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Baba O Zeine Mohamed Anouar Sadat
Research Scholar, Laboratory of Biochemical-Pharmacodynamic, Training Unit and Research in Biosciences, Félix Houphouët-Boigny University Cocody, Abidjan, Côte d'Ivoire

Bedou Kouassi Denis
Research Scholar, Laboratory of Biochemical-Pharmacodynamic, Training Unit and Research in Biosciences, Félix Houphouët-Boigny University Cocody, Abidjan, Côte d'Ivoire

Konkon N' dri gilles
Senior Lecturer, Laboratory of Botany, Training Unit and Research in Biosciences, Training Unit and Research in Biosciences, Félix Houphouët-Boigny University Cocody, Abidjan, Côte d'Ivoire

Djaman A. Joseph
Professor, Laboratory of Biochemical-Pharmacodynamic, Training Unit and Research in Biosciences, Félix Houphouët-Boigny University Cocody, Abidjan, Côte d'Ivoire

N'guessan Jean-David
Professor, Laboratory of Biochemical-Pharmacodynamic, Training Unit and Research in Biosciences, Félix Houphouët-Boigny University Cocody, Abidjan, Côte d'Ivoire

Correspondence:
Baba O Zeine Mohamed Anouar Sadat
Research Scholar, Laboratory of Biochemical-Pharmacodynamic, Training Unit and Research in Biosciences, Félix Houphouët-Boigny University Cocody, Abidjan, Côte d'Ivoire
Email: mohamedzeine78[at]gmail.com

Ethnobotanic and toxicological study of some medecinal plants used in treatment of diabetes

Baba O Zeine Mohamed Anouar Sadat*, Bedou Kouassi Denis, Konkon N'dri gilles, Djaman A. Joseph, N'guessan Jean-David

ABSTRACT

Aim: These ethnobotanical investigations within drug sellers of medicinal plants in Côte d'Ivoire (CI) were performed in order to contribute to a better knowledge of plants with antidiabetic effect. They were carried in Adjamé "Quartier rouge" in the district of Abidjan. **Methods and Results:** The results obtained allowed to inventory 16 species of medicinal plants belonging to 13 families. All of these species are used in the treatment of various pathologies such as diabetes. In order to establish the safety of these plants in the diabetic treatment, acute toxicity tests were performed. To this end, the LD_{50} was determined in rats. It was determined haematological and biochemical parameters after repeated dosing of 2000 mg/kg of body weight (bw) of aqueous extract of *Calotropis procera*'leaf, *Bauhinia thonningi*'fruit, *Fagara zanthoxyloides*'barks and *Cassia siberiana*'roots to those rats during 14 days. The aqueous extracts had no effect on most of blood parameters tests. These studies have shown that aqueous extracts of these plants were not toxic in the experimental dose. **Conclusion:** This study was conducted in the context to perform pharmacological and toxicological experiments for implementation of innovative initiatives in Côte d'Ivoire. That may lead in the future, to the manufacture of improved traditional drugs (TID).

Keywords: Ethnobotanical Investigations, Diabetes, Acute toxicity, LD_{50}, Blood parameters.

INTRODUCTION

Diabetes is one of no communicable diseases (NCD) the most widespread in the world.[1] It is a metabolic disease characterized by a disorder in the regulation of blood glucose.[1] According to Word Health Organization,WHO, more than 176 million peoples are affected by this disease in the world.[2] It is directly responsible for 3.5% of deaths caused by NCD.[3] Furthermore, estimated to 2.8% in 2000, its prevalence will reach 4.4% of world population in 2030.[4; 5]

Among all continents, Africa is the most affected by this disease.[6] In Côte d'Ivoire, 2014 recorded 500,000 diabetics with a prevalence rate of 4.94 % according to the coordinator of the National Program for the Fight against Metabolic Diseases (DFI).[7] Faced with the expansion of this disease whose support is high, WHO encouraged ethnobotanical studies and pharmaceutical research. This could improve drugs based to medicinal plants (DMP) to promote their optimal uses in health care delivery systems.[9,8]

Although many ethnobotanical investigations were performed on the antidiabetic plants in African countries [5,6] and elsewhere [1,2,10,11], it should be noted that few studies have been carried out on those used in Cote d'Ivoire.

otherwise, according to the OECD directives establishing the safety and efficacy of a new drug, toxicology is an important aspect of pharmacology. It treats the deleterious effect of the organic active substance given by organic material before its use as a drug or chemical in clinical use.[12]

So we felt it necessary to conduct an ethnobotanical investigation followed by an assessment of acute toxicity on: *Calotropis procera*'s leaves, *Bauhinia thonningi*'s fruit, *Fagara zanthoxyloides'*s bark and *Cassia siberiana*'s roots. This is intended to provide the scientific community with a database on the medicinal plants used in the treatment of diabetes and sold in the district of Abidjan.

MATERIALS AND METHODS

Material

Description of the study area

Ethnobotanical investigation

We collected some parts (leaves, fruit, bark or root) of medicinal plants commonly used in the treatment of diabetes in Adjamé, a township of Abidjan. These are: *Uapaca togoensis*, *Cataranthus roseus*, *Bauhinia thonningii*, *Picralima nitida*, *Khaya senegalensis*, *Boscia senegalensis*, *Cassia sieberiana*, *Sclerocarya birrea*, *Coelocaryon oxycarpum*, *Ziziphus mauritiana*,*Fagara zanthoxyloides*, *Calotropis procera*, *Crescentia cujete*, *Hallea ledermannii*, *Opilia celtidifolia* and *Terminalia catappa*.

Acute toxicity

Vegetal material

We used some parts of most used plants such as *Calotropis procera*'s leaves, *Bauhinia thonningi's* fruit, *Fagara zanthoxyloides*'s bark and *Cassia siberiana'*s roots. Each of these different parts of plants were dried outdoors in the shade at room temperature and then crushed by an electric grinder (Vorwerk Thermomix 3000) to obtain the powder.

Animal material

We used "Wistar" nulliparous and non gravidic female rats from the pet of the National High School(NHS) in Abidjan.They were aged 8 to 10 weeks and had a body weight between 94 and 126g. They were fed with pellets (IVOGRAIN), dried fish, grains and tap water in bottles without interruption. The temperature was 27 ± 5 ° C, 12 hours of light and 12 hours of darkness during the experiment. They were used for the acute toxicity tests by oral route.

Methods

Ethnobotanical investigation

Study methods

Our investigations were based on the method of Semi-Structured interview [13,14]. They were held with 19 of medicinal plants sellers at "Plants market" in Adjamé "quartier rouge" from March to May, 2015. These sellers haveanswered to our surveys through dialogue in local languages (Malinke or Baoule Moré) or in French. The informationswere concerned to the resource person's profile (age, sex, region, and level of education) and ethnopharmacological data such as local or common names, the usually parts of plants, preparation methods, ways of administration, banned and side effects associated with each recipe.

Identification of plant species

The plants collected on the sales site (plants market in Adjamé, Quartier-rouge) were identified at the National Centre for Floristic of Felix Houphouet-Boigny University using analytical flora.

Method of preparation

The sellers ignore the weight and specific measures in the preparation and the dosage form of herbal drugs. The accuracy is lacking on several plants such quantities of plant organs to prepare, the solvent used, the time required for preparation of solutions (decoction, infusion, fumigation, poultice, maceration and brushing) and the precise dose to prescribe.

Preparation of the aqueous extract

Using a magnetic stirrer, 50 g of the powder from each organ of used plants were soaked in 1 liter of distilled water for 2 hours. The macerated was then filtered using a filter paper (Whatman No. 1). The filtrate obtained was finally dried in an oven at 50 ° C for one week.

Acute toxicity

Distribution of rats

15 female rats were divided into 5 groups of 3 rats

Lot 1: Normal Witnesses Rats (RTN) stuffed with distilled water.

Lot 2: normal rat treated with the extract A (*Fagara zanthoxyloides'*s Bark).

Lot 3: normal rat treated with extract B (*Calotropis procera*'s leaves).

Lot 4: Normal Rats treated with the extract C (*Cassia siberiana's* roots).

Lot 5: Normal Rats treated with the extract D (*Bauhinia thonningi*'s fruit).The change in body weight was monitored periodically throughout the experiment.

Haematological analysis

Blood samples collected in tubes containing anticoagulant (EDTA) were immediately used to determine levels of white blood cells, red blood cells, hemoglobin and hematocrit platelets according to standard methods.[15,16]

Biochemical parameters

Blood samples in tubes without anticoagulant were centrifuged at 3000 revolutions/min during 10 min Collected serum were stored at -20 °C. Thus, they were used to assay the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by the colorimetric method of Reitman and Frankel.[17] Creatinine was measured though the method of reaction with picrate in alkaline centre.[18]

Statistical analysis

The data recorded on the investigation sheets were processed by the GraphPad Prism 6.01 software. The citation frequency (Fc) of each plant was determined by the formula:

$$Fc = \frac{\text{Number of citations for considered plant}}{\text{Number of citations for all plants}} \times 100$$

The values derived from biological tests, are expressed as mean ± standard deviation. After variance analysis, comparing mean values between different lots of rats was performed by the "Student test" with the graphpad Prism 6.01 software. Significant value was obtained for (P<0.05)

RESULTS

Ethnobotanical investigation

Distribution of Sellers according to the sex

Ethnobotanical instigations in the field have allowed to interview 19 people including 92.31% female.

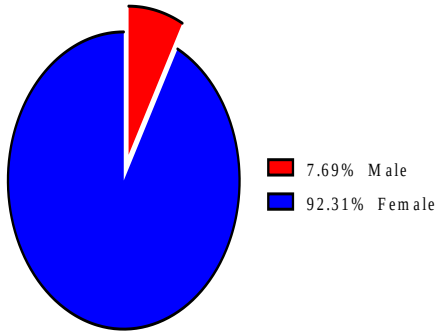

Figure 1: Distribution of Sellers according to the sex

Distribution of sellers according to age and level of study

Sale of medicinal plants in this area were mainly practiced by adults whose age ranged within 41 and 50 years (65.22% of sellers) (Figure 2). 37.04% of those interviewed were illiterate while 33.33% had a primary level of study (Figure 3).

Distribution of plants according to the botanical families

The collected data have identified 16 species of plant belonging to 13 botanical families. The most represented were the Apocynaceae and the Caesapinaceae (Figure 4).

Distribution of plants according to the method of preparation, method of use and the used part

The aqueous decoction (62.79%) and the infusion (23.26%) remain the most used methods of preparation (Figure 5-a).

The oral route is the route of administration which is the most recommended by traditional healers (80.95%) (Figure 5b).

The leaves (37.04%) are the most used in herbal medicine. Then come the fruits and bark used to 25.93% for each of these parts (Figure 5-c).

We found an increase in body weight (bw) in control rats with a growth rate of about 19.70g after oral gavage with 2000 mg/kg of bw. 17g. During 14 days of observations, this increase was near to lots 3 and 5, respectively 19g and 17g. The Lot 2 had a slower growth an order of 15g in contrary to Lot 4, which had a slight increase of 23g.However, body weight observed in animals of these 4 lots treated with 2000 mg/kg of bw have shown no significant difference (Table 2).

The hematology analysis showed no significant change between the numbers of white blood cells, platelets, red blood and hematocrit cells in dose of 2000 mg/kg of bw between the control group and the test lots (Table 3).

In dose of 2000 mg/kg of bw aqueous extracts have induced no significant changes in creatinine, urea, GOT (glutamic oxaloacetic transaminase) and TGP (glutamic pyruvic transaminase) in the blood of rats all lots.

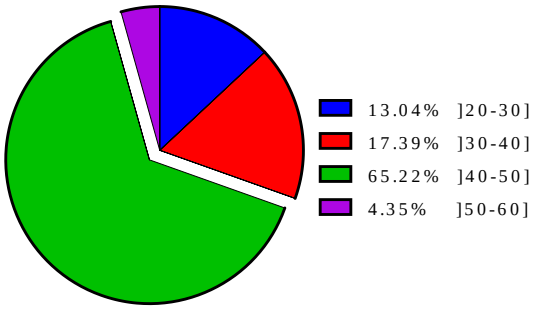

Figure 2: Distribution of sellers according to age

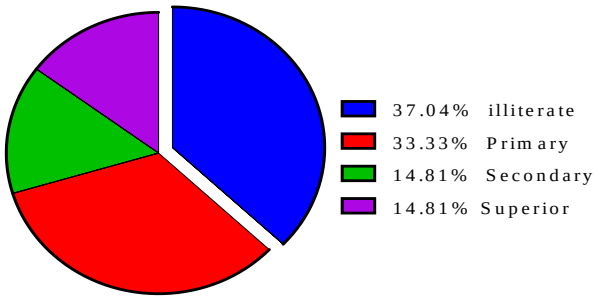

Figure 3: Study level informants

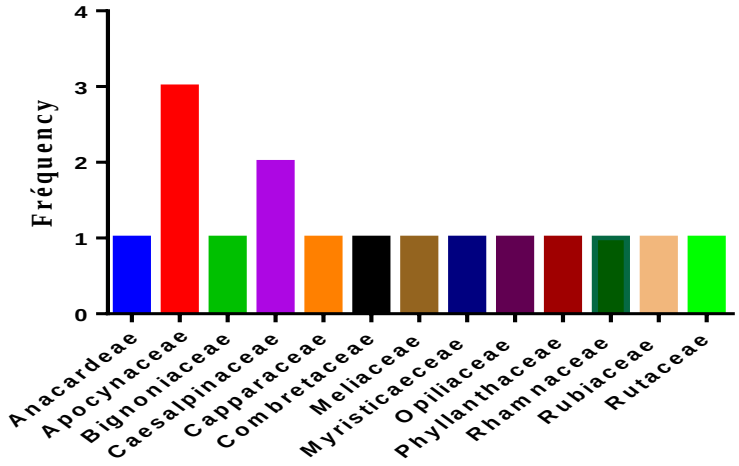

Fig 4: Frequency of botanical families

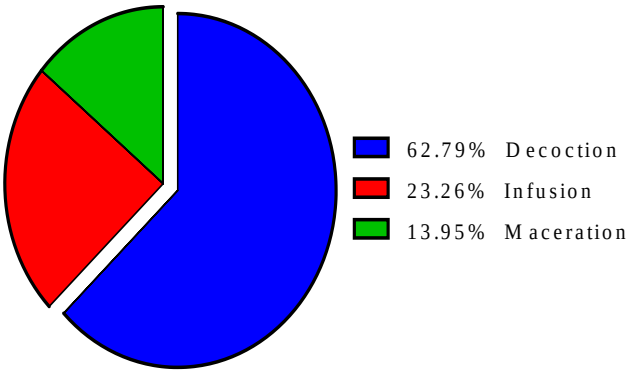

Figure 5-a : Method of preparation

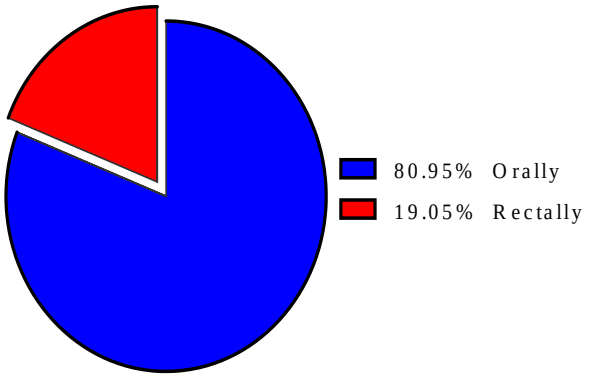

Figure 5-b : Method of use

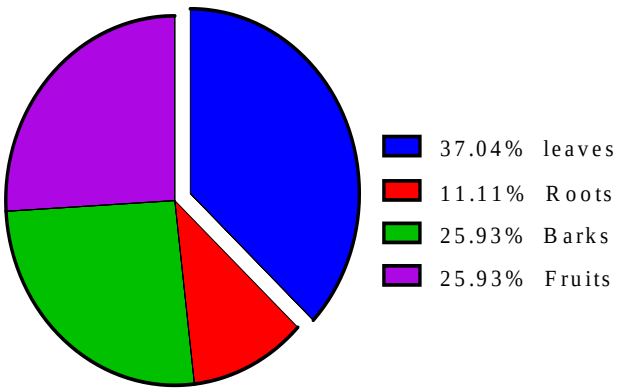

Figure 5-c : Used part of plant

Table 1: General state of the animals after administration of the aqueous extract of different plants

Lot/temps clinical signs	Lot 1		Lot 2		Lot 3		Lot 4		Lot 5	
	24h	48h	24h	48h	24h	48h	24h	48h	24h	48h
Fur	N	N	N	N	N	N	N	N	N	N
Eyes	N	N	N	N	N	N	N	N	N	N
Mucous	N	N	N	N	N	N	N	N	N	N
Absence	N	N	N	N	N	N	N	N	N	N
Salivation	N	N	N	N	N	N	N	N	N	N
Lethargies	N	N	N	N	N	N	N	N	N	N
Heartbeat	N	N	N	N	N	N	N	N	N	N
Aggressiveness	A	A	A	A	A	A	A	A	A	A
Drowsiness	No	No	No	No	Yes	No	No	No	Yes	No
Food	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Mobility	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Mortality	No	No	No	No	No	No	No	No	No	No

N : Normal ; A : Absence

During observation period, the rats of Lots 1 and 3 showed no abnormal behavior. However, those of lots 2 and 4 had mild drowsiness, weakness, mobility and lack of appetite in the early hours followed by a rapid recoveryAfter 14 days, all lots have recorded no deaths or morbidity of sustainable state.

Table 2: Evaluation of body weight of rats during two weeks

Lots Days	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5
D_1	89.30±3.39	118.13 ± 6.36	96.54 ± 6.27	101.15 ± 10.16	113.00± 4.47
D_2	92.89± 3.60	121.57± 8.18	99.93±7.67	106.29± 8.34	115.93± 4.62
D_5	93.16± 3.09	122.47± 9.04	102.72± 6.98	106.91± 9.06	117.53± 3.96
D_8	96.59± 4.54	127.00± 9.93	107.05±4.25	111.17± 9.29	122.97± 4.24
D_{11}	103.03± 3.91	129.80± 13.13	111.70± 1.20	117.23± 7.64	130.17± 5.44
D_{14}	109.03± 3.71	133.97± 12.98	115.45± 0.85	124.03± 7.24	130.07± 4.71

1: normal control rats (NCR) stuffed with distilled water
2:Lot of rats receiving the extract of *Fagara / Zanthoxylum zanthoxyloides*
3:Lot of rats receiving the extract of *Opilia celtidifolia*
4: Lot of rats receiving the extract of *Cassia sieberiana*
5:Lot of rats receiving the extract of *Bauhinia thonningii*
D: Day

Table 3: Assessment of blood formed elements after two weeks

Lots / Parametersl haematological		Lot 1	Lot 2	Lot 3	Lot 4	Lot 5
Blood count	Red blood cells	6.89	6.46	7.47	6.53	7.06
	Hemoglobin	11.17	11.87	12.87	10.30	12.77
	Hematocrit	33.27	37.10	40.60	31.55	40.30
	MCV	59.20	59.70	54.33	57.10	56.93
	MCHC	19.63	17.57	18.77	18.65	18.03
	MCCH	33.20	32.57	35.80	36.50	36.20
	Platelets	795.67	850.67	859.00	871.00	791.67
	White blood cells	9.10	10.08	8.84	9.09	8.29
	Leukocyte count					
	Neutrophil	10.03	10.55	12.58	11.64	11.83
	Eosinophil	0.08	0.13	0.20	0.57	0.17
	Lymphocytes	40.93	38.75	38.03	34.75	34.83
	Monocytes	0.08	0.25	0.16	0.31	0.32

MCV: Mean Corpuscular Volume
MCHC: MeanCorpuscular Hemoglobin Content
MCCH: Mean Concentration of Corpuscular Hemoglobin

Table 4: Determination of some of biochemical parameters for each lot

Lot / biochemical parameter	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5
Urea g/l	0.34± 0.05	0.39 ±0.02	0.34±0.13	0.34±0.13	0.22±0.02
Creatinine mg/l	4.50±0.71	5.33±1.53	6.33±0.3	6.33±1.15	6.67±1.15
TGO (UI/l)	186.35±15.20	210.63±29.46	265.57±0.52	199.23±0.49	149.50±0.74
TGP (UI/l)	35.95± 0.03	30.43±0.02	41.23±0.02	31.43±0.01	33.83±0.03

Table 5: Average weight of organs (liver, heart, kidneys) from different lots of plant

Lot / Organ	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5
Rat	109±5.01	134 ±12.1	103±1.13	122±11.8	132±8.29
Kidney	0.74±0.1	0.72±0.03	0.65±0.06	0.71±0.06	0.63±0.33
Liver	3.85±0.4	3.8±0.29	2.79±0.52	3.98±0.49	2.88±0.74
Heart	0.43±0.03	0.48±0.02	0.4±0.02	0.46±0.01	0.42±0.03

DISCUSSION

Ethnobotanic investigations

Sex of sellers

Ethnobotanical investigations in the field have allowed to interview 19 people including 92.31% of women. These results confirm other ethnobotanical studiessuch as Mehdioui and Kahouadji's one (2007) [21] in Maroc intoAmsittène forest (Province of Essaouira) that have shown that women are holders of traditional herbal knowledge.This can be explained by the fact that women use medicinal plants in other areas that therapy and their responsibility as mothers. In fact, they are the bodies whose give first aid especially for their children.The results of Fah *et al.*, In 2013 in Benin are similar because according to them, herbalists are predominantly females.[19] Also, this could be justified by the fact that in Benin, selling items to the market is usually reserved for women.

Age and Study level of sellers

Sale of medicinal plants was mainly exercised by adults, predominantly among people belonging to the age group ranging from 41 to 50 years (65.22% of sellers) (Figure 3). The average age was 43 years. In fact, seniors are expected to provide more reliable information, because they hold much of the ancestral knowledge that is transmitted orally. The transmission of this knowledge is threatened now because it is not always ensured.[20,22] Moreover, the majority of interviewed were illiterate or had a primary school level (70.37%) (Figure 3). They are people whose have spent most of their lives in rural areas where school enrollment remains low. According to Orch *et al.*, 75% of interviewed were illiterate or had a primary school level.

Plants according to the botanical families

The collected data have identified 16 species of plant belonging to 13 botanical families of which the most represented are the Apocynaceae and Caesapinaceae (Figure 4). These results are almost similar to those of Tra Bi *et al*. in 2008 during a study in Ivory Coast.[8] In fact, these have shown that the Euphorbiaceae, Asteraceae and Poaceae were respectively the most represented. Then, came in second place, the Caesalpiniaceae and the Apocynaceae. This slight difference is due to the fact that their studies were focused on therapeutic plants used in the treatment of high blood pressure and diabetes, while ours was focused specialy on diabetes and in one district of Abidjan. According to Tra Bi, this is also explained by the fact that these families are part of the majority species and kinds of Ivorian flora.[23,24] Futhermore, our investigations have shown that 50% of the plants sold come from ouside the country especially from Mali, Burkina Faso and sometimes of Guinea. The results of Fa *et al.* in 2013 are contrary to ours. In fact, they have shown in their study that rather the family of Asteracea was the most represented. This difference is understandable because the geographies area differ among studies. The use of plants is different according to the countries. Futhermore, this study relates to the plants used against diabetes in both sexes while those studied by Fah et al. were intended exclusively to pregnant women with diabetes.[19]

Method of preparation, method of use the part of plant used

The majority of herbalists was unaware about the toxicity and the methods of use (the method of preparation and the recommended doses) of plants. Futhermore, informations concerning the quantities vegetal material of plant to prepare the solvent or the vehicle used, the time required for preparation of solutions (decoction, infusion, powder, fumigation, poultice, maceration and brushing) varies according to the traditional healer. The use of medicinal plants should be streamlined in the objective to profit and avoid the risks. Studies of this aim are needed. However, the aqueous decoction (62.79%), infusion (23.26%) and maceration (13.95%) remain the most used methods of preparation (Figure 5-a). These preparations are generally administered orally (Figure 5-b). This requirement can be explained by the fact that this pathology is linked to deep organs. To reach them any compound must pass through the digestive system to facilitate its assimilation.[8] Furthermore, the results also show that the sheets are the most used organs, followed by the fruit, bark and roots (Figure 5-c). This observation is characteristic of many ethnobotanical studies in Africa and in the world.[8,25,26] Sweet food consumption is prohibited during the treatment. As part of this study, herbalists reported that no adverse effect was associated with the use of these revenues.

Acute toxicity

The extract A that was administered at a dose of 2000 mg/kg of bw did not result in any abnormal behavior and no mortality in rats of Lot 1.

These results are close to those obtained by Ghosh in 1984 showing that *Fagara zanthoxyloides* was not orally toxic but could be slightly toxic by intraperitoniale way since the LD50 was between 0.5 and 5 g/kg.[29]

However, other species such as *Zanthoxylum zanthoxyloides* (Lam), *Zepernick, TimlerZanthoxylum Macrophyllum Oliv*, *Zanthoxylum madagascariensis* are known for their toxicity by sub dermal, intramuscular and intravenous routeThey are used to advantage in West Africa to manufacture poisons for hunt using bark, roots and stems.[27] In accordance with the study of Clarke and Clarke in 1977, a plant whose LD_{50} is greater than 1000 mg/kg of bw is considered as non-toxic in animal tests.[28]

It can be concluded that the aqueous extract of F. *zanthoxyloides* is relatively nontoxic in normal doses and orally. Therefore it could be recommended.

Compared with controls, rats of Lot 3 had presented no mortality after receiving a dose of 2000 mg/kg of bw of the extract B. Nevertheless, they had slight difficulties such as lower mobility, drowsiness and loss of appetit. however, they had hematological and biochemical values similar to those of control rats. It was the same for the weight of donated organs. These observations are similar to those obtained by Ghosh in 1984 who found that the viscera (liver, kidney and heart) of animals (rats) after oral gavage with aqueous extract of *Opilia celtidifolia* showed no macroscopic change which could result in death.[29] They are also similar to the results obtained by Makan Soumare in 2012 revealing that the aqueous extract of *Opilia celtidifolia*'s leaf did not result in acute toxicity at the dose of 2000 mg/kg of bw in mice.[30]

The limit dose of 5000 mg/kg of bw aqueous extract of *Cassia bark siberiana* has caused any consequence or abnormal clinical sign: No mortality observed during the study of acute toxicity on mice and rats during 48 hours in short term and 14 days in long-term of observation. It suggest that the LD_{50} of the extract (5000 mg/kg of bw) in both species has led to no significant differences between the test and control. Therefore, the extract may not have deleterious effects on bone marrow function.[31]

Similarly, in our study, rats of Lot 4 those had received 2000 mg/kg of bw of aqueous extract of *Cassia siberiana*'s root have shown no abnormal behavior and no mortality. This goes in the same direction as the results of studies of Nartey *et al*. 2012, which revealed that the LD_{50} inrats is 2000 mg/kg of bw because the gavage wi the aqueous extract of *Cassia sieberiana*'s root and bark produced no morbidity or mortality.[32]

According to the balance of Hodge *et al.* in 1943, the fruit of Cassia sieberiana whose LD_{50} is between 500 and 2000 mg / kg have a low toxicity.[33]

This could be related to the fact that drugs and orally administered compounds undergo some events that potentially decrease the systemic circulation. That would prevent the attainment of sufficient quantity for pharmacological effects.[31]

The aqueous extract of *Bauhinia thonningii*'s fruit has led to no deaths after being administered to rats of Lot 5. However, some passenger abnormal behaviors related to immobility, drowsiness, and anorexia were observed. As for hematological and biochemical values, they did not show significant differences with the controls. The weights of the organs were no lethal micro or macroscopic change.

This is similar to the results of Daniyan S.Y *et al*. in 2011 that showed that acute and sub-acute toxicity of the extract of *Bauhinia tonningii*'s leaf with doses of 2000 mg/kg and 5000 mg/kg had led to no death during the experimental periodHematological, biochemical and weight of different collected organs, have shown no significant difference in acute toxicity.[34]

CONCLUSION

Four plants were the subject of this study: *Fagara/Zanthoxylom zanthoxyloide*, *Opilia celtidifolia*, *Cassia siberiana* and *Bauhinia thonningii*.The toxicity study in vivo involving each of these plants showed that the LD_{50} was greater than 2000 mg/kg of body weight. Consequently, they are not harmful.These results shall contribute to the evolution of diabetes pharmacotherapy.However, further histological studies on rat organs should be carried out subsequently to verify whether there is any harmful action of the extracts at this stage.

Acknowledgments

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