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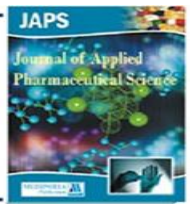

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Effect of aqueous extract of *Terminalia catappa* leaves on the glycaemia of rabbits

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ABSTRACT

Diabetes is a disease which affects 5% of Côte-d'Ivoire population. This is a worrying prevalence rate. Our search for means of fighting this affection made us to develop an herbal medicine from decoction of *Terminalia catappa* leaves. During the experience we carried out, rabbits received, orally, a solution of glucose (4 g/l). As treatment, the hyperglycaemic rabbits were given, glibenclamide (0.25 mg/ml) and herbal medicine to drink, 0.6 ml per 20 grams of body weight. Before administration of glucose overload, the animals had a basal glycaemia of 1.11 g/l. The not treated rabbits' glycaemia increased and reached 1.39 g/l. The oral administration of glibenclamide lowers blood sugar at 0.86 g/l, after 180 minutes. At 2.5 mg/ml, the herbal medicine does not induce a significant hypoglycaemic effect. At 10 mg/ml, it decreases the hyperglycaemia to 1.05 g/l. At 40 mg/ml, it induces a significant decrease in blood glucose. A fall of 30% was observed. At 40 mg/ml, its effect on hyperglycaemic rabbits is compared to glibenclamide (0.25 mg/ml). The glibenclamide exerts on normoglycaemic rabbits a significant basal glucose-lowering effect unlike herbal medicine. The herbal medicine appears like an antidiabetic and produces its hypoglycaemic effect mainly through alkaloids, sterols or triterpens.

Keywords: Côte-d'Ivoire, Diabetes, Ethnopharmacology, Medicinal plants, Traditional Healers.

INTRODUCTION

Diabetes is a metabolic disease which exists everywhere in the world and interests approximately 6% of the world population. Côte-d'Ivoire has about 5% of diabetics (Djédjé, 2002). This prevalence rate places the diabetes like most frequent of endocrinien diseases (Gentilini, 1993). This disorder concerns genetic and exogenic factors (viral, chemical) and damages the β cells of Langerhans (Kadja, 1998). As a result, the body becomes unable to produce insulin, a pancreatic hypoglycaemic hormone. This disorder is characterized by polyuria (frequent and abundant urines), glycosuria (presence of glucose in urines) and hyperglycaemia (glucose rate on an empty stomach higher than 1.2 g/l in plasma blood and confirmed in at least two occasions). Diabetes comes with other complications (kidney, eye) and appears as a major cause of disability and death (Dièye et al., 2008). In modern medicine, no satisfactory effective therapy is still available to cure diabetes (Paris and Amarnath, 2004). Currently, diabetes therapy is based on the use of hypoglycaemics (sulfonamides, biguanides, insulin), on hygieno-diet measures and exercises (Reichard et al., 1993). Even if the injections of insulin or other products make it possible diabetic to remain in life, the diabetes requires a long treatment, which the patients have of the evil to support. In the search of means of fighting, man recognized and used the medicinal properties of many cultivated or wild plants and many drugs to combat this worrying affection.

It is in this context that studies have been conducted to provide a scientific basis of traditional therapeutic uses. We mention, for examples, the works of Kadja (1998) that reported the antidiabetic properties of DIOCODA, a vegetable natural substance. There are also those of Kwashie et al. (1998) which indicated the hypoglycaemic effect of aqueous extract prepared with leaves of *Stereospermum kunthianum* (Bignoniaceae). Kamtchouing et al. (2004) highlighted the hypoglycaemic effect of hexane extract of *Anacardium occidentale* (Anacardiaceae) on diabetic rats. Bhandari et al. (2005) related that ethanolic extract of *Zingiber officinale* (Zingiberaceae) produced significant antihyperglycaemic effect in diabetic rats. In their study, N'Guessan et al. (2008) indicated the hypoglycaemic activity of aqueous extract of leaves of *Crescentia cujete* (Bignoniaceae). N'Guessan et al. (2009a) reported the antidiabetic effect of seeds of *Persea americana* (Lauraceae). N'Guessan et al. (2011) related the hypoglycaemic effect of *Boerhavia diffusa* leaves on rabbits.

The ethnopharmacological survey conducted in Aboudé-Mandéké in the region of Agboville (Côte-d'Ivoire), made us discover that *Terminalia catappa* L. (Combretaceae) is used in traditional medicine to treat diabetes. Concerning this plant, we reported its empirical antidiabetic effect (N'Guessan, 2008; N'Guessan et al, 2009b), but no experimental study on its hypoglycaemic activity has been carried out. This study aims at finding new affordable therapies, inexpensive and able to normalize and stabilize the glycaemia. Its objective is to experimentally study the effect of the total aqueous extract of the plant's leaves on the glycaemia of hyperglycaemic rabbits in order to provide scientific evidence of the effectiveness of the traditional use of *Terminalia catappa*, as antidiabetic.

MATERIAL AND METHODS

Plant material

The leaves of *Terminalia catappa* L. (Combretaceae) were collected, freshly, within the village of Aboude-Mandeke in the Department of Agboville (South of Côte-d'Ivoire). From the collected samples and specimens of the herbarium of the National Floristic Center, we identified the plant, by its scientific name. A voucher specimen (Moutcho, Cote-d'Ivoire, 20 août 1998, N'guessan Koffi n° 298) was deposited in National Floristic Center (University of Cocody-Abidjan, Cote-d'Ivoire).

Preparation of plant extract

Eight hundred (800) grams of the drug (fresh leaves of *Terminalia catappa*) were collected and rinsed then dried for 3 weeks in the shade, well-ventilated place, to avoid contamination by mould. The leaves were pulverized with an electric grinder (type RETSCH) and a powder was obtained. Two hundred (200) grams of the dry powder were obtained and introduced in 500 ml of distilled water. The mixture, bulled during 30 minutes, was wrung in a neat cloth square, filtered successively twice on absorbent cotton and on Wattman 3 mm paper. The volume of the filtrate obtained was concentrated and evaporated in a drying oven at 60°C, during 2-3 days. The pulverized crystals made it possible to obtain fine powder used for the experimentation. The total water extract, codified KCTC, is then kept in sterilized glass bowls, hermetically closed, in a fridge.

Animal material

We used rabbits (*Oryctolagus cuniculus*, Leporidae) we bought in a farm located in Bingerville, suburbs of Abidjan (Côte-d'Ivoire). They were twenty four (24), with as many males as of females. These animals were old 6 to 10 weeks and weighed between 1200 and 1800 grams. They were placed in ventilated metal cages containing litters of shavings which are regularly renewed. They are acclimatized to the conditions of the animal house, during 7 days before the treatment and fed with the granules produced by the Ivorian Compound Food Manufacturing Society (F.A.C.I.). We used tap water. The rats were divided into 8 batches of 3, as follows:

Batch 1: sample rabbits with normal glycaemia.
Batch 2: sample hyperglycaemic rabbits treated with glucose (4 g/l).
Batch 3: hyperglycaemic rabbits treated with glibenclamide at 0.25 mg/ml.
Batch 4: hyperglycaemic rabbits treated with herbal medicine at 40 mg/ml.
Batch 5: hyperglycaemic rabbits treated with herbal medicine at 10 mg/ml.
Batch 6: hyperglycaemic rabbits treated with herbal medicine at 2.5 mg/ml.
Batch 7: normal glycaemic rabbits treated with glibenclamide at 0.25 mg/ml.
Batch 8: normal glycaemic rabbits treated with herbal medicine at 40 mg/ml.

Technical material

Pasteur pipettes were used to take blood samples we collected in hemolysis tubes. Electrical scales for weighing powders were needed. The glycaemia level determination device included a spectrophotometer of KENZA type.

Chemicals

Surgical spirit was necessary to treat injured rabbits. The glucose, a glucidic agent, known to cause hyperglycaemia, was used. For the treatment of induced hyperglycaemic rabbits of control group, we used glibenclamide (DAONIL tablet, 5 mg), the reference product having hypoglycaemic effect. Oxalate of sodium and sodium fluoride was needed in order to stabilize the process of glycolysis in blood. To carry out the phytochemical screening, we used solvents (ether of oil, methanol and distilled water) and various classic reagents (N'Guessan, 2008). Classical methods described in the works of Ronchetti and Russo (1971), Hegnauer (1973), Wagner (1983), Bekro et al. (2007) were used to characterize the chemical groups.

Induction of hyperglycaemia

We used glucose whose hyperglycaemic property is established with rabbits (Kwashie et al., 1998; Gharras et al.,

1999). Lukens (1948), Siliart and Andre (1987) were interested in the glycaemia disorders and therapeutic consequences on dogs. Instead of dogs, we used rabbits, easier to handle and in which the diabetogenic property was also observed (Kadja, 1998; Djédjé, 2002). The glucose absorption depends on the body weight of the animal: 0.6 ml of glucose for 20 g of rabbit weight. Except rabbits of batches 1, 7 and 8**,** all the animals receive a glucose overload at the moment T=0, after basal glycaemia determination. The administration of glucose (4 g/l) is done by oral way, with a nozzle of intubation. Then, the status of rabbits is closely monitored and is detected every thirty minutes by determination of blood sugar quantity.

Treatment of hyperglycaemic rabbits with glibenclamide and herbal medicine (KCTC)

The rabbits of batch 3 are treated with glibenclamide (5 mg/20 ml distilled water, that to say 0.25 mg/ml), 30 minutes, after the cramming by glucose. The rabbits of batches 4, 5 and 6 are treated with the herbal medicine that we call "KCTC", 30 minutes, after the cramming by glucose. To do things like the traditional healers, the hyperglycaemic rabbits received, orally, 0.6 ml of glibenclamide and herbal medicine for 20 g of body weight.

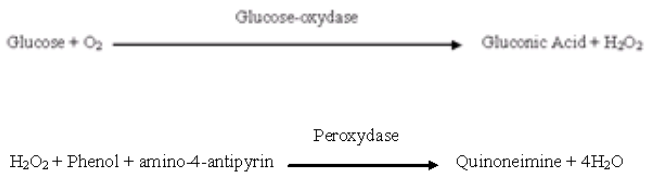
Rabbits' blood sampling

All the animals (rabbits) used for experimentation were deprived of food overnight. Pasteur pipettes were used to take blood samples done, intravenously, through the marginal vein of the ear, to determine glycaemia level. The blood (3 ml) is collected in hemolysis tubes containing an anticoagulant (oxalate of sodium and sodium fluoride) in order to stabilize the process of glycolysis in blood. Thirty (30) minutes before treatment, the blood of all the animals was taken, for determination of the basal glycaemia. Thereafter, blood samplings were made, every 30 minutes after the treatment, according to the constituted batches. On the whole, 7 blood tests were carried out on each animal, during 180 minutes.

Rabbits' glycaemia determination

Principle of determination

The method used is that related to the enzyme (Djédjé, 2002). It consists in oxidizing glucose by the glucose oxydase, enzyme with production of gluconic acid and hydrogen pyroxyde (H_2O_2). The hydrogen pyroxyde reacts with phenol and 4-amino-antipyrine in the presence of peroxydase to form a compound of red brick, quinoneimine and water. The optical density of quinoneimine to 500 nm is proportional to the concentration of glucose in the sample. Below we present the following reaction of blood sugar quantity determination.



Protocol

A milliliter of enzymatic solution works in 10 microliters of serum. The blood is centrifuged to 3500 rpm for 10 min and then the serum is collected. After a bain-marie at 37 ° C, the serum is immediately analyzed with a spectrophotometer KENZA type. A reading is made with a spectrophotometer at 500 nm against the white composed of enzymatic solution. The glycaemia is then determined each hour, during experience. Below, we present formula used to calculate the glucose rate:

$$\text{Glucose rate (g/l)} = \frac{D_0 \text{ sample}}{D_0 \text{ standard}} \text{ X n, with n = standard value.}$$

The dosage of glycaemia has been achieved in Medical Analysis Laboratory located in City of Arts (L.A.M.C.A) in Cocody (Abidjan, Cote-d'Ivoire).

Statistical analysis

Data on the variations of glycaemia were expressed in the form Mean ± SEM of 3 observations, on the histograms we traced with the STATISTICA software. Data were analyzed statistically by one way analysis of variance ANOVA statistical test using STATISTICA version 6.05 (Windows XP) to test for significance. $P < 0.05$ was considered significant. We used Mauchley test to verify the condition of sphericity and Newman Keuls test for the comparison of the means (α *=5 %*).

RESULTS AND DISCUSSION

Effects of glucose overload on rabbits with normal glycaemia level

The figures 1 to 6 show the level of blood glucose in normal, hyperglycaemic control and experimental groups of rabbits. Before treatment, all the animals had a basic glycaemia of about 1.11 g ± 0.05. This result on the basic glycaemia in rabbits deprived of food overnight confirms work of Djédjé (2002). A few moments (30 minutes) after administration of glucose to all the animals, the glycaemia rise gradually to reach 1.4 g/l: the rabbits showed a significant level of blood glucose. The glucose overload induces on rabbits a hyperglycaemia, after its administration. That confirms the property of glucose as a product able to create hyperglycemia. This result confirms that of Kwashie et al. (1998) on rabbits' glycaemia.

Evolution of glycaemia after glucose overload

The figure 1 reports result on rabbits of batches 1 and 2. The rabbits of batch 1 are the sample rabbits not treated by glucose (4 g/l). Their glycaemia fluctuates between 1.12 and 1.18 g/l: glycaemia remains basically stable, during the experiment. We notice two stages in the evolution of glycaemia with the rabbits of batch 2 (sample rabbits induced with glucose overload but not treated): an increase phase from basic glycaemia (1.09 g/l) to the peak (1.39 g/l) during which the rats showed a significant level of blood glucose and a decreasing phase during which glycaemia goes from 1.39 to 1.16 g/l. A fall of 18 % is noted, after the glycaemic

peak. At the end of the experimentation, the blood glucose value (1.16 g/l) is near normal level. The induced hyperglycaemia is transitory: the organism is able to restore normal glycaemia, after a glycaemic overload.

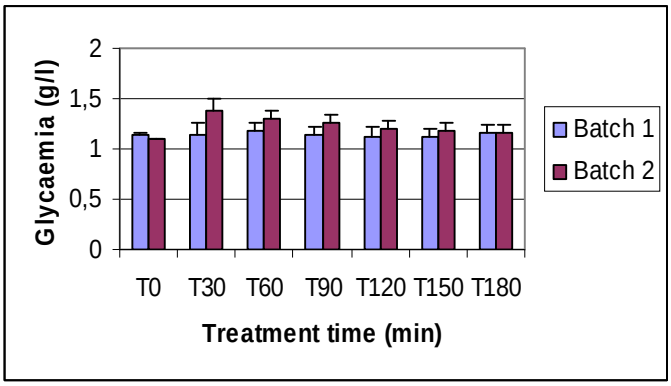


Fig. 1: Glycaemia variation histogram for sample untreated rabbits with normal glycaemia and sample hyperglycaemic rabbits treated with glucose (4 g/l); Mean ± SEM, n =3, P < 0.05. Batch 1: sample untreated rabbits with normal glycaemia. Batch 2: sample hyperglycaemic rabbits treated with glucose (4 g/l).

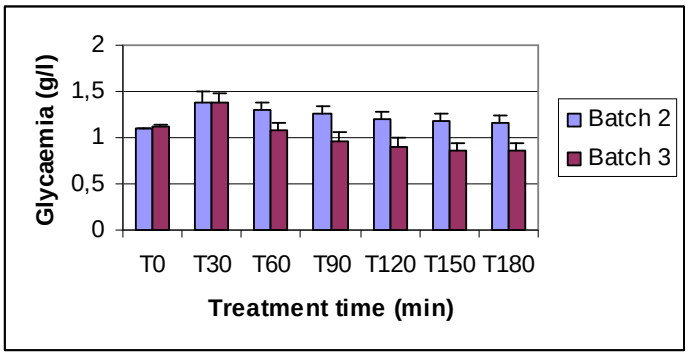


Fig. 2: Glycaemia variation histogram for sample hyperglycaemic rabbits treated with glucose and sample hyperglycaemic rabbits treated with glibenclamide; Mean ± SEM, n =3, P < 0.05. Batch 2: sample hyperglycaemic rabbits treated with glucose (4 g/l). Batch 3: hyperglycaemic rabbits treated with glibenclamide (0.25 mg/ml)

Effects of glibenclamide on hyperglycaemic rabbits

The administration of glibenclamide to hyperglycaemic rabbits of batch 3 shows a significant decrease in the level of blood glucose that pass from 1.38 g/l to 0.86 g/l. A fall of 38 % is observed, 180 minutes later (fig. 2): glibenclamide exerts a hypoglycemic effect, in accordance with the results of Gharras et al. (1999). The glibenclamide contribution corrects therefore the hyperglycaemia created by glucose overload. The fixing of glibenclamide to its receptor allows the entry of glucose into the cell, preventing the accumulation of glucose in the blood that explains hyperglycaemia reduction. The glibenclamide induces a significant hypoglycaemic effect, 60 minutes, after glucose overload. Three (3) hours after administration, the glycaemia of treated rabbits with the reference product decreases significantly but its normal value is not restored. This result does not tally with that of Kwashie et al. (1998) on albino's rabbits; in their study, glibenclamide exerts significant hypoglycaemic effect, 120 minutes, after administration.

Effects of herbal medicine on the glycaemia of hyperglycaemic rabbits

The figure 3 shows the level of blood glucose in hyperglycaemic control and experiment groups. The herbal medicine has a significant hypoglycaemic effect. The glycaemia of the rabbits of batch 4, treated with the herbal medicine at 40 mg/ml, decreases but does not go back to a normal level. The fall (30 %) is slightly weaker than that of glibenclamide (38 %); at a rate of 40 mg/ml, the herbal medicine has a glucose-lowering effect. Herbal medicine (KCTC) and glibenclamide treatment to hyperglycaemic rabbits significantly reversed the level of blood glucose. However, the effect of KCTC is not more prominent when compared with glibenclamide (fig. 4).

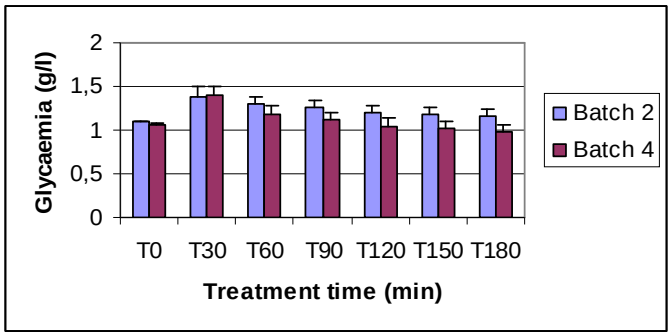


Fig. 3: Glycaemia variation histogram for sample hyperglycaemic rabbits treated with glucose and hyperglycaemic rabbits treated with herbal medicine at 40 mg/ml; Mean ± SEM, n =3, P < 0.05. Batch 2: sample hyperglycaemic rabbits treated with glucose (4 g/l). Batch 4: hyperglycaemic rabbits treated with herbal medicine at 40 mg/ml.

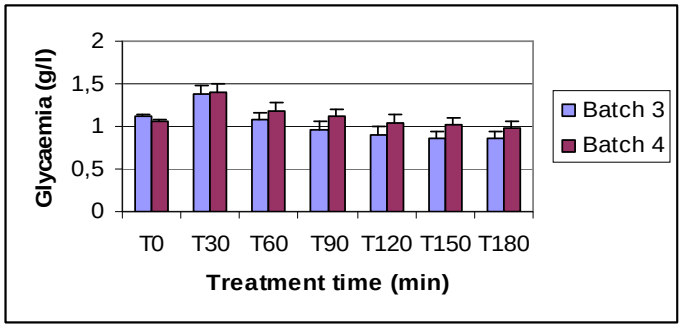


Fig. 4: Glycaemia variation histogram for hyperglycaemic rabbits treated with glibenclamide and hyperglycaemic rabbits treated with herbal medicine; Mean ± SEM, n =3, P < 0.05. Batch 3: hyperglycaemic rabbits treated with glibenclamide (0.25 mg/ml). Batch 4: hyperglycaemic rabbits treated with herbal medicine at 40 mg/ml.

The use of the aqueous decoction from leaves of *Terminalia catappa* revealed that it has glycaemic properties, which vary from one dose to another (Figure 5). The glycaemia of rabbits of batch 5, treated with the herbal medicine at 10 mg/ml, goes down from 1.31 g/l to 1.05 g/l, 180 minutes later. From the peak, we observed a fall of 20 %. Until the end of the experiment, there is no stabilization of glycaemia at its normal value. The glycaemia of rabbits of batch 6, treated with herbal medicine at 2.5 mg/ml, experienced a similar evolution to that of the sample hyperglycaemic rabbits non treated (rabbits of batch 2); despite treatment, the glycaemia rate which rised to 1.25 g/l ± 0.10, after

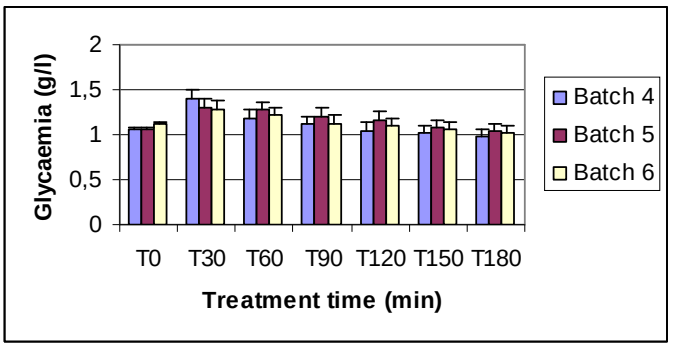


Fig. 5: Glycaemia variation histogram for hyperglycaemic rabbits treated with herbal medicine at 40 mg/ml, 10 mg/ml and 2.5 mg/ml; Mean ± SEM, n =3, P < 0.05. Batch 4: hyperglycaemic rabbits treated with herbal medicine at 40 mg/ml. Batch 5: hyperglycaemic rabbits treated with herbal medicine at 10 mg/ml. Batch 6: hyperglycaemic rabbits treated with herbal medicine at 2.5 mg/ml.

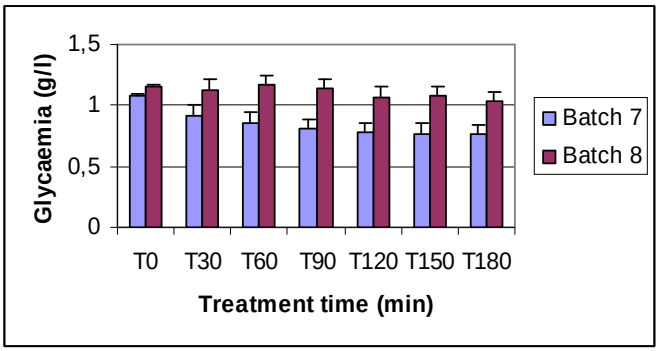


Fig. 6: Glycaemia variation histogram for normal glycaemic rabbits treated with glibenclamide and herbal medicine; Mean ± SEM, n =3, P < 0.05. Batch 7: normal glycaemic rabbits treated with glibenclamide (0.25 mg/ml). Batch 8: normal glycaemic rabbits treated with herbal medicine at 40 mg/ml.

administration of glucose practically does not vary: herbal medicine therefore does not exert a significant hypoglycaemic effect at the subliminal dose of 2.5 mg/ml. A fall of 17 % is noted, after the glycaemic peak that is comparable to result with animals of batch 2.

The administration of the herbal medicine at lower doses (≤ 2.5 mg/ml) does not induce significant hypoglycemic effect; at low doses (subliminal doses), the herbal medicine would have normoglycaemic activity. The administration of the herbal medicine at 10 mg/ml highlights the hypoglycaemic effect. The plant medicine lowers the hyperglycemia level without bringing back the glycaemia to its normal value of 1.11 g/l. At 40 mg/ml, the herbal medicine lowers the hyperglycemia level, but does not restore normal glycaemia, after 180 minutes of treatment. The effect of the herbal medicine at 40 mg/ml approximates that of glibenclamide at 0.25 mg/ml. An herbal medicine (codified DIACODA), used in the treatment of diabetes mellitus, exerts a hypoglycemic effect, restores and stabilizes normal glycaemia to 0.99 g/l when a dose of 30 mg/ml is administered to rabbits (Djédjé, 2002).

This experience was conducted to study the antidiabetic activity of *Terminalia catappa* leaves in rabbits as well as to provide an introductory approach for the evaluation of its traditional preparation in order to scientifically validate the therapeutic preparation of the plant in the control of diabetes. The results show that the effect of herbal medicine (KCTC) at 40 mg/ml is compared to glibenclamide (0.25 mg/ml). The effect of herbal medicine was more prominent when the dose used is higher: the herbal medicine exerts dose-dependant hypoglycemic effect and appears like an antidiabetic.

Effect of glibenclamide and herbal medicine on basal glycaemia of rabbits

The figure 6 shows the level of basal blood glucose in normo-glycaemic experiment groups treated with the glibenclamide (rabbits of batch 7) and with the herbal medicine (rabbits of batch 8). The reference product exerts a significant basal glucose-lowering effect unlike herbal medicine (KCTC). The noninsulinic treatment of diabetes utilizes oral hypoglycaemiants type of sulphamides and type of biguanides. Sulphamides to which belonged glibenclamide act by stimulating the secretion of insulin (Kwashie et al., 1998). The biguanides reinforce the peripheral use of glucose and appear to inhibit the gluconeogenesis. The herbal medicine (KCTC) would have an extra-pancreatic action by stimulating peripheral use of glucose, similar to that observed with the biguanides. The antidiabetic effect of KCTC would be due to an increase in the membrane permeability to glucose blood similar to that observed after biguanides administration. Administration of herbal medicine significantly increased the activities of membrane enzymes for glucose utilization in hyperglycaemic rabbits.

Experimental validation for the medicinal activity of the plant using phytochemistry

We performed a primary validation of the traditional medical practices, by looking for the chemical groups that explain the antidiabetic effect of the herbal medicine “KCTC”. Thus *Terminalia catappa* leaves were chemically screened and yielded alkaloids, flavonoids, polyphenols, saponosides, sterols and triterpenes. Among these compounds, the alkaloids, sterols and triterpens can be incriminated in the antidiabetic activity of the plant. Alkaloids would be used as stimulatives of the hepatic glycogenogenesis (Neuwinger, 1996). Sterols and triterpens are recognized for their properties to decrease the rate of blood glucose (Nacoulma, 1996). Alkaloids, Sterols or triterpens highlighted in the leaves of the plant would be responsible for the observed antidiabetic effect.

CONCLUSION AND PROSPECT

The aqueous decoction from leaves of *Terminalia catappa* exerts a dose-dependent hypoglycemic effect. It has a normoglycaemic activity at lower doses (≤ 2.5 mg/ml) and a hypoglycaemic activity, at higher doses (> 2.5 mg/ml). The dose of 40 mg/ml is the most effective among the administered doses. Indeed, at 40 mg/ml, the herbal medicine reduces hyperglycaemia and brings back glycaemia to its normal value of about 1.11 g/l ± 0.05, after 90 minutes of experiment. The plant proves to be an antidiabetic. Subsequent studies are needed to deepen the mechanism of action and identify the active principle of

Terminalia catappa leaves which have a significant hypoglycaemic effect and appear like an antidiabetic due to chemical components as alkaloids, sterols and triterpens.

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