

Chronophysiology of Rat Wistar under Extracts from *Khaya Senegalensis*

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Abstract: Generally in Africa and particularly in Benin, the population is increasingly confronted with several pathologies such as diabetes, colds, chest pain, gastric disorders, malaria, bechia, colic and so on. Although modern medicine is well developed, this population for the treatment of these diseases uses traditional medicine because of their low purchasing power. The frequent use of these medicinal plants by traditional healers and the satisfactory results which follow in certain cases has led us to carry out a more thorough reflection on *Khaya senegalensis* in order to relate the use made by traditional healers and scientific evidence. The present work was carried out in order to evaluate the bioactivity of the ethanol extract of the *Khaya senegalensis* barks according to the time of day in the Wistar rat. After phytochemical screening of the extracts, glycaemia, triglyceridemia, total cholesterol, transaminases (ASAT and ALAT) and urea were measured spectrophotometrically in three (03) batches of three (03) Wistar rats each. Lots 2 and 3 received oral doses of 2.5 mg / kg and 5 mg / kg body weight of the extracts, respectively, at 10 am during the day. Control batch 1 received distilled water in place of the extract. The results of phytochemical screening revealed the presence of polyphenolic compounds (gallic tannins, catechic or condensed tannins, anthocyanins, and leuco-anthocyanins), flavonoids, mucilages of reducing compounds, alkaloids, certain anthracene derivatives (Free anthracenics, O-heterosides), steroids, and quinone derivatives. There was a significant decrease ($p < 0.05$) in the blood glucose level 12h after treatment with the extract. Batch 3 which received 5 mg / kg by weight had a lower rate than the batch received 2.5 mg / kg body weight. Triglyceridemia, cholesterol, transaminases and urea did not differ significantly from the control batch ($p < 0.05$), but these values are high compared to the normal values of wistar rats and are due to feeding of these rats. The long-term use of the ethanolic extract of *Khaya senegalensis* bark could compromise liver and kidney function and inhibit apoptosis, that is, can induce cancer in the wistar rat.

Keywords: *Khaya senegalensis*, Bark, Extracts, Biological rhythm, Biochemical parameters

1. Introduction

According to the first global report on the WHO diabetes, published in April 2016 on the occasion of World Health Day, 422 million adults are living with diabetes, mostly in [1] developing countries. According to the report more than 80% of diabetes deaths occur in low- and middle-income as Benin. Diabetes could become the seventh leading cause of death worldwide by 2030 [1].

Furthermore WHO estimates the prevalence of diabetes in Benin in 2016 to 5.1% among both men and women? Ce rate is one of the highest rates in the sub-region. [2]

Current diabetes treatments are effective in lowering blood sugar, however the daily adequate glycemic control is very difficult to achieve in most cases, and this leads to long term to the emergence of very serious complications. The recent growth of herbal medicine offers an opportunity to find natural compounds that may have beneficial effects on the regulation of glucose metabolism avoiding the side effects of synthetic substances [3]. The effectiveness of *Khaya senegalensis*; this tropical plant, the drop in blood sugar is no longer in doubt at present [4] [5] [6]. It reduces hepatic glucose release and this effect is stronger than the extracted insulin 2.5UI [4].

Chronobiology is the science of rhythmic organization of living things. Interpreted as an adaptation of living in regular change of its habitat, the biological rhythm must be understood as an anticipation of imminent and foreseeable regular event. It is the gradual selection of the most appropriate forms of life to their environment that phylogeny has gradually entered the rhythmic function in the genes and because it anticipates the coming changes, the biological rhythm has become the most link effective between the living and its habitat. [7]

The chronophysiology is the application of chronobiological knowledge to the field of physiology. The chronophysiology provides a dynamic view of understanding the workings of the human body. It takes into account natural fluctuations in body functioning, the scale of a day, month or year. This work aims to demonstrate the mastery of chronophysiology could be useful in improving treatment of diabète par extracts from the bark of *Khaya senegalensis*.

2. Materials and Methods

The study was conducted at the Laboratory of Cellular Signaling and Biomembranes, Faculty of Science and Technology, University of Abomey Calavi in southern Benin, between June 2016 and October 2016. The extraction was performed in the laboratory of pharmacognosy and Oils

essential to the Institute of applied biomedical sciences (ISBA), Cotonou, Benin.

2.1. Assumptions

- Extract *Khaya senegalensis* would be more effective for lowering blood sugar at a certain time of day;
- Extract *Khaya senegalensis* would act on biochemical parameters (triglycerides, LDL, HDL and cholesterol) differently depending on the time of its decision.

2.2. Materials and methods

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2.2.1. Rootstock

Khaya senegalensis of bark were collected in June 2016 in the city of Abomey, agroecological zone VI, in the south of Benin. This area has a Guinean climate with two rainy seasons (April-July, September-November) precipitation varies from 1000 to 1400 mm and the soil is laterite, ironstone or HYDROMORPH. The plant material was dried in air and ground into powder.

2.2.2. Preparation of extract

The dry bark extracts of *Khaya senegalensis* were cut into small pieces and then ground in the mill knives. 100 g of the resulting powder, weighed using an analytical balance Sartorius® and placed in a container prepared for this purpose, were soaked in 500 ml of 96% ethanol for 72 hours. Then, the macerate is filtered through cotton wool fiber. The obtained filtrate was evaporated at 40 ° C using the Rotavapor evaporator. The paste deposited in the evaporator flask bottom was recovered in pots and dried in an oven at 45 ° C. After complete drying, the merged solid deep pots were scraped, crushed and stored in jars.

2.2.3. Phytochemical Screening

It is based on the reactions (color and precipitation) large differential groups of chemical compounds in the plants according to the method of Houghton PJ and A. RAMAN (1998) reviewed and adapted to the conditions of pharmacognosy laboratory and essential oils ISBA.

2.2.4. Biological Material

Nine Wistar rats of body weight between 205g and 250g, provided by the pet department of the University of Abomey Calavi were used for the test.

2.2.5. Determination of biochemical parameters

To assay blood glucose, triglycerides, urea and transaminases and cholesterol in Wistar rats, the material is taken at the olphatique vein, blood is collected in tubes and ependolfs is then centrifuged at 3000 rpm for 10 minutes and the supernatant serum was decanted and stored for the determination of 2.5.1. Gavage rats

The principle is to administer the ethyl extracts of *Khaya senegalensis* in Wistar rats (male and female) of about 200g and having the same food intake, orally at various doses. These animals do not receive any other medication during the experimental period outside the extract. The rats were randomly divided into 03 batches of 03, then the batch is assigned respectively the doses per kg body weight. The beginning of the experiment were weighed each of the rats of each batch in order to find the average weight and calculating the effective dose of extract to be administered to him.

Lot 1 is the control group. The rats of this batch will receive distilled water. At the lot 2, the animals receive 2.5 mg / kg body weight of ethyl extract of *Khaya senegalensis* and animals lot3 receive 5 mg / kg body weight. The administration of the various solutions will orally using a syringe with a probe. After feeding, the samples are taken at 4 interval to see the effect of the extract on biochemical parameters and thus the duration of action of the extract on these parameters.

2.2.5.1. Gavage rats

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2.2.5.2. The blood sample

The blood sample is carried out according to the experimental protocol used by WOUETOLA (2014). The puncture of the retro-orbital sinus was performed without anesthesia. The animal is kept a hand in lateral recumbency, and held by the scruff of the neck. Thumb pressure on the neck behind the jaw angle, allows a compression of the jugular vein, and thus venous stasis to the head, favoring filling the retro-orbital sinus.

By making a slight pull on the upper eyelid with the index, we create exophthalmia facilitating blood sampling using heparinized hematocrit tube or not. The end of the tube is introduced slowly in the lateral angle of the eye. Progression through the tissue is facilitated by printing a slight rotation in the pipette. As soon as one reaches the venous plexus, blood flowed in the periorbital space and rises by capillary action into the tube. The volume of collected blood is 0.5 to 2 ml.

Before removing the tube, releasing the compression and the bleeding stops spontaneously when the eye pressure normalizes. The recovered blood is used for the determination of various biochemical parameters. Blood is collected in anticoagulant without hemolysis tubes and

centrifuged at 3000 rev / min for 15 minutes at a temperature of 4 ° C. Following centrifugation of blood, the obtained serum is stored in tubeseppendorf at a temperature of -4 ° C for the analysis of various biochemical parameters.

3. Results and Discussion

In this part we will present the results based on the average per group of rats at each sampling time. Recall that we have three groups:

- The control group (T) receiving only distilled water
- The rat group receiving 2.5 mg of *Khaya* (R 2.5)
- The group of rats that received 5 mg of *Khaya* (R 5)

3.1. Coefficient extraction

The mass of solids obtained after extraction with alcohol is obtained 42.79 g, corresponding to a yield R (alcohol) = $(42.79 \text{ g} / 100 \text{ g}) \times 100 = 42.79\%$

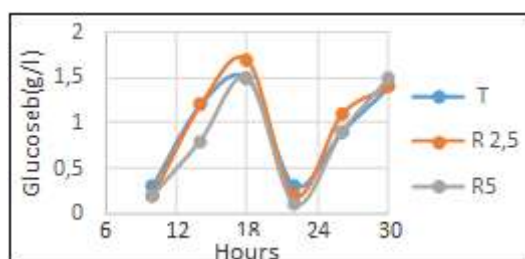
3.2. Results of phytochemical analysis

Extracts of the bark of *Khaya senegalensis* contain abundant polyphenolic compounds such as tannins, catechin and leucoanthocyanins tannins and saponins such as abundant sanosides with a foam index of 4. other polyphenolic compounds, such as anthocyanins derivatives anthracene such as O-glycosides aglucones are rare in these extracts Unlike steroids that are there in small quantities. (See Table I)

Table I: Results of phytochemical analyzes

chemical groups	Subgroups	Observation
Polyphenolic compounds	Tannins	+++
catechin	tannins	++
anthocyanins		+++
Leuco anthocyanin		+++
Saponosides	Sanosides	+++
Index of the foam		is 4 +++
Steroids	steroids	+
anthracene derivatives	O-glycosides with reduced	genins ++
Abundant	+++ ++ + Scarce	Low

3.3. Chronophysiologie glycemic Wistar rats



Graph 1: Change in mean levels of blood sugar over time (gavage made 09 h).

The previous graph shows the variation in the different average rates of glucose from our three groups of rats in

function of time. It is apparent from this graph several observations:

- 1) The three glycemic variation curves have the same general appearance
- 2) They all have a higher average rate of glucose from 10h to 18h and 22h to 06h with peaks at 18h and 06h.
- 3) They all have lower average rate between 18h and 22h.
- 4) So we could hold on chronophysiologique basis of blood glucose in rats following 24 the following chronology:
 - From 10 to 18 it rises to a first peak around 18h
 - From 18h to 22h it decreases to its lowest value around 22h
 - From 22h to 06h we have a new increase and a new peak around 06h
 - And from 06h to 10h we have a new decrease.
- 5) The increased glucose in rats occur during periods of high food activity against the reduction would occur during periods of rest
- 6) They all have a higher average rate of glucose from 10h to 18h and 22h to 06h with peaks at 18h and 06h.
- 7) They all have lower average rate between 18h and 22h.
- 8) So we could hold on chronophysiologique basis of blood glucose in rats following 24 the following chronology:
 - From 10 to 18 it rises to a first peak around 18h
 - From 18h to 22h it decreases to its lowest value around 22h
 - From 22h to 06h we have a new increase and a new peak around 06h
 - And from 06h to 10h we have a new decrease.

The increased glucose in rats occur during periods of high food activity against the reduction would occur during periods of food break.

This first observation allows us to think that already fall significantly glycemic rats it would be preferable to administer the *Khaya* between 10 and 18h and between 06h and 22h and when the food rat activity is highest.

3.4. Changes in blood sugar under *Khaya*

The Graph 1 also shows that the R2.5 curve which represents the rats receiving 2.5 mg of *Khaya* is above the curve T of the control rats that received only the eau distiller which means that glucose these rats increased. Moreover, the curve R5 rats received 5mg of *Khaya* is that which is below all other curves therefore having the lowest values of blood sugar. This is conceived that extracts *Khaya* not lower their blood sugar as from a certain amount below which they will instead lead to the opposite effect.

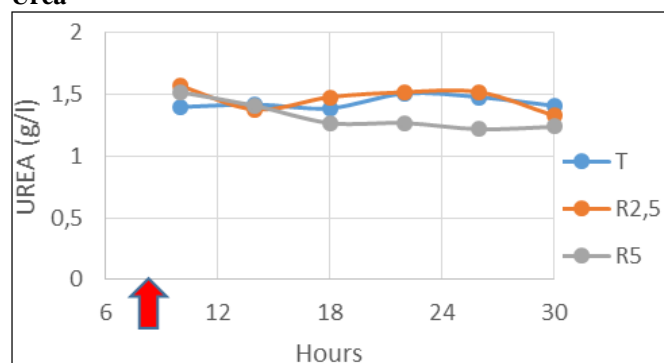
Glucose was measured for each concentration of the extracts of *Khaya senegalensis* and for each instant spectrophotometrically (reading be wavelength 500 nm) using the reagent of GOD-PAP. This is an enzymatic method based on the oxidation of glucose. The increase in mean blood glucose could be explained by the activation of glycogen synthase, glycogen phosphorylase, a phosphatase enzyme and molecules such as ATP.

The reduction rate may be explained by the glycogen synthase phosphatase inactivated form of glycogen. Which causes the activation of glycogen phosphorylase by phosphorylation (ATP contribution).

Our initial hypothesis regarding the effectiveness of *Khaya* in lowering blood sugar at a certain time of day to be completely checked should therefore be considered as the dose of *Khaya* (Greater than or equal to 5 mg)

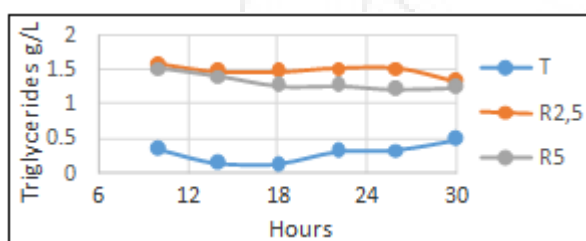
3.4.1 Change in other biochemical parameters

Urea



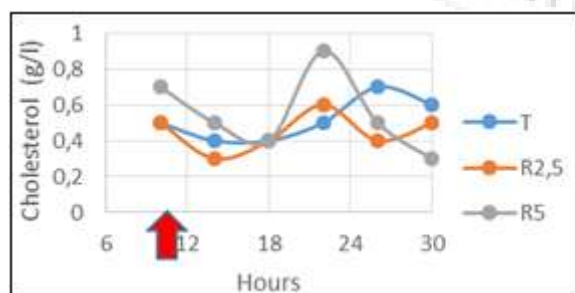
Graph 2: Change in average rates of urea in different groups of rats in function of time

3.4.2. Triglycerides



Graph 3: Change in mean levels of triglycerides among the different groups of rats over time

3.4.3 Cholesterol

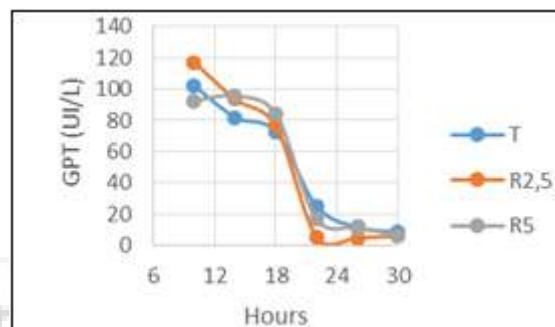


Graph 4: Change of average cholesterol levels among the different groups of rats in function of time

3.4.4. Transaminases AST



Graph 5: Change of average AST among different groups of rats over time.



3.5 Figures and Tables

Chemical groups	Subgroups	Observation
Polyphenolic compounds	Tannins	+++
	catechin tannins	+++
	Anthocyanins	++
	Leuco-anthocyanin	+++
Saponosides	Sanosides	+++
	Index of the foam is 4	
Steroids	Steroids	+
anthracene derivatives	O-glycosides with reduced genins	++

+++ Abundant
 ++ Little abundant
 + Low

Diabetes mellitus is a heterogeneous group of metabolic diseases whose main characteristic is hyperglycemia resulting from a defect in secretion, from the action of insulin or from these two associated abnormalities. It affects more than 5% of the population and represents the major source of morbidity in developed countries (Sharma et al, 2008). Given the considerable increase in the number of diabetics and the secondary failures of antidiabetic drugs, many researchers have evaluated the pharmacological action of traditional plants and thus their interests in traditional medicine.

Several hundred plants are known and used as antidiabetics by traditional medicine but a crippled part has been the object of study or validation of their antidiabetic activities through experiments.

Khaya senegalensis is a plant that is used for its various effects on blood parameters (Adebayo et al., 2003; Kolawolé et al., 2011); In the treatment of several diseases (Gill, 1992). Little work has been devoted to the antidiabetic activities of *Khaya senegalensis*. Zohoun in 2011 showed in vitro that the ethanolic extracts of *Khaya senegalensis* inhibit hepatic release of glucose at low concentrations (5, 10 or 20 µg / l). This work reveals that *Khaya senegalensis* contains the main

groups of active ingredients polyphenolic compounds (predominantly), saponosides, steroids and O-heterosides.

The hypoglycemia observed in normoglycemic rats suggests that the ethanolic extracts of *Khaya senegalensis* have been able to act in the same way as certain oral antidiabetic agents such as glibenclamide by closing K^+ / ATP channels, membrane depolarization, Influx Ca^{2+} , the first key step for insulin secretion (Henquin, 2005). It is demonstrated that *Genderma lucidum* polysaccharides (a fungus) do not stimulate insulin synthesis, but can directly stimulate its release from the remaining pancreatic β cells by facilitating the influx of Ca^{2+} into pancreatic β cells in Rats rendered diabetic by streptozotocin (Zhang et al., 2004).

The hypoglycemic effect of the ethanolic extract of *Khaya senegalensis* can also be assimilated to both the effects of the organic constituents and those of the inorganic constituents. Among other things, it is important to note that the inorganic constituents that medicinal plants contain play a primary role in improving their medicinal properties, including hypoglycaemic activity. For this purpose, Bhaskar et al. (2008), who studied the effect of the aqueous extract of *Mucuna pruriens* "200mg / kg" in rats rendered diabetic by streptozotocin, clearly indicates that certain numbers of essential minerals such as Na, K, Ca, Zn, Mg, Fe, Cu, and Mn may be associated with an insulin release mechanism and its activity. It has also been reported that several bioactive molecules isolated from plants such as terpenes and flavonoids influence pancreatic β cells and stimulate insulin secretion by their antioxidant activities (Sarkhail et al., 2007).

Since oxidative stress and free radicals affect and destroy β cells during diabetes, the ethanolic extract of *Khaya senegalensis* can also increase the secretion of insulin via its antioxidant activity (El-Alfy et al., 2005).

The objective of our work is to see specifically the effect of the ethanol extract of *Khaya senegalensis* on the biochemical parameters over a period of 24 hours at an interval of 4 hours of time.

The lipid profile of the rats after treatment has not changed much. This shows that the ethanolic extracts of *Khaya senegalensis* would not have an instantaneous hypoglycaemic activity. In their work, Masuma et al (2010) report that several studies have indicated that elevated total cholesterol is strongly associated with coronary atherosclerosis and increases cardiovascular risk. They enrich their remarks by continuing that clinical studies have shown that a decrease in cholesterol by using diet or drugs decreases the incidence of coronary heart disease. In these rats, the cholesterolemia increased with the dose of 5mg to 22h therefore 12h after the treatment. The rats of lot1 (control) and those of lot2 did not undergo a significant difference in cholesterolemia. Extracts of *Khaya* at 5mg / kg body weight may affect some blood enzymes (Kolawolé et al., 2011) or liver enzymes especially those involved in cholesterol metabolism. Triglyceridemia was also lowered at *Khaya* at a dose of 5 mg / kg body weight 12 hours after that at 22 hours, which may be due to a reduction in the synthesis of liver triglycerides and / or A

reduction in lipolysis due to an increase in insulinaemia (Sivaraj et al., 2009) under *Khaya senegalensis*.

The urea levels at lot 2 and lot 3 (lots receiving *Khaya* at different doses) did not undergo a particular increase compared to lot 1 (control batch) at the different sampling times. This requires good functioning of the kidneys of the rats undergoing treatment. Increased uraemia may be associated with impaired renal excretion (renal failure). During a chronic renal wait, there is not only a deficit of urea removal but also sulphates, phosphates and ions (Valdiguíe, 2008).

Prolonged treatment of these rats with *Khaya* extracts causes a rise in uremia with a proportional increase in dose. (Kolawolé et al., 2011). Creatinine, just like urea, increases with dose. The increase in creatinine is an indicator of kidney damage (Valdiguíe, 2008), supports the idea of a renal attack both with ethanolic extracts and with aqueous extracts of *Khaya senegalensis*. The ethanolic extracts of *Khaya senegalensis* therefore have no immediate action on the kidneys.

The harmful effects of prolonged treatment with extracts of *Khaya senegalensis* do not seem to affect the kidney. The group of Kolawolé et al (2011) found that aqueous extracts of *Khaya senegalensis* raises the level of alkaline phosphatase. Increases in alkaline phosphatase are observed in liver disease (Valdiguíe, 2008), which supports a hepatic attack during prolonged treatment.

Other indicators of renal function were explored under *Khaya senegalensis*. These are alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT). The increase of these enzymes (transaminases) is moderate in chronic hepatitis and translates the parenchymatous involvement by cell necrosis. Also, it is due to obstruction of the biliary tract (Valdiguíe, 2008). Transaminase levels did not increase after gavage compared to lot1 (control group). This assumes that *Khaya senegalensis* has no immediate action on the liver.

In our work, the treatment of the animals by extracts causes the decrease of the glucose 12h after the treatment. This confirms the work of Abdoulaye ISSOTINA ZIBRILA in 2012 which showed the antidiabetic activity of the extracts of *Khaya* in the rabbit. Treatment at a dose of 5mg / kg results in a greater decrease in blood glucose than in the dose of 2.5mg / kg. These results confirm the work of Kolawolé et al, (2011).

This decrease may be due to an increase in tissue sensitivity to insulin affecting peripheral cells such as muscle, adipose tissue and liver, to an activation of the signaling pathways of insulin which affects in particular the number of receptors To insulin and / or their affinity for the hormone and the number of insulin-dependent membrane transporter which allows the entry of glucose into the cells.

4. Conclusions

All of our work has highlighted the hypoglycaemic activity in normoglycemic rats extracts of the bark of *Khaya senegalensis* over 24h at 4h interval justifying its traditional use as antidiabetic. Thus, we were able to observe the effect of these extracts on the lipid profile, the transaminases as well as on the uremia.

First, we validated the hypoglycaemic activity of ethanolic extracts of *Khaya senegalensis* in rats 12h after administration at a dose of 5mg / kg. Its effect over a period of 24 hours on the lipid profile, uremia and transaminases is not remarkable. These results show overall low activity on blood glucose and lipid profile also its effect on the liver and kidneys is not instantaneous. Our results thus bring to the surface the question of the inadequacies of the traditional treatments by the plants and especially the traditional self-medication. These treatments do not take into account the therapeutic specificity of each disease in relation to chronopharmacology and the biological rhythm of the organs.

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