Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(5):310-318

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Evaluation of the quality and *in vivo* therapeutic efficacy of a generic Glimepiride manufactured in Algeria, compared to the brand name drug Amarel on alloxan diabetic rats

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ABSTRACT

The present study aims to evaluate physicochemical characteristics and the effectiveness of pharmacological effects of a Glimepiride generic product, compared to its originator Amarel a sulfonylurea used to treat type 2 diabetes mellitus. Two doses 2 and 4 mg per day were tested on male albino rats diabetics with alloxan. Body weights, glycemia, HbA1c, lipid profile, total protein, the activity of certain enzymes and some renal parameters were determined. The results showed that physicochemical characteristics are compliant with standards of the American Pharmacopeia compared with the used reference substance. However, the biological study revealed a dose-dependent effect of Amarel on body weights, blood glucose and lipid profile of rats during and after the treatment, which was not obtained with the generic. Total protein and enzymes activities of serum transaminases, amylase and lipase were almost identical in groups treated with 4 mg of originator and generic. The 2 mg dose has not exerted the expected therapeutic effect. These results show that the studied generic exhibited less efficacy than the originator despite compliance of physicochemical characteristics. A supply of the generic with the aqueous extract of a local medicinal plant (Zygophyllum cornutum) was performed where the results of measuring blood glucose before and after sacrifice of rats were similar to those of healthy controls. No significant difference was recorded for renal parameters in all treated groups.

Keywords: Generic; Branded drug; Glimepiride; Alloxan diabetes.

INTRODUCTION

Type 2 diabetes, a chronic widespread disease, is one of the major challenges of the 21st century in terms of health and development, WHO estimates that diabetes, has reached critical levels, each year, not less than four million people die of diabetes and about ten million are suffering from other disabilities and life-threatening complications [1]. The goal of treatment is to target glycemic control by maintaining hemoglobin glycated (HbA1c) as close to normal as possible while avoiding hypoglycemia.

Glimepiride, an oral sulfonylurea, indicated for the treatment of type 2 diabetes, it acts by stimulating the release of insulin in β cells of the pancreatic islets. This action is not glucose-dependent, it can lead to hypoglycemia. Stimulation occurs by closing the potassium channels of the β cell membrane, allowing the opening of calcium channels and the entry of calcium into the cell, thereby stimulating insulin secretion. Glimepiride also increases the number of active glucose transport molecules, the sensitivity of extra-pancreatic tissue is then raised (adipocytes, myocytes) and the speed of action of glucose slowed. Finally, it decreases the uptake of insulin by the liver by inhibiting gluconeogenesis [2].

Although the generic of a drug (originator or original molecule), are considered by the legislation as a medication that has the same qualitative and quantitative composition in active ingredient, the same pharmaceutical form, and

which the bioequivalence with the branded name product is demonstrated by bioavailability studies [3]. The effectiveness of these drugs is still questioned by physicians, as well as by patients; however, their prescription is increasing worldwide [4]. In addition, due to the high cost of drugs, Algeria, like all developing countries, has opted for generic drugs, by importing or producing these drugs, instead of original medicines protected by patents in developed countries [5].

This study aims to verify the antidiabetic effect of a glimepiride generic product, manufactured by a national pharmaceutical company and marketed in Algeria, and to evaluate its effectiveness in two different doses, recommended in glimepiride dosage, 2 and 4 mg per day, compared to the brand Amarel. This, leads to confirm the supposed effect of generic and to eliminate doubt on their supposed lack of efficacy compared to the originator [6], it will permit doctors to prescribe and patients to use generic drugs instead original drugs with confidence and avoid unnecessary costs, which will allow access to treatment for the poorest patients.

EXPERIMENTAL SECTION

Pharmaceuticals

In this study, we used Amarel the branded product of the molecule glimepiride and one of its generic manufactured in a national Algerian company, the two products were commercially purchased.

Biological material

Wistar albino male rats (180 - 200 g) were purchased from Pasteur institute of Algiers. They were separated and divided into groups of 6 rats per cage with access *ad libitum* to water and a standard diet for rats (UAB: National unit of animal feed, Bejaia). They were also kept and maintained under laboratory conditions of temperature and light (24 ± 1°C and 12 h light/dark cycle) respectively and strict hygiene for a few days, for acclimatization. The experiments were performed according to the guidelines of the Guide for Care and Use of Laboratory Animals [7].

Laboratory quality control testing

The determination of the physicochemical properties of the two drugs, Amarel and the generic, were performed according to the American Pharmacopoeia (Active ingredient assay, dissolution test and disintegration time) [8, 9].

Assay: The analysis was performed on Waters e2695 HPLC system equipped by a binary pump, an UV/Vis Waters 2489 Detector and column (4mm x 12.5 cm, packing L1). The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Mobile phase consisted of phosphate buffer at pH of 2.1 to 2.7 and acetonitrile at equal volumes. The diluent was a mixture of acetonitrile and water (9:1). A standard solution of glimepiride reference standard (RS) at 0.1 mg/ml concentration was used as reference. Assay preparation: five Tablets were transferred into a suitable volumetric flask to prepare a solution of approximately 0.1 mg/ml of glimepiride. 10 % of the volume of the flask was filled with water. About 70 % of the volume of the flask of acetonitrile was added. The samples were sonicated in a water bath for 5 to 10 minutes with occasional shaking. Acetonitrile was added to volume and the sample was mixed and filtered. 10 µl of standard solution and samples were injected separately into the chromatograph at 1 ml/min flow rate and the eluent was measured at 228 nm. The percentage of the labeled amount of glimepiride (C24H34N4O5S) in the portion of Tablets taken was calculated by the formula: $\mathbf{100(}C_S / C_U\mathbf{)(}R_U / R_S\mathbf{)}$. In which $\mathbf{C_S}$: the concentration, in mg/ml, of glimepiride in the Standard solution; $\mathbf{C_U}$: the concentration of glimepiride in the sample; and $\mathbf{R_U}$ and $\mathbf{R_S}$ are the peak responses for glimepiride of the sample and the Standard solution, respectively.

***In vitro* dissolution test:** The dissolution test was carried out according to USP Dissolution Test 1. The tablets were disposed separately in pH 7.8 phosphate buffer; 900 ml for 15 min at 37±0.5 °C at 75 rpm, using SOTAX AT 7 Smart 1022-197 Dissolutest. The standard solution was prepared as recommended in USP monographs to get a solution of 0.75 µg/ml of glimepiride RS. After 15 min 10 ml of sample was withdrawn from the dissolution medium and was centrifuged for 5 min at 2500 rpm. To 3ml of the supernatant, 7ml of a mixture of methanol and water (1:1) was added to get the sample solution. The mobile phase was prepared as directed in the assay. 50µl of standard solution and the sample solution were injected separately in the same conditions of assay.

Disintegration time test: Disintegration were carried out using SOTAX DT 2, 5023-016 disintegration tester using distilled water as disintegration medium at 37 ± 2 °C, six tablets were examined.

Biological Study
We evaluated the antidiabetic effects of the two medications, brand and generic glimepiride product, on Wistar albino rats diabetics with alloxan. For the two drugs, the same batches were used in the quality control analysis, as well as in the biological study.

Diabetes induction
The rats were treated by a single intraperitoneal injection of 150 mg / kg body weight of alloxan monohydrate (Sigma-Aldrich Co., USA) [10]. To ensure the installation of diabetes, we measured blood glucose of rats after 72 hours of alloxan injection, only rats with fasting glycemia greater than 300 mg/dl were selected for the rest of the study [11].

Experimental protocol and animal treatment
Rats were randomly divided into 7 groups of 6 rats per cage **(Table 1):** two control groups (healthy and diabetics), 4 subgroups treated with 2 and 4 mg of the two drugs and a group treated with 2 mg of the generic supplemented by an aqueous extract of an antidiabetic plant according to the local traditional medicine.

Treatments were administered daily to rats by a single oral dose [12], for 32 days. The rats were weighed and their fasting blood glucose levels (FBG) were measured using an Accu-check glucometer every three days throughout the treatment period.

Table 1: Experimental design

Groups	Characteristics
HC	Healthy controls received water under the same conditions as other groups.
DC	Diabetic controls received water under the same conditions as other groups.
2mg-G	Diabetics treated with 2 mg of the generic drug in water.
2mg-A	Diabetics treated with 4 mg of the generic drug in water.
4mg-G	Diabetics treated with 2 mg of Amarel in water.
4mg-A	Diabetics treated with 4 mg of Amarel in water.
G+Plt	Diabetics treated with a morning dose of 2 mg of the generic in water and 80 mg/kg b.w. of the aqueous extract of the plant.

Biochemical assay
At the end of experiment, overnight fasted rats were sacrificed; blood samples were immediately collected in labeled tubes. After centrifugation, the serum obtained will be used for assays of serum glucose, total cholesterol (TC), total lipids (TL), triglycerides (TG), low density lipoprotein cholesterol (LDLc), high density lipoprotein cholesterol (HDLc) levels, the activity of serum aminotransferases GOT and GPT, amylase and lipase, and even the renal parameters; Glycated Hb was determined in whole blood. The assays were performed according to the supplier's specifications from the standard Kits. LDLc have been calculated using the following formula: **LDLc = TC – (HDLc) – (TG/5)** [13].

Statistical analysis of results
The results were presented as mean plus or minus standard deviation (Mean ± SEM). The statistical analysis was performed by one way analysis of variance (ANOVA) followed by Dunnett's or Tukey multiple comparisons tests using MINITAB 16 package. Level of significance was: Significant when $P \leq 0.05$; highly significant when $P \leq 0.01$ and very highly significant when $P \leq 0.001$.

RESULTS AND DISCUSSION

Quality control of products
The in vitro analysis of the generic drug and the branded product Amarel are presented in **Table 2.**

Despite the compliance with USP standards [8, 9]; results obtained from glimepiride assay, disintegration time and dissolution test for the generic drug are inferior to those of Amarel.

Table 2: Results of the quality control of the two glimepiride drugs

Analysis	USP limits	Amarel	Generic
Glimepiride assay (%)	90,0 - 110,0	109,8	107,0
Disintegration time (min)	≤ 15	3	1
Dissolution after 15 min (%)	≥ 80	98,4	82,7

USP: *United States pharmacopeia.*

Changes in body weights and fasting glycemia before sacrifice

The following figures show the results of measurements of body weights and fasting blood glucose levels of animals monitored during the whole period of treatment.

Body weights

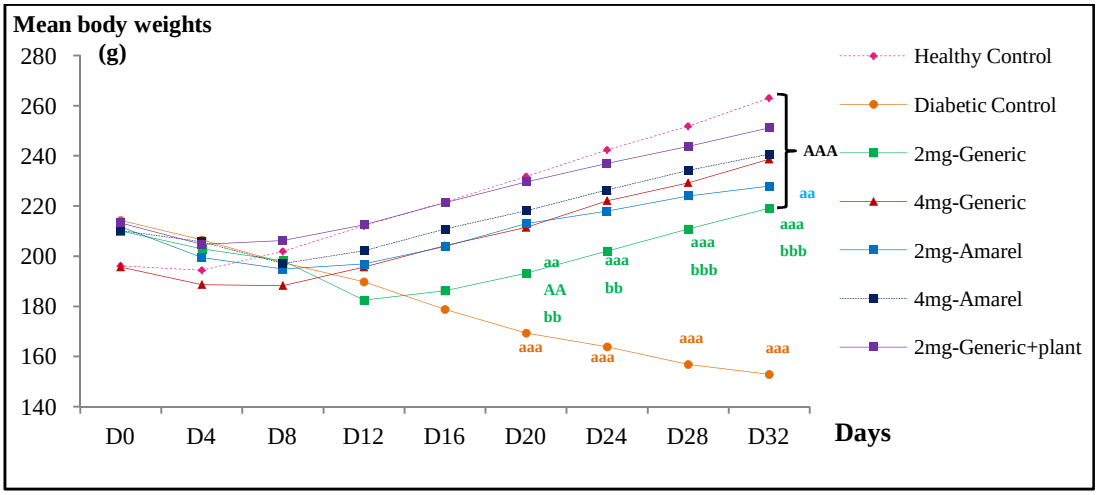

Fig.1: Changes in body weights of rats during the whole period of treatment

Vs HC: $^{aa}P \leq 0,01$, $^{aaa}P \leq 0,001$; Vs DC : $^{AA}P \leq 0,01$, $^{AAA}P \leq 0,001$; 2mg-G Vs 4mg-G : $^{bb}P \leq 0,01$, $^{bbb}P \leq 0,001$.

The results obtained **(Fig.1)** shows an increase in body weights of the healthy controls (HC) which is related to the normal growth of animals as well as a fall in weights of the diabetic controls (DC) which would be linked to metabolic disorders due to diabetes. The lack of insulin activates lipolysis in adipose tissue and would cause weight loss **[**14]; moreover, these animals received no treatment.

An increase in weights of the diabetic groups treated with the two doses of drugs has been observed, but it remains lower than that observed in healthy control rats, HC. This would suggest that both generic drug and Amarel have exerted a slight effect on insulin activity of the pancreas, resulting a slight lipogenesis, that allowed the recovery of body weights of rats, this weight gain is also due to normal growth of rats. Studies of the effect of glimepiride on body weight in diabetic man show that this medication is not associated with weight gain [2, 15].

While the group treated with the mixture, generic and plant extract (***Zygophyllum cornutum***), showed a better result similar to that of healthy controls.

Fasting blood glucose

Measurements of fasting blood glucose performed in the treatment period are shown in **Figure 2**; the healthy control group shows no change in blood glucose concentrations during 32 days of experiment.

However, in the diabetic control group, a very highly significant increase in blood glucose levels was observed **(29,74%)** during this period, which would be linked to the cytotoxic effect of alloxan on the pancreatic beta cells [16, 17], the lack of treatment of animals [18].

Diabetic groups, treated with 4 mg per day of generic and originator drugs show lower blood glucose levels of **57,52 %** and **60,53 %** respectively, this reduction is higher than that obtained by the dose 2 mg per day (**54,20 %** for the generic and **54,66 %** for Amarel). This reduction of the antidiabetic effect of the generic could be related to its active ingredient content which is lower to that of the originator (Table 2) or its excipient, different from that of the original, which could influence the release rate of the principle active [19]. The combination of the generic, at a rate of 2 mg per day, with the aqueous extract of *Zygophyllum cornutum Coss*, at a dose of 80 mg/kg, resulted in a significant decrease in blood glucose levels compared to the other used treatments and very highly significant compared to diabetic controls, DC **(72,67%).**

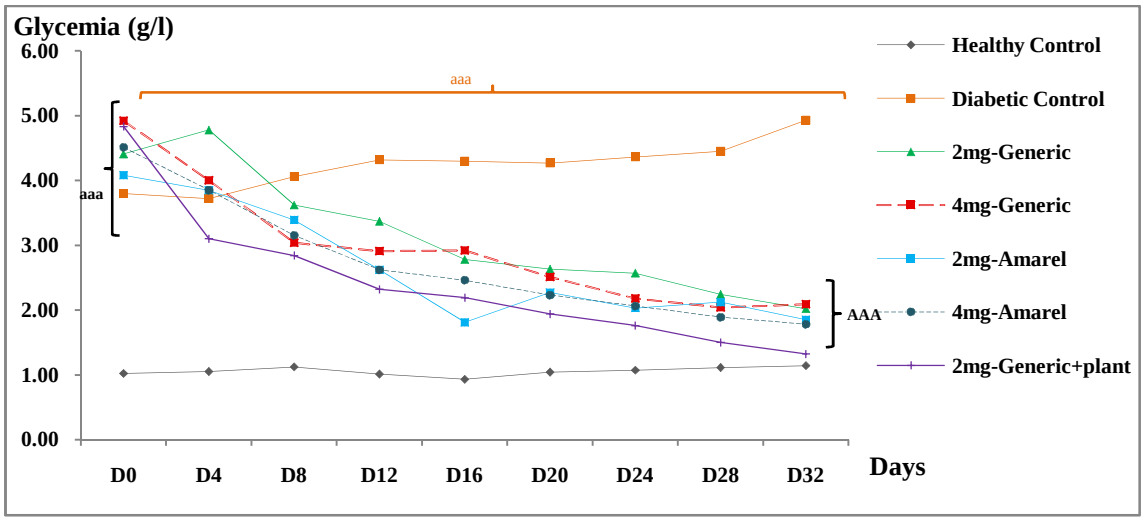

Fig.2: Changes in fasting glycemia of rats during the treatment period
Vs HC: $^{aaa}P \leq 0{,}001$; Vs DC: $^{AAA}P \leq 0{,}001$.

Biochemical parameters after sacrifice

Results of generic glimepiride effects, compared to Amarel, on some biochemical parameters, after sacrifice, (blood glucose, lipid profiles, enzymes activities and renal parameters) are presented in **Figures 3, 4, 5, 6** and **Tables 3, 4**.

Glycemia and $HbA1_C$

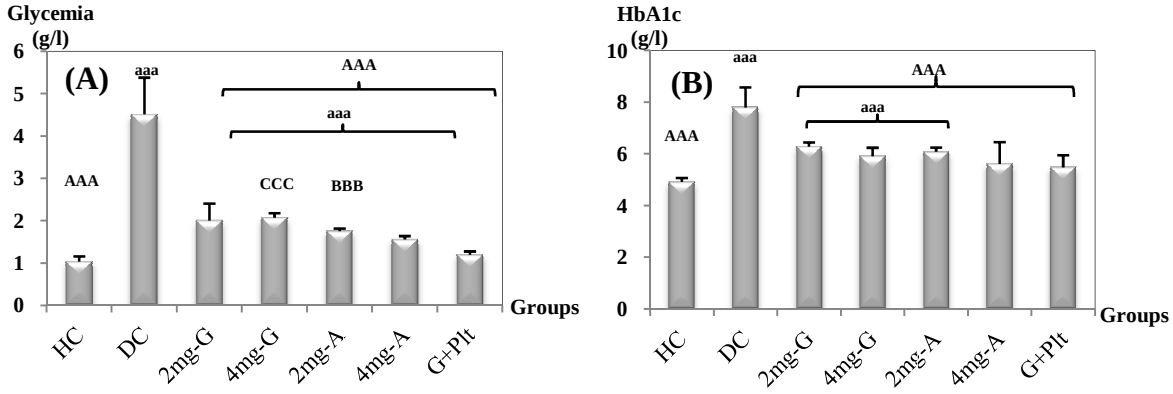

Fig.3: Evaluation of glycemia (A) and HbA1c levels (B) of rats after sacrifice
Vs HC: $^{aaa}P \leq 0{,}001$; Vs DC: $^{AAA}P \leq 0{,}001$; 2 mg-A Vs 4 mg-A: $^{BBB}P \leq 0{,}001$; 4 mg-G Vs 4 mg-A: $^{CCC}P \leq 0{,}001$.

The results obtained after 32 days of treatment **(Fig.3 A)** show a high level of blood glucose in diabetic controls compared to healthy ones, which could be the result of diabetes **[**18]. In contrast, treatment with glimepiride exhibited a decrease in blood glucose levels in all treated groups [20]; this reduction remains relatively elevated compared to the healthy control group. We noted a dose-dependent effect of Amarel; indeed a very highly significant difference was observed between fasting glycemia in rats treated with 2 mg **(1,76 g/l)** compared to those treated with 4 mg **(1,56 g/l).** Whereas, for the two doses of generic, we noticed no significant difference between the glucose levels (**2,01 g/l** for the 2 mg dose and **2,08 g/l** for the 4 mg dose). Only the mixture drug-plant extract revealed an hypoglycemic effect higher than that obtained in treated groups by both drugs; glucose levels observed in this group are similar to those of HC. This result was also obtained with glycemia before sacrifice.

The follow-up of $HbA1_C$ in diabetics reflects the glycemia stability over a given period (three months in human), allows to evaluate the effectiveness of treatments and is even used for predicting of dyslipidemia risks in the human diabetes [21]. $HbA1_C$ levels observed in treated groups are in the range of **5,62** to **6,28 %** and are in accordance with decreases in fasting glucose levels before and after sacrifice of animals **(Fig.3 B)** showing also efficacy of these treatments. However, $HbA1_C$ levels are very elevated in untreated diabetics DC having very highly significant differences compared to healthy controls and treated groups; this increase is associated to high concentrations of blood glucose in this group [22]. Animals treated with all doses of the generic or the branded drug revealed no significant differences between their glycated Hb levels, but these values are slightly higher than the HC ones.

Supplementation of the generic by the plant extract seems to have the most potent effect on blood glucose and $HbA1_C$ levels. This result is similar to those found by other authors [23, 24], which have shown that the combination of a low dose of certain anti-diabetic agents combined with a dose of herbal extracts could assure a good glycemic control.

Lipid profile

Table 3: Results of lipidic parameters assessment

Parameters Groups	TG (g/l)	LT (g/l)	CT (g/l)	LDLc (g/l)	HDLc (g/l)
HC	1,49 ± 0,14	1,91 ± 0,25	1,22 ± 0,09	0,81 ± 0,16	1,36 ± 0,28
DC	**aaa** 3,97 ± 0,30	**aaa** 8,43 ± 0,58	**aaa** 2,36 ± 0,37	**a** 1,41 ± 0,62	**aa** 0,90 ± 0,18
2mg-G	**aaa AAA** 2,32 ± 0,27	**aaa AAA** 4,11 ± 0,47	**aa A** 1,68 ± 0,46	**a** 1,26 ± 0,47	**A b** 1,27 ± 0,32
2mg-A	**aa AAA cc** 1,86 ± 0,23	**aaa AAA** 4,16 ± 0,63	**AAA** 1,42 ± 0,41	0,92 ± 0,54	**A BB** 1,33 ± 0,35
4mg-G	**aaa AAA b** 1,98 ± 0,21	**aaa AAA** 4,35 ± 0,24	**aa AAA** 1,46 ± 0,21	0,82 ± 0,31	**AAA CC** 1,61 ± 0,14
4mg-A	**aa AAA** 1,76 ± 0,15	**aaa AAA** 4,52 ± 0,79	**AAA** 1,42 ± 0,35	**A** 0,73 ± 0,33	**aaa AAA** 1,95 ± 0,14
G+Plt	**AAA** 1,52 ± 0,08	**aaa AAA** 4,47 ± 0,09	**AAA** 1,40 ± 0,20	0,87 ± 0,25	**aa AA** 1,83 ± 0,14

Vs HC: *^{a} P ≤ 0,05, ^{aa} P ≤ 0,01, ^{aaa} P ≤ 0,001;* ***Vs DC:*** *^{A} P ≤ 0,05, ^{AA} P ≤ 0,01, ^{AAA} P ≤ 0,001;*
2mg-G Vs 4mg-G : ^{b} P ≤ 0,05; 2mg-P Vs 4mg-P: ^{BB} P ≤ 0,01; 2mg-G Vs 2mg-P: ^{cc} P ≤ 0,01; 4mg-P Vs 4mg-P: ^{CC} P ≤ 0,01.

According to the results, there was a very highly significant increase in the concentration of TG in the DC group compared to HC **(Table 3)**, which is linked to the insulin-deficiency responsible for lipolysis in adipose tissue [18]. In all treated groups, the rate of TG is reduced, indicating a hypolipemic effect of Glimepiride [25]. We also observed a concentration of TG in the group treated with the mixture of the generic- plant extract similar to that of healthy control one, this result has been obtained previously with glucose and $HbA1_C$.

Very high levels of total cholesterol (TC), LDLc and total lipids (TL) in diabetic control rats (DC) were obtained, compared to healthy controls. In contrast, all treated groups have lower rates than DC group, with very highly significant differences.

The measurement of HDLc, revealed a lower serum level in the DC group compared to HC, with highly significant difference. This concentration in the group treated with 2 mg of Amarel (2mg-A) is similar to that of healthy control one. Compared to healthy and diabetic controls, 4mg-A and G+plt groups exhibited high levels of HDLc, with very highly significant differences. These results are in agreement with those reported by Araki et al. [26]; studying the effect of Glimepiride on increasing rates of HDLc.

Total proteins

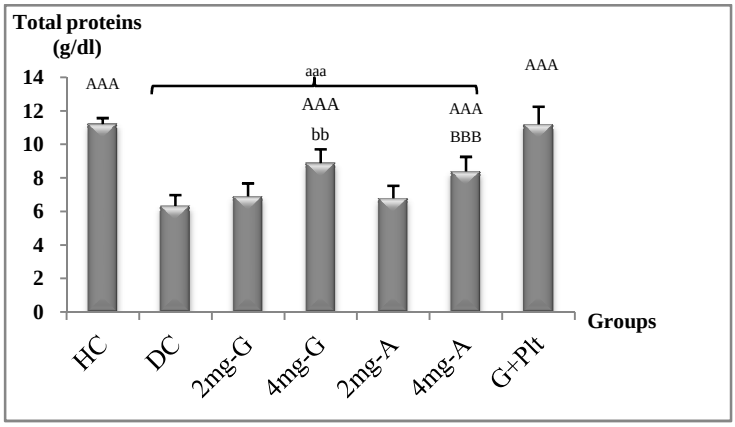

Fig. 4: Evaluation of total proteins in rats at the end of the experiment
Vs HC: ^{aaa} P≤ 0,001; Vs DC: ^{AAA} P≤0,001; 2mg-G Vs 4mg-G: ^{bb} P ≤ 0,01; 2mg-A Vs 4mg-A: ^{BBB} P ≤ 0,001.

The results presented in **Figure 4** indicate a rate of total serum proteins in untreated diabetic rats lower than that of healthy controls, with a very highly significant difference. This could be due to a loss in the urine (proteinuria)

related to a long lasting hyperglycemia [27], to the toxic action of alloxan on the kidneys [28] or the result of increased protein catabolism associated with insulin deficiency [29].

Total proteins of treated groups with 4 mg of both drugs are similar to each other but remain lower than those of HC, whereas proteins of the group treated by mixing drug-extract are similar to those of the HC.

Enzymatic activities

- **Serum aminotransferases**

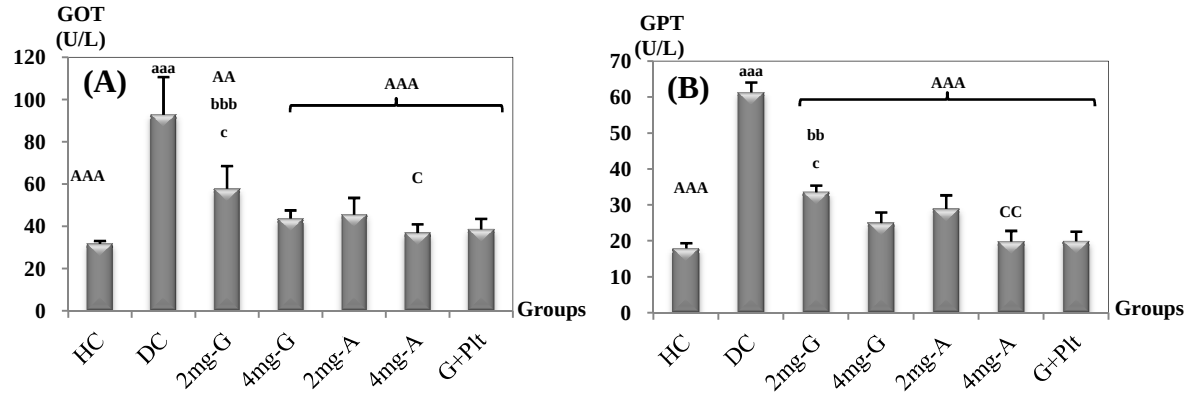

Fig. 5: Evaluation of serum transaminases GOT (A) and GPT (B) in rats after the treatment period

Vs HC : $^{aaa}P\leq0,001$; Vs DC: $^{AA}P\leq0,01$, $^{AAA}P\leq0,001$; 2mg-G Vs 4mg-G : $^{bb}P\leq0,01$, $^{bbb}P\leq0,001$; 2mg-G Vs 2mg-A : $^{c}P\leq0,05$; 4mg-G Vs 4mg-A: $^{C}P\leq0,05$, $^{CC}P\leq0,01$.

A very highly significant increase in the activity of serum aminotransferases in diabetic control rats was observed compared to healthy controls. The high enzymatic activity of GOT and GPT can be explained by the hepatotoxic effect of alloxan [28, 30]. In contrast, treatment of diabetic rats by Amarel and its generic revealed decreased activities of these two enzymes, with very highly significant differences compared to DC **(Fig.5)**.

These activities were higher in the group treated by 2 mg of the generic compared to the group treated with 4 mg, with a highly significant difference ($P\leq0.01$). While, both doses of Amarel showed no significant differences. The treatment resulted in a reduction in the activity of these two enzymes and therefore, exerted a protective effect against liver damage caused by alloxan; the best effect was obtained with the 4 mg dose of Amarel and the combination of the generic with the plant extract.

- **Serum amylase and lipase activity**

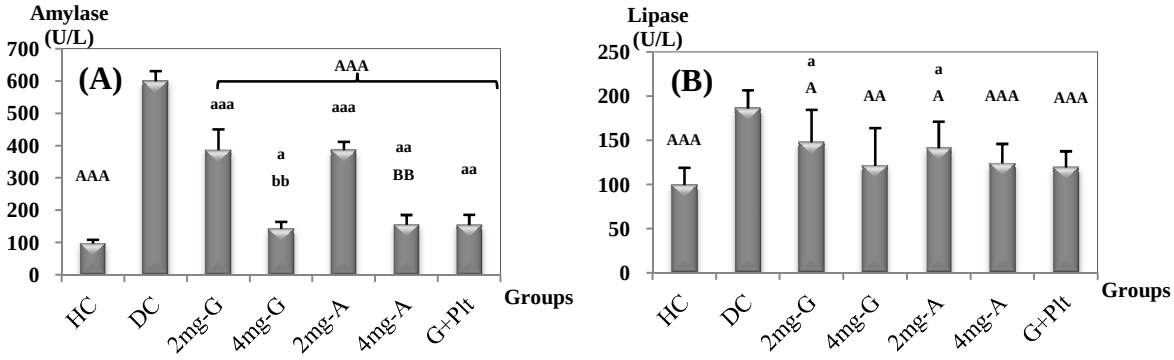

Fig.6: Evaluation of serum amylase (A) and lipase (B) activities after sacrifice of rats after treatment

Vs HC: $^{a}P\leq0,05$, $^{aa}P\leq0,01$, $^{aaa}P\leq0,01$; Vs DC: $^{A}P\leq0,05$, $^{AA}P\leq0,01$, $^{AAA}P\leq0,001$; 2mg-G Vs 4mg-G: $^{bb}P\leq0,01$; 2mg-A Vs 4mg-A: $^{BB}P\leq0,01$.

The determination of amylase and serum lipase allows the diagnosis of pancreatic damage [31]. In diabetic controls, we noticed a very highly significant increase of serum amylase and lipase activities, compared to the healthy control group, suggesting an alteration of the pancreas caused by alloxan [32]. The 4 mg dose of both generic and even the combination of the generic with the plant extract caused very highly significant decreases in the activity of amylase **(Fig.6 A)**, compared to diabetic controls ($p \leq 0.001$). Reduced activities of serum amylase were also observed in diabetic groups treated with 2 mg of the two medicaments compared to DC group but remained elevated compared

to healthy controls ($p \leq 0.001$ Vs HC). The lipase activity, in all treated groups was lower than that of DC; only the groups treated with 4 mg of both drugs and the mixture generic-plant showed decreases with highly significant differences for the generic and very highly significant for Amarel and the mixture, compared to DC **(Fig.6 B)**.

Renal parameters

Chronic hyperglycemia and dyslipidemia are associated with metabolic disorders in humans and animals with diabetes **[**32], which causes oxidative stress, resulting high levels of ROS [33]. Oxidative environments can cause damage in hepatic and renal cells and tissues [34]. High levels of urea and creatinine (indicators of renal dysfunction) observed in untreated diabetic rats **(Table 4)** would resulted in from the action of ROS and the toxic effect of alloxan on the **kidneys [28].**

Table 4: Evaluation of renal serum parameters in rats

Parameters Groups	Uric acid (mg/dl)	Urea (g/l)	Creatinine (mmol/l)
HC	**AA** 2,58 ± 0,44	**AAA** 0,66 ± 0,08	**AAA** 63,64 ± 15,34
DC	 3,37 ± 0,42	 1,34 ± 0,36	**aaa** 111,68 ± 13,99
2mg-G	**A** 2,84 ± 0,21	**AA** 0,78 ± 0,18	**NS** 90,88 ± 28,84
2mg-A	**A** 2,80 ± 0,37	**AA** 0,70 ± 0,19	**AA** 75,03 ± 17,12
4mg-G	**NS** 3,05 ± 0,40	**AA** 0,80 ± 0,13	**aa** 97,56 ± 14,26
4mg-A	**NS** 2,99 ± 0,38	**AAA** 0,74 ± 0,07	**A** 87,16 ± 21,23
G+Plt	**A** 2,71 ± 0,57	**AAA** 0,67 ± 0,08	**AAA** 73,54 ± 14,10

Vs HC: ^{aa} P ≤ 0,01, ^{aaa} P ≤ 0,001; Vs DC: ^{A} P ≤ 0,05, ^{AA} P ≤ 0,01, ^{AAA} P ≤ 0,001; ^{NS}: Not Significant.

The treatment was effective in improving these two parameters. No significant differences were observed between the different treatments for the three renal parameters studied.

CONCLUSION

This study aimed to evaluate the pharmaceutical quality of a generic glimepiride, an oral antidiabetic agent, compared to the originator product Amarel, and to verify its effects, according to two selected doses namely 2 and 4 mg per day, in rats with alloxan diabetes. Despite the compliance of their physicochemical characteristics with American standards, the results of the biological study revealed: a recovery of body weights in rats treated with the mixture generic - plant, followed by groups treated with 4 mg of Amarel and the generic respectively. These results are in accord with those obtained for glycemia declines following different treatments **(Fig.2).** After sacrifice, the most important decreases of fasting glycemia and HbA1c levels were obtained with the combination "generic-plant extract", and with doses 4 and 2 mg of Amarel. For the lipid profile, Amarel was more effective than the generic; and the mixture still shows a beneficial effect on these parameters. Total proteins and also enzymatic activities of serum transaminases, amylase and lipase were improved in groups treated with 4 mg of both drugs and the mixture. The different treatments exerted similar effects on serum urea, creatinine and uric acid. No toxic effects were observed in rats treated with the two drugs, Amarel and its generic product, at doses of 2 and 4 mg per day, during the period of treatment. The analyzed generic glimepiride exhibits lower therapeutic potency compared to the originator drug Amarel, which requires dose adjustment for treatments. According to this study, it is suggested to manufacturers to carry out studies on their finished generic products, in order to adjust the recommended doses to avoid overdosing or under dosing which could be dangerous for patients.

Acknowledgments

This study was partly supported by the Ministry of Higher Education and Scientific Research (MESRS) of Algeria (PNR, Health project 2011). Authors thank assistance of Inpha-Médis laboratories.

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