

American Journal of
Drug Discovery
and Development

ISSN 2150-427X



Academic
Journals Inc.

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Anti-diabetic Activity on Ethanolic Extracts of Fruits of *Terminalia chebula* Retz. Alloxan Induced Diabetic Rats

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ABSTRACT

The present study intended to evaluate the beneficiary effects of ethanolic extract of *Terminalia chebula* Retz. fruits (EETC) by using alloxan-monohydrate induced diabetic control by using Wistar Albino rats. The toxicity study was performed on aliquot doses of EETC (100 to 500 mg kg⁻¹ b.wt.) and predetermined the LD₅₀ value on 30 days evaluation; also the behavioral changes, symptoms and mortality have been checked, the EETC showed the nil toxicity up to 500 mg kg⁻¹ b.wt. The effect of EETC (200 mg kg⁻¹ b.wt.) was compared with the glibenclamide (600 mg kg⁻¹ b.wt.) that is often used as a standard drug and the anti-diabetic activity has been conducted for 30 days. After the completion of the study, animals were dissected through cervical dislocation and collected the blood, serum and pancreas. The collected samples were performed under parameters like biochemical and anti-oxidant enzymes related to diabetes such as, weight variation, blood glucose, plasma insulin, serum and liver protein, serum and liver cholesterol, serum and liver triglyceride, serum and liver phospholipids, SGOT (Serum Glutamate Oxaloacetic Transaminase), SGPT (Serum Glutamate Pyruvate Transaminase), ACP (Acid Phosphatase), ALP (Alkaline Phosphatase), GSH (Glutathione reductase), GPT (Glutamate Pyruvate Transaminase), GPX (Glutathione Peroxidase), CAT (Catalase) and histopathological sections of the pancreas, the above parameters calculated and showed that the significance at p<0.001 to 0.05. The histopathological changes caused after induction of alloxan showed the granular cytoplasm, dilatation, shrunken nuclei and inflammation, which were reduced after treatment of the EETC (200 mg kg⁻¹ b.wt.). Excess proliferation of epithelium in the pancreas was observed in diabetic rats, which was reduced after administration of the EETC (200 mg kg⁻¹ b.wt.). From the evaluation of the present study on EETC has been confirmed that having the pharmacological action against the diabetic condition, even though the mechanism of the action is unknown, also it can be used further molecular compound analysis and define the chemical to the action.

Key words: *Terminalia chebula*, anti-diabetic, serum and liver parameters, pancreas

INTRODUCTION

The Diabetes Mellitus (DM) is being one of five leading causes of death and debilitating disease in the world. One hundred and fifty million people were suffering from diabetes wide reaching, which is almost five times more than the estimates one decade ago and it may double in the year

2030. India leads the way with its largest number of diabetic subjects in India is expected to increase 57.2 million by the year 2025 (King *et al.*, 1998). *Diabetes mellitus* is a complex multisystemic disorder characterized by abnormal insufficiency of insulin secretion, Insulin Dependent Diabetes Mellitus (IDDM) or concomitant resistance of the metabolic action of insulin on target tissues (Garber, 1998). Hence, search for a drug with low cost, safety, efficacy, non-toxic, potential and without adverse side effects are being pursued in several laboratories around the world. Throughout the countries, many traditional plants have been found successful for anti-diabetic activity, further most, the marked medicines are distillations, combinations, reproductions or variations of substances that are found in nature. Our ancestors recommended some of the substances that are found such as secondary metabolites in nature long before their value was demonstrated and understood by scientific methods. However, few have received scientific or medical scrutiny and the World Health Organization (WHO) has recommended the traditional plant treatments for diabetes warrant further evaluation (WHO, 1980). Moreover, today it is necessary to provide scientific proof as to whether it is justified to use a plant or its active principles for treatment (Singh *et al.*, 2000).

Due to the above stated about the herbal medicine; our objective is to be found the resolution for the prevalent disease DM from the nature. Medicinal herbs are great demand in the developed countries as well as developing countries were having the awareness of primary healthcare because of their wide biological and medicinal activities, higher safety margins and lesser costs. *Terminalia chebula* Retz. (Combretaceae) is also known as “King of Medicines” in Tibet and is always listed first in the Ayurvedic Materia Medica because of its wide spectrum of biological and pharmacological activity against the debilitating disease. It is a flowering evergreen tree and in Tamil called as Kadukkai; in English called as the black Myrobalan; Sanskrit and Bengali they calling as Haritaki; in Hindi named as Harad; in Telugu called as Karkchettu; Marathi and Gujarati named as Harada. It is widely available in Indian subcontinent and the adjacent areas of Pakistan, Nepal, south-west of China, Kerala, Sri Lanka (Chopra *et al.*, 1956). *T. chebula* Retz., a native plant in India and Southeast Asia, it is extensively cultivated in Taiwan. Its dried ripe fruit has traditionally been used to treat various ailments in Asia (Perry, 1980).

It is a popular folk medicine and has been studied for its homeostatic laxative, diuretic and cardiogenic activities (Singh, 1990; Barthakur, and Arnold, 1991). *T. chebula* has been reported to exhibit a variety of biological activities, including anti-diabetic (Sabu and Kuttan, 2002), anti-cancer (Saleem *et al.*, 2002), anti-mutagenic (Kaur *et al.*, 2002) and anti-viral (Ahn *et al.*, 2002) activity. The plant *T. chebula* was found that various bioactive phytoconstituents such that tannin, chebulic acid, chebulagic acid, corilagin and gallic acid also the presence of citri is being used for the disease of citrus canker (Afzalakhtar *et al.*, 1997). The present study intended to reveal that the anti-diabetic activity on ethanolic extract of *Terminalia chebula* fruits by using Wistar albino rats and analyzed by various biochemical and anti-oxidant parameters with histopathological analysis of pancreas.

MATERIALS AND METHODS

Fruit collection and authentication: Fresh matured *T. chebula* fruits were collected from a tree in Kolli hills, Namakkal District, Tamil Nadu, India and got an authentication from the Botany department of Bharathidasan University, Tiruchirappalli, Tamil Nadu, India.

Extraction: The dried fruits were powdered in an electrical grinder and stored at 5°C until further use. One hundred grams of the powder was extracted with petroleum ether (60-80°C) to remove

lipids. It was then filtered and the filtrate was discarded. The residue was extracted with 95% ethanol by Soxhlet extraction. The ethanol was evaporated in a rotary evaporator at 40-50°C under reduced pressure and yielded 8.5 g extract from 100 g of dried fruit.

Chemicals procurement: Alloxan was purchased from Sigma Aldrich Chemical Co., St. Louis, MO, USA. In addition, all other chemical other chemical were purchased in an analytical grade.

Animals: Adult male Wistar albino rats strain weighing approximately 150 to 180 g was procured from Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India. They were acclimatized to animal house conditions, fed with standard rat pellet feed supplied by Hindustan Lever Ltd., Bangalore, India.

Toxicity studies: To study any possible toxic effects and changes in behavioral pattern of rats were treated with graded dose on ethanolic extract of fruits of *T. chebula* (100-500 mg kg⁻¹ body weight/rat/day) and kept under close observation for 8 h daily up to 30 days. All symptoms including changes in awareness, motor activity, posture, muscle tone and reflexes were recorded for 30 days (The report was not included in this article).

Alloxan induction in animal model: The rats were injected with Alloxan monohydrate dissolved in sterile normal saline at a dose of 150 mg kg⁻¹ b.wt., intraperitoneally since, Alloxan is capable of producing fatal hypoglycemia because of massive pancreatic insulin release and rats were treated with 20% glucose (15-20 mL) intraperitoneally 6 hours after the injection of Alloxan. The rats were then kept for the next 24 h in their cages with 5% glucose bottles to prevent hypoglycemia (Ragunathan and Sulochana, 1994).

Anti-diabetic activity: The animals were divided into four groups and each comprising six animals. Group I was served as normal pellet food with *ad libitum* termed as negative control; Group II was served as positive control induced with Alloxan (150 mg kg⁻¹ b.wt.), Group III was served as standard control which was Glibenclamide (600 mg kg⁻¹ b.wt.), Group IV was served as herbal treatment with EETC fruit (200 mg kg⁻¹). The overall study was performed for thirty days, after the completion of thirty days, animals were dissected by cervical dislocation, collected the blood samples and organ as pancreas for biochemical and histopathological analysis of pancreas respectively. During the experimental period, the blood glucose level and body weight has been measured (Aruna *et al.*, 1999).

Biochemical parameters analysis: The various biochemical parameters were analyzed on different four groups. The parameters were blood glucose, plasma insulin, serum and liver protein by Lowry's method (Lowry *et al.*, 1951), serum and liver cholesterol, serum and triglyceride, phospholipid and liver phospholipid, acid phosphatase, alkaline phosphatase, SGOT/AST (Serum glutamate oxaloacetic transaminase/Aspartate amino transferase), SGPT/ALT (Serum glutamate pyruvate transaminase/Alanine aminotransferase), Catalase (CAT), Glutathione reductase (GSH), Glutamate pyruvate transaminase (GPT), Glutathione peroxidase (GPX).

Statistical analysis: All data are presented as Mean±SD and were analyzed with Duncan's Multiple Range Test (DMRT). Values of p<0.01-0.001 were considered significant anti diabetic activity.

RESULTS AND DISCUSSION

The present study expressed that the anti-diabetic activity of the ethanolic extract of fruits of *Terminalia chebula* by using Wistar albino rats. The animal groups were separated into four different groups; the results were tabulated in Table 1 and calculated for mean, standard deviation and significance. The EETC (200 mg kg⁻¹ b.wt.) and Glibenclamide (600 mg kg⁻¹ b.wt.) were given positive significant results against the Alloxan monohydrate dangerous; such that both the EETC and standard drug retain the body weight from the abnormal weight loss. Even though, the standard drug having more significant than the EETC, also the EETC showed potential activity against the diabetic condition, which is comparable results to the Glibenclamide when treated. From the results; measurement of body weight, the negative control showed that increased body weight without any abnormal condition. The second group (positive control) i.e., the diabetic control group showed that decreasing the body weight, which suggested that they are destroyed the β -cells in the pancreas, In third group i.e., EETC (200 mg kg⁻¹ b.wt.) treated group was significantly retaining the body weight to the normal condition from Alloxan action in pancreas. In fourth group as standard drug treatment as Glibenclamide (600 mg kg⁻¹ b.wt.) showed that highly significant in body weight; which were shown in Table 1.

Sansevieria senegambica Baker. (Agavaceae) treated upon Alloxan induced diabetic Wistar rats has been reported as significant hypoglycemic, hypocholesterolemic and ocular protective effects on aqueous extract. The study has been reported that may a chance to protective to lipid metabolism of the plant extract in three different doses with dose dependent activity by observed twenty-nine different flavonoids detection (Chigozie and Chidinma, 2012). Such that a familiar plant species *Terminalia chebula* also produced a significant report like hypocholesterolemic agent. Furthermore, another the study has been reported that antidiabetic activity of *Feronia limonia* and *Artocarpus heterophyllus* in Streptozotocin induced diabetic rats with reduced blood glucose level, body weight and serum cholesterol level. Since, the present study also showed that evidence, revealed and suggested that significant activity in the body weight reduction and blood glucose level (Priya *et al.*, 2012).

As wells as, the biochemical parameters were analyzed in the present study was shown in (Table 2). The effective parameters such that, blood glucose and cholesterol was taken as an important evidence for the diabetic control. Those parameters were monitoring the blood circulate the glucose and cholesterol in to the cells and producing the effects to pancreas whether altering the β -cells or damage and insulin secretion. The levels of serum lipid is usually elevated the *Diabetes mellitus* and such an elevation represents the risk factor for coronary heart disease; lowering the serum lipids concentration through dietary with or drug therapy seems to be associated with a decrease in the risk of vascular disease. The rise in blood sugar is accompanied with the increase in total cholesterol, triglycerides, phospholipids, EETC (200 mg kg⁻¹ b.wt.) and Glibenclamide (600 mg kg⁻¹ b.wt.) exhibited hypercholesterolemia and hypophospholipidemic effects (Rhoads *et al.*, 1996). In the present study the plasma insulin, serum protein, liver protein,

Table 1: Body weight of anti-diabetic activity treatment upon EETC in Wistar albino rats

Groups	Initial weight (g)	Final weight (g)	Change in body weight (g)	Significance (p-value)
Negative control	130±15.81	150±13.20	+30	0.000
Positive control (diabetic control)	150±7.58	132±8.99	-18	NS
Diabetic control with Glibenclamide	140±19.58	164±14.19*	+24	0.001
Diabetic control with EETC	150±8.45	172±8.99*	+22	0.001

Values are given as Mean±SD (n = 6 rats), At p<0.001 compared with diabetic control using DMRT, NS: Not significant, *Indicating that the dose of the drugs given were significant

Table 2: Biochemical parameters of anti-diabetic activity treatment upon EETC in Wistar albino rats

Parameters	Group I	Group II	Group III (<p value)	Group IV (<p value)
Blood glucose (mg dL ⁻¹)	98.51	38.00	108 (0.01)	90 (0.001)
Plasma insulin (μU mL ⁻¹)	35.83	14.61	31.32 (0.05)	23.69 (0.001)
Serum protein (g dL ⁻¹)	7.20	5.90	7.49 (0.001)	6.9 (0.001)
Liver protein (g dL ⁻¹)	15.14	12.98	15.18 (0.01)	14.98 (0.01)
Serum cholesterol (mg dL ⁻¹)	94.12	283.90	130.6 (0.01)	110.48 (0.001)
Liver cholesterol (mg dL ⁻¹)	360.46	790.12	342.42 (0.001)	384.89 (0.5)
Serum triglyceride (mg dL ⁻¹)	66.31	165.77	84.22 (0.5)	62.4 (0.01)
Liver triglyceride (mg 100 g tissue)	582.62	921.36	534.88 (0.1)	650.36 (NS)
Phospholipids (mg dL ⁻¹)	112.62	251.26	148.73 (0.1)	161.36 (NS)
Liver Phospholipid (mg/100 g tissue)	1380.22	2464.55	1408.16 (NS)	1436.38 (NS)
SGOT (IU L ⁻¹)	86.35	181.38	99.62 (0.01)	107.28 (0.01)
SGPT (IU L ⁻¹)	62.83	134.22	111.89 (NS)	86.91 (0.5)
Acid phosphatase (IU L ⁻¹)	7.36	8.82	7.04 (0.01)	8.16 (0.5)
Alkaline phosphatase (IU L ⁻¹)	8.94	7.18	16.00 (NS)	10.28 (0.5)
GSH (U mg ⁻¹ protein)	42.63	21.14	34.39 (0.5)	36.21 (0.1)
GPT (U mg ⁻¹ protein)	462.26	314.30	420.23 (0.1)	396.02 (NS)
GPX (U mg ⁻¹ protein)	368.20	201.80	360.40 (0.01)	342.08 (0.5)
Catalase (U mg ⁻¹ protein)	35.83	14.61	31.32 (0.5)	23.69 (NS)

The study was reported the significance of the anti-diabetic activity in the table in between the bracket, NS was referred as Non-significant. Study was carried for the six animals, only one animal was taken for the biochemical analysis and they are significantly compared with diabetic control groups. Single group variant comparison has been made in the values

ALP, GSH, GPT, GPX, CAT were decreased in the diabetic control rats, although EETC (200 mg kg⁻¹ b.wt.) and Glibenclamide (600 mg kg⁻¹ b.wt.) were retained the diabetic control to the normal levels in the above parameters when compared to diabetic controlled rats.

The rest of the parameters in the present study, blood glucose, serum and liver cholesterol, serum and liver triglycerides, serum and liver phospholipids, SGPT, SGOT and ACP were showed that increased values when compared to negative control group. The Glibenclamide and EETC treated groups were showing significant depletion in values when compared with the positive control.

Alloxan induced Diabetic rabbits were reported on Aqueous methanol extract of *Acacia nilotica* Pods on various biochemical parameters, namely blood glucose levels, total cholesterol, High Density Lipids (HDLs), triglycerides, serum glutamate oxaloacetate and pyruvate transaminase (SGOT, SGPT) and serum creatinine clearance (Ahmad *et al.*, 2008). Such that the SGOT and SGPT, Total cholesterol, triglyceride and LDL were reported significantly reduced and HDL alone increased while treating while treated with Anp, this is the evidence while treating the extract of plant material the SGOT and SGPT levels will be reduced. Since the present study also being the same condition of the reduced state of SGOT, SGPT, liver and blood cholesterol and triglycerides; suggested that the extract was reducing the diabetic condition to normal.

Reduced conditions of ALP, Total protein, Phospholipids were reported in anti-diabetic activity while treating with methanol leaf extract of *Costus pictus* (Jothivel *et al.*, 2007). The present study was evidence of the previous reported evaluation ALP, Total protein and phospholipids were reduced while treating with EETC.

In addition, the liver, kidney and pancreas cells were reported that there was any no inflammation or infiltration while treating with *Costus pictus*. Histopathological studies were

reported that the reinforced healing power to pancreas, by *Vinca rosea* extracts, as a possible mechanism of their antidiabetic activity (Ahmed *et al.*, 2010). Antidiabetic and antioxidant effect of methanol extract of *Artanema sesamoides* in Streptozotocin-induced diabetic rats also showed that the significant reduction of the diabetic condition by reducing the cell damage, abnormal tissue infiltration fatty changes and inflammation (Selvan *et al.*, 2008). Similarly, the histopathological analysis of the pancreas was showed in Fig. 1 also showed that significant changes in the EETC

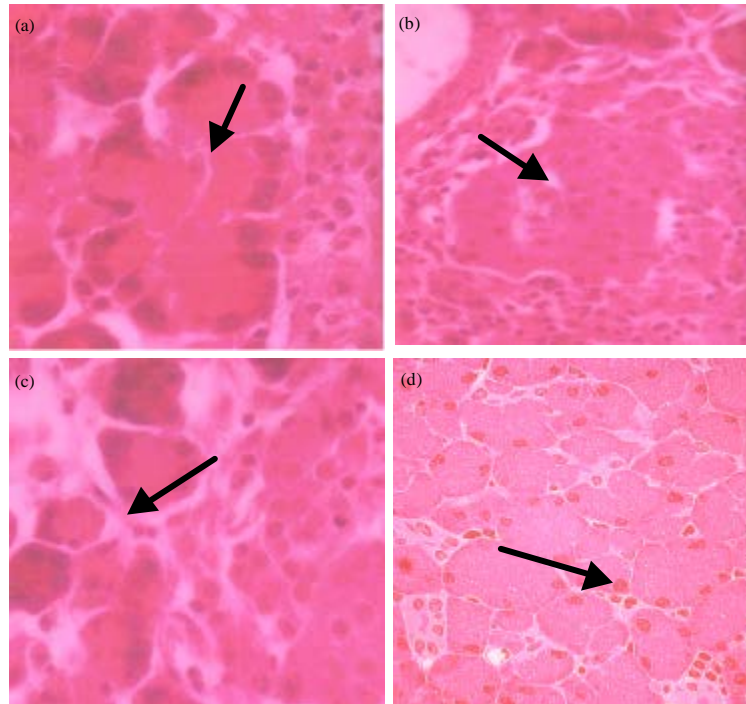


Fig. 1(a-d): Histopathological analysis of anti-diabetic activity Pancreas upon EETC fruits in Wistar Albino rats, (a) Negative control. The pancreatic cells were found that normal architecture without any damage due to the normal condition without any fatty changes or infiltration nor inflammation, 10x magnification with eosin and hematoxylin staining, (b) Diabetic control. The pancreatic cells were found that abnormal damaged architecture with inflamed cells, also, it may be a cause of β -cells damage due to the induction of Alloxan-monohydrate. 10 magnification with eosin and hematoxylin staining, (c) Diabetic control+glibenclamide. The pancreatic cells were found that normal cell structure without any damages, infiltration and inflamed cells, also, it may be reduced the dangerous of alloxan-monohydrate due to the retaining of the damaged β -cells to normal cells, 10x magnification with eosin and hematoxylin staining, (d) Diabetic control+EETC. Even the selected medicinal herb Ethanolic Extract of T Chebula (EETC) also revert the mechanism of Alloxan toxicity to the pancreatic cells to normal condition without any damage, fatty changes or inflammation. 10 magnification with eosin and hematoxylin staining

(200 mg kg⁻¹ b.wt.) and Glibenclamide (600 mg kg⁻¹ b.wt.) when compared with the diabetic control. The cells damages and infiltration of tissue, redness, fatty changes or inflammation were not found in the drugs treated groups i.e., group III and IV.

CONCLUSIONS

The present study demonstrated that a larger number of plants were screened in India and elsewhere for the anti-diabetic activity. The EETC has been confirmed that they are having potential anti-diabetic activity without any toxicity and side effects. Besides, the study confirming that the EETC having anti-diabetic activity, by having previously reported bioactive compounds present in the fruits of the *T. chebula*, the preliminary work of pharmacology may help to the further molecular analysis.

ACKNOWLEDGMENT

The authors sincere thanks to Department of Microbiology, Bharathidasan University, Tiruchirappalli-620024. Tamil Nadu, India for providing the laboratory facility for carry out the research work.

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