Vol. 17(36), pp. 1111-1118, 5 September, 2018
DOI: 10.5897/AJB2018.16445
Article Number: 030EB9558491
ISSN: 1684-5315

http://www.academicjournals.org/AJB

African Journal of Biotechnology

Full Length Research Paper

Evaluation of the effects of plant aqueous extracts as anti-diabetic agents on alloxan induced diabetic male rabbits

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Received 28 February 2018, Accepted 30 July 2018

This study investigates the effect of barley *(Hordeum vulgare),* black plum *(Syzygium cumini)* and Chinese tree leaves (*Pistacia chinesis*) aqueous extracts on serum glucose, cholesterol, urea, uric acid level and body weight of normal and alloxan-induced diabetic male rabbits. Rabbits were kept in fasting condition for 12 h, then diabetes was induced using alloxan monohydrate (150 mg/Kg). From the 7th day of diabetes induction, blood serum was collected for glucose analysis. Rabbits having fasting glucose level ≥ 250 mg/dL were considered as diabetic. Rabbits were treated with 1% barley, black plum and Chinese tree aqueous extract to check their effects on the serum glucose, serum cholesterol, serum urea, uric acid and body weight of the animals. Samples were collected after every 72 h for biochemical analysis. It was noted that 1% barley, black plum and Chinese tree aqueous extract reduced 43.92, 39.05 and 32.47% glucose level. Results suggest that oral administration of aqueous extract of barley, black plum and Chinese tree reduced glucose, cholesterol, urea, and uric acid level. Therefore, these medicinal plants should be supplemented as herbal drugs in the treatment of various complex diseases and specially to control diabetes.

Key words: Chinese tree leaves, antidiabetic agents, barley, black plum, rabbits, diabetes mellitus.

INTRODUCTION

Diabetes mellitus is one of the chronic diseases that occur either due to decrease in insulin secretion or lack of insulin peripheral activity (Mutalik et al., 2003); it approximately causes half of all deaths occurring at the age of 70. Literature reports that 415 million adults were living with diabetes in 2015 and this would increase to 642 million by 2040 (Rahelic, 2016). Diabetic complications include increased gluconeogenesis and ketogenesis (Kumar et al., 2011) and increased risk of heart attacks and strokes (Jousilahti et al., 2010). Diabetes mellitus has two types, Type 1 occurs due to β-cell destruction, and is mostly insulin dependent diabetes (Alberti and Zimmet, 1998); type-2 is triggered by mutation in β-cell gene, and is the most common forms of adulthood onset diabetes caused by change in glucokinase and HNF-1 alpha genes. Type2 diabetes remains undiagnosed because hyperglycaemia does not show any symptoms; such patients may develop micro

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or macrovascular complications (Chisholm et al., 1997; Lillioja et al., 1993).

Medicinal plant has been used for the cure of diabetes mellitus before the invention of insulin therapy in 1921 (wadood et al., 2007). Medicinal plants are good sources of hypoglycemic compounds and these plants are used as adjuncts to the existing therapies for the treatment of diabetes mellitus (Sharma et al., 2008). Plants' extract has effect on blood glucose level through different mechanisms: some plants have insulin-like compounds, some might inhibit insulin activity (Hussain et al., 2013) and other mechanisms could enhance the regeneration of the β-cells in the pancreas (Hosseini et al., 2015). More than 400 medicinal plants have been used for the treatment of diabetes mellitus, and screened for anti-diabetic agents (Thomson, 2006). Various parts of plant such as fruit, seeds, and leaves have been reported for the treatment of type 2 diabetes (Mahesar et al., 2010, Khushk et al., 2010). Bitter melon (*Momocardia charantia*), karela is a member of the cucumber family grown for its edible fruit. Bitter melon decreases the level of glucose in the blood (Dans et al., 2007). Presently, there is growing interest in herbal remedies due to the side effects associated with the oral hypoglycemic agent (therapeutic agent) used for the treatment of diabetes mellitus.

Type 2 diabetes can be controlled by taking *M. charantia* capsules over a period of three months (Dans et al., 2007). Corn silk (*Zea mays*) is mostly used in China against diabetes (Mendoza-López et al., 2017). Various ether soluble fractions of onion (*Allium cepa* L.) and soluble fractions of dried onion powder show anti hyperglycemic activity against diabatic rabbits. Onion (*A. cepa* L.) is also known to have anti-oxidant and hypolipidemic activity (Jain and Vyas, 1974).

Garlic (*Allium sativum*) is a member of the Liliaceae family, which is one of the most popular herbs used worldwide to reduce various risk factors associated with several disease (Thomson, 2006). Garlic has been found to be effective in lowering serum glucose levels in STZ-induced as well as alloxan-induced diabetic rats and mice. Most studies showed that garlic can reduce blood glucose levels in diabetic mice, rats and rabbits. Some hypoglycemic activity was found in garlic as compared to diabetic control groups (Nadir Ali et al., 2013).

Soybean (*Glycine max*) belongs to the family Leguminosae or Fabaceace, which contains vegetable protein, oligosaccharides, dietary fiber, phytochemicals and minerals. Soybean reduces coronary heart disease and lowers cholesterol level. Also, it has anti-inflammatory and anti-carcinogenic effect on digestive system (Aparicio et al., 2008). In Pakistan, soybean is cultivated for oil extraction (Malik et al., 2006).

Barley (*Hordeum vulgare*) is a rich source of magnesium, a mineral composed of more than 300; enzymes, including those involved in glucose metabolism and insulin secretion. Black plum has been used for centuries as anti-diabetic medicines. Barley has gained popularity in recent years owing to its association with the soluble β-glucan fiber and the phytochemical compounds it contains with various health benefits (Alu'datt et al., 2012). Epidemiological studies have associated the regular consumption of barley with its potential to reduce the risk of certain diseases, such as chronic heart disease (Sullivan et al., 2013), colonic cancer (Dongowski et al., 2002), high blood pressure (Behall et al., 2006), and gallstones (Hoang et al., 2011). Reports of barley focused on maintaining a healthy colon (Kanauchi et al., 1999), inducing immune stimulation (Tada et al., 2009), and generally boosting the immune system (Kemp et al., 2013). Barley extract has not been evaluated for its antidiabetic efficiency, thus in present study, barley extract was found to be the best antidiabetic agent against alloxan induced rabbits. Chinese tree (*Pistacia chinesis*) has been used for medicines (TCM) and local herbal crops for abdominal sickness, abscesses, amenorrhea, bruises, chest aliments, circulation, dysentery, gynecopathy, pruritus, rheumatism, sclerosis of the liver, sores and trauma (Blascakova and Poracova, 2011). The aim of the present study was to investigate the potential of an aqueous extract of barley, black plum, and Chinese tree in controlling serum glucose, cholesterol, urea, uric acid and body weight level in alloxan induced diabetic male rabbits compared to normal control and diabetic control male rabbits.

MATERIALS AND METHODS

Animals

Male rabbits were taken from animal house of Institute of Biotechnology and Genetic Engineering University of Sindh Jamshoro and maintained on a normal diet with filtered tap water. The average weight was observed to be 1.4 ± 0.15 kg. The animals were kept for 7-days of acclimatization period.

Experimental design

The rabbits were divided into five groups of 3: (1) alloxan control, (2) normal control and (3-5) diabetic control treated through water extract of barley, black plum and Chinese tree extracts. Diabetes was induced in the rabbits with alloxan monohydrate of 150 mg/dL body weight except normal and control. In the next step, rabbits were screened for diabetes. Rabbits having blood glucose level above 250 mg/dL (in fasting condition) were chosen for the study (as diabetes rabbits). The experiment continued for 21 days. Throughout the period of the treatment all tests were performed, and the body weight was also determined.

Numerical analysis

The data were calculated as mean values and the final value minus initial value, and then divided by the initial value. The answer was multiplied by 100%. The results were compared with control.

Chemicals

Glucose, urea, and cholesterol (Globe diagnostic Itly-GDO34000-GA434000) kits were used for performing the above mentioned tests. Alloxan monohydrate was purchased from Sigma chemical company, U.S. The other chemicals used were of analytical grade and purchased from Sigma, E. Merck and Fluka.

Plant materials

The fresh barley, black plum seeds, and Chinese tree leaves were purchased from local seeds dealers in Hyderabad, Sindh, Pakistan. They were identified by the experts of Institute of Biotechnology and Genetic Engineering, University of Sindh, Jamshoro, Pakistan.

Preparation of plant extracts

Healthy seeds of black plum and barley were selected and kept for 5 min in ethanol and they were dried on filter paper. To prepare water extract, 1 g of barley, black plum seeds, and Chinese tree leaves powder was grinded separately in distilled water. Contents were mixed with glass rod; final volume was made up to 100 mL with distilled water. Clear solution was separated through centrifugation at 5000 rpm for 10 min and samples were stored for further study. Daily dose was used after mixing on magnetic stirrer for 5 min.

Induction of diabetes

Induction of diabetes, alloxan monohydrate was prepared by dissolving 10 g in 100 mL sterilized water. Diabetes was induced in fasting rabbits by administration of 150 mg/kg body weight alloxan to each rabbit.

Administration of extract

100 mL of barley, black plum, and Chinese tree extracts was poured into separate drinking feeders in the morning and then the animals were given free access to water after finishing their extract. 50 mL of extracts was again given orally per rabbit once in the afternoon.

Blood sample collection

Blood samples were collected from marginal vein of the posterior side of the ear of the animals through sterilized syringe and needle. Then the samples were transferred to sterilized micro centrifuge tube for biochemical analysis (serum glucose, serum cholesterol, serum urea, serum uric acid and body weight).

RESULTS AND DISCUSSION

Diabetes mellitus is the most common endocrine metabolic disorder that affects patients' health (Nadir Ali et al., 2013). It occurs due to excess amount of glucose present in blood reacting with haemoglobin to form glycosylated haemoglobin. Glycation rate is directly proportional to the amount of blood glucose (Sheela and Augusti, 1992). There is a proof that in diabetic condition, glycation induces the formation of oxygen-derived free radicals (Gupta et al., 1997).

Plants are used for the treatment of diabetes because they contain several compounds that could act as anti-diabetic agents. These could preserve β-cell function and avoid diabetes (Valsta et al., 2005). Antidiabetic herbal medicines are suggested and given worldwide due to their less side effects and cheaper cost (Shukia et al., 2000). Leaves of *Cydonia oblonga* were used for the treatment of cold, cough, bronchitis, diarrhoea, nervousness and against hyperglycemia (Tabata et al., 1988; Ermis, 2012; Sezik et al., 2001; Tuzlacı and Tolon, 2000). Alloxan behaves as a cytotoxin for β-cells of the islet Langerhans, cause diabetes and induce cell necrosis (Jorns et al., 1997). Intracellular accumulation of alloxan in rabbits leads to β-cell membrane disruption (Mathew and Augusti, 1973). Recently, several researchers have evaluated many traditionally important medicinal plants such as onion, bitter melon, ginger etc that can act as antidiabetic agents (Ramkumar et al., 2007; Pari and Rajarajeswari, 2010).

In alloxan induced diabetic rabbits, the blood glucose levels raised because of permanent destruction of pancreatic β-cell resulting in the reduction of serum insulin level (Hala et al., 2006). It was also reported in Khushk et al. (2010) soya bean extract showed lower blood glucose level as compared to the diabetic control group; therefore it shows that not only barley, black plum, and Chinese tree have antidiabetic effect but some other plants also lower blood glucose level. The rate of reduction in serum glucose level was most effective. The results of barley, black plum, and Chinese tree were obtained by performing blood serum analysis for glucose, cholesterol, urea, uric acid, and body weight. Results are shown in Figures 1 to 5.

The effect of different medicinal plant extract on diabetic male rabbits was observed. Serum glucose level was reduced from 321 to 150 mg/dL when 1.0% barley extract was used. Black plum blood reduced glucose from 297 to 181 mg/dL and Chinese tree serum decreased glucose from 311 mg/dL to 210 mg/dL as shown in Figure 1a to c. According to Virdi et al. (2003), the water extract of fresh unripe whole fruits at a dose of 20 mg/kg was found to trim down fasting glucose level by 48%. The hypoglycemic effect of barley might be due to the presence of β-glycan (Sullivan et al., 2013) and hypoglycemic effect of black plum could be due to the presence of gallic acid.

Alloxan induced rabbits were treated with the water extract of barley and it was observed that serum cholesterol level decreased from 146 to 90 mg/dL; Chinese tree reduced serum cholesterol level from 137 to 120 mg/dL. Black plum cholesterol increased from 136 to 290 mg/dL as reported in another medicinal plant which shows that ginger stimulated the conversion of cholesterol to bile acids, an important path way of eliminating cholesterol from the body and reducing cholesterol level (Nadir Ali et al., 2013). Another study

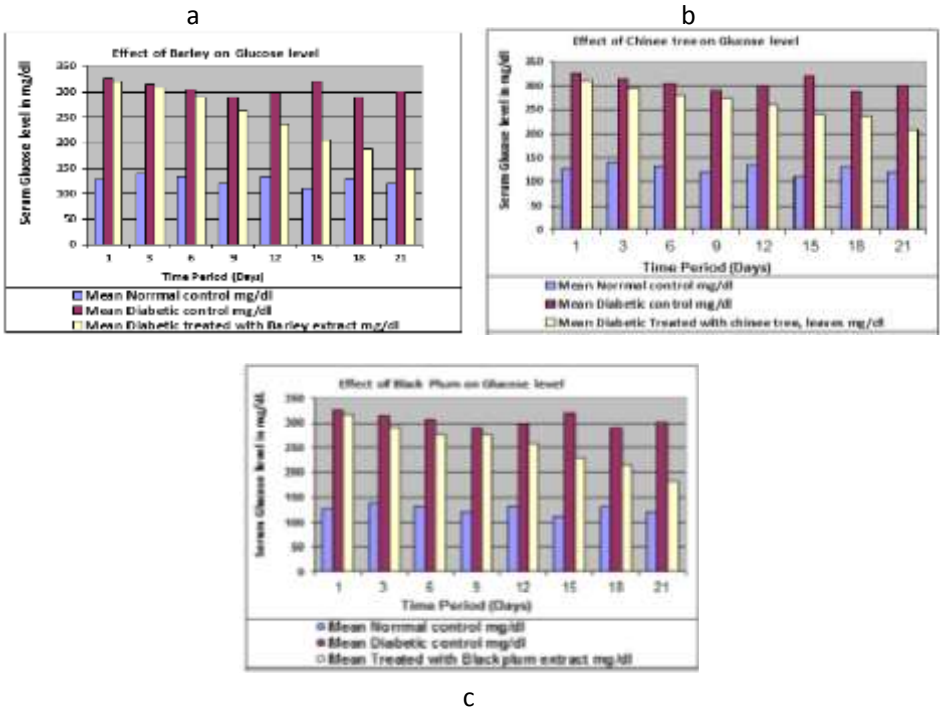

Figure 1. Effect of plants extracts on glucose level in alloxan induced rabbits. (a) Barley extract; (b) Chinese tree leaves extract; and (c) Black plum extract.

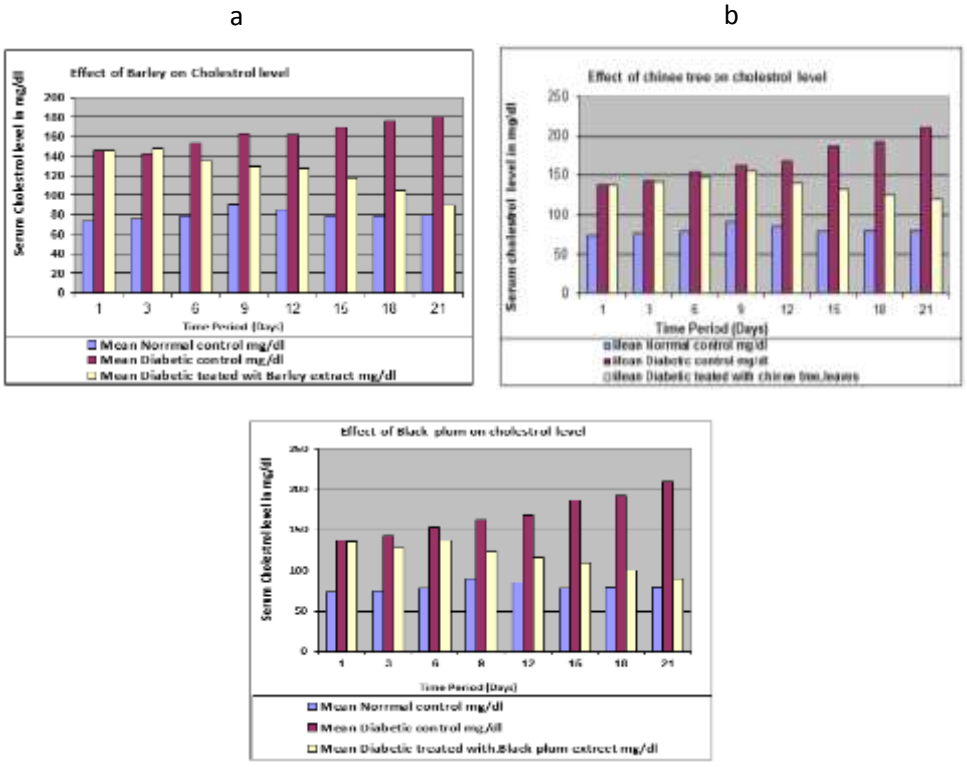

Figure 2. Effect of medicinal plants on cholesterol level in alloxan-induced rabbits; (a) Effect of barley extract; (b) Effect of Chinese tree extract, and (c) Effect of black plum extract.

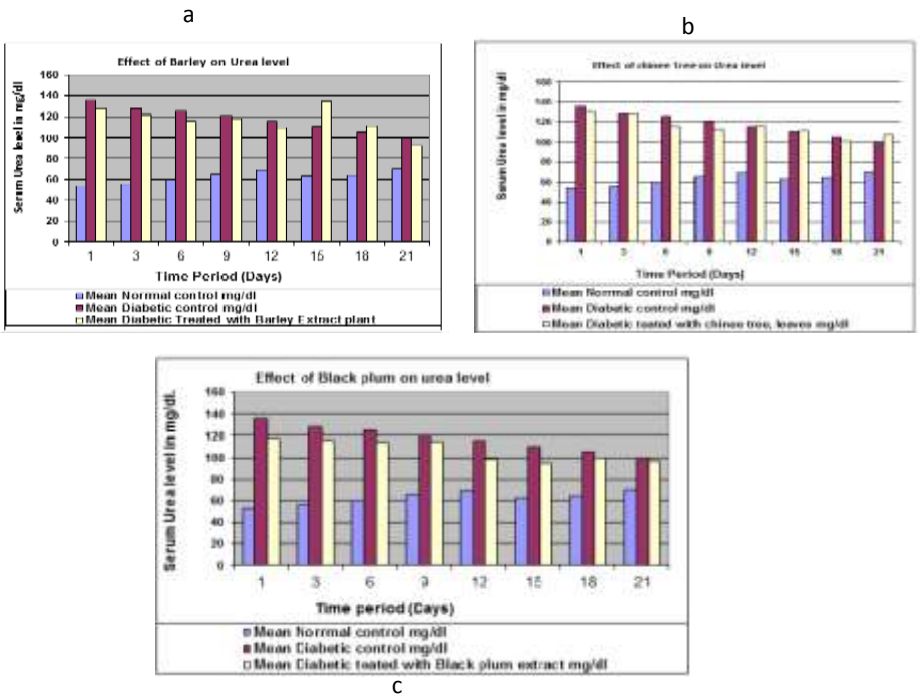

Figure 3. Effect of medicinal plants on urea level in alloxan-induced rabbits; (a) Effect of barley extracts; (b) Effect of Chinese tree extract, and (c) Effect of black plum extract.

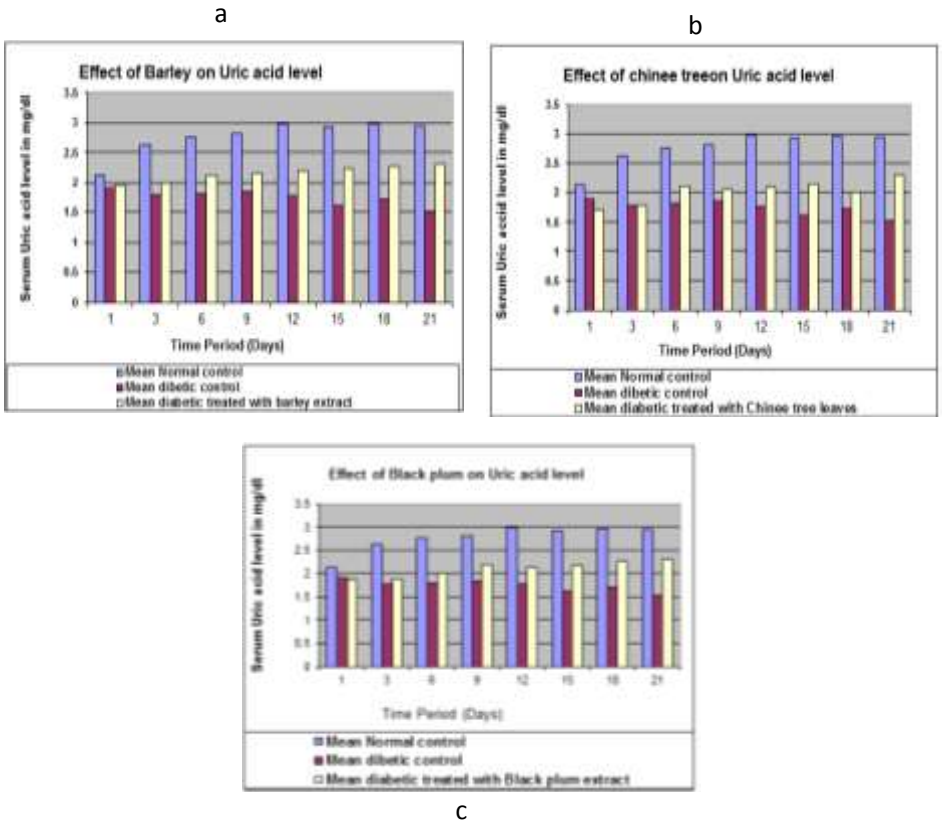

Figure 4. Effect of medicinal plants on serum uric acid in alloxan induced male rabbits. (a) Effect of Barley; (b) Effect of Chinese tree extract; and (c) Effect of black plum extract.

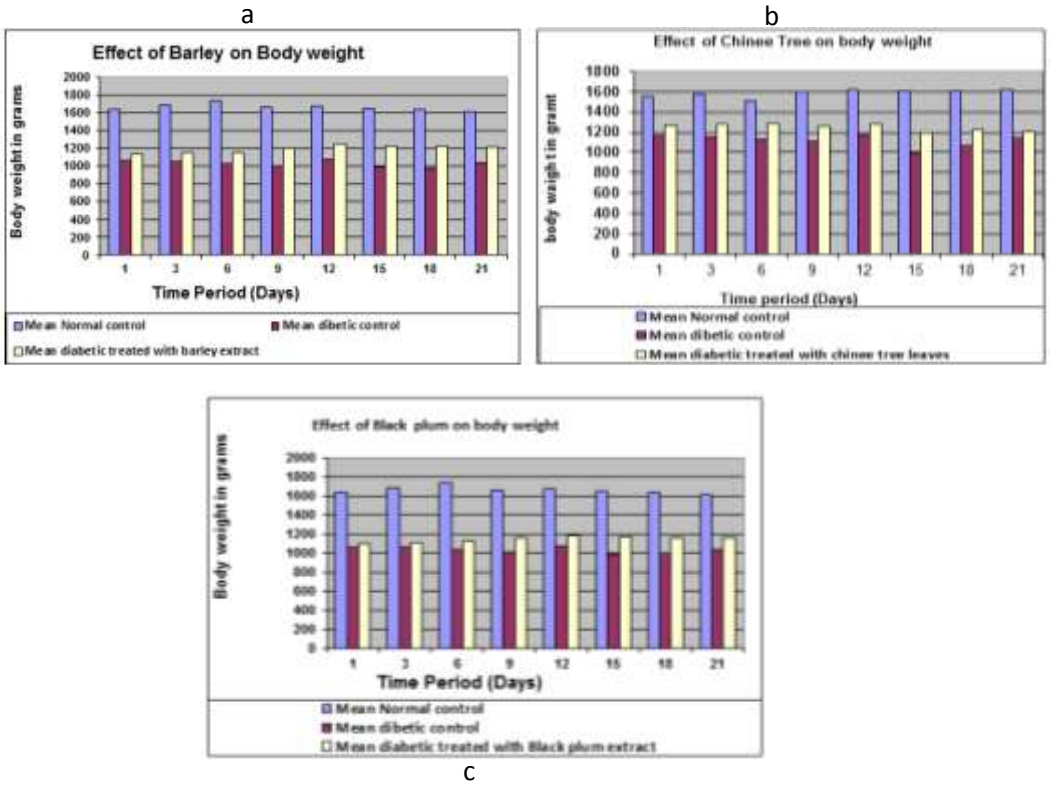

Figure 5. Effect of medicinal plant aqueous extract on body weight of alloxan induced male rabbits. (a) Effect of barley extract; (b) Effect of Chinese tree extract; and (c) Effect of black plum extract.

suggests garlic as a potential antilipidemic, antihypertensive, ant antiglycemic, antithrombotic and antiatherogenic agents which decrease serum triglycerides and cholesterol in diabetic rats (Nadir Ali et al., 2013). The plants with hypoglycemic constituents may have hypolipidemic effects as well. Figure 3 shows the effect of medicinal plants on serum urea level of alloxan induced rabbits. Serum urea level gradually reduced in barley from 127 to 92.31 mg/dL; in black plum it slightly increased from 135 to 137 mg/dL and in Chinese tree leaves, it decreased from 125 to 110.12 mg/dL on the 21st day of the treatment (Figure 3). Untreated diabetic control rabbits reduced the level of serum urea from 135 to 120 mg/dL and Chinese tree, from 135 to 125 mg/dL. Plant extracts were applied on different rabbits group, and slight increase in serum urea level was observed. This might be due to the effect of extract on renal function (Ahmed et al., 2005). Alloxan treatment increased the serum enzymes levels such as cholesterol, LDL, Creatinine, urea and alkaline phosphate and decreased the HDL level, but not glibenclamide (Mohammad et al., 2010). Diabetes cause disturbance in renal function so that the blood urea level is elevated. Extract treated group exhibited reduction in serum urea level, indicating the extract may have effect on renal function as shown in our result (Khushk et al., 2010).

Effect of medicinal plants' aqueous extract on uric acid level in alloxan-induced rabbits was investigated. The results are depicted in Figure 4. Serum uric acid level increased from 1.96mg/dL to 2.5 mg/dL in barley extract, increased from 1.87 to 2.31 mg/dL in black plum and similar pattern was observed in Chinese tree, from 1.71 to 1.99 mg/dL on the 21st day of treatment as shown in Figure 4. Previous studies have also shown similar effect of plant extract on increasing pattern of uric acid (Mahdi et al., 2003). The results of the effect of medicinal plant aqueous extract on body weight of alloxan induced male rabbits are presented in Figure 5. Body weight increased in rabbits treated with barley from 1140 to 1215 g; in diabetic control, from 1040 to 1065 g; in normal male rabbit, body weight decreased from 1638 to 1615 g. The body weight of rabbits treated with black plum increased from 1100 to 1160 g; in diabetic control it increased from 1040 to 1065 g; in normal male rabbits, it increased from 1638 to 1650 g. While in rabbits treated with Chinese tree their body weight increased from 1230 to 1270 g; in diabetic control, it decreased from 1240 to 1065 g; in normal male rabbit, it decreased from 1638 to 1615 g on the 21st day of the treatment as shown in Figure 5. It shows that the body weight of normal rabbits had greater value compared to diabetic and treated rabbits. In soya bean, it was also reported that the weight gain of the group treated with extract had corrected body metabolism; the results revealed that the soya bean alcohol exhibited

antidiabetic activity in a dose dependent manner (Khushk et al., 2010). The lipolysis, proteolysis, and acute fluid loss during diabetes cause weight loss (Alberti and Zimmet, 1998). Results suggest that oral administration of aqueous extract of barley, black plum and Chinese tree reduced glucose, cholesterol, urea, and uric acid level. Therefore, these medicinal plants should be supplemented as herbal drugs in the treatment of various complex diseases and specially to control diabetes. The active ingredients of anti-diabetes in barley, black plum and Chinese tree leaves should be identified.

Conclusion

This study investigates the effect of medicinal plants (barley, black plum, and Chinese tree leaves) aqueous extract as anti-diabetic agents and their effects on the serum cholesterol, urea, and uric acid and body weight of alloxan induced male rabbits. Herbal medicines have an excellent potential to reduce diabetes in alloxan induced male rabbits. Barley greatly controls diabetes in alloxan induced diabetic male rabbits compared to black plum and Chinese tree. Barley extract reduced diabetes level to 43.92%, black plum to 39.5%, and Chinese tree to 32.47%. Therefore, these medicinal plants should be supplemented as herbal drugs in the treatment of various complex diseases and specially to control diabetes.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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