



Anti-hyperglycaemic, Anti-dyslipidaemic and Hepatoprotective Effects of the Polyherbal Mixture Diarth in Alloxan-induced Diabetic Rats

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Authors' contribution

This work was carried out in collaboration among all authors. Author ONB designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Authors KNEA and CO wrote the protocol and managed the literature searches. Author FCE managed the analyses of the study. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JOCAMR/2020/V9i330145

Editor(s):

(1) Assist. Prof. Suma B. V., Ramaiah University of Applied Sciences, India.

Reviewers:

(1) Shailja Puri, India.

(2) Dashputre Neelam Laxman, Savitribai Phule Pune University, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/57368>

Original Research Article

Received 09 March 2020

Accepted 14 May 2020

Published 26 May 2020

ABSTRACT

Aim: This study evaluates the anti-hyperglycaemic, anti-dyslipidaemic and hepatoprotective effects of the polyherbal mixture diarth, in alloxan-induced diabetic rats.

Methodology: A total of 35 male Wistar albino rats weighing between 120-140 g were used for this study. Diabetes was induced by a single intraperitoneal injection of freshly prepared alloxan-monohydrate (140 mg/kg body weight). Fasting plasma glucose (FPG) was determined using the glucose oxidase method. Total Cholesterol (TC), Triglyceride (TG) and High density lipoprotein cholesterol (HDL-C) were determined using enzymatic methods. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald's equation. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined using Reitman-Frankel method,

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while alkaline phosphatase (ALP) was determined using the colorimetric phenolphthalein method. Phytochemical analysis was done on the herbal mixture, using classical methods.

Results: The results revealed the presence of the phytochemicals saponins, alkaloids, cardiac glycosides, flavonoids and tannins in the polyherbal mixture diarth. The results revealed significantly lower FPG levels in the negative control and treatment groups compared to the diabetic control. FPG level was significantly higher in the glibenclamide treated group, but showed no significant differences in the diarth group and the combination group (glibenclamide + diarth), compared to negative control. TC levels in the diabetic control was significantly higher compared to the negative control and treatment groups. There were no significant differences in TC levels in the negative control and the treatment groups. The diabetic control had significantly higher TG level compared to the negative control. TG level in the glibenclamide treated group was not significantly different from that of the diabetic control. TG level in the diarth treated group was significantly lower than the diabetic control, but also significantly higher than that of the negative control. TG levels in the combination group (diarth + glibenclamide) was significantly lower than the diabetic control, and showed no significant difference compared to the negative control. The negative control and treatment groups had significantly higher HDL-C levels compared to the diabetic control. The treatment groups showed no significant difference in HDL-C levels, compared to the negative control. The negative control and treatment groups had significantly lower LDL-C levels compared to the diabetic control. The treatment groups showed no significant difference in LDL-C levels, compared to the negative control. The results show significantly elevated ALT, AST and ALP in the diabetic rats compared to the negative control and treatment groups. The treatment groups showed no significant differences in ALT and AST levels compared to the negative control.

Conclusion: 140 mg/kg body weight of alloxan produced significant diabetes in the Wistar rats with dyslipidaemia and elevated liver enzyme levels. Treatment with the polyherbal mixture diarth showed anti-hyperglycaemic, anti-dyslipidaemic and hepatoprotective effects. The effects were equipotent compared to treatment with glibenclamide, thus could be incorporated in the management of diabetes.

Keywords: *Diabetes mellitus; hyperglycaemia; complementary and alternative medicine; diarth; pax herbal; glibenclamide; dyslipidaemia; liver enzymes; phytonutrients; alloxan.*

1. INTRODUCTION

The use of complementary and alternative medicine (CAM) has become a common practice and a mainstay in the management of diabetes mellitus, one of the most important diseases worldwide. Most patients even resort to self-medication and polypharmacy. This is so because of the disease burden, cost and dissatisfaction in the use of the current conventional therapies [1,2]. However, there is the concern of safety and efficacy in the use of CAM, especially in Nigeria where there is a lack of regulation of CAM use and its integration into the mainstream health care systems [3]. This study looks at the efficacy and safety in the use of an anti-diabetic herbal mixture, thus evaluates the anti-hyperglycaemic, anti-dyslipidaemic and hepatoprotective effects of the polyherbal mixture diarth, in alloxan-induced diabetic rats.

2. MATERIALS AND METHODS

2.1 Experimental Animals

A total of thirty five (35) male Wistar rats weighing between 120 to 140 g were used for the

study. The rats were housed in standard cages at regulated room temperature, with controlled 12 hour light-dark cycles, and allowed access to feed and water *ad libitum*. The rats were allowed to acclimatize for two (2) weeks prior to the commencement of study.

2.2 Drugs

A commonly used anti-diabetic herbal mixture diarth was used for the study. Diarth is manufactured by Pax Herbal Clinic and Research Laboratories, Nigeria. Glibenclamide, a sulfonylureas and a standard anti-diabetic drug was also used for the study. It was manufactured by Glanil Pharmaceuticals, Nigeria.

2.3 Acute Toxicity Study

Acute Toxicity Study was done by the fixed dose procedure [4], using a group of 3 rats. 10 ml/kg body weight of diarth was orally administered to each of the rats. The rats were then observed for signs of toxicity for 48 hours. After observation, there were no signs of toxicity, hence the polyherbal mixture diarth was deemed safe up to

a dose of 10 ml/kg body weight. Glibenclamide is a standard anti-diabetic drug, and the dose was translated from the human dose.

2.4 Dose Calculation

2.4.1 Diarth

The daily dose was extrapolated from the manufacturers' dose of 180 ml/70 kg body weight.

A rat of 1 kg would require; $1/70 \times 180$ [4,5] = 2.57 ml/kg/day.

2.4.2 Glibenclamide

The administered rat dose was extrapolated from the human daily dose [6] as shown below:

Human daily dose is 1 tablet (5 mg) twice daily, which is 10 mg/day.

Rat dose (mg/kg) = Human daily dose \times 0.018 \times 5

= $10 \times 0.018 \times 5$

= 0.9 mg/kg body weight

2.5 Study Design and Diabetes Induction

The rats were weighed and grouped into 5 groups of 7 rats each. Diabetes was induced by a single intraperitoneal injection of freshly prepared alloxan (140 mg/kg body wt.) dissolved in physiological saline, after a 6 hour fast. Diabetes was confirmed after 48 hours in all the rats, with fasting blood glucose levels above 14 mmol/L (250 mg/dl) [7]. Treatments (drugs) were administered daily according to the groupings by means of oral gavage for 28 days.

Group 1: Negative control group. Injected only physiological saline intraperitoneally

Group 2: Diabetic control

Group 3: Diabetic rats treated with glibenclamide.

Group 4: Diabetic rats treated with diarth.

Group 5: Diabetic rats treated with the combination of diarth and glibenclamide.

2.6 Reagents and Biochemical Analyses

All reagents were commercially purchased and the manufacturer's standard operating procedures strictly followed. Quality control (QC) samples were run together with the biochemical analysis. Alloxan was gotten from Qualikems Fine Chem Pvt Ltd, India. Fasting plasma glucose (FPG) was determined using Glucose oxidase method [8], as modified by Randox Laboratories Limited (UK). Total Cholesterol (TC) was determined by enzymatic method [9], as

modified by Randox laboratories limited (UK). Triglyceride was determined by enzymatic method [10], as described by Randox laboratories limited (UK). High Density Lipoprotein Cholesterol (HDL-C) was determined by enzymatic method [11], as modified by Randox laboratories limited (UK). Low Density Lipoprotein Cholesterol (LDL-C) was calculated from the Friedewald's equation [12]. The liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined using the Reitman-Frankel method [13], as modified by Randox laboratories limited (UK). Alkaline phosphatase (ALP) was determined using the Colorimetric endpoint method [14] as modified by Randox laboratories limited (UK). Qualitative phytochemical analysis was done on the herbal mixture using classical methods [15].

2.7 Statistical Analysis

Data was analysed using Graph Pad Prism version 8.0.2. Groups were compared using one way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Results were considered statistically significant at 95% confidence interval ($p \leq 0.05$). Values are expressed as Mean \pm SD.

3. RESULTS AND DISCUSSION

Table 1 shows the results of phytochemical analysis. The results revealed the presence of the phytochemicals saponins, alkaloids, cardiac glycosides, flavonoids and tannins in the polyherbal mixture diarth in variable amounts. These phytonutrients have the ability to affect diabetic pathways and could be responsible for the alteration of biochemical parameters [16].

Table 2 shows results of fasting plasma glucose (FPG) and lipid profile parameters of the rats after treatment. The results revealed significantly lower ($P < .05$) FPG levels in the negative control and treatment groups compared to the diabetic control. FPG level was significantly higher ($P < .05$) in the glibenclamide treated group, but showed no significant differences ($P > 0.5$) in the diarth group and the combination group (glibenclamide + diarth), compared to negative control. This implies treatment with the polyherbal diarth and the combination treatment were more effective than treatment with glibenclamide alone in reducing glucose levels to baseline control values. Plant and plant nutrients

have shown different degree of efficacies in both experimental and clinical studies by producing different glycemc responses. The results agree with the works of Sarfraz et al. [17], in which glibenclamide and the aqueous extract of black pepper and ajwa seed significantly reduced glucose levels in alloxan-induced diabetic rats. Al-Omaria et al. [18] reported that a concurrent treatment of ginger and glibenclamide significantly reduced blood glucose levels, compared to when glibenclamide was used alone in STZ-induced diabetic rats.

Total cholesterol (TC) levels in the diabetic control was significantly higher ($P < .05$) compared to the negative control and treatment groups. Also there were no significant differences ($P > .05$) in TC levels in the negative control and the treatment groups. This implies the treatment with the polyherbal diarth, glibenclamide and their combination were effective in reducing TC levels to normal control levels.

The diabetic control had significantly higher ($P < .05$) TG level compared to the negative control, indicating an increased rate of lipolysis in the diabetic rats. TG level in the glibenclamide treated group was not significantly different ($P > .05$) from that of the diabetic control. TG level in the diarth treated group was significantly lower ($P < .05$) than the diabetic control, but also significantly higher ($P < .05$) than that of the negative control. TG levels in the combination group (diarth + glibenclamide) was significantly lower ($P < .05$) than the diabetic control, and showed no significant difference ($P > .05$) compared to the negative control. This implies treatment with glibenclamide had no effect on elevated TG levels, also, diarth was not as effective as it did not return the TG levels to normal control levels. However, the combination proved very effective in reducing TG levels to normal control levels, showing drug-herb synergy, in which the polyherbal mixture diarth potentiated the effect of glibenclamide.

Table 1. Qualitative Phytochemical Analysis of the Herbal Mixture Diarth

Phytochemicals	Presence
Saponins	+
Alkaloids	++
Terpenes	-
Coumarins	-
Cardiac glycosides	++
Flavonoids	+
Polyphenols	-
Tannins	++
Phlobatannins	-

+ Present, - Not present

Table 2. Effect of treatment on fasting plasma glucose (FPG) and lipid profile parameters of the rats

Groups	FPG (mmol/l)	TC (mmol/l)	TG (mmol/l)	HDL-C (mmol/l)	LDL-C (mmol/l)
Group 1 (Negative Control)	5.36 ± 0.50 ^b	2.33 ± 0.13 ^b	0.74 ± 0.10 ^b	1.63 ± 0.05 ^b	0.36 ± 0.08 ^b
Group 2 (Diabetic Control)	17.14 ± 2.72 ^a	3.57 ± 0.44 ^a	1.29 ± 0.05 ^a	1.19 ± 0.15 ^a	1.79 ± 0.54 ^a
Group 3 (Gli)	7.57 ± 0.95 ^{a,b}	2.71 ± 0.53 ^b	1.10 ± 0.15 ^a	1.51 ± 0.10 ^b	0.69 ± 0.12 ^b
Group 4 (Dia)	7.42 ± 0.69 ^b	2.43 ± 0.19 ^b	0.99 ± 0.16 ^{a,b}	1.58 ± 0.21 ^b	0.40 ± 0.11 ^b
Group 5 (Gli + Dia)	6.16 ± 0.84 ^b	2.27 ± 0.17 ^b	0.72 ± 0.15 ^b	1.43 ± 0.04 ^b	0.52 ± 0.14 ^b
p-value	< 0.0001	< 0.0001	< 0.0001	0.0002	< 0.0001
F-value	68.59	12.96	17.80	9.41	14.35
Remark	S	S	S	S	S

^a – significantly different from negative control, ^b – significantly differently different from diabetic control, TC – total cholesterol, TG – triglycerides, HDL-C – high density lipoprotein cholesterol, LDL-C- low density lipoprotein cholesterol, Gli – Glibenclamide, Dia – Diarth

The negative control and treatment groups had significantly higher ($P<.05$) HDL-C levels compared to the diabetic control. Also the treatment groups showed no significant difference ($P>.05$) in HDL-C levels, compared to the negative control. This implies the reduced HDL-C caused by diabetes was effectively improved by the treatments to normal control levels.

The negative control and treatment groups had significantly lower ($P<.05$) LDL-C levels compared to the diabetic control. Also the treatment groups showed no significant difference ($P>.05$) in LDL-C levels, compared to the negative control. This implies the elevated LDL-C caused by diabetes was effectively reduced by the treatments to normal control levels.

From this study, the diabetic rats present with diabetic dyslipidaemia, having significantly elevated TC, TG, LDL-C and reduced HDL-C. This was however resolved by the administration of the anti-diabetic treatments. Diabetes is not only associated with defective glucose metabolism, but also disturbances in lipid metabolism, which mostly presents as the characteristic diabetic dyslipidaemia and is a risk factor for cardiovascular disease [19]. Apart from the changes in the concentration of the different lipoproteins, their content and composition could also be affected. Hypertriglyceridaemia and the presence of triglyceride-rich lipoproteins are thought to play a central role in the disease process and the presentation of diabetic dyslipidaemia [20]. The findings are in agreement with our earlier work, Briggs et al. [21], in which STZ-induced diabetes produced significant dyslipidaemia in experimental rats. Gupta et al. [22] found that treatment with a polyherbal plant extract and treatment with glibenclamide

significantly reduced total cholesterol and triglyceride levels when compared to the diabetic control. Treatment with glibenclamide was more effective in reducing the lipid levels than the polyherbal plant extract. The lipid levels however, did not return to normal control values. Arshadi et al. [23] reported significant improvements in lipid profile after treatment with fenugreek extract and glibenclamide in STZ-induced diabetic rats, when compared to the diabetic control.

Table 3 shows the results of the liver enzymes ALT, AST and ALP of the rats after treatment. The results show significantly elevated ($P<.05$) ALT, AST and ALP in the diabetic rats compared to the negative control and treatment groups. The liver has been associated with diabetes related oxidative stress. Injury to the liver is a common occurrence in patients with uncontrolled diabetes, with biochemical, histopathological and physiological changes [24]. The treatment groups showed no significant differences ($P>.05$) in ALT and AST levels compared to the negative control. This implies administration of diarth, glibenclamide and their combination effectively reduced the elevated liver enzymes ALT and AST in the diabetic rats. Glibenclamide effectively reduced ALP levels to normal control levels. Treatment with the polyherbal diarth and the combination of diarth and glibenclamide reduced ALP levels, but not to control levels. The results reveal the polyherbal diarth, glibenclamide and their combination had hepatoprotective effect on the liver of the diabetic rats.

The results are in consonance with the works of Khajuria et al. [25], in which experimental induced diabetes significantly elevated levels of transaminases (AST and ALT) and phosphatases (ALP and ACP) in rats. The results also agree with the works of Briggs et al. [26], in

Table 3. Effect of treatment on the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) levels of the rats

Groups	ALT (IU/l)	AST (IU/l)	ALP (IU/L)
Group 1 (Negative Control)	8.6 ± 0.79 ^b	42.63 ± 5.81 ^b	46.86 ± 2.27 ^b
Group 2 (Diabetic Control)	12.37 ± 1.55 ^a	61.10 ± 4.57 ^a	71.90 ± 4.49 ^a
Group 3 (Gli)	9.50 ± 1.43 ^b	45.86 ± 6.53 ^b	43.41 ± 3.53 ^b
Group 4 (Dia)	8.79 ± 1.17 ^b	42.96 ± 4.57 ^b	57.53 ± 3.65 ^{a b}
Group 5 (Gli + Dia)	9.90 ± 1.04 ^b	44.87 ± 3.72 ^b	82.45 ± 4.70 ^{a b}
p-value	< 0.0001	< 0.0001	< 0.0001
F-value	10.65	13.68	138.0
Remark	S	S	S

^a – significantly different from negative control, ^b – significantly differently from diabetic control, Gli – Glibenclamide, Dia – Diarth

which treatment with a polyherbal capsule glucoblock and glibenclamide had equipotent hepatoprotective effect and restored liver enzyme levels to normal, as well as improving liver histology. Otunola & Afolayan [27] found that glibenclamide significantly reduced levels of the liver enzymes ALP, AST, ALT, gamma glutamyltransferase (GGT) and cholinesterase in diabetic rats. Also, administration of a polyherbal mixture brought about equipotent results as compared to glibenclamide treated rats.

4. CONCLUSION

140 mg/kg body weight of alloxan produced significant diabetes in the Wistar rats with dyslipidaemia and elevated liver enzyme levels. Treatment with the polyherbal mixture diarth and its combination with glibenclamide showed anti-hyperglycaemic, anti-dyslipidaemic and hepatoprotective effects, effectively resolving the lipid and liver disturbances associated with diabetes. The polyherbal mixture diarth was effective, had equipotent effects compared to glibenclamide, and could be incorporated in the management of diabetes.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written animal ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:

The peer review history for this paper can be accessed here:
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