



Effect of *Trema guineensis* leaves (celtidaceae) on glucose-induced hypertension in Wistar rats

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ABSTRACT

Trema guineensis leaves are used in Togolese's traditional medicine as an antihypertensive remedy. This study aims at evaluating the protective effect of *T. guineensis* extract on glucose-induced hypertension to Wistar rats. Hypertension has been induced to rats through oral administration of 10% D-glucose for 3 weeks. Animals have received the treatments for 3 weeks. At the end of the treatments, blood pressure, reduced glutathione (GSH), malondialdehyde (MDA), superoxide dismutase (SOD), nitric oxide (NO) activity in heart, aorta, liver, and kidney and biochemical parameters in serum have been measured. At the doses of 200 and 400 mg/kg/day, *T. guineensis* has significantly prevented the increase in high blood pressure in glucose's presence. The extract has significantly prevented the high concentrations of total cholesterol, and triglycerides, low-density lipoprotein (LDL), atherogenic index, urea, and uric acid induced by glucose treatment as compared to untreated glucose's rats group. *T. guineensis* (400 mg/kg) has prevented the increase in glutamic-oxaloacetic transaminase, GOT but did not affect serum creatinine's rates. Treatment with plant's extract has significantly prevented the increase in SOD, MDA, and the decrease in GSH and NO's concentration in aorta, heart, kidney, and liver. These results have proved that the extracted leaves of *T. guineensis* could prevent glucose-induced hypertension. These results have allowed the traditional use of *T. guineensis*.

1. INTRODUCTION

Hypertension is one of the most wide-spread and modifiable factors of cardiovascular diseases throughout the world [1,2]. It is also one of the main causes of disability, morbidity, and mortality [3]. From far away, it has been the most common affection among cardiovascular diseases, and it is considered as a serious problem of public health's matter. Indeed, there is about 80 million of hypertensive in Sub-Saharan Africa, and the projections based on epidemiological data suggest that this figure will reach 150 million patients before 2025 [4]. Among the 17 million patients who die every year from cardiovascular diseases, it is thought that 7–8 million are hypertensive [4]. African countries are particularly concerned because they, in fact, think that in 2025 almost 3/4 of the hypertensive world's population will live in developing countries. Despite the availability of several antihypertensive agents, who successfully reduce blood pressure in many hypertensive subjects, numerous patients remain unresponsive to treatment and are left with high blood pressure [2]. For example, hypertension is not adequately managed in approximately 10% of patients who are compliant with

prescriptive therapeutics [5]. Existing review has shown that in many developing countries, about 70–80% of the population, have relied ardously on medicinal plants in their vicinity to meet their basic health-care needs [6].

Fructose and glucose are two carbohydrates source blood pressure's increased [7,8]. Several mechanisms are the source of this blood pressure's increase, of which the most important are dyslipidemia [9], sodium retention and fluid volume expansion [10], stimulation of the sympathetic nervous system [11], endothelial dysfunction [12], and also the increase in oxidative stress [13].

Some plants are used to treat hypertension by traditional healers in Africa. Among them, *Trema guineensis* is a plant commonly used in traditional medicine to treat several pathologies. The leaves' decoction of *T. guineensis* is drunk in case of high blood pressure associating it with *Gardenia ternifolia* leaves [14]. Wooden fragments are roasted and used to make the tea which fights against dysentery; the bark is used for cough's treatment. Bark's decoction is used against bronchial congestion, asthma, sore throat, teeth, and against mouth's infections. Our previous studies have shown that the extract of *T. guineensis* leaves had vasodilator effects [15].

Therefore, the present study has been conceived to investigate on antihypertensive activities of *T. guineensis* on a rat model of glucose-induced hypertension.

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2. MATERIALS AND METHODS

2.1. Plant Material and Extraction

Fresh pieces of *T. guineensis*' leaves have been harvested in December 2016 in Badou, a village located at 220 Km from Lomé (Togo) and authenticated by the Department of Botany and Plant Ecology in Science Faculty (University of Lomé) where voucher specimen (N 15379TG) was deposited. Leaves are washed in the tap water then dried in light's shelter. Once these leaves are dried, they are reduced in powder evaluated at 250 g. This quantity was mortified by uninterrupted agitation during 72 h in an extraction's solvent composed of water and ethanol in a voluminal ratio 20:80. After soaking, the product was first filtered on the cotton wool, and after, on the filter paper and then, the filtrate evaporated in a rotavapor R-210 (Buchi) at 45°C. We obtained 28.2 g of extract which corresponds to 11.28%.

2.2. Phytochemical Screening

Phytochemical analyses of the ethanolic extract have been done following the procedure described by Odebiyi and Sofowora [16]. The plant's extract was screened in the presence of alkaloids, saponins, tannins, and flavonoids. The total phenols were determined from the Folin–Ciocalteu method after polyvinylpyrrolidone tannin fixation. The determination of total flavonoids is based on flavonoids' property to form with aluminum chloride aluminum chelates of Mimica-Dukic.

2.3. Animals

Albinos Wistar rats, weighting between 150 and 180 g, have been used. Animals were raised in the Animal House of Science Faculty (University of Lomé) in plastic cages, under standard light (12-h day/night natural cycle) and temperature (25°C). Rats were fed with standard diet and water *ad libitum*. The research protocol was approved by the Institutional Animal Ethical committee with proposal number: 018/2017/CB-FDS-UL Date: 01/10/2017.

2.4. Experimental Design

The extract's effect of *T. guineensis* on D-glucose-induced hypertension has been evaluated. Normotensive rats were randomly divided into five groups composed of five animals each which have received different treatments by gavage. Group one has received tap water and has served as negative control (NC), group two has received 10% D-glucose solution in drinking water serving as positive control (PC). Groups III and IV were the treated groups which have received each 10% D-glucose in drinking water and the plant's extract by gavage at 200 mg/kg/day and 400 mg/kg/day, respectively. Group five has received D-glucose in drinking water and nifedipine at 10 mg/Kg by gavage. The experiments have lasted 3 weeks. At the end of the experiment, systolic arterial blood pressure rate was measured as described by Mtopi *et al.* [17]. After blood pressure measurement, blood was collected at the level of the retro-orbital sinus. Serum was separated and total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, urea, glutamic-oxaloacetic transaminase (GOT), and GTP rates using commercial diagnostic kits BC 3000 + Mindray. After blood collection, heart, aorta, liver, and kidney were removed, weighted, crushed, and homogenized in McEwen solution for aorta and heart or Tris-HCl buffer solution for liver and kidney. Serum and homogenate were stored at -20°C. Reduced glutathione (GSH) was determined by the method of Sedlak and Lindsay [18]. Superoxide dismutase (SOD) was determined using the method of Misra and Fridovich [19]. Nitric oxide (NO) was determined

according to the method of Tom *et al.* [20]. Malondialdehyde (MDA) was determined using the procedure of Satoh [21]. Total proteins are determined using the method [22].

2.5. Statistical Analysis

Results are expressed in average \pm S.E.M. One-way analysis of variance (ANOVA) as followed by Tukey test was used for statistical evaluation. *p* value < 0.05 was considered as statistically significant.

3. RESULTS

3.1. Phytochemistry

The phytochemical analysis of the extract reveals the presence of saponosides, tannins, flavonoids, and but no alkaloids. The dosage of polyphenols, flavonoids, and tannins is summarized in Table 1.

3.1. Effects Of The Extract On Glycemia Value

Glucose has increased the glycemia's value. *T. guineensis* extract has decreased the glycemic rates as compared with the PC [Figure 1].

3.2. Effects of the Extract on Blood Pressure

After 3 weeks of treatment, the arterial blood pressure's average of rats which have received only glucose has increased significantly ($P < 0.001$). The *T. guineensis* extract has prevented this increase in arterial blood pressure's average in this model. At 400 mg/kg dosage, the extract has reduced the arterial blood pressure from 153 ± 4.34 mmHg to 126.4 ± 2.06 mmHg. This blood pressure reduction is similar with nifedipine treatment group [Figure 2].

Table 1: Proportion of polyphenols in the extract

Compounds	Content
Total polyphenols (mg eqQ/g of extract)	27.185
Total flavonoids (mg eqQ/g of extract)	14.29
Tannins (mg eqQ/g of extract)	10.93

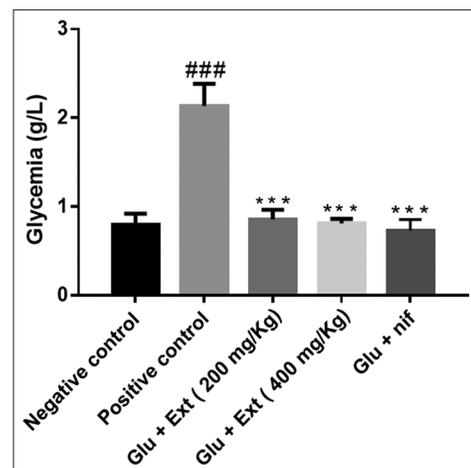


Figure 1: Effects of *Trema guineensis* extract on the glycemia of the rats. Every value represents the mean \pm standard error of mean, ($n = 5$). ** $P < 0.01$ *** $P < 0.001$ significant difference in comparison with the positive control. ### $P < 0.001$ significant difference in comparison with the negative control

3.3. Effects Of The Extract On Body Weights

Glucose has significantly ($P < 0.001$) increased the body's weight of PC (53.00 ± 2.98 g) as compared to the NC (27.2 ± 2.15 g). There was no significant difference between weights gained in *T. guineensis* (400 mg/kg) glucose-treated animals as compared to NC [Figure 3].

3.4. Effects of the Extract on Lipid Profile

As shown in Table 2, glucose has significantly increased ($P < 0.001$) the total cholesterol by 39.20%, triglycerides by 82.91%, atherogenic index by 242.66, LDL-cholesterol by 324.52%, and the decrease of HDL-cholesterol by 49.46%, respectively, as compared to the NC. The administration of *T. guineensis* extracts reduced these parameters.

3.5. Effects of the Extract on Oxidative Stress Markers

Glucose has significantly ($P < 0.001$) increased MDA, SOD rates and reduced that of GSH and NO in aorta, heart, liver, and kidney as compared to NC. *T. guineensis* extract has markedly suppressed the increase of SOD, MDA and has increased the GSH and NO levels as compared to PC [Figures 4-7].

3.6. Effects of the Extract on Liver and Kidney

Glucose has induced a significant increased ($P < 0.001$) of urea (29.88%), uric acid (78.98%), GOT (102.37%), and GTP (68.23%), respectively, as compared to NC. *T. guineensis* has significantly ($P < 0.001$) reduced GOT, GTP, urea, and uric acid rates as compared to the PC. There is no difference between creatinine's rates of other groups and the control group [Table 3].

4. DISCUSSION

T. guineensis is used in Togo by traditional practitioners to treat many sicknesses, including cardiovascular diseases such as hypertension. In the present study, we evaluated the antihypertensive activities of *T. guineensis* extract on glucose-induced hypertension on rats. Glucose in our study has induced an increase in treated rats glycemia in relation to NC. The plant extract has significantly prevented that increase. This result can be explained by the fact that either the extract would

increase insulin release to reduce the increase in blood glucose's rate or act on the liver by accelerating the formation of glycogen or on the muscles by their sensitization using glucose.

Our data have shown a significant increase in weight gain of hypertensive rats as compared to normal rats. The administration of *T. guineensis* extract has significantly prevented this weight gain. It

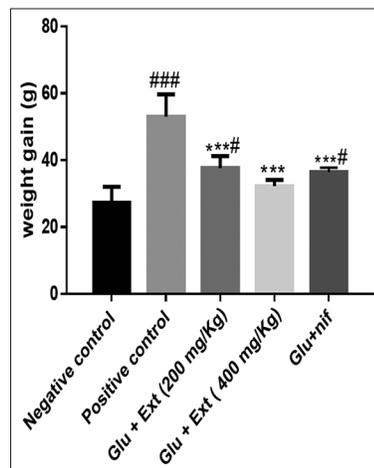


Figure 3: Effects of *Trema guineensis* extract on the weight of the rats. Every value represents the mean \pm standard error of mean, ($n = 5$). *** $P < 0.001$ significant difference in comparison with the positive control. # $P < 0.05$, ### $P < 0.001$ significant difference in comparison with the negative control

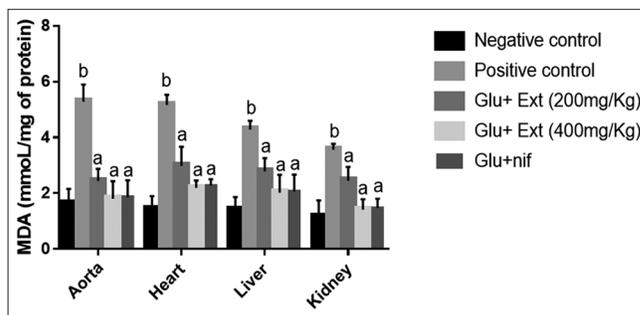


Figure 4: Effects of *Trema guineensis* extract on the reduced glutathione. Every value represents mean \pm standard error of mean, ($n = 5$). ^a $P < 0.001$ significant difference in comparison with the positive control. ^b $P < 0.001$ significant difference in comparison with the negative control

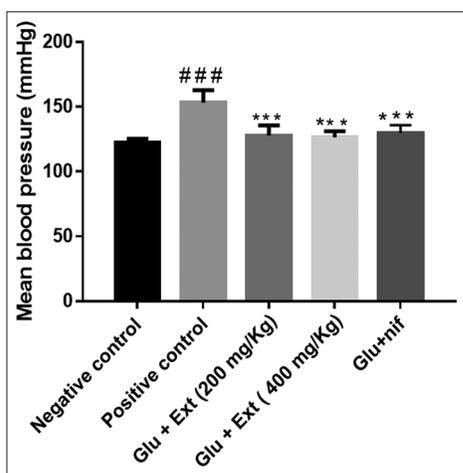


Figure 2: Effects of *Trema guineensis* extract on mean arterial blood pressure of the rats. Every value represents the mean \pm standard error of mean ($n = 5$). *** $P < 0.001$ significant difference in comparison with the positive control. ### $P < 0.001$ significant difference in comparison with the negative control

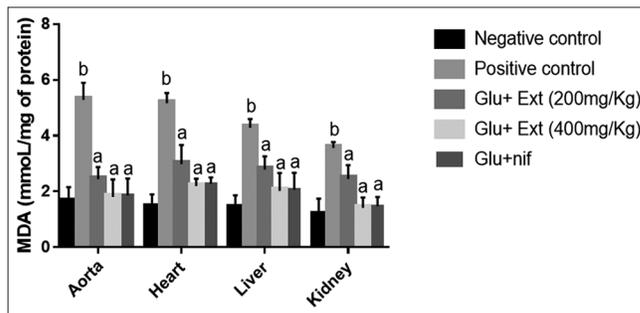


Figure 5: Effects of *Trema guineensis* extract on the malondialdehyde levels. Every value represents mean \pm standard error of mean, ($n = 5$). ^a $P < 0.001$ significant difference in comparison with the positive control. ^b $P < 0.001$ significant difference in comparison with the negative control

Table 2: Effects of *T. guineensis* extract on the lipid profile parameters of the rats

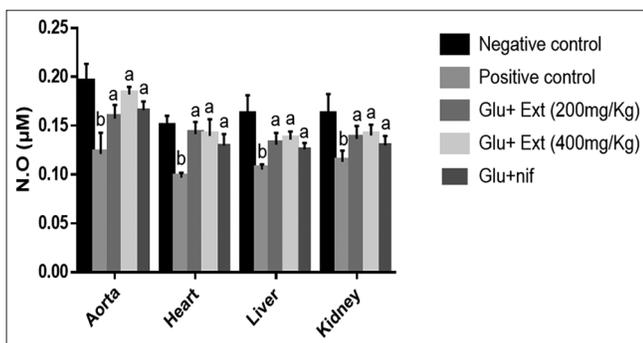
Parameters	NC	PC	Glu+Ext (200 mg/Kg)	Glu+Ext (400 mg/Kg)	Glu+nif (10 mg/Kg)
Triglycérides (mg/dL)	39.80±5.28	72.40±0.81###	47.80±2.10***	38.20±1.56***	42.5±2.21***
Cholesterol (mg/dL)	55.60±3.01	77.40±4.20###	52.40±0.87***	52.25±0.25***	55.30±1.40***
HDL (mg/dL)	37.20±2.05	18.80±1.98###	37.80±1.77 ***	37.00±2.75***	25.33±3.10***
LDL (mg/dL)	10.44±2.76	44.32±5.29###	5.20±2.07***	7.56±3.16 ***	12.41±1.25***
Indice atherogénique	1.50±0.10	5.14±0.66###	1.39±0.084 ***	1.44±0.13***	1.88±2.21***

Every value represents the mean ± ESM, with (n = 5). *** P < 0.001, significant difference in comparison with the positive control. ### P < 0.001, significant difference in comparison with the negative control, NC: Negative control, PC: Positive control, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

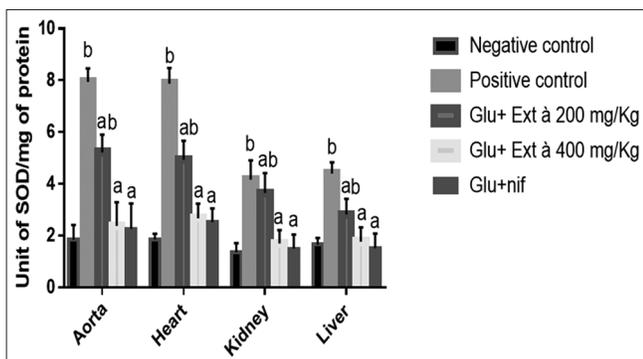
Table 3: Effects of *T. guineensis* extract on serum parameters of liver and kidney

Parameters	NC	PC	Glu+Ext (200 mg/Kg)	Glu+Ext (400 mg/Kg)	Glu+nif (10 mg/Kg)
GOT (UI)	134.80±5.15	272.80±5.1###	159.20±3.80***##	149.60±2.40***	155.24±2.40***
GTP (UI)	72.40±4.47	121.80±3.85###	96.00±2.62**	85.80±2.20***	73.45±1.25***
Urea (mg/dL)	41.46±1.47	53.85±2.49###	38.76±1.79***	36.68±2.66***	33.52±1.33***
Uric acid (mg/L)	14.23±0.22	25.47±1.11 ###	13.87±1.20 ***	13.62±0.92***	17.41±1.56***
Creatinine (mg/dL)	7.08±0.43	6.16±0.24	6.54±0.57	6.96±0.20	7.36±0.20

Every value represents the mean ± ESM, (n = 5), ** P < 0.01, ***P < 0.001, significant difference in comparison with the positive control. ## P < 0.01, ### P < 0.001, significant difference in comparison with the negative control, GOT: Glutamic-oxaloacetic transaminase, NC: Negative control, PC: Positive control

**Figure 6:** Effects of *Trema guineensis* extract on the nitric oxide of the rats.

Every value represents mean ± standard error of mean (n = 5). ^bP < 0.001 significant difference in comparison with the positive control. ^aP < 0.001 significant difference in comparison with the negative control

**Figure 7:** Effects of *Trema guineensis* extract on SOD levels. Every value represents mean ± standard error of mean (n = 5). ^aP < 0.001 significant difference in comparison with the positive control. ^bP < 0.001 significant difference in comparison with the negative control

is suggested that the chronic consumption of glucose stimulates more food intake and leads to more weight gain [23].

In our study, we have observed a significant reduction in medium arterial pressure rate to the rats treated at the same time with glucose and extract. This pressure reduction caused by the *T. guineensis* extract is due to the vasodilatory action of the extract, as demonstrated *in vitro* on the isolated aorta [15].

An increased consumption of fructose and glucose, two carbohydrates are a source of the increase in blood pressure by dyslipidemia, endothelial dysfunction, and also by the increase in oxidative stress. In the present study, glucose feeding has significantly increased total cholesterol, triglycerides, and atherogenic index. Dyslipidemia enhances vascular resistance and leads to an increase in blood pressure [24]. *T. guineensis* has significantly prevented total cholesterol's rise, triglycerides and atherogenic index, LDL. and increase in HDL observed in untreated glucose's rats. The vasodilator effect of the extract and its action on blood pressure decreasing may be explained by the lowering of total cholesterol, triglycerides, atherogenic index, LDL, and the increase in HDL that it causes. Furthermore, HDL increase protects heart against cardiovascular diseases risks [25]. It is suggested that the extract possesses an antihypertension effect through its antihyperlipidemic and antihypercholesterolemic's action. The increased oxidative stress and excessive formation of free radicals resulting from LDL's conversion in oxidized LDL are involved in the development of atherosclerotic lesions in the vascular endothelium [26]. This suggests that *T. guineensis* may stimulate HDL synthesis or enhance lipase protein's activity. The antihyperlipidemic's effect of the extract could represent a protective mechanism against atherosclerosis' development in rats. This suggests that lipid's improvement of a profile by the plant's extract may be responsible at least partially for arterial hypertension's prevention. Moreover, in hypertensive patients, lower concentrations of antioxidants have been documented [27]. Our inquiry is that: Does the extract of *T. guineensis* have its effect on oxidative stress parameters?

Cardiovascular dysfunctions in glucose-induced hypertension are the source of the increase in reactive oxygen species (ROS) and the antioxidant's alteration defense status as shown by Kasdallah-Grissa et al. [28]. Furthermore, we have measured GSH, SOD, and MDA rates

as being the peroxidation lipid's index resulting from the activated oxygen species' reaction with membrane fatty acids [29]. The results have shown a significant increase in MDA, SOD and the decrease in GSH rates in heart, kidney, liver, and aorta. The treatment with the extract of *T. guineensis* has significantly prevented the decrease in GSH, and the increase in MDA, SOD's rates. These findings are in accordance with those found by Husain *et al.* [30] which have shown that glucose dose-dependently increases MDA and decreases GSH. The decrease of GSH can be explained by an increase in its use by hepatic cells, and by a decrease in the synthesis of GSH or an increase in its degradation during oxidative stress [31], because it participates in the ROS detoxification reactions [32]. It is then converted into its oxidized form (GSSG) under the GSH peroxidase's effect. This leads to GSH's consumption which is the reason for its decrease in PC rats [33]. Therefore, the extract favors GSH's synthesis and stops its degradation by fighting against the oxidative stress. Thus, treatment with plant's extract has shown antioxidant properties by preventing tissues' lipid peroxidation and increasing GSH. The increase in SOD is due to high oxidative stress causing the increase in this enzyme's production to fight against the stress. The reduction observed in SOD antioxidant enzyme's concentrations in all extract's treated groups may occur due to an oxidative stress status' total reduction. Our results suggest that the extract induces an antioxidant effect, which may due to this plant richness in bioactive compounds and antioxidant that inhibit the lipoperoxidation and alteration caused by the excessive production of free radicals as shown by Liu *et al.* [34].

In the current study, glucose has significantly decreased the NO. Plant extract, given simultaneously with glucose, has prevented the decrease in NO. The extract has corrected this deficit in NO's rate. It suggests that the extract could prevent the endothelial dysfunction caused by NO's deficit.

We have evaluated the glucose's toxicity on liver and kidney's functions by assessing transaminases (GOT and GTP), uric acid, and urea's rate. The hepatic injury induced by glucose has resulted in an increase in serum GOT and GTP rates due to cellular enzymes' leakage in the circulation. *T. guineensis* has inhibited the raising in GOT, GTP serum's rates and without reducing them to normal control values; this is similar with the effect on oxidative stress markers. This may indicate that oxidative stress is involved in hepatotoxicity's mechanisms due to glucose chronic consumption. This reduction in transaminases can also be explained by the gluconeogenesis reduction's process; an essential step requiring the GOT and GTP's intervention [35]. Serum enzymes' low rate after the concomitant treatment with *T. guineensis* as compared to NC suggests liver and kidney's protective effects of the extract.

Phytochemical studies of the extract have revealed polyphenols' presence such as flavonoids and tannins. The main characteristic of polyphenols is that they are very powerful antioxidants [36]. Indeed, flavonoids are also known to have a preventive role against cardiotoxicity, their inhibition of lipid peroxidation and their ability to prevent various hematological disorders [37]. Indeed, flavonoids provide protection against free radicals by preventing their binding with cell membrane lipids; which results in a decrease in MDA (lipid peroxide) and the hematological composition's protection by allowing good erythrocyte regeneration and prevention against leukopenia and thrombocytopenia observed in the presence of free radicals [38]. Flavonoids have an ability to capture and deactivate free radicals. Flavonoids are known for their protective effect on cardiovascular health by modifying several pathological processes involved in cardiovascular development diseases by inhibition of the oxidation

of LDL cholesterol (bad cholesterol) by free radicals. These results obtained during our experiment would be due to the polyphenols contained in the extract and in particular the flavonoids.

5. CONCLUSION

The side effects of chronic administration of glucose have been established in this study, and we can suggest lipid accumulation, oxidative stress and tissue damage as a bridge linking the high consumption of sugar to arterial hypertension. These results scientifically confirm the antihypertensive properties of the extract of *T. guineensis* as used in Togolese traditional medicine and suggest that this effect may result from its blood pressure or lipid-lowering and its antioxidant or vasodilator effects.

5. ACKNOWLEDGMENT

Nil.

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