \leq 0.01$) in serum glucose concentration by percent change as 283.68% compared to normal controls. Intervention with GLE (200, 400, 600 to 800 mg/kg BW) in feeding rats for 28 days led to significantly ($P \leq 0.05$) decrease the levels of serum glucose, which recorded 256.07, 223.82, 158.94 and 141.13% change compared to the normal controls, respectively. The opposite direction was observed for insulin level. Treatment of rats with STZ caused a significant decreasing ($p \leq 0.01$) in serum insulin concentration by the ratio -49.75% change compared to normal controls. Intervention with GLE (200, 400, 600 to 800 mg/kg BW) in feeding rats for 28 days led to a significantly ($p \leq 0.05$) increase the levels of serum insulin which recorded -44.38, -41.09, -32.43, and 30.64% change versus the normal controls, respectively. The decreasing in BWG, FI and FER as the result of $G. \text{ lucidum}$ consumption could be attributed to its bioactive compounds content and the consequences thereof biological effects. In the same context, Tahoon, (2019), and Elhassaneen et al., (2021) reported that injection of rats by $\text{CCL}_4$ induced hepatotoxic and diabetic effects led to decrease in BWG, FI and FER. Consumption of plant components containing bioactive chemicals, like as those found in GLE, helped such illnesses. Hamzawy et al., (2013) and Abd El-Rahman (2021) discovered that hepatic rat problems caused by diabetes result in a considerable reduction in BW and FI. Furthermore, multiple studies have shown that people with diabetes and liver problems are at risk of malnutrition. Poor eating habits, maldigestion, malabsorption, and anomalies in macro and micronutrient metabolism and storage are among them (Morresion and Hark, 1999; Elhassaneen et al., 2014; Sayed Ahmed et al., 2016; Aly et al., 2017; and Abd El-Rahman, 2021).
rate of increase in serum glucose and insulin were exhibited a dose-dependent boost with GLE intervention. When comparing the diabetes (model) group to the control/normal group, serum insulin levels were found to be considerably lower in the diabetic (model) group. These findings are consistent with Kocak et al., (2000); Melhem et al., (2002) and Kandeil et al., (2007).

Streptozotocin is a commonly utilized DM inducer in laboratory animals. It can cause chronic or persistent diabetes in these animals by selectively destroying pancreatic islet cells (Mathe, 1995; Elhassaneen et al., 2021). The results demonstrated that serum glucose concentrations in diabetic rats were substantially higher than in normal rats. As in the case of insulin-dependent diabetes mellitus IDDM, chronic hyperglycemia can be caused by a deficiency in insulin secretion (Kandeil et al., 2007). STZ generates several types of reactive oxygen species/radicals (ROS) that attack DNA generating DNA-strand breaks in β-cell, as stated by Lenzen, (2008) in experimental diabetes that may represent a model of T2D. The breaks cause the poly adenosine diphosphate-ribose (ADP-ribose) polymerase (PARP) to be activated, which uses nicotinamide adenine dinucleotide+ NAD+ as a substrate to repair the DNA. As a result, NAD+ levels within cells decrease. NAD+ deficiency limits ATP synthesis and cellular processes, as well as insulin synthesis and secretion, and the β-cell eventually dies (Pusztai et al., 1996). This would result in decreased glucose uptake by peripheral tissues such as muscles and adipose tissue, as well as increased glycogenolysis, gluconeogenesis, and hepatic glucose synthesis. (Gold, 1970; Caro, 1990; Raju et al., 2001; Beck-Nielsen, 2002 and Jung et al., 2011). Perhaps this notion is supported by the current study's findings, which show that serum glucose levels in the diabetic group intervention GLE were much lower and serum insulin levels were significantly higher than in the diabetic/model group. The numerous bioactive components discovered in GLE may be responsible for its hypoglycemic impact in STZ-induced diabetic mice. Skalicka-Wozniak et al., (2012), Liu et al., (2017), and Darija et al., (2018) discovered
that G. lucidum is a rich source of bioactive components such as phenolic, lycopene, Polysaccharides, terpenoids, flavonoids, triterpenoids, and vitamins (A, B, and E). Sterols, amino acids, soluble proteins, oleic acid, cyclo-octasulfur, ergosterol peroxide, and cerebrosides are all found in Reishi (Mizuno, 1995; McKenna et al., 2002; Gao et al., 2003).

These compounds are known for their antioxidant properties, lipid oxidation suppression, and free radical/ROS scavenging action, all of which aid type 2 diabetes patients with glycemic control, metabolic dysregulation of free fatty acids, and insulin resistance (Elhassaneen et al., 2012-2015; Aly et al., 2017; Elbasouny et al., 2019).

Several previous studies, along with others, have proven that bioactive compounds (Phenolic, flavonoids and lycopene) which was spotted in this study inside G. lucidum play an important vital role in preventing and/or treating many diseases including diabetes (Elhassaneen et al., 2014; 2016, Sayed Ahmed et al., 2016; Aly et al., 2017 and Abd El-Rahman, 2021). In addition, Tiwari and Madh-usudana (2002) reviewed that bioactive compounds found in G. lucidum, such as polyphenolics, have been reported to inhibit alpha-amylase and sucrose, and have been shown to be the primary substance for suppressing postprandial hyperglycemia, in addition to their well-known antioxidant properties. Furthermore, Wasser (2005) demonstrated in experimental animals that the polysaccharide fractions of G. lucidum had potential hypoglycemic and hypolipidemic effects. In addition, a water extract of G. lucidum reduced the increase in blood glucose and blood insulin levels in rats (50 mg p.o.) following oral glucose test. Additionally, G. lucidum glycan’s have shown significant hypoglycemic activity in mice.

**Effect of GLE intervention on glycosylated hemoglobin (HbA1c) level of diabetic rats**

Data in Table (3) and Figures (4-5) were shown the effect of GLE on glycosylated hemoglobin (HbA1c) level of STZ-induced diabetic rats. Such data indicated that treatment of rats with STZ caused a significant increased ($p \leq 0.01$) in HbA1c concentration by the ratio 97.93% change.
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Intervention with GLE (200, 400, 600 to 800 mg/kg BW) in feeding rats for 28 days led to significantly ($p \leq 0.05$) decrease the levels of HbA$_1c$, which recorded 80.04, 62.15, 40.30 and 32.02%, change compared to the normal controls, respectively. The rate of increasing in HbA$_1c$ was exhibited a dose-dependent boost with GLE intervention. The HbA1c measurement results show that diabetic rats treated with dose of 800 mg/kg BW GLE has the best outcome compared to the other treatments. HbA1c measurement may become a parameter for the capability of GLE in producing anti-diabetes effect on diabetic rats. This is fending in line with the results of plasma glucose and insulin level measurement. Some researches show close relationship between HbA1c concentration and mean blood glucose level (Begley, 2012 and Nuniek et al., 2018).

HbA1c is a form of hemoglobin (Hb) that is chemically linked to a sugar (all monosaccharides, including glucose, galactose and fructose). The formation of the sugar hemoglobin linkage indicates the presence of excessive sugar in the bloodstream, often indicative of diabetes (Bunn and Higgins, 1981). Because it is so easy to identify, A1C is of particular interest. It is utilized to detect the three-month average blood glucose level and a DM diagnostic test as well as a glycemic management assessment test in persons with diabetes (WHO, 2011). As the average amount of plasma glucose increases, the fraction of glycated hemoglobin (HbA$_1c$) increases in a predictable way. The International Diabetes Federation (IDF) recommend HbA$_1c$ values below 48 mmol/mol (6.5 DCCT % , Diabetes Control and Complications Trial,), while the American Diabetes Association (ADA) recommends HbA$_1c$ be below 53 mmol/mol (7.0 DCCT %) for most patients (Miedema, 2005). Persistent elevations in HbA$_1c$ increase the risk of long-term vascular complications of diabetes, such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy etc. (Shubrook and Shubrook, 2010; Saleh, 2015). In the current study HbA$_1c$, levels significantly decreased in diabetic group intervention GLE the...
diabetic / model group. Such hypoglycemic (HbA1c) effect of GLE in STZ-induced diabetic rats may be related to the diverse bioactive compounds found in GLE. Gao et al., (2003) found that treatment with Ganopoly (GL poly-saccharide extract) significantly decreased the mean HbA1c from 8.4% at baseline to 7.6% at 12 weeks.

**Effect of GLE intervention on liver functions of diabetic rats**

The effect of GLE intervention on serum liver functions enzymes activities AST, ALT and ALP of diabetic rats induced by STZ were shown in Table (4) and Figure (6-7). Such data indicated that STZ caused a significant (p≤0.05) increased in AST, ALT and ALP with 30.79, 29.85 and 45.68% change compared to normal control group, respectively. Intervention with GLE (200, 400, 600 to 800 mg/kg BW) in feeding rats for 28 days led to significantly (p≤0.05) decrease the levels of those enzymes activities, which recorded 21.87, 17.75, 11.35 and 10.53% (for AST), 28.62, 25.42, 18.94 and 12.44% (for ALT), and 39.74, 22.51, 16.02 and 14.14% (for ALP) compared to the normal controls, respectively. The rate of decreasing in serum liver enzymes activities were exhibited a dose- dependent increase with GLE intervention.

Intracellular enzymes include aminotransferases (ALT and AST) as well as ALP. As a result, high levels of aminotransferase (AST and ALT) and ALP in the blood indicate that cells that produce these enzymes have been damaged. Cell lysis in the liver and pancreas, for example, might result in the release of intracellular enzymes into the bloodstream (Pagana and Pagana, 1997 and Sayed-Ahmed et al., 2020). G. lucidum has long been used to treat chronic hepatitis caused by a variety of reasons G. lucidum powder and extracts (primarily polysaccharides or triterpenoids) appear to protect against liver injury caused by toxic substances (e.g., CCl4), according to data from in vitro and animal experiments (Sayd-Ahmed et al., 2020). The mechanisms underlying G. lucidum's hepato-protective effects are unknown. Antioxidant and radical scavenging activities, modulation of hepatic Phase I and II meta-bolizing enzymes, inhibition of -glucuronidase, anti- fibrotic and antiviral activity,
modulation of NO production, maintenance of hepatocellular calcium homeo-stasis, and immunomodulatory effects are all possible mechanisms (Gao et al., 2003; Sayed-Ahmed et al., 2020). Also, G. lucidum are a rich source of different bioactive compounds including phenolic, lycopene, polysaccharides, terpenoids, flavonoids, triterpenoids and vitamins (A, B and E) (Skalicka-Woźniak et al., 2012), Liu et al. (2017) and Darija et al., 2018). Bioactive compounds could be lowered liver serum enzymes through many suggested effects including blocking the hepatocellular uptake of bile acids. Improving the antioxidant capacity of the liver. Diminishing the bilirubin concentration reducing the damage of hepatocytes. Scavengers of reactive oxygen species” (Beattic et al., 2005; El-Nashar, 2007; Aly et al., 2017; Mahran et al., 2018 and Sayed-Ahmed et al., 2020).

**Effect of GLE intervention on kidney functions of diabetic rats**

The effect of GLE intervention on serum kidney functions parameters (urea and creatinine concentrations) of diabetic rats induced by STZ were shown in Table (5) and Figure (8-9). Such data indicated that STZ caused a significant (p≤0.05) increased with percent change in urea (65.37%) and creatinine (43.62%) parallel to normal controls, respectively. Presence of GLE (200, 400, 600 to 800 mg/kg BW) in feeding rats for 28 days led to a significantly (p≤0.05) decrease the levels of those parameters recorded 58.25, 47.57, 26.86 and 25.89% (for urea), and 35.77, 33.17, 27.25 and 16.48% (for creatinine), respectively. The rate of decrease in kidney functions parameters has exhibited a dose-dependent increase with GLE intervention.

The liver produces urea as a byproduct of protein metabolism. Protein is broken down into amino acids during digestion, which are catabolized, resulting in the formation of free ammonia. The ammonia are mixed to make urea (Pagana and Pagana, 1997). Ammonia is highly toxic, it is detoxified through conversion to urea, which is nontoxic and water-soluble and is excreted through urine by the kidneys. Hence, blood urea level can be considered a predictor of hepatic or renal
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

functional status (Bennett et al., 1995 and Pagana and Pagana, 1997). Creatinine is a breakdown product of creatine phosphate in a muscle that the body produces at a relatively consistent pace (depending on muscle mass). It is an easily detectable by product of muscle metabolism that is eliminated unchanged by the kidneys. Serum creatinine (a blood measurement) is an essential indicator of renal health (Pagana and Pagana, 1997). The decreasing in serum urea and creatinine as the result of GIE could be attributed to its high content of bioactive compounds such phenolics, lycopene, polysaccharides, terpenoids, flavonoids, triterpenoids and vitamins (A, B and E) (Elhassaneen et al., 2012, Skalicka – Wozniak et al., 2012, Liu et al. (2017) 2016b and Darija et al., 2018). Similar research (Bedawy, 2008) found that eating plant parts resulted in lower serum urea and creatinine levels due to their increased phenolic component content. Furthermore, El-Sayed et al., (2012) discovered that increasing the amount of henada, lemon balm leaves, hawthorn leaves, rose of Jericho, and corn cob silk in the diet by 5 and 10% in the presence of CCl4 resulted in significant improvements in all kidney functions, including serum urea and creatinine levels. One or more of the following processes could explain the proposed mechanisms of kidney serum parameters reducing the investigated by-products. GLE polyphenols boosted the activity of superoxide dismutase in the kidney and improved kidney weight and serum levels of urea nitrogen, creatinine, and creatinine clearance (reviewed in El-Nashar, 2007). Flavonoids also reduced plasma creatinine and urea levels, indicating improved kidney function following surgery (Van Hoorn et al., 2006).

Correlation studies

The correlation analysis revealed significant differences between biological (BW) and biochemical [serum glucose, serum insulin, HbA1c, liver functions (AST, ALT and ALP) and kidney functions (urea and creatinine)] parameters in diabetic rats administrated GLE (Table 6). It was discovered from the data that BW and serum glucose had a negative significant (p≤ 0.05) association ($r^2 = - 0.6331$) and
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

HbA1c ($r^2 = -0.5964$) while the relevance was positive with serum insulin ($r^2 = 0.6057$). Also, high positive significant ($p \leq 0.05$) relation with recorded between serum glucose and HbA1c ($r^2 = 0.7796$), serum creatinine ($r^2 = 0.6117$) and urea ($r^2 = 0.5974$) and negative with insulin ($r^2 = -0.7998$). Furthermore, no significant rapport was observed between serum glucose and all liver functions parameters including AST, ALT and ALP. These findings corroborated our findings, which indicated a significant rise ($p \leq 0.05$) in mean BWG in diabetic rats given GLE compared to diabetic rats; although still lower than control rats. GLE is also an insulin sensitizer, according to Wasser (2005), since it can promote insulin-stimulated glucose absorption, improve insulin sensitivity, and hence increase BW. Furthermore, GLE is potential to improve insulin sensitivity and speed pancreatic-$\beta$-cells regeneration can nearly reverse metabolic changes associated with diabetes and boost BW. The HbA1c measurement results show that diabetic rats treated with dose of 800 mg/kg BW GLE have the best outcome compared to the other treatments. Thus, HbA1c measurement may become a parameter for the capability of GLE in producing an anti-diabetic effect on diabetic rats. This is in line with the results of serum glucose and insulin levels measurement. Such as shown in the present correlation analysis, some researches show close interrelation between HbA1c concentration and mean serum glucose level (Sultanpur et al., 2010 and Begley, 2012).

CONCLUSION

The results of this investigation show that the selected (Ganoderma lucidum) extract is effective to ameliorate hyperglycemia and its complications in diabetic rats. The mechanisms of the anti-diabetic effects of G. lucidum have been not fully understood. However, accumulating evidence by the present study suggests several possible mechanisms: accelerating recovery of pancreatic $\beta$-cells, i.e. increasing the insulin secretion / sensitivity, improving insulin stimulated glucose uptake, and reducing the damage of liver and kidney cells. Such strategies can almost completely reverse the metabolic changes caused by
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

diabetes. These findings provide the use of the Ganoderma lucidum extract for the protection and improvement of type 2 diabetes.

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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

<table>
<thead>
<tr>
<th>Reference</th>
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<tr>
<td><strong>IDF, (International Diabetes Federation) (2021):</strong></td>
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen


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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Table 1. Effect of GLE intervention on BWG, FI and FER of diabetic rats induced by STZ

<table>
<thead>
<tr>
<th>Groups</th>
<th>BWG (%)</th>
<th>FI (g/day/rat)</th>
<th>FER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>0.85 ± 0.07\textsuperscript{a}</td>
<td>11.76 ± 0.86\textsuperscript{a}</td>
<td>0.073 ± 0.008\textsuperscript{a}</td>
</tr>
<tr>
<td>Model control</td>
<td>0.52 ± 0.03\textsuperscript{bcd}</td>
<td>8.03 ± 0.91\textsuperscript{c}</td>
<td>0.056 ± 0.010\textsuperscript{bc}</td>
</tr>
<tr>
<td>GLE intervention (200 mg/kg BW)</td>
<td>0.59 ± 0.06\textsuperscript{bc}</td>
<td>8.56 ± 0.53\textsuperscript{c}</td>
<td>0.058 ± 0.009\textsuperscript{b}</td>
</tr>
<tr>
<td>GLE intervention (400 mg/kg BW)</td>
<td>0.64 ± 0.05\textsuperscript{bc}</td>
<td>8.73 ± 0.55\textsuperscript{c}</td>
<td>0.059 ± 0.006\textsuperscript{b}</td>
</tr>
<tr>
<td>GLE intervention (600 mg/kg BW)</td>
<td>0.70 ± 0.02\textsuperscript{bc}</td>
<td>8.97 ± 0.69\textsuperscript{c}</td>
<td>0.062 ± 0.009\textsuperscript{b}</td>
</tr>
<tr>
<td>GLE intervention (800 mg/kg BW)</td>
<td>0.73 ± 0.04\textsuperscript{b}</td>
<td>9.35 ± 0.67\textsuperscript{b}</td>
<td>0.064 ± 0.007\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SD (n = 6). Different superscript letters on the same column indicate significant difference (P ≤ 0.05). Normal control: healthy rats without intervention; Model control: STZ induced diabetic rats without intervention; GLE intervention: STZ induced diabetic rats with GLE intervention.

Figure 1. Effect of GLE intervention on BWG, FI and FER (% of change) of diabetic rats induced by STZ
Reishi Mushroom (Ganoderma lucidum) Extract Ameliorate Hyperglycemia and Liver / Kidney Functions in Streptozotocin-induced Type 2 Diabetic Rats
Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Table 2. Effect of GLE intervention on serum glucose and insulin levels of diabetic rats induced by STZ

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum glucose conc. (Mean ±SD, mg/dl)</th>
<th>Insulin level (Mean ±SD, µIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>89.34 ± 10.25 e</td>
<td>13.97 ± 1.14 a</td>
</tr>
<tr>
<td>Model control</td>
<td>342.78 ± 21.23 a</td>
<td>7.02 ± 2.21 bcd</td>
</tr>
<tr>
<td>GLE intervention (200 mg/kg b w)</td>
<td>318.11 ± 15.78 b</td>
<td>7.77 ± 2.01 bc</td>
</tr>
<tr>
<td>GLE intervention (400 mg/kg b w)</td>
<td>289.30 ± 13.24 c</td>
<td>8.23 ± 0.99 bc</td>
</tr>
<tr>
<td>GLE intervention (600 mg/kg b w)</td>
<td>231.34 ± 22.23 d</td>
<td>9.44 ± 1.34 b</td>
</tr>
<tr>
<td>GLE intervention (800 mg/kg b w)</td>
<td>215.43 ± 9.4d</td>
<td>9.69 ± 0.76 b</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SD (n = 6, one-way ANOVA). Different superscript lowercase letters on the same column indicate significant difference (P ≤ 0.05). Normal control: healthy rats without intervention; Model control: STZ induced diabetic rats without intervention; GLE intervention: STZ induced diabetic rats with GLE intervention.

Figure 2. Effect of GLE intervention on serum glucose and insulin level (values) of diabetic rats induced by STZ
Reishi Mushroom (Ganoderma lucidum) Extract Ameliorate Hyperglycemia and Liver / Kidney Functions in Streptozotocin-induced Type 2 Diabetic Rats
Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Figure 3. Effect of GLE intervention on serum glucose and insulin level (values) of diabetic rats induced by STZ

Table 3. Effect of GLE intervention on Glycosylated hemoglobin (HbA1c) level of diabetic rats induced by STZ

<table>
<thead>
<tr>
<th>Group</th>
<th>HbA1c (m mol/mol)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>34.64 ± 1.55f</td>
<td>5.31 ± 0.25e</td>
</tr>
<tr>
<td>Model control</td>
<td>91.48 ± 6.45a</td>
<td>10.51 ± 1.04a</td>
</tr>
<tr>
<td>GLE intervention (200 mg/kg BW)</td>
<td>81.09 ± 5.27b</td>
<td>9.56 ± 0.85b</td>
</tr>
<tr>
<td>GLE intervention (400 mg/kg BW)</td>
<td>70.71 ± 2.91c</td>
<td>8.61 ± 0.47c</td>
</tr>
<tr>
<td>GLE intervention (600 mg/kg BW)</td>
<td>58.03 ± 3.22d</td>
<td>7.45 ± 0.52cd</td>
</tr>
<tr>
<td>GLE intervention (800 mg/kg BW)</td>
<td>53.22 ± 3.04e</td>
<td>7.01 ± 0.49d</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SD (n= 6). Different superscript letters on the same column indicate significant difference (P ≤ 0.05). Normal control: healthy rats without intervention; Model control: STZ induced diabetic rats without intervention; GLE intervention: STZ induced diabetic rats with GLE intervention.
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Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Figure 4. Effect of GLE intervention on Glycosylated hemoglobin (HbA1c, mmol/mol) level of diabetic rats induced by STZ

Figure 5. Effect of GLE intervention on Glycosylated hemoglobin (HbA1c, % of change) level of diabetic rats induced by STZ
Table 4. Effect of GLE intervention on liver functions of diabetic rats induced by STZ

<table>
<thead>
<tr>
<th>Group</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>ALP (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>$68.56\pm3.77^{ab}$</td>
<td>$29.51\pm2.17^{b}$</td>
<td>$104.65\pm9.11^{d}$</td>
</tr>
<tr>
<td>Model control</td>
<td>$89.67\pm5.87^{a}$</td>
<td>$38.32\pm4.31^{a}$</td>
<td>$152.45\pm21.20^{a}$</td>
</tr>
<tr>
<td>GLE intervention (200 mg/kg BW)</td>
<td>$83.56\pm4.63$</td>
<td>$37.95\pm3.46^{a}$</td>
<td>$146.24\pm14.12^{a}$</td>
</tr>
<tr>
<td>GLE intervention (400 mg/kg BW)</td>
<td>$80.73\pm5.18^{a}$</td>
<td>$37.01\pm1.98^{a}$</td>
<td>$128.21\pm12.20^{b}$</td>
</tr>
<tr>
<td>GLE intervention (600 mg/kg BW)</td>
<td>$76.34\pm5.5^{ab}$</td>
<td>$35.10\pm2.90^{ab}$</td>
<td>$121.42\pm16.57^{bc}$</td>
</tr>
<tr>
<td>GLE intervention (800 mg/kg BW)</td>
<td>$75.78\pm4.53^{ab}$</td>
<td>$33.18\pm3.11^{b}$</td>
<td>$119.45\pm11.20^{bc}$</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SD (n = 6). Different superscript letters on the same column indicate significant difference (P ≤ 0.05). Normal control: healthy rats without intervention; Model control: STZ induced diabetic rats without intervention; GLE intervention: STZ induced diabetic rats with GLE intervention. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.
Reishi Mushroom (Ganoderma lucidum) Extract Ameliorate Hyperglycemia and Liver / Kidney Functions in Streptozotocin-induced Type 2 Diabetic Rats
Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Figure 7. Effect of GLE intervention on liver functions (% of change) of diabetic rats induced by STZ

Table 5. Effect of GLE intervention on kidney functions of diabetic rats induced by STZ

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum creatinine conc. (µmol/L)</th>
<th>Serum urea concentration (mmol/L)</th>
</tr>
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<tbody>
<tr>
<td>Normal control</td>
<td>43.56 ± 4.76&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.09 ± 0.82&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Model control</td>
<td>62.56 ± 7.43&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.11 ± 1.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GLE intervention (200 mg/kg BW)</td>
<td>59.14 ± 3.95&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.89 ± 1.08&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GLE intervention (400 mg/kg BW)</td>
<td>58.01 ± 5.01&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>4.56 ± 0.98&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>GLE intervention (600 mg/kg BW)</td>
<td>55.43 ± 7.22&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.92 ± 0.57&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td>GLE intervention (800 mg/kg BW)</td>
<td>50.74 ± 6.43&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.89 ± 0.61&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SD (n = 6). Different superscript letters on the same column indicate significant difference (P ≤ 0.05). Normal control: healthy rats without intervention;
Reishi Mushroom (Ganoderma lucidum) Extract Ameliorate Hyperglycemia and Liver / Kidney Functions in Streptozotocin-induced Type 2 Diabetic Rats

Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Model control: STZ induced diabetic rats without intervention; GLE intervention: STZ induced diabetic rats with GLE intervention.

**Figure 8.** Effect of GLE intervention on kidney functions (Value) of diabetic rats induced by STZ

**Figure 9.** Effect of GLE intervention on kidney functions (% of change) of diabetic rats induced by STZ
Table 6. Correlation studies between biological and biochemical parameters in diabetes rats administrated with GLE* +

<table>
<thead>
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<th>$r^2*$</th>
<th>Parameters</th>
<th>$r^2*$</th>
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<td>BW/Serum glucose</td>
<td>-0.6331</td>
<td>Serum glucose/AST</td>
<td>0.4945</td>
</tr>
<tr>
<td>BW/ Serum insulin</td>
<td>0.6057</td>
<td>Serum glucose/ALT</td>
<td>0.4734</td>
</tr>
<tr>
<td>BW/ HbA1c</td>
<td>-0.5964</td>
<td>Serum glucose/ALP</td>
<td>0.4821</td>
</tr>
<tr>
<td>Serum glucose /Insulin</td>
<td>-0.7998</td>
<td>Serum glucose/Urea</td>
<td>0.5974</td>
</tr>
<tr>
<td>Serum glucose /HbA1c</td>
<td>0.7796</td>
<td>Serum glucose/Creatinine</td>
<td>0.6117</td>
</tr>
</tbody>
</table>

* $P \leq 0.05$
Reishi Mushroom (Ganoderma lucidum) Extract Ameliorate Hyperglycemia and Liver / Kidney Functions in Streptozotocin-induced Type 2 Diabetic Rats
Samah A Elsemelawy, Mai A Gharib and Yousif A Elhassaneen

Bulletin of the National Nutrition Institute of the Arab Republic of Egypt. June 2021 (57) 107

Reishi Mushroom (Ganoderma lucidum) Extract Ameliorate Hyperglycemia and Liver / Kidney Functions in Streptozotocin-induced Type 2 Diabetic Rats
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