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Comparative study of the effect of ethanolic extract of *swietenia mahagoni* seeds with rosiglitazone on experimentally induced diabetes mellitus in rats

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Abstract

The study was performed to compare the blood glucose lowering effect of *Swietenia mahagoni* seeds with an oral antidiabetic drug, rosiglitazone in experimentally induced diabetic rats. Twentyfour healthy Long Evans Norwegian strain of rats were included in the study and divided into four groups (A, B, C and D) comprising 6 rats each. Group A (control group) received standard rat food for 14 days. Diabetes was induced by a single intraperitoneal administration of alloxan 120mg/kg body weight in Group B, C and D. Group B was given standard food for 10 days and considered as diabetic control. Group C and D were treated with ethanolic extract of *Swietenia mahagoni* seeds 1000mg/kg and rosiglitazone 10mg/kg orally respectively. Administration of ethanolic extract of *Swietenia mahagoni* seeds in group C and rosiglitazone in group D produced a significant reduction in blood glucose level as compared to diabetic control (group B). Histological examination of pancreas showed destruction of beta cells in Islets of pancreas in group B whereas retaining of islets and few degranulations of beta cells of pancreas found in group C and group D. The observations and results of the present study provide information that ethanolic extract of *Swietenia mahagoni* seeds has hypoglycaemic effect in experimentally induced diabetic rats which requires further investigation.

Introduction

Diabetes mellitus is a metabolic disorder resulting in raised blood glucose (hyperglycaemia) from defects in insulin secretion, insulin action or both that arise from genetic as well as environmental factors. It is defined by documenting raised blood glucose in fasting state (≥7.0mmol/L) or 2 hours after an oral standard glucose drink (≥11.1mmol/L)[1]. The chronic hyperglycaemia is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, liver, heart and blood vessels[2].

The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030[3]. Traditional medicine is fostered particularly in countries where scientific medicine is not accessible to large populations for economic reasons. Complementary and alternative medicine does not compete with the successful main stream of scientific medicine. Users of complementary and alternative medicine commonly have chronic conditions and have tried conventional medicine but found that it has not offered a satisfactory solution, or has caused adverse effects[4].

Bangladesh is a rich emporium of medicinal plants, some of which are used therapeutically in the treatment of various diseases by both traditional healers and local people. Many of them are highly efficacious and are internationally recognized as useful drugs[5]. Herbal medicines have several advantages such as fewer side-effects, better patient tolerance, relatively less expensive and well accepted due to a long history of use.The more important cause is that herbal medicines provide rational means for the treatment of many diseases that are obstinate and incurable in other systems of medicine[6].

Swietenia mahagoni is one of the most significant plants of the family, Meliaceae. This plant has various types of medicinal values like antimalarial and antidiarrhoeal effects. The plant extracts have been accounted to possess antibacterial and antifungal activities. Limonoids obtained from *Swietenia mahagoni* have antifungal activity[7].

Study has clearly indicated the significant antidiabetic activity of *Catharanthus Roseus* (Nayantara), *Azadirachta Indica* (Neem) and *Allium sativam* (Garlic) and supports the traditional

usage of the herbal preparations by Ayurvedic physicians for the therapy of diabetics[8].

The seed of *Swietenia mahagoni* is a natural agonist of peroxisome-proliferator activated receptor (PPAR γ)[9]. The functions of these PPAR receptors after activation by drugs include an increase in lipid and cholesterol metabolism, adipocyte differentiation, and improvement in insulin sensitivity. It has been demonstrated that PPAR γ is the receptor of the thiazolidinedione (TZD) class ligands. Among the TZD type antidiabetic drugs, Rosiglitazone and Troglitazone are potent adiopocyte-differentiating agents, which activate ap 2 gene expression in a PPARγ-dependent manner[9].

With this background information, in this study, attempt has been made to compare the glucose lowering effect of *Swietenia mahagoni* seeds with an oral antidiabetic drug, rosiglitazone in experimental diabetic rats. Alloxan has been chosen to induce diabetes mellitus in rat. Blood glucose level has been estimated to detect the extent of pancreatic damage. Pancreatic histology has also been performed to confirm the findings.

Materials and Methods

This experimental study was carried out at the Department of Pharmacology and Therapeutics, Dhaka Medical College (DMC), Dhaka, during the period July 2009 to June 2010.

A total number of 24 Long Evans rats of either sex were used for the present study. The rats were fed normal diet and allowed to drink water ad libitum.The rats were divided into four groups(A, B, C and D). Each group consists of six rats.

Experiment design : It comprised of 24 rats which were divided into 4 groups each group having 6 rats (Group-A, Group-B, Group-C and Group-D). All the rats were fasted overnight before collection of blood. Group-A (Control group) received standard rat food for 14 days. Fasting blood glucose (FBS) level was estimated on day 1, 4 and day 15 of the experiment.

Group-B (Diabetic control group)-was given alloxan 120 mg/kg intraperitoneally for induction of diabetes on day 1. After alloxan rats were given standard food. Fasting blood glucose level was estimated on day 1 (before alloxan), on day 4 and on day 15 of the experiment.

Group-C was given alloxan 120 mg/kg intraperitoneally on day 1. After alloxan rats were given standard food. Then after 3 days ethanolic extract of *Swietenia mahagoni* seeds 1000mg/kg orally along with standard food was given for 10 days. Fasting blood glucose level was estimated on day 1 (before alloxan), on day 4 and on day 15 of the experiment.

Group-D was given alloxan 120 mg/kg intraperitoneally on day 1. After alloxan rats were given standard food. Then after 3 days, rosiglitazone orally along with standard food was given for 10 days. Fasting blood glucose level was estimated on day 1 (before alloxan), on day 4 and on day 15 of the experiment.

On day 15 all the rats were sacrificed and pancreas was preserved in 10% formalin for histological study.

Results

*Effect of Alloxan on blood glucose level of group Aand B rats on day 1, day 4 and day 15:*In group-A, blood glucose levels (mean±SD) were 5.80±0.52 mmol/L, 5.8±0.50 mmol/L and 5.80±0.46 mmol/L on day 1, day 4 and day 15 respectively. Percentage change was 3.45% (Table-I).

Table I: Effect of alloxan on blood glucose level of group A and B rats on day1, 4 and 15.

Group	FBG (mmol/L) on day 1 (before Alloxan) mean ± SD	FBG (mmol/L) on day 4 (after alloxan) mean ± SD	FBG (mmol/L) on day 15 (after alloxan) mean ± SD
A	5.8 ± 0.52	5.8 ± 0.52	5.8 ± 0.46
B	5.5 ± 0.65^{ns} (P < 0.05)	15.0 ± 3.38*** (P < 0.001)	16.0 ± 2.83*** (P < 0.001)

N = 6, ns = not significant, *** = highly significant

Effect of Alloxan, EESM seeds and rosiglitazone on blood glucose level of group B, C and D rats on day 1, 4and day 15: In group B, the blood glucose levels (mean±SD) were 5.50±0.64 mmol/L, 15.00±3.38 mmol/L and 16.00±2.83 mmol/L on day 1, day 4 and day15 respectively. Percentage change was 172.73% and 190.91% respectively. In group C, the blood glucose levels (mean±SD) were 5.80±0.64 mmol/L, 15.05±3.45 mmol/L and 8.03±2.04 mmol/L on day 1, day 4 and day 15 respectively. Percentage change was 159.48% and 38.45% repectively. In group D, the blood glucose levels (mean±SD) were 5.60±0.46 mmol/L, 14.08±3.27 mmol/L and 7.22±0.90 mmol/L on day 1, day 4 and day 15 respectively. Percentage change was 151.43% and 28.93% repectively. Unpaired t test was done between group B and group C, between group B and group D and between group C and group D on day 4 and day 15 (Table-II).

Table II: Effect of on EESM (ethanolic extract of *Swietenia mahagoni*) seeds and rosiglitazone on blood glucose level in diabetic rats:

Group	FBG (mmol/L) on day 1 (before Alloxan) mean ± SD	FBG (mmol/L) on day 4 (after alloxan) mean ± SD	FBG (mmol/L) on day 15 (after alloxan) mean ± SD
B (Alloxan treated)	5.5 ± 0.64	15.0 ± 3.38	16.0 ± 2.83
C (EESM treated)	5.8 ± 0.64^{ns} (P < 0.05)	15.05 ± 3.45^{ns} (P < 0.001)	8.03 ± 2.04*** (P < 0.001)
D (Rosiglitazone treated)	5.6 ± 0.46^{ns} (P < 0.05)	14.08 ± 3.27^{ns} (P < 0.05)	7.22 ± 0.90^{ns} (P < 0.05)

N = 6, ns = not significant, *** = highly significant

Percentage change of blood glucose level in diabetic rats after EESM (ethanolic extract of Swietenia mahagoni) seeds and Rosiglitazone treatment: In group B, the blood glucose levels (mean ± SD) were 5.50 ± 0.64 mmol/L and 16.00±2.83 mmol/L on day 1 and day 15 respectively. Percentage change was 192.37%. In group C, the blood glucose levels (mean±SD) were 5.80±0.64 mmol/L and 8.03±2.04 mmol/L on day 1 and day 15 respectively. Percentage change was 41.50%. In group D, the blood glucose levels (mean±SD) were 5.60±0.46 mmol/L and 7.22±0.90 mmol/L on day 1 and day 15 respectively. Percentage change was 29.68%. Unpaired t test was done between group B and group C and between group B and group D, differences on day 15 were significant statistically (P < 0.001) (Table-III).

Table-III: Effect of EESM (ethanolic extract of Swietenia mahagoni) seeds and rosiglitazone on blood glucose level in diabetic rats:

Group	FBG (mmol/L) on day 1 (Mean±SD)	FBG (mmol/L) on day 15 (Mean±SD)	Percent change
B (n=6)	5.50±0.64	16.00±2.83	+192.37
C (n=6)	5.80±0.64	8.03±2.04***	+41.50
D (n=6)	5.60±0.46	7.11±0.90***	+29.68

*** = significant at P <0.001.

Effect of EESM (ethanolic extract of Swietenia mahagoni) seeds and rosiglitazone on pancreatic islets of Langerhans in diabetic rats: In group B the islet of pancreas is destroyed and dilated ducts are filled with secretory product. Complete beta cell degranulation is seen. In group C (received ethanolic extract of Swietenia mahagoni seeds after alloxan) the islets configuration is retained and beta cells are partially degranulated. The islets of pancreas is increased in size. In group D (received rosiglitazone after alloxan) the islets configuration of pancreas is retained and partial degranulation of beta cells is seen. There is increase in size of the islets of pancreas (figure:1-5).

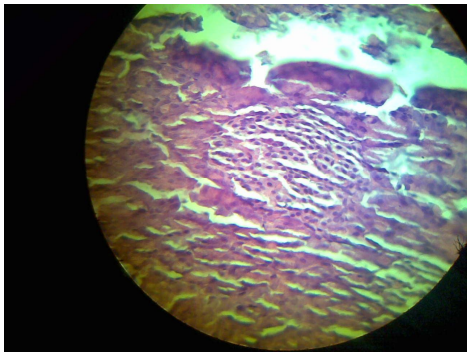

Figure-1: Normal rat pancreas, showing section of islet packed with beta cells. Acinar and islet components are clearly separated from each other (H & E stain x 40).

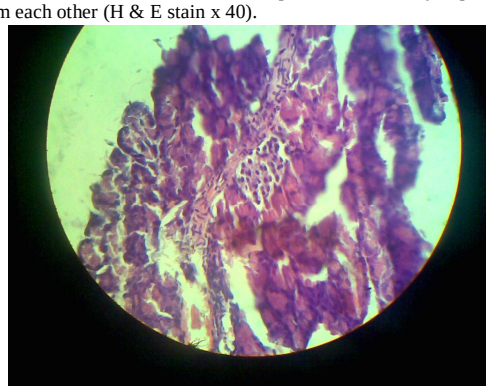

Figure-2: Showing the destroyed islet of pancreas and dilated ducts filled with secretory product Alloxan treated rats. Degranulation of beta cell occurred (H & E stain x 40).

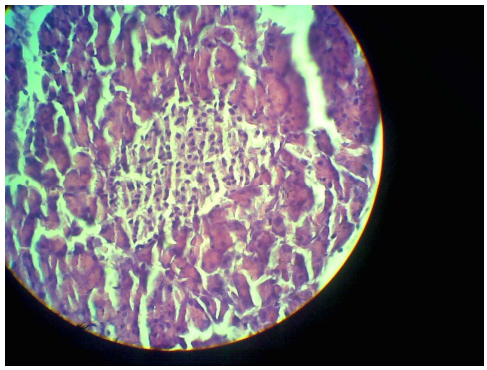

Figure-3: Rat pancreas in ethanolic extract of *S Mahagoni* treated group after Alloxan treatment showing retention of islet configuration and partial degranulation of beta cells (H &E stain x 40).

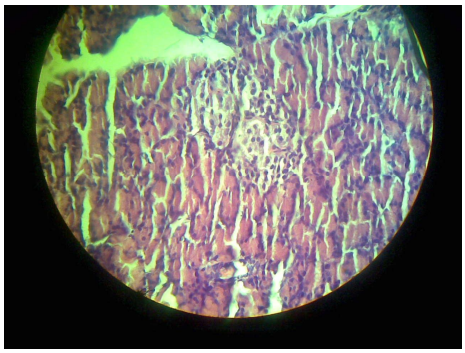

Figure-4: Rat pancreas treated with Rosiglitazone showing least destruction of beta cells within the islets. Acinar and islet components are clearly separated from each other (H & stain x 40).

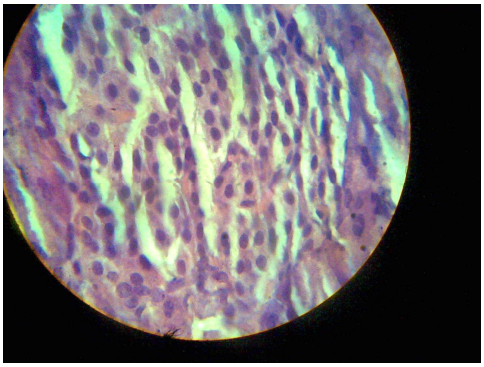

Figure-5: Normal rat pancreas showing enlarged islet in high power. Acini and beta cells are clearly separated. Exocrine ducts are seen around the acini (H & E stain x 100).

Discussion

The present study was carried out to compare the glucose lowering effect of ethanolic extract of *Swietenia mahagoni* seeds with rosiglitazone on experimentally induced diabetes mellitus in rats.The ethanolic extract of *Swietenia mahagoni* seeds and rosiglitazone were given for 10 days in alloxan induced diabetic rats. In addition, histological studies of rat pancreas following administration of ethanolic extract of *Swietenia mahagoni* seeds, rosiglitazone and alloxan were also done.

In the present study, diabetes was induced by alloxan. The dose and route of administration of alloxan monohydrate was selected from Andrade et al (2000)[10] and Kim et al (2006)[11] respectively.The blood glucose levels in animals were measured 72 hours after administration of alloxan which was done according to experiment of Etuk EU et al(2010)[12]. In this study, intraperitoneal (ip) administration of single dose of alloxan (120mg/kg), increased blood glucose level significantly. Similar observations were reported by number of researchers. Ghosh et al (2004)[13] observed the condition of diabetes after 24 hours of intravenous injection of sterile, freshly prepared 1% alloxan monohydrate solution at a dose of 40mg/kg in albino rats.In the present study, the rise in blood glucose level in experimental diabetic rats was also very high.

The dose of *Swietenia mahagoni* (1000mg/kg body weight), used in this study was selected in keeping conformity with the dose used in different research work by Li DD et al (2005)[9]. The duration(15 days)of study was selected according to Bokaeian et al(2010)[14].

Decrease in the mean value of blood glucose level was observed in the experimental diabetic group when treated with EESM (ethanolic extract of *Swietenia mahagoni*)seeds at a dose of 1000mg/kg and rosiglitazone and these changes were significant ($P<0.001$). Therefore, the findings of this study are in well agreement with the findings of other researcher Li DD et al (2005)[9]. It may be concluded that *Swietenia mahagoni* seeds have hypoglycaemic effect in experimentally induced diabetic rats.

The histology of the islets and the beta cells of pancreas were observed in diabetic, *Swietenia mahagoni* and rosiglitazone treated diabetic rats.This was done in addition to the research of Li DD et al(2005)[9] and to confirm the findings.The destruction of islets, filling of dilated ducts with secretory product and complete degranulation of beta cell were seen in Alloxan treated diabetic group. The islets configuration was retained and beta cells were partially degranulated in *Swietenia mahagoni* and rosiglitazone treated diabetic group, suggesting regeneration of islets mass.This is complimentary to other studies where rosiglitazone inhibited the well-characterized progressive loss of β-cell mass in rodents by maintaining β-cell proliferation, thereby preventing increases in overall net β-cell death[15]. Thiazolidinediones (TZDs) enhance insulin sensitivity, reduce blood glucose levels, and also preserve β-cell mass[15]. De et al (2011)[16] in their study showed that aqueous-methanolic extract of *Swietenia mahagoni* is useful in correction of diabetes and its related complications like oxidative stress and hyperlipidemia. These antioxidant activities also protect the metabolic enzymes in cells that resettled the cellular homeostasis towards the normal level[16]. This mechanism may be proposed to the cause behind the regeneration or retention of islets tissue activity.

Maiti et al (2009)[17] isolated the hypoglycaemic phytoconstituent named Swietenine from seeds of a related species *Swietenia macrophylla* and the effect was comparable to that of human insulin.

The active constituent of *Swietenia mahagoni* that might be responsible for hypoglycaemic activity is yet to be isolated.

The exact mechanism of ethanolic extract of *Swietenia mahagoni* in reducing blood glucose level is not well understood. The scientists of China claimed that the hypoglycaemic activity of *Swietenia mahagoni* is mediated by agonistic activity to PPAR γ receptor which after activation improves insulin sensitivity.

It was observed that the EESM (ethanolic extract of *Swietenia mahagoni*) seeds has hypoglycaemic effect in Alloxan treated diabetic rats.The result suggested that the ethanolic extract of *Swietenia mahagoni* seeds may be a useful hypoglycaemic

agent in the treatment of diabetes mellitus. It is recommended that further studies regarding pharmacokinetics, pharmacodynamics, toxicology and posology of extract of *Swietenia mahagoni* seeds should be undertaken to develop it as a useful antidiabetic agent for human.

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