Research Article

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DOI: 10.36648/2572-5432.6.1.33

Journal of Clinical and Molecular Endocrinology ISSN 2572-5432

Vol. 6 No. 1 :33

2021

An Evaluation of Diabetes Ameliorating Capacity of *Terminalia bellerica* Ethanolic Extract on Alloxan-Induced Diabetic Rat Including Safety Profile Study

Abstract

Diabetes is one of the world's most widespread diseases. It is a chronic, metabolic condition, and to treat this condition; plant extracted products are used. Plants are multifarious sources of different medicinal compounds that can be used to improve diabetes. The fruit of T. bellerica (commonly known as 'Bohera') is used for this purpose. Our present investigation was designed to investigate the hypoglycemic effect, lipid profile, and safety profile and thus, monitored an ethanolic extract of T. bellerica fruit in alloxan-induced diabetic rats. In rats, diabetes was induced by intraperitoneal alloxan injection at a dose of 150 mg/kg body weight, and *T. bellerica* fruit extract was fed to the rats at a dose of 750 mg/kg. Blood glucose levels, lipid profile, and safety profile were assessed by measuring serum cholesterol, free fatty acids, phospholipids and triglycerides, SGOT, SGPT, and creatinine levels in diabetic non-diabetic rats before and after extract administration. After evaluating the amount of blood glucose, the hypoglycemic efficacy was found to be equivalent to that of metformin (p> 0.05) given at a dose of 500 mg/kg. Lipid profile and safety profile were analyzed by measuring the levels of tissue cholesterol, free fatty acids, phospholipids and triglycerides, SGOT, SGPT and creatinine. It was found that both fruit extract of T. bellerica and metformin strengthened the diabetes-induced pathological condition. Besides, both fruit extract of *T. bellerica* and metformin did not substantially affect healthy individual rats' normal physiological condition. So, it could be also be concluded that the fruit extract of T. bellerica could be used as a successful alternative therapy for the treatment of diabetes.

Keywords: Terminalia bellerica; Diabetic Mallitus; Safety Profile; SGPT; SGOT; Creatinine

Received: December 19, 2020; Accepted: January 15, 2021; Published: January 22, 2021

Introduction

Diabetes mellitus (DM) is a branch of metabolic disorder distinguished by chronic hyperglycemia [1] due to impaired insulin secretion [2-4]. Untreated diabetes results in some acute complications like ketoacidosis, hypoglycemia, nonketotic hyperosmolar coma [4], and chronic conditions including nephropathy, retinopathy, atherosclerosis, various organ failures, microangiopathy, and infections [5,6]. To control this complicated situation, a wide range of medication is prescribed to control blood glucose levels. The most commonly used antidiabetic drugs include insulin and its derivatives, thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists, sodium-glucose

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Citation: Tahsin MdR, Jannat B, Mostafa A, Purni FA, Khondoker S, et al. An Evaluation of Diabetes Ameliorating Capacity of *Terminalia bellerica* Ethanolic Extract on Alloxan-Induced Diabetic Rat Including Safety Profile Study. J Clin Mol Endocrinol. 2021, 6:1.33

cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, biguanides, sulfonylureas, amylin analogues and glucosidase inhibitor, and this range is widening day by day [7-10]. The conventional antidiabetic drugs have some adverse reactions. The most common side effect is the urinary tract infection. The glucose increases in the urine, and the infection occurring by bacteria are mainly associated with diabetes. Hypotension occurs due to intravascular volume contraction, hyperkalemia, ketoacidosis, the risk of bone fractures, dehydration [11]. Some medicinal plants are used for the treatment of diabetes mellitus. The bark of *Acacia Arabica* [12], seed of *Boerhaavia diffusa* [13], the fruit of *Capsicum annuum* [14], and the fruit of *Coccinia indica* [15], and so on are used.

The scientific name of bohera is *Terminalia bellerica*. It grows wildly throughout the Indian Subcontinent, Srilanka, and South East Asia; an elevation up to 1200 meters with extended etiological diversity can be found [16]. Mainly it is used in antibacterial drugs, but nowadays, it has been used in the treatment of diabetes mellitus [17].

It is as such a tree that is deciduous in nature and possesses a supported trunk, a dense brownish-gray bark including depthless longitudinal fissures, accomplishing a height of within 30 to 20 meters. The leaves are jammed around the edges of the branches, alternately arranged, margins entire, elliptic to elliptic obovate, rounded tip or subacute, midrib prominent, pubescent when young, and becoming glabrous with maturity. The flowers hold an unpleasant odor and are fade greenish-yellow in color and produced in axillary spikes bigger than the petioles but shorter than leaves. The fruit comes ovoid grey drupes, unclearly 5-angled, narrowed into a very tiny stalk [18-21].

It contains several phytochemical constituents such as glucoside (bellericanin) [22], gallo-tannic acid, coloring matter, resins and a greenish-yellow oil [23], ellagic acid, gallic acid, lignans (termilignan and thannilignan), 7- hydroxy 3'4' (methylenedioxy) flavone and anolignan B [24], tannins, ethyl gallate, galloyl glucose, and chebulagic acid, phyllemblin, β -sitosterol, mannitol, glucose, fructose, and rhamnose [18,25].

Different parts of *Terminalia bellerica have been recognized as capable of inducing diverse pharmacological response for example*- immunological activity[24], β -lactamase inhibitor activity [26], immune response In vitro [24], wound healing activity [27], analgesic activity, antihypertensive effect [28], Anti-diarrheal activity [29], anti-salmonella activity [30], anti-microbial activity [31], antimicrobial and toxicity studies [32], antimutagenic activity [33], antipyretic activity [34], hepatoprotective activity [35], antithrombotic and thrombolytic activity [36], anti-spasmodic and bronchodilatory properties [37], antibiofilm activity [38], acute and sub-acute toxicities [39], antiulcer activity [40], antioxidant activity [23], anticancer activity [41] etc.

In this experimental investigation, our principal aim was to examine the antidiabetic and hypoglycemic effect of *Terminalia bellerica* in diabetic rodents.

Method and Materials

Chemicals

Metformin, an antidiabetic drug, was obtained from Square Pharmaceuticals Limited, Salgaria, Pabna, Bangladesh, Which is an Active Pharmaceutical Ingredient (API). Alloxan was brought from Sigma Aldrich, Germany. All the Blood parameter measuring kits were purchased from Plasmatic Laboratory Product Ltd. Humalyzer 3000 (Semi-Automated Clinical Chemistry Analyzer derived from Medigroup Asia limited, Combodia) was used to assess several blood parameter parameters, the glucometer Alere GI of Alere Inc, the USA was obtained from Shahbag, Dhaka, Bangladesh.

Extraction Procedure

The fruits of *Terminalia bellerica* Roxb were obtained from Botanical Garden, Mirpur, Dhaka. Fruits were washed with distilled water and then dried at less than 45°C temperature for 21 days and then the properly dried fruits were crushed into powder. Next, the dry powder was shocked in 95% ethanol at a ratio of 1: 6 (Powder: Solvent) and kept for 7 days with occasional vigorous shaking. The same procedure was done thrice. After that, the extract was made to evaporate using Evaporator. The extract was then gathered. The yield of the extract was 12.4% (Modified) [42].

Experimental Design and Animal Handling

Healthy adult male Wistar rats (120-140 gm) were assembled from the Department of Pharmacy of Jahangirnagar University, Savar, Bangladesh, and held at the Institute of Nutrition & Food Science, University of Dhaka at 25°C temperature and a 12±1 h light/dark cycle was strictly controlled. Standard pellet diet and water were provided (*ad libitum*) to the animals. The rats were kept there for acclimatization before starting the analysis. After that, the body weight of each rat was determined; animals were divided into 6 groups. The rodent was equally distributed according to its body weight, and each group included 5 rats.

Group 1: Negative Control.

Group 2: Alloxan Control.

Group 3: Alloxan induced animals treated with metformin, 200 mg/kg [43].

Group 4: Alloxan induced animals treated with the extract of *Terminalia bellerica*, 750 mg/kg.

Group 5: Non-diabetic rats treated with 200 mg/kg metformin [43].

Group 6: Non-diabetic rats receiving the extract of *Terminalia bellerica*, 750 mg/kg.

The rats were treated without persuading diabetes in the first two weeks with their respective specimens. Alloxan, a chemical agent, was then injected intraperitoneally into all rats belonging to groups 2, 3 and 4, at a dose 150 mg/kg [44,45]. These rats' blood glucose levels were tested to see whether or not, after three days, they were affected by diabetes. The negative control group and alloxan injected Alloxan control group was held untreated, where treatment with drugs and extracts was started in animals in groups 3, 5, and 4, 6, respectively. Forty-two days of treatment continued, and blood glucose levels were tested thrice in a week. Then, drug and plant extract doses were administered orally.

Statistical Analysis

The findings were expressed as mean±SD for all study parameters belonging to different groups. "One Way Anova Test of SPSS 16" software was used to evaluate intra-group

and inter-group discrepancies in outcomes to assess the statistical significance. The statistical significance level was set at a 'p' value of p>0.05. In terms of outcomes, the intragroup difference was considered statistically important when the 'p' value was found at 0.05.

Results

Change in body weights

The pre-treatment & post - treatment Body weight of rats belonged to the different groups is shown below in Figure 1.

Change in blood glucose level

The blood glucose level (mg/dl) of all test groups from day 1 to day 42 are expressing below as mentioned in Figure 2.

Safety Profile Study (Liver function test)

The SGOT level of all rats belonged to all 6 groups are denoting the condition of the liver (Figure 3).

The level of SGPT of all rats belonged to 6 groups are expressing the condition of livers (Figure 4).

Safety Profile Study (Kidney functioning Test)

The below - mentioned values regarding the level of Creatinine (mg/dl) of rats belonged to all 6 groups as a requirement of measuring the kidney functioning test Figure 5).

Safety Profile Study (Lipid profile)

The Total Cholesterol level of rats belonged to all 6 groups is denoting the condition of Lipid profile (Figure 6).

Safety Profile Study (Lipid profile)

The level of HDL all rats belonged to 6 groups are expressing the condition of lipid profile (Figure 7).

Safety Profile Study (Lipid profile Test)

The below mention values regarding the level of LDL (mg/dl) of rats belonged to the 6 groups as a requirement of measuring the lipid profile (Figure 8).

Safety Profile Study (Lipid profile Test)

The level of Triglyceride level (mg/dl) of all rats belonged to 6 groups are expressing the lipid profile (Figure 9).





Journal of Clinical and Molecular Endocrinology ISSN 2572-5432







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Discussion

Body weight measurement

Groups 2 and 3 had almost equal body weight, but significantly higher body weight was found in rats belonging to group 4 compared to groups 2 and 3. The control group and group 6 displayed a significantly identical but significant decrease in body weight, as was also detected in group 5. When correlated to the diabetic control group, with the metformin and extract-treated group, a significant reduction was observed in the metformintreated group. Because metformin has been reported to cause weight loss [46]. But the extract-treated group is nearly identical to the control group. However, both metformin and the extracttreated group were fed correspondingly as the control group. In the case of plant *Costus pictus*, a similar consequence was noticed [47].

Blood Sugar level

Group 2 appeared higher blood glucose levels than group 3 and group 4. Thus, contrasted to group 2, a significant decrease was observed in group 3 and group 4. Blood glucose levels in group 1 rats were encountered to be normal. The elevated blood glucose level was significantly reduced in the same pattern in the metformin and the extract-treated group as in the control group. It was precedently denoted that both metformin and plant *Terminalia bellirica* did not cause hypoglycemia [48]. Furthermore, the reduction of blood glucose in the group treated with metformin was slightly higher than that of the group treated with extract, but it has no statistical significance. A resemblant outcome was observed in the case of plant *Panicum maximum* [49].

Lipid profile

In the existing study, we have recognized a notable increase in total cholesterol, LDL, triglycerides levels in blood serum. Still, a significant decline in serum HDL levels was noticed in alloxan-induced diabetic rats than in group 3 and group 4. Total cholesterol, LDL, and triglyceride levels were nearly identical between groups 3 and 4 with null statistical significance. Again, the HDL level of group 3 revealed a little bit better condition than group 4 and significantly nullified. Whole lipid profiles were almost indistinguishable in the control group of normal healthy rats treated with *Terminalia bellirica* and metformin and were also statistically nullified. A consistent result was found in the case of the plant *Sigesbeckia orientalis* [5].

Liver functioning test

Group 2, which corresponds to alloxan-induced diabetes rats, displayed higher SGOT and SGPT levels than group 3 and group 4. So, a significant decline was found in group 3 and group 4 compared with group 2. The drug-treated group was a little better condition between the drug and extract-treated group, which occupies statistical significance. In addition, SGPT and SGOT levels were almost identical in the control group of normal healthy rats treated with *Terminalia*

bellirica and metformin, along with no statistical significance. When group 3 and group 4 are compared with the control group, significant results are seen. Rats were given drugs and extracted in group 5 and group 6, but in group 3 and group 4, rats were given alloxan with drug and extract. It can be assumed that alloxan is responsible for the significant result, not for the plant itself. In the case of plant *Ocimum sanctum*, a similar result was found [50].

Kidney functioning test

Group 2, which considers alloxan-induced diabetes, reported higher creatinine levels in rats relative to group 3 and group 4. Thus, compared to group 2, a significant decrease was noted in group 3 and group 4. A marginally better situation between the drug and the extract-treated group was the drug-treated group, which exhibits statistical significance. Besides, in the control group of normal healthy rats treated with *Terminalia bellerica* [51] and metformin, creatinine serum concentration was found to be approximately uniform with no statistical significance. Significant differences are found when group 3 and group 4 are compared to the control group. In group 5 and group 6, rats were given drug and extract, but in group 3 and group 4, rats were given alloxan with drug and extract. Alloxan can be said to be responsible for the essential outcome, not for the plant itself. An identical result was found in the case of the plant *Murraya koenigii* [52].

Conclusion

The above-discussed outcome may be presumed that the *T. bellerica* fruit extracts impart alike but slightly lower effect than metformin with null statistical significance. Additionally, it ameliorates the state of pathological parameters in diabetic rats like SGOT, SGPT, and Creatinine and imparts an anti-diabetic effect. Furthermore, it is also noticed that these parameters remain unchanged when non-diabetic rats were fed with *T. bellerica* with a similar dose. Thus, we put an end to the research by saying that this herbal cure can be merged for disease management of diabetes mellitus.

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