JOURNAL OF INTERCULTURAL ETHNOPHARMACOLOGY, 2018
VOL 7, NO. 1, PAGES 1–7
10.5455/jice.20170909091946

eJManager

ORIGINAL ARTICLE

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Comparative study of *Annona senegalensis* (Annonaceae) and *Hallea ledermannii* (Rubiacaceae) effects on glycemia in rats

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ABSTRACT

Aim: In order to promote African traditional pharmacopoeia, studies have been undertaken to evaluate the effects of aqueous extracts of *Annona senegalensis* (Annonaceae) (EAAs) and *Hallea ledermannii* (Rubiaceae) (EAHl) in white rats of Wistar strain.
Methods: A phytochemical screening and a toxicological study according to the Organisation for Economic Co-operation and Development guidelines 423 were carried out. Pharmacological effects on blood glucose were evaluated. The different treatments were performed orally.
Results: The aqueous extracts of EAAs and EAHl, respectively, at the maximum doses of 3,000 and 5,000 mg/kg bw, did not cause death in rats. Phytochemical screening revealed the presence of polyphenols, flavonoids, and quinonic compounds in both extracts. This study showed that in addition to the common compounds, the *Annona senegalensis* extract contained sterols, polyterpenes, catechic tannins, and alkaloids, while that of *Hallea ledermannii* showed the existence of saponosides. *Annona senegalensis* (100 mg/kg bw) and *Hallea ledermannii* (200 mg/kg bw), provoked more hypoglycemia, respectively, of 40% and 35.34% in rats. EAAS (27.78% vs. 25.41%) showed better anti-hyperglycemic effect in pretreated rats while EAHl (40.30% vs. 29.37%), provoked more anti-hyperglycemic activity in post-treated animals.
Conclusion: The effects of EAAs and EAHI on blood glucose value may be related to the presence of chemical compounds such as flavonoids and saponosides highlighted in a phytochemical study. These compounds recall those of certain insulin-secreting agents and justify their use in traditional medicine.

ARTICLE HISTORY

Received September 09, 2017
Accepted January 03, 2018
Published January 09, 2018

KEYWORDS

Annona sengalensis; Hallea ledermannii; Glibenclamide; hypoglycemia; anti-hyperglycemia; rat

Introduction

Diabetes is a metabolic disorder due to insufficiency or misuse of insulin characterized by a fasting hyperglycemia, verified twice. This disease affects more and more people in the world and is today a real public health problem. According to Danaei et al. [1], this disease caused, following its complications, the death of nearly 3.4 million people. In Côte d'Ivoire, 3–7% of the population suffers from diabetes [2]. The therapeutic management of this disease is costly given the low purchasing power in most developing countries [3]. The traditional pharmacopoeia offers a solution for the populations with low income. To enable access to health care at lower cost, ethnobotanical studies of medicinal plants have been carried out to develop improved traditional medicines. Thus, extracts of certain plants have been tested for their antidiabetic activity [4–6]. It is in this perspective that we undertook to study the effects of aqueous extracts of *Annona senegalensis* (Annonaceae) (EAAs) and *Hallea ledermannii* (Rubiaceae) (EAHl), two plants of the traditional African pharmacopoeia, known, as antidiabetic plants.

Annona senegalensis, a medicinal plant used to treat numerous infectious pathologies [7], also has antiparasitic activity on a resistant strain of Plasmodium falciparum [8]. In addition,

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antibacterial activities have been reported by More et al. [9]. The stems, leaves, fruits, and roots of *A. senegalensis* have been used in the treatment of skin cancer, cough, and to heal wounds [10,11]. According to Konaté et al. [12], the aqueous extract of bark from the root of this plant would be used in Burkina as a remedy against epilepsy and convulsions.

As for *Hallea ledermannii*, it is used as a local anesthetic, decreases blood pressure, and causes disorders in the lymphatic system of the intestine [13]. This plant also has antimicrobial and antioxidant activity [14].

The aim of this work was to evaluate the effects of EAAs and EAHl on blood glucose levels in rats.

Material et Methods

Plant material

The plant material consists of dry leaves of *Annona senegalensis* (Annonaceae) and *Hallea ledermannii* (Rubiaceae) harvested, respectively, in Bouaflé and yopougon, a neighborhood in Abidjan (Côte d'Ivoire). They were identified at the National Floristic Center of the Félix Houphouët Boigny University (Côte d'Ivoire) by the late Professor Aké Assi. Samples of *Annona senegalensis* (Annonaceae) and *Hallea ledermannii* (Rubiaceae) are kept, respectively, under the herbarium numeros 9,809 Lamto 06/12/1967 and 2,538 Forest of the banco 14/10/1954.

Preparation of extracts

To three hundred (300) grams of dried leaves of *Annona senegalensis* or *Hallea ledermannii*, which were cut into pieces, 1.5 l of distilled water is added and the whole is brought to a boil for 1 hour. The decoctate obtained is filtered several times on hydrophilic cotton. The filtrate is dried in an oven at 60°C. After drying, we obtained, respectively, 18 g (7.2%) and 22.5 g (9%) powder of *Annona senegalensis* and *Hallea ledermannii*.

Animal material

The experiments were carried out on rats of the species Rattus norvegicus of Wistar strain weighing between 90 and 150 g and bred in the animal house of Biosciences of the Felix Houphouët-Boigny University, at the ambient temperature (25°C). These rats had access to food and water *ad libitum*, enjoying 12 hours of light and darkness. The animals were acclimatized to laboratory condition before the start of experiment. They were used for the toxicological study and for the evaluation of pharmacological effects on blood glucose.

Phytochemicals studies of the aqueous extracts of Annona senegalensis and Hallea ledermannii

The aim of this study was to identify the chemical groups contained in the EAAs and EAHl, showing pharmacological interest, namely, sterols, polyterpenes, flavonoids, tannins, quinone compounds, saponosides, and alkaloids. For this, we used a qualitative method based on specific chemical reactions described by Bechro et al. [15], Nene Bi et al. [16], and Abo [17]. These tests are based on visual observation of color change or formation of precipitate after specific reactions.

Toxicity study of Annona senegalensis and Hallea ledermannii

This study was carried out according to the principles of Organisation for Economic Co-operation and Development [18] and covered a total of 20 rats for each extract. The healthy rats, weighing between 90 and 150 g, are divided into four batches of five rats, comprising one control batch and three test batches. After subjecting the animals to an 18-hour fast, each animal received a single dose orally with a gastric tube and different doses of the test substances were administered to the rats of the three test batches. The rats of the control group each received distilled water at a rate of 10 ml/kg. The maximum volume administered for each dose does not exceed 2 ml/100 g body weight. Animals are observed individually during the first 30 minutes after the administration of the substances, then every 8 hours and finally every day for 14 consecutive days in order to observe changes in behavior and possible mortality.

Pharmacologic study

This study consisted of determining blood glucose levels in temporary normoglycemic and hyperglycemic rats using the Accu-Chek glucose meter with reagent strips. The blood glucose value is given in mg/dl [19].

Normoglycemic rats

For this study, a total of 60 rats was used, each of these experiments was made from a total of 30 Wistar rats for each extract. The animals were divided into five batches of six rats and were fasted

for 18 hours. Prior to the administration of the test substances, blood glucose is measured in all animals at a T0 time. The rats of batch 1 (control batch) receive 2 ml of distilled water and those of batches test 2, 3, 4, and 5, respectively, receive doses of 50, 100, 200, and 300 mg/kg bw of *Annona senegalensis* or *Hallea ledermannii*. The effect of *Annona senegalensis* (Annonaceae) and that of *Hallea ledermannii* (Rubiaceae) on blood glucose in normoglycemic animals are followed for 3 hours at regular intervals of 30, 60, 90, 120, 150, and 180 minutes after administration of test substances.

Temporary hyperglycemic rats

For this experiment, 40 normoglycemic rats (20 pretreated rats and 20 post-treated rats) weighing between 90 and 150 g were fasted 18 hours before the start of the experiment. They had four (4) lots of five rats for each type of experiment. Blood glucose was measured at regular time intervals of 0, 30, 60, 90, 120, and 180 minutes.

For pretreated rats, the distribution is as follows:

- Lot 1: (R-T) Control rats treated with 2 ml of distilled water (p.o),
- Lot 2: (R-Glib) treated with glibenclamide (10^{-2} g/kg bw) and then 30 minutes afterwards, with 4 g/kg bw anhydrous glucose (p.o),
- Lot 3: (R-EAAs) treated with 100 mg/kg bw of EAAs and then 30 min afterwards, with 4 g/kg bw of anhydrous glucose (p.o),
- Lot 4: (R-EAHl) treated with 200 mg/kg bw of EAHl, then 30 min after with 4 g/kg bw of anhydrous glucose.

For tests with post-treated rats, groups were formed as above, with the only difference that the animals first receive the glucose and then the test substance.

Statistical analysis

Graph Pad Instat (San Diego, Calif., USA) and Graph Pad Prism 5 (San Diego, Calif., USA) were used for the statistical analysis of the values and the graphical representation of the data. The statistical difference between the results was obtained by using the variances (ANOVA), followed by the Tukey–Kramer multiple comparison test, with a significance level $p < 0.05$.

Resultats

Phytochemical study of Annona senegalensis and Hallea ledermannii

Phytochemical screening of EAAs and EAHl revealed certain types of compounds (Table 1).

This study showed that both extracts contain polyphenols, flavonoids, and quinone compounds.

In addition to these compounds, the *Annona senegalensis* extract contains sterols, polyterpenes,

Table 1. Chemical composition of the aqueous extract of *Annona senegalensis* (EAAs) and *Hallea ledermannii* (EAHl).

Chemical compounds		EAAs	EAHl
Polyphenols		+	+
Sterols and polyterpenes		+	–
Flavonoids		+	+
Saponosides		–	+
Quinonic compounds		+	+
Alkaloids		+	–
Tannins	Catechic	+	–
	Gallic	–	–

Presence (+); Absence (–)

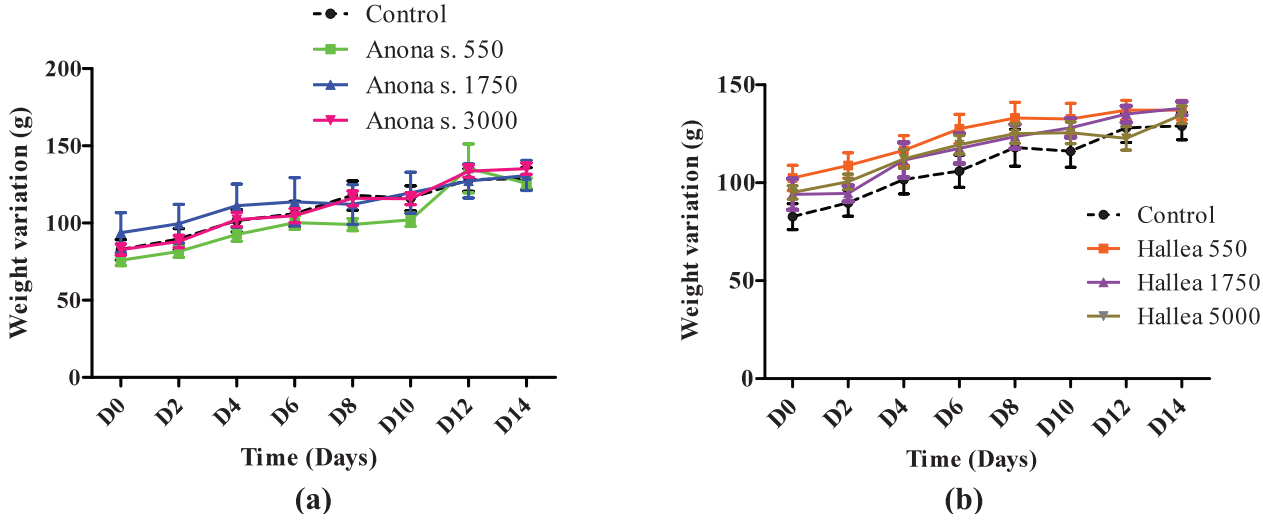

Figure 1. Effect of aqueous extracts of *Anona senegalensis* (a) and *Hallea ledermanii* (b) on weight in rats after 14 days. Values are expressed as mean ± ESM.

alkaloids and catechic tannins, in contrast to the extract of *Hallea ledermannii* which contains saponosides.

Toxicological study of aqueous extracts of Annona senegalensis and Hallea ledermannii

In rats, the extracts of *Annona senegalensis* (550, 1,750, and 3,000 mg/kg bw) and *Hallea ledermannii* (550, 1,750, and 5,000 mg/kg bw) were administered orally by causing a brief decrease of motricity without death in these animals.

Effects of the administration of EAAs and EAHl on the weight of rats

Increasing doses of EAAs (550, 1,750, and 3,000 mg/kg bw) and EAH1 (550, 1,750, and 5,000 mg/kg bw) were administered to the rats of different test batches. After two weeks of the study, no significant variation ($p > 0.05$) of weight was observed in these animals. The experiments were carried out several times ($n = 5$) and the mean values obtained allowed to plot the dose–response curves of different doses of EAAs (Fig. 1(a)) and EAHl (Fig. 1(b)).

Effects of aqueous extracts of Annona senegalensis and Hallea ledermannii on blood glucose in normoglycemic rats

Figure 2 shows the effects of increasing doses (50, 100, 200, and 300 mg/kg bw) of EAAs and EAHl on blood glucose in normoglycemic rats.

EAAs, at the doses of 50, 200, and 300 mg/kg bw, do not significantly ($p > 0.05$) alter blood glucose values after T180 (180 minutes) in treated rats compared to T0 (each T0 represents the control for the concerning group). For the dose of 100 mg/kg bw, there is a significant ($p < 0.05$) effect from 30 to 150 minutes, 60 to 150 minutes, and 90 to 150 minutes, on blood glucose when T30, T60, and T90 are compared to T150. The dose of 100 mg/kg bw reduced glycemia of 40% compared to its T0 (Fig. 2(a)).

Figure 2(b) shows the effect of EAHl on glycemia in rats. At the dose of 200 mg/kg bw, this extract significantly ($p < 0.05$) decreases the blood glucose level, from 30 to 150 minutes and 30 to 180 minutes, when T30 is compared to T150 and T180. EAHl significantly reduced ($p < 0.05$) glycemia of 35.34 % after 180 minutes compared to its T0.

Blood glucose measurement in temporary hyperglycemic rats

Figure 3 shows the effects of EAAs (100 mg/kg bw) and EAHl (200 mg/kg bw) on blood glucose level in pretreated (Fig. 3(a)) and post-treated rats (Fig. 3(b)).

In pretreated rats (Fig. 3(a)), with the test substances and then 30 minutes with glucose solution (4g/kg bw), hyperglycemic peaks were observed at 60 ($p < 0.01$) and 90 ($p < 0.01$) minutes with EAAs. EAAs reduced hyperplycemia compared to the peaks (60 and 90 minutes) of 27.78% and 25.57% after 150 minutes. In EAHl pretreated animals, hyperglycemia was observed at 90 minutes. EAHl induced the decrease of blood glucose value in rats after 120 minutes of 25.41% compared to the peak value.

In post-treated animals (Fig. 3(b)) with EAAs, peaks of hyperglycemia were observed at 30 and 60 minutes and glycemia level decreased after 180 minutes of 27.94% and 29.37% compared to T30 and T60. In animals post-trated with EAHl, hyperglycemia peak was observed at 30 minutes. Compared to the peak glycemia level, EAHl reduced hyperglycemia in rats of 40.30% after 180 minutes. Blood glucose values in all test batches returned to normal and were not statistically

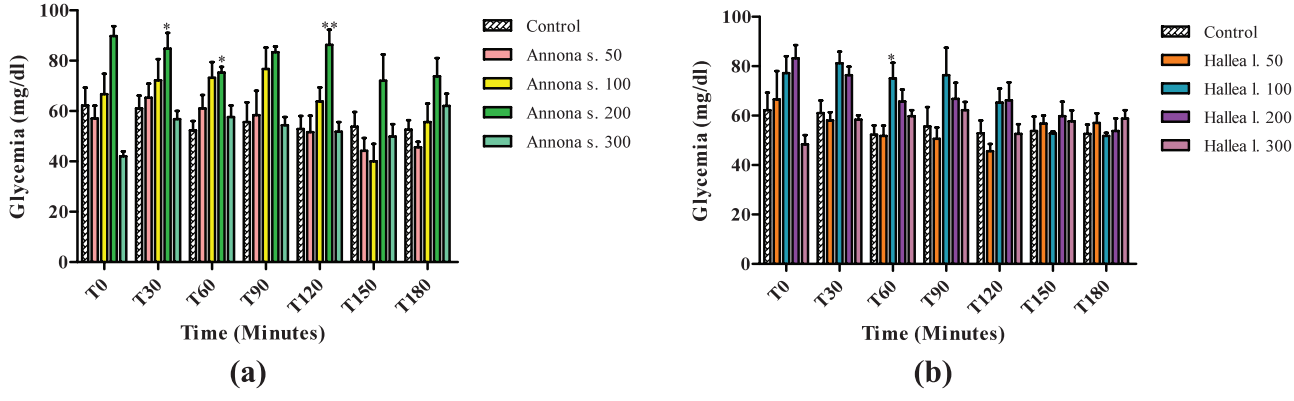

Figure 2. Dose-response effects of *Annona senegalensis* (a) and *Hallea ledermannii* (b) aqueous extracts on blood glucose in normoglycemic rats. Data are presented as mean ± SEM, $n = 6$ (*$p < 0.05$, **$p < 0.01$).

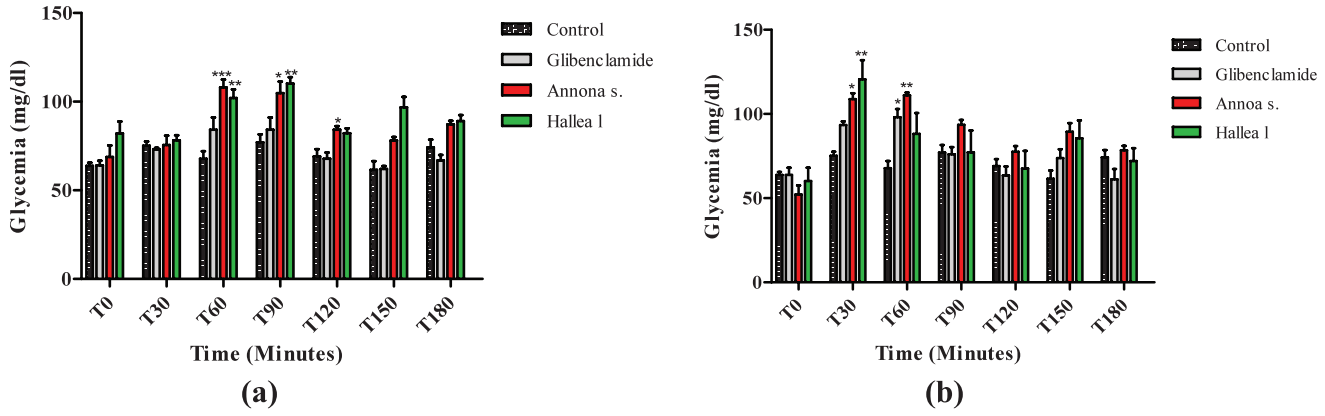

Figure 3. Effects of EAAs and EAHl in pre-treated (a) and post-treated (b) temporary hyperglycemic rats. Results are presented as mean ± SEM, $n = 5$ (*$p < 0.05$, **$p < 0.01$, $p < 0.001$).

different ($p > 0.05$) from the normal control values after 180 minutes.

Discussion

The phytochemical screening carried out with the aqueous extract of *Annona senegalensis* (Annonaceae) revealed the presence of sterols and polyterpenes, polyphenols, flavonoids, quinones, catechic tannins, and alkaloids. This test did not reveal the presence of saponosides. These results are in agreement with those obtained by Konaté et al. [12], with the aqueous extract of the root bark of this plant. On the other hand, studies by Yéo et al. [20] did not reveal the presence of alkaloids and quinone compounds in the ethanolic extract of the leaves of *Annona senegalensis*.

As for the EAHl, this study revealed the presence of polyphenols, flavonoids, quinones, and saponosides. According to our work, this extract would not contain sterols and polyterpenes, tannins, and alkaloids. Previous work by Sofowora [21] with the methanol extract of leaves of this plant, contrary to our results, revealed the presence of alkaloids. This difference could be due to the type of solvent used.

Toxicological studies with the EAAs and EAHl in rats, at the respective doses of 550 mg/kg to 3,000 mg/kg bw and 550 mg/kg to 5,000 mg/kg bw, did not result in deaths. Similar results were obtained with the aqueous extract of the root barks of *Annona senegalensis* by Konaté et al. [12]. These authors showed that the extract of this plant was not toxic in rats at doses lower than or equal to 3,000 mg/kg bw. According to these results, the extracts of *Annona senegalensis* and *Hallea ledermannii* are non-toxic plants.

In addition to the absence of toxicity, these plants do not cause significant variations in the weight in the treated animals.

The results of work on the measurement of blood glucose in normoglycemic rats showed that extracts of *H. ledermannii* and *A. senegalensis* cause hypoglycemia in these animals at the respective doses of 200 mg/kg and 100 mg/kg bw. However, after glucose overload, EAAs exhibited better anti-hyperglycemic effect in the pretreated rat, unlike EAHl. In the post-treated animals, EAHl showed more anti-hyperglycemic effect than EAAS.

Similar properties have been observed in many medicinal plants derived from the African Pharmacopoeia. Indeed, Sy et al. [22–24], studying the activity of the acetonic extract of *Vernonia colorata* leaves on blood glucose levels in rabbits, showed that this extract caused hypoglycemia in these animals. Similar results were obtained with extracts of *Rauvolfia vomitoria* [25], *Boscia senegalensis* [26], *Gnetum africanum* and *Gnetum bulchozzianum* [27], which presented hypoglycemic activities in rats.

Extracts of *Annona senegalensis* and *Hallea ledermannii* showed antihyperglycaemic properties in rats. Similar results were obtained with the F2 fraction of Vernonia coloratapar [28]. These authors demonstrated that the F2 fraction of Vernonia colorata caused a drop in blood glucose in rats with temporary hyperglycemia.

The results of our studies on the phytochemical screening of the extracts of *Annona senegalensis* and *Hallea ledermannii* have made it possible to demonstrate the presence of certain chemical compounds such as flavonoids, tannins, alkaloids, and saponins. Indeed, authors N'Diaye et al. [29] and Olagbende-Dada et al. [30] demonstrated the antihyperglycaemic properties of flavonoids, which act by improving

the body's sensitivity to insulin [31,32]. According to Kambouche et al. [33] the saponins possess an antihyperglycemic effect. Thus, the antihyperglicemic effects of the extract of *Annona senegalensis* and *Hallea ledermannii* in rats are likely due to the presence of chemical compounds such as flavonoids and saponins.

Conclusion

The phytochemical studies of *Annona senegalensis* revealed the presence of sterols and polyterpenes, polyphenols, flavonoids, quinones, catechic tannins, and alkaloids. Those of *Hallea ledermannii* made it possible to demonstrate the presence of polyphenols, flavonoids, quinones, and saponosides.

The EAAs and EAHl, administered orally, are nontoxic in rats at the maximum respective doses of 3,000 mg/kg and 5,000 mg/kg bw. These plants have effects on blood glucose value which are likely due to the presence of chemical compounds such as flavonoids and saponins.

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