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Management Of Diabetes Mellitus And Associated Liver Challenges With Delonix Regia Seed Solution, Pioglitazone And Simvastatin In Streptozotocin-Induced Diabetic Rats

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Abstract: ***Pioglitazone (PG) and Simvastatin (ST) are known anti diabetic and dyslipidaemia drugs that target insulin resistance, have beneficial effects on glucose and lipid metabolism in some tissues, but more especially in the liver. Current researches are focussing on the use of plant products like Delonix regia(DR) seed for management of diabetes and its associated liver challenges. This research reports on the use of PG, ST and powdered DR seed in management of diabetes mellitus and the associated liver challenges. Seventy-two Wistar rats were divided into seven groups with group one as normal control, while groups two to seven were made diabetic with streptozotocin (60 mg/kg body weight of rat) and treated with distilled water, 100, 200, 300 (mg/kg of powdered solution of DR), 10mg/kg of PG, and 10 plus 15 mg/kg of PGST respectively for six weeks. Blood was collected at 14 days intervals and was analyzed for glucose, Aspartate Amino Transferase (AST), Alanine amino Transferase (ALT) and alkaline phosphatase (ALP). After six weeks, Streptozotocin significantly (p<0.05) increased the levels of glucose (mmol/l) from a normal level of 122.00± 2.82 to a diabetic 146.5± 2.12, liver markers AST(U/l) a diabetic level of 31.00±0.00; ALT(U/l) a diabetic level of 42.00±0.00 while ALP level 193.00±0.00. The glucose level of diabetic rats were significantly reduced (p<0.05) after six weeks to 102.50±23.33 and 98.00±0.00 in groups 4 and 5 mimicking PGZ and PGST value of 119.50±9.19 and 97.00±14.14. The AST (U/L) diabetic level (31.00±0.00) was significantly (p<0.05) reduced to 10.00±0.00, 11.50±2.12, 7.00+0.00, 13.00±0.00 and 10.00±0.00(U/L) respectively in groups 3-7. ALT also was significantly reduced (p<0.05) from a common diabetic level of 42.00±0.00 to 25.00±5.65; 17.00±0.00; 17.00±0.00; 17.00±0.00 and 38.00±2.82 after treatment with 100mg/kg, 200mg/kg , 300mg/kg of GRS, PG and PGST respectively. Delonix regia mimicked pioglitazone + simvastatin on reduction of elevated glucose, AST and ALT levels. The management was maximal and effective at 28 days and declined on 42 days, indicating that Delonix regia could be a promising source of managing diabetes and associated liver challenges.***

Keywords: Diabetes mellitus, Glucophage, Delonix regia, Pioglitazone, Simvastatin, Streptozotocin-induced,

I. INTRODUCTION

The plant botanically called *Delonix regia* is a tropical tree that is native to Madagascar now widely planted around the world in tropical and semi-tropical areas. It is generally called flamboyant or royal poinciana [1], Krishnachura, Gulmohar or Malinche [2] and Tabachine [3]. The flowers give way to flattened bean-like fruit pods (each to 24" long) [1].The pods contain the seeds that look like beans.

The leaves and seeds of *Delonix regia* are used in folk medicine for the treatment of diabetes[4].FACAE which is now acclaim to be relevant to health services globally with

about three-quarters of world population relying on plants and plant products for health care [4] accounting to thee rationale behind the designs of novel drugs from traditional medicine that offers new proposal in modern healthcare [4].

Delonix regia is implicated in the treatment of diabetes mellitus (DM) - an endocrine chronic disease characterized by hyperglycemia, hyperlipidemia, negative nitrogen balance and sometimes ketonemia [5]. DM is also a known risk factor of hepatocarcinoma [6,7], oxidative stress, inflammation, and insulin resistance [8]. Its incidence is increasing with western way of living. It is estimated that 323 million adults are affected and 5.1 million deaths recorded [9, 10] currently in the world. With currently available hypoglycemic agents, the management of DM has not shown to be improved [10]. In DM, high levels of glucose can lead to oxidative stress via glucose auto-oxidation and can damage various organs including the liver [9] which are kept in check by complex network of antioxidant defense and repair systems [11].

Recent researches has establish a close inter-relationship between inflammation and damage of the liver, insulin resistance, lipid disorders, the metabolic syndrome and the development of atherosclerosis in diabetic and non-diabetic patients resulting in the thiazolionediones (TZDs) being widely used in the treatment of type 2 diabetes [12]. Pioglitazone improves insulin sensitivity, glycemic control and dyslipidemia, hypertension and microalbumin [13]. It decreases fasting and postprandial plasm glucose levels by improving the sensitivity of hepatic and peripheral tissues to insulin [13].Simvastatin on the other hand shown improvement in the degree of oxidative stress in patients with type 2 diabetes through its effects on serum lipids and lipid peroxidation. It therefore acts as lipid-lowering agents that specifically, compitively and reversibly inhibits HMG-CoA a rate limiting step in the formation of cholesterol [14].

An agent that mimics the effects of Pioglitazone and Simvastatin will tend to points to its usefuness in liver damage. This reearch intends investigate the usefulness in the management of DM and associated liver damange of Delonix Regia seed solution whoes leaf have been reported to have maximum hypoglycemic activities which is known to contain proteins, flavonoids, tannins, phenolic compounds, glycerol, sterols and triterpenoids [15].

II. MATERIALS AND METHODS

A. ANIMALS

The experimental animals consisting of Sixty-three albino rats, weighing 125 - 145g were bred in the animal house of Department of Biochemistry University of Port Harcourt,Choba. The animals were kept under standard laboratory conditions with water and feed (Bendel feeds and Flour mill Ltd.) *ad libithum.*

B. DRUGS USED

Pioglitazone and Simvastatin were purchased from Capino pharmacy.

C. PREPARATION OF PLANT EXTRACT

The seeds of *Delonix regia* were dried by sunlight and pulverized into a fine powder. The powder was sieved and 10g dissolved in water, boiled for 10 minutes and cooled. Three doses of 100mg, 200mg and 300mg/Kg body weight were prepared from this stock using distil water as a vehicle.

D. ANIMAL TREATMENT AND DRUG ADMINISTRATION

The rats were divided into seven groups of nine (9) rats per group. Groups II to VII were made diabetic by using intraperitoneal injection of 60 mg/kg body weight of rat. Group I served as normal control and was given only feed and water. Group II served as Diabetic control and was not treated either with the plant or drugs; Groups III-V received the three different doses of *Delonix regia* seed solution; while Groups VI and VII received 15 mg/kg body wt of Pioglitazone and 15mg/kg body wt + 10mg/kg body wt of Pioglitazone and Simvastatin respectively. The treatment was done daily and at weekly interval, three rats were sacrificed from each group and blood was collected for analysis. The experimental design is further explained below

Group I: Normal Control; Non – diabetic and No Treatment

Group II: Diabetic control - Diabetic and No Treatment

Group III Diabetic and Treated with Extract (100mg/kg body weight of rat)

Group IV: Diabetic and treated with Extract (200mg/kg body weight of rat)

Group V: Diabetic and treated with Extract (300mg/kg body weight of rat)

Group VI: Diabetic and treated with Pioglitazone (15mg/kg body weight of rat)

Group VII: Diabetic and treated with Pioglitazone + Simvastatin (15 mg/kg + 10 mg/kg body weight of rat)

E. COLLECTION OF BLOOD SAMPLE

The rats were sacrificed painlessly under chloroform anesthesia. Blood was collected at weekly intervals by cardiac puncture, centrifuged at 3000rpm for 10minutes and serum was collected for further analysis.

F. DETERMINATION OF BIOLOGICAL VARIABLES

The serum activities were determined using the spectrophotometric methods of Monica [16], for Glucose; Reitman and Frankel [17] for Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) and GSCC [18] method for Alkaline phosphatase (ALP).

G. STATISTICAL ANALYSIS

The data obtained were expressed as Mean + Standard Error of Mean (M±SEM). The significance of difference among the various treated groups and control group were analyzed by means of one-way Analysis of Variance ANOVA

followed by Dennett's multiple comparison tests (San Diego, CA.USA). The level of significance was set at p <0.05.

III. RESULTS AND DISCUSSION

Table 1 shows the effects *Delonix regia* seed solution on glucose level in streptozotocin-induced diabetes. There was a significant increase (p <0.05) in glucose level after 42hrs of streptozotocin induction from a normal range level of 114.00±12.78 to 122.00±2.84 to a diabetic range value of 146.5 ±2.12 148.5±2.82 mg/dl. Group III-V glucose level were significantly (p <0.05) reduced within a range of 98.00± 0.00 to 135.50 ± 9.19 when compared to the normal level. The level of glucose was seen to be significantly reduced (p <0.05) as the concentration of the extract was increasing and also as the time in weeks, increased, hence 100g/kg(135.5±9.19), 200mg/kg(102.5±23.33) and 300mg/kg(98.00±0.00 body weight. *Delonix regia* seed solution at 300mg/kg(98.0±0.00) was able to reduce the glucose level to almost the same level with that of 15mg/kg of Pioglitazone+ 10mg Simvastatin(97.0±14.14)

Group	Treatment	After 14days	After 28days	After 42days
1	Normal rats(non diabetes)	114.0±12.78^{ab}	125.0± 2.82^{ab}	122.0± 2.82^{a}
2	Diabetic rats(no treatment)	146.5±2.12^{ab}	148.5±2.12^{b}	147.5±2.12^{b}
3	Diabetic rats(Treatment with 100mg/kg of *Delonix regia*)	134.5±4.95^{a}	136.0±1.41^{ab}	135.5±9.19
4	Diabetic rats(Treatment with 200mg/kg of *Delonix regia*)	107.5±3.53^{b}	105.0±2.82^{b}	102.5±23.33^{b}
5	Diabetic rats(Treatment with 300mg/kg of *Delonix regia*)	125.0±4.24^{b}	123.0±8.48^{b}	98.0±0.00
6	Diabetic rats(Treatment with 15mg/kg of Pioglitazone)	126.5±0.70^{b}	120.0±4.24^{b}	119.5±9.19
7	Diabetic rats(Treatment with 15mg/kg of Pioglitazone + 10mg simvastatin)	127.5± 0.70^{ab}	78.00±0.00^{ab}	97.0±14.14^{b}

[a] show significant (p<0.05) difference when group 1 is compared with other group

[b] show significant (p<0.05) difference when group 2 is compared with other group

Table 1: Effect of Delonix regia powdered seed solution on glucose level(mmol/l) in streptozotocin induced diabetic rats

Table 2 shows the effects of *Delonix regia* seed solution, and standard drugs on Aspartate transaminase(AST) level (mg/dl) in streptozotocin-induced Wister rats after 6 weeks (42 days). Significant(p <0.05) increase was observed in the level of AST from normal of 9.00± 0.00 at 42 days to the level of 31.00± 0.00 in the diabetic rats. The treatment with the DR produced the significant (p <0.05) result of 100mg(10.00± 0.00), 200mg(11.50± 2.19) and 300mg(7.00± 0.00).There was significant(p <0.05) mimics of the standard drugs of 15mg/kg of pioglitazone (13.00±0.00) and 15mg/kg of pioglitazone + 10mg simvastatin (10.00±0.00) mmol/l

Group	Treatment	After 14days	After 28days	After 42days
1	Normal rats(non diabetes)	7.00±0.00^{ab}	9.00±0.00^{ab}	9.00±0.00^{ab}
2	Diabetic rats(no treatment)	25.00±8.48^{ab}	19.00±0.00^{ab}	31.00±0.00^{ab}
3	Diabetic rats(Treatment with 100mg/kg of *Delonix regia*)	18.00±7.07^{b}	31.00±0.00^{a}	10.00±0.00^{a}
4	Diabetic rats(Treatment with 200mg/kg of *Delonix regia*)	25.00±2.82^{b}	29.00±2.82^{a}	11.50±2.12^{a}
5	Diabetic rats(Treatment with 300mg/kg of *Delonix regia*)	27.00±0.00^{b}	29.00±2.82^{a}	7.00±0.00^{ab}
6	Diabetic rats(Treatment with 15mg/kg of pioglitazone)	21.00±2.82^{b}	29.00±2.82^{a}	13.00±0.00^{a}
7	Diabetic rats(Treatment with 15mg/kg of pioglitazone + 10mg simvastatin)	25.00±2.82^{b}	27.00±0.00^{a}	10.00±0.00^{ab}

[a] show significant (p<0.05) difference when group 1 is compared with other group

[b] show significant (p<0.05) difference when group 2 is compared with other group

Table 2: Effect of Delonix regia powdered seed solution on Aspartate transaminase (AST) level (mmol/l) in streptozotocin-induced diabetic rats

Table 3 shows the effects of *Delonix regia* seed solution, and standard drugs on Alanine Aminotransaminase level (mg/dl) in streptozotocin-induced Wister rats after 6 weeks (42 days). The significant (p <0.05) increase of the Alanine Aminotransaminase level of 42.00± 0.00 at day 42, of diabetic rats being the reduced to 17.00± 0.00 by the 200mg and 300mg of the stock solution DR while the 100mg/gm reduction was 25.00± 5.63.The standard drug Pioglitazone (15mg/kg body wt) recorded a level of 17.00± 0.00 while PZ + ST showed 38.00± 2.82 mmol/l at day 42.

Group	Treatment	After 14days	After 28days	After 42days
1	Normal rats(non diabetes)	06.00±2.82[ab]	34.00±0.00[ab]	18.50±9.19
2	Diabetic rats(no treatment)	34.00±12.72[ab]	39.00±0.00[ab]	42.00±0.00
3	Diabetic rats(Treatment with 100mg/kg of *Delonix regia*)	30.00±2.82[a]	36.50±3.53	25.00±5.65
4	Diabetic rats(Treatment with 200mg/kg of *Delonix regia*)	32.00±5.65[a]	34.00±0.00[a]	17.00±0.00
5	Diabetic rats(Treatment with 300mg/kg of *Delonix regia*)	33.00±5.65[a]	29.00±0.00[ab]	17.00±0.00
6	Diabetic rats(Treatment with 15mg/kg of pioglitazone)	38.00±0.00[a]	34.00±0.00[a]	17.00±0.00
7	Diabetic rats(Treatment with 15mg/kg of pioglitazone + 10mg simvastatin)	10.00±2.82[a]	36.50±3.53	38.00±2.82

[a] *show significant (p<0.05) difference when group 1 is compared with other group*
[b] *show significant (p<0.05) difference when group 2 is compared with other group*

Table 3: Effect of Delonix regia powdered seed solution on Alanine Aminotransaminase level(mmol/l) in streptozotocin-induced diabetic rats

Table 4 shows the effects of *Delonix regia* seed solution, and standard drugs on Alkaline Phosphatase (ALP) level (mg/dl) in streptozotocin-induced Wister rats after 6 weeks (42 days). There were significant (p <0.05) increases in ALP level from the normal range of 105.00± 32.52 – 108.50± 19.09 to diabetic range level of 139.00±50.91 to 193.00± 0.00 after the 42 days treatment with Streptozotocin. The diabetic range of 139.00±50.91 to 193.00± 0.00 were reduced to 280.00± 1.72, 103.00±1.41 and 173.00± 0.00 by 100mg, 200mg and 300mg/kg body of *Delonix regia* seed solution respectively after the 42 days treatment. This mimics the standard drugs 15mg/kg of pioglitazone (103.00±0.00) and 15mg/kg of pioglitazone + 10mg simvastatin (99.00±0.00) mmol/l.

Group	Treatment	After 14days	After 28days	After 42days
1	Normal rats(non diabetes)	105.00±32.52[b]	109.50±75.66	108.50±19.09[b]
2	Diabetic rats(no treatment)	139.00±50.91[a]	175.00±0.00[a]	193.00±0.00[a]
3	Diabetic rats(Treatment with 100mg/kg of *Delonix regia*)	304.50±3.53[ab]	331.50±7.05[a]	280.00±1.72[ab]
4	Diabetic rats(Treatment with 200mg/kg of *Delonix regia*)	128.50±4.44	117.00±7.78	103.00±1.41
5	Diabetic rats(Treatment with 300mg/kg of *Delonix regia*)	157.00±36.77	142.50±10.60	173.00±0.00
6	Diabetic rats(Treatment with 15mg/kg of pioglitazone)	305.50±92.63[ab]	188.50±109.60	103.00±0.00
7	Diabetic rats(Treatment with 15mg/kg of pioglitazone + 10mg simvastatin)	191.00±72.12	168.50±13.43	99.00±0.00

[a] *show significant (p<0.05) difference when group 1 is compared with other group*
[b] *show significant (p<0.05) difference when group 2 is compared with other group*

Table 4: Effect of Delonix regia powdered seed solution on Alkaline Phosphatase (ALP) level(mmol/l) in streptozotocin-induced diabetic rats

In this study, the mean glucose level (mg/dl) of untreated diabetic rat (diabetic control) (122.00±2.82) increased significantly, (p<0.05) after day 42 with a level of 147.5± 2.12 mmol/l. This confirms the necrosis of pancreatic beta cell by streptozotocin[19]. With the treatment at day 42 the 100mg/kg of DR(135.5± 9.19), 200mg/kg(102.5± 23.5) and 300mg/kg(98.0± 0.00) mmol/l. It could be inferred that *Delonix regia* had ameliorating effect on hyperglycemic glucose level as the concentration especially with increasing concentration of DR significantly (p<0.05)[20]. It is speculated that Sterols, triterpeniods or glycosides presents in the plant extracts may be responsible for the observed activities [21].

Delaney *et. at.* [22] reported the hepatic toxicity and membrane labializing effect on organ of *Delonix regia.* In this study there was significant (p<0.05) elevation in the untreated diabetic rats in the level of liver enzymes (AST, ALT, and ALP) across the weeks compared to the normal rats and other groups respectively in conformity with the report of Shanmukha *et al* of 2011[23].In the report of by Hanefeld *et al* [12] the discussed the ability of Pioglitazone to reduce insulin resistance and the additive anti-inflammatory effects of to simvastatin in non-diabetic subjects with cardiovascular diseases. This study affirms the synergistic effects of Pioglitazone and Simvastatin in the treatment of liver damage and its associated complications which is mimicked by the increasing concentration of DR. The presence of flavonoids

may be responsible for piloting these activities [1, 4,22]. A report by Videla [24], indicated a rapid mobilization of liver-ALP in blood, resulting increase serum levels at early stages of liver damage.

Similarly, the extract administration decreases the elevated Alanine Transferase Level. This is attributed to the ability of the antioxidant supplement to balance off free radicals generated hence preventing peroxidation of the lipid components of the cell membrane. Disruption of membrane integrity is a common causative factor attributed to increase release or leakage of cellular contents [25].This finding is was consistent with the reports of Li *et al*. [26].

The result of the treatment at day 42 in the treatment of Pioglitazone combination Simvastatin is indicative of likely toxicity as indicated with the elevated level of Alanine Aminotransferase. This could be the reason for the gradual withdrawal of Simvastatin in the treatment of liver damage due to the toxicity [27].

IV. CONCLUSION

Delonix regia was shown to possess anti diabetic properties and able to ameliorate liver hepatotoxicity effects.

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