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Acute Toxicity and Effects of Hydroethanolic Leaf Extract of Annona senegalensis Pres. and Detarium microcarpum Guill. & Perr. on Biochemical and Hematological parameters in Wistar rats

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ABSTRACT

Annona senegalensis and Detarium microcarpum are two medicinal plants used in the treatment of bacterial infections in Benin. The interest in using leaves of these two plant species requires that an approach to its capacity be undertaken to evaluate its safety in humans. The objective of present study was to compare acute influence of hydro-ethanolic extracts of these plants. Thus, leaves of A. senegalensis and D. microcarpum were used to prepare hydro-ethanolic extracts by maceration. The acute effect of crude Hydroethanolic extract was induced by oral administration to Wistar rats. A single dose of 2000 mg/kg body weight was administered and effects on biochemical and hematological parameters were evaluated. The direct radiation test on rats orally at a dose of 2000 mg/kg body weight showed no adverse effects or deaths during 14 days of observation. On the basis of these data, it appears that The two plants studied do not show any toxicity. In view of the pharmacological and chemical data previously available, these plants are good candidates for the development of improved traditional medicines.

Keywords: Annona senegalensis, Detarium microcarpum, acute toxicity, biochemical and

1. INTRODUCTION

Traditional medicine is a major source of cultural heritage in Africa, to which population remains attached for primary healthcare [1].

According to World Health Organization (WHO), approximately 65 to 80% of population in developing countries rely primarily on traditional medicinal plants for their primary healthcare [2]. This percentage increases in developing countries with a higher rural and tribal population due to its low cost [3]. Recent findings have revealed that over 80% of African population relies on medicinal plant species for their primary healthcare [4]. A. senegalensis Pers. and D. microcarpum are among the plants traditionally used for this purpose.

Thus, to help development of traditional medicine, Beninese State has established a collaboration between traditional medicine and modern medicine. This collaboration was translated as a Priority in National Health Development Plan [5]. by creation in 2020 of a National Program for Promotion of Traditional Medicine (PNPMT). The mission assigned to this program is improvement of national health coverage through effective and efficient use of traditional medicine and pharmacopoeia through regulation, rehabilitation and organization of this sector, in order to achieve true collaboration

between actors of two medicines. To achieve this objective, it is imperative to evaluate clinical efficacy, ensure safety of medicinal plants, strengthen knowledge and performance of traditional practitioners and guarantee sufficient patient monitoring. A renewed interest in traditional medicine in recent years has allowed for a deeper analysis of its therapeutic efficacy and especially its toxicological aspect [2]. Indeed, several studies carried out on traditional herbal treatments have reported toxicity problems [6].

The use of these medicinal plants by traditional healers and resulting satisfactory results in some cases have led some countries, mainly African, to consider revaluing herbal medicine. However, for most of them, scientific evidence is not always clear. Adjanohoun and de Souza [6] identified nearly 501 species used in traditional medicine. Adjanohoun [7], listed 814 species belonging to 130 botanical families with medicinal properties including A. senegalenis, and D. microcarpum. The phytochemistry (quantitative and qualitative) analysis of these plants revealed presence of bioactive molecules capable of having analgesic, anti-inflammatory and bacterial properties [8]. It is therefore necessary to verify by a pharmacological study through variations of biochemical parameters after absorption of hydroethanolic extracts of leaves of A. senegalensis, and of D. microcarpum compared to a reference molecule and to study their acute toxicity in vivo.

2. MATERIALS AND METHODS

2.1. Materials

2.1.1 Plant Material

It is composed of leaves of two plant species (D. microcarpum Guill. & Perr and A. senegalensis Pers. ssp.). The leaves were collected in the commune of Kandi, Alibori department, Benin. They were authenticated respectively under names YH756/HNB and YH754/HNB by National Herbarium of Benin, University of Abomey-Calavi. These leaves were dried at 25 °C for two weeks. After drying, they were ground into powder in the laboratory using a Retsch grinder type SM 2000/1430/Upm/Smfet, Germany. The powders were used to prepare a hydroethanolic extract.

2.1.2 Animal material and acclimatization conditions

The animal material used was female Specific Pathogen-Free (SPF) Wistar rats, approximately eight weeks old and weighing between 150 and 200 g. The animals were housed in polypropylene cages equipped with water bowls, under optimal hygienic conditions, with standard rat diet and free access to water. After two weeks of acclimation at a constant temperature of 22 ± 2 °C and a 12 h/12 h light/dark cycle, rats were divided into groups for different tests. The body weight of rats was recorded at the beginning and end of experiment.

2.2. Methods

2.2.1 Preparation of extracts

The extracts were prepared according to method described by Kabré [11]. The powder (100 g) of each plant (D. microcarpum and A. senegalensis) was macerated for 48 h with continuous stirring in 500 mL of a mixture of water and ethanol (30:70/v:v). The macerates were then filtered 3 times through cotton and once through Whatman paper. The filtrates obtained were then evaporated using a rotary evaporator (IKA HB10S40, Germany) under reduced pressure. The concentrate was dried at 40 °C in an oven until complete evaporation. The residues obtained after drying constitute hydro-ethanolic extracts of each plant and were used for study of different biological activities.

2.2.2 Evaluation of the toxicological effect of hydroethanolic extracts

Acute toxicity was assessed in vivo according to Organization for Economic Co-operation and Development 423 guidelines [12].

2.2.2.1 Conditioning of rats

Adult Wistar rats were used in this study. These animals received no other drug treatment during the experimental period, except for the extracts.

After acclimatization, animals were divided according to their weight into three (3) groups of three (4) animals, including two (2) experimental groups and one (1) control group. The principle consists of administering plant extracts orally to animals on same diet at a single dose of 2000 mg/kg of body weight. Thus, treatment of groups was carried out as follows:

Group 1: Rats receiving hydroethanolic extract of D. microcarpum;

Group 2: Rats receiving hydroethanolic extract of A. senegalensis;

Group 3: Control rats receiving physiological saline.

2.2.2.2 Observation

After various treatments, animals were observed every 30 minutes for 8 hours on the first day, then daily for 14 days. During this period, symptomatic disturbances (agitation, lack of appetite, eye discoloration, motor difficulties,

diarrhea, lethargy, and dyspnea) were not observed.

2.2.2.3 Blood sampling

A blood sample was taken by puncture of the retro-orbital sinus of animals (under diethyl ether anesthesia) on 14th day after the treatments. These samples were used for biochemical and hematological analyses. Biochemical parameters were as follows: urea, creatinine and transaminases (ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase). The hematological analyses included complete blood count (CBC): red blood cells (RBC), hemoglobin (Hb), content), mean corpuscular hemoglobin concentration (MCHC), white blood cells (WB), lymphocytes (Lym), triglycerides (TRY), blood corpuscular volume (BCV) …). These biochemical parameters were determined using BIOLABO diagnostic kits.

2.3. Statistical analysis

GraphPad Prism 9.5.1. (733) software was used to perform graphs and statistical analysis of biochemical parameters. A comparison of means was performed with analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Differences are considered significant with $p < 0.05$ and highly significant with $p < 0.001$.

3. RESULTS

3.1. Assessment of acute toxicity

In the acute oral toxicity assessment, after careful observation for 14 days, no mortality was recorded in rats receiving hydroethanolic extracts of D. microcarpum and A. senegalensis at 2000 mg/kg body weight. However, the weight of animals during treatment was measured. ANOVA analysis of variance does not show any change in body weight of animals during treatment. Indeed, no significant difference was observed between weights recorded on first day (D0) and those recorded on last day (D14) of treatment, considering control group that received distilled water and the experimental group treated with tested extracts (Figure 1). This observation shows that treatment does not affect physical appearance of animals and is therefore an indication of safety of extracts.

3.2 Observations on parameters after 14 days of acute toxicity.

Acute toxicity is defined as a short-term exposure and rapid absorption of toxic product through skin, lungs or mouth of a single or multiple doses not exceeding 24 hours in general, Table 1 shows different observations from toxicity test. From analysis of this table, no signs of toxicity were recorded during 14 days of observation of toxicity test on control rats as well as on treated rats. On 14th day, a significant difference was noted. This means that no significant difference ($p>0.05$) exists between hematological parameters of control rats and rats treated with extracts regardless of day of sampling. Oral administration of extracts did not cause any significant toxic effects in treated rats. Secondary signs of acute toxicity such as decreased sensitivity to pain, noise, or locomotion were not observed. After 14 days of observation, no deaths were observed in treated rats, which did not allow determination of lethal doses 50 (LD50). These results are similar to those of Legba et al. [13] in a study on toxicological characterization of plants used in treatment of salmonellosis.

3.2.1. Weight evolution during the toxicity test

Figure 1 shows evolution of the rats' weight over 14 days. It emerges from interpretation of these results that there is no significant increase in weight in all rats treated with hydroethanolic extracts of plants retained, between D0 and D14 as well as in control rats which received distilled water.

From analysis of weight gain in female rats, a non-significant increase in weight was observed in the test group compared to control group. Significant differences in body weight changes between treated group and control animals over time were observed. Therefore, the average weight gain was moderately high in groups that received hydroethanolic extracts of leaves of investigated plants.

Table 1: Results of observations made on rats during the acute toxicity test

Hydroethanolic extract	Number of deaths	Tremor	Motility	Reaction to noise	Coat
Annona senegalensis	0	No	No	No	No
Detarium microcarpum	0	No	No	No	No
Distilled water	0	No	No	No	No

After consumption of aqueous extract of leaves, animals showed a slight stimulation of appetite for food and water. Then, no statistically significant differences, compared to control animals, in values of some biochemical and hematological parameters were observed in this study.

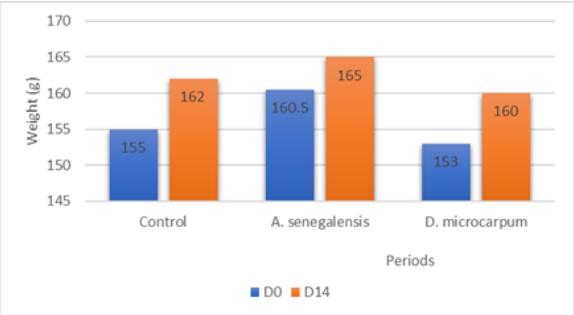


Figure - 1: Rats weight evolution after 14 days of treatment with plant extracts.

A. senegalensis: Annona senegalensis; D. microcarpum : Detarium microcarpum.;

3.2.2 Effect of the tested extracts on hematological and biochemical parameters

In order to confirm or invalidate the harmlessness of the extracts, the biochemical parameters were evaluated 14 days after the administration of the extracts to the rats. The different dosages carried out 14 days after treatment show that the results of blood tests do not vary remarkably ($p > 0.05$).

3.2.2.1 Effect of acute treatment with hydroethanolic extracts of 2 plants on rats hematological parameters

The results of hematological parameters are presented in Table 2. The compared action of extracts with negative control having received only distilled water shows that there is no variation ($p > 0, 05$) between most hematological parameters. These observations show that treatment with extracts of two plants does not induce any toxicity in blood parameters of treated rats. In addition, an increase in platelet rate is noted when comparing control to hydroethanolic extracts of A. senegalensis ($p = 0.0002$) and D. microcarpum ($p < 0 .0001$). Indeed, platelet counts decrease in the following order 825.00±83.43 (control), 900.5±50.20 (A. senegalensis), 908.5±36.06 (D. microcarpum).

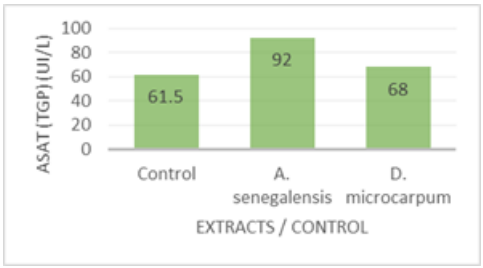
Table 2: Variation of hematological parameters

Parameters	Control	*A. sen*	*D. mic*	*P-value*
NR	6.28±1.30	7.62±0.36	7.32±1.47	$p > 0.05$
Hb	13.25±1.48	13.9±0.14	13.45±1.48	$p > 0.05$
Hte	50.50±7.77	52.5±0.70	52.5±7.77	$p > 0.05$
VGM	70.00±2.82	68.00±2.83	72.00±4.24	$p > 0.05$
TCMH	18.5±0.70	18.00±0.00	18.00±0.00	$p > 0.05$
CCMH	26.5±0.70	26.5±0.70	25.5±0.70	$p > 0.05$
NB	7.80±2.36	4.48±1.58	8.70±0.94	$p > 0.05$
Neut	43.5±19.09	39.5±24.74	56.00±4.24	$p > 0.05$
Eos	2.00±1.41	5.5±3.53	4.00±2.82	$p > 0.05$
Mono	1.00±1.41	1.5±0.70	0.5±0.70	$p > 0.05$
Lym	22.5±10.60	27.00±22.62	14.00±0.00	$p > 0.05$
Plaq	825.00±83.43	900.5±50.20	908.5±36.06	$p < 0.001$

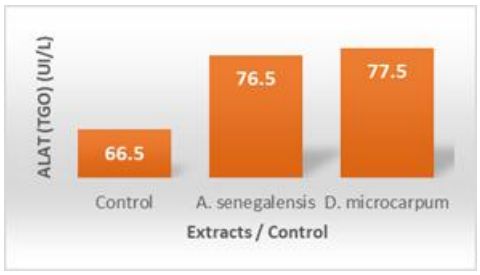
Red Blood Cell (NR), Hemoglobin (Hb), Hematocrit (Hte), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Hemoglobin Concentration (MCHC), White Blood Cell (NB), Neutrophil (Neut), Eosinophil (Eos), Monocyte (Mono), Lymphocyte (Lym), Platelets (Plaq). *A. senegalensis : Annona senegalensis ; D. microcarpum : Detarium microcarpum.*

3.2.2.2 Effect of acute treatment with hydroethanolic extracts of 2 plants on the rats hepatic parameters

The results of hepatic parameters are shown in figure2. The action of extracts on hepatic function was carried out by measuring enzymatic activity of transaminases, Alanine amino transferase (ALAT) and Aspartate amino transferase (ASAT). Enzyme activity is the amount of enzyme present in a tissue or organ. It is difficult to measure the amount of enzyme in units of mass or molar concentration. Enzyme activity is defined in terms of reaction rate. It is the equivalent of a maximum speed and is expressed in International Units (IU). ANOVA analysis of the results obtained shows that treatment did not cause any variation ($p > 0.05$) in quantity of enzyme (ASAT) between control and treated groups. ALAT rate varies from 61.5±17.67 U.I/L (control) to 92.00±14.14 U.I/L (A. senegalensis) while ASAT rate varies from 51.5±10 to 95.5±12.02 U.I/L (D. microcarpum).



[a]



[b]

Figure 2: Variation in ASAT [a] and ALAT [b] transaminases of controls and rats treated with the hydroethanolic extract of the four plants

A. senegalensis : Annona senegalensis ; D. microcarpum : Detarium microcarpum;

4. DISCUSSION

Overall, there was no difference in hematological and biochemical parameters between control rats (physiological water) and treated rats (extracts) regardless of the day of sampling. Analysis of uremia and creatinine levels revealed that administration of the extracts did not result in any significant changes. Serum urea and creatinine are considered the main markers of nephrotoxicity, although serum urea is often considered a more reliable predictor of renal function than serum creatinine [14]. Also, transaminases or aminotransferases (ASAT and ALAT) are tissue enzymes generally present in the liver, but also in muscle, kidneys, pancreas and other tissues. These enzymes are synthesized in the cytoplasm where they play an important role and are released into the bloodstream when cells are damaged [15]. Both enzymes are specific for liver damage, but AST is somewhat more sensitive [16]. Thus, 14 days after oral administration of a single dose of 2000 mg/kg of hydroethanolic extract of two plants selected, no deaths were observed in treated rats, likewise in the rats, no more or less significant changes were observed. Similarly, no signs of toxicity including a decrease in sensitivity to pain or noise or locomotion were observed. This implies that LD50 is greater than 2000 mg/kg of body weight and according to the OECD Globally Harmonized Classification System [12], the hydroethanolic extract of leaves of two plants can be classified in category 5 and considered as a non-toxic substance by oral route.

The evaluation of hematological parameters can be used to determine extent of deleterious effect of foreign compounds, including plant extracts on blood. The non-significant increase ($P < 0.05$) in mean values of red blood cell (RBC) count, and hemoglobin (Hb) concentration at different doses of hydroethanolic extract of A. senegalensis, D. microcarpum leaves, used in this study implies that plant extracts have potential hematological effects. These effects on RBCs, WBCs and Hb imply an increase in oxygen-carrying capacity of blood and the amount of oxygen delivered to tissues, as RBCs are very important in transfer of respiratory gases [17]. This suggests that extracts have potential to stimulate release of erythropoietin in kidney which is humoral regulator of RBC production [18,19]. Thus, it can also be deduced that investigated plants have a stimulating effect on bone marrow, which is responsible for production of red and white blood cells [20]. The significant increases in RBC, and Hb showed that plants can be useful in treatment of anemia and other blood disorders. The mean values of total white blood cell count showed a dose-dependent increase throughout 14 days (2 weeks) of the treatment period. This could suggest possible immunomodulatory effects of extract through their dynamic regulation of information molecules such as cytokines.

Biochemical and hematological parameters were measured. ALAT and ASAT provide information on a possible hepatotoxic effect of a substance. The results of ALAT and ASAT dosage showed no

significant increase in rats treated with hydroethanolic extract of investigated plants compared to control rats, but these enzymes increase in cases of myopathy, rhabdomyolysis or myocardial infarction and ASAT, particularly in cases of hemolysis. Therefore, plants are non-hepatotoxic at a dose of 2000 mg/kg.

Further evaluation of toxicity profile was observed in hematological parameters and pathological status of laboratory animals and humans, as this may be an indicator of the direct effect caused by extract [21]. In herbal toxicity studies, elevation in the level of leukocytes, lymphocytes, and neutrophils may be an indicator that plant extract has induced immune response of treated animals [22]. On the other hand, a significant decrease ($P > 0.05$) in these blood parameters may indicate that there is insufficient production of leukocytes, which means that the body is susceptible to diseases and infections and is less likely to fight infections. Thus, hematological analysis of the study did not reveal a significant decrease ($P > 0.05$) in the level of leukocytes, red blood cells, and lymphocytes at 200 mg/kg compared to control. These results suggest that plant extracts of D. microcarpum and A. senegalensis possess a chemical constituent capable of decreasing leukocyte production or suppressing its activity [23]. According to [24], mean corpuscular volume (MCV) or hematocrit (Hte), hemoglobin (Hb), Mean Corpuscular Hemoglobin Content (MCHC), Mean Corpuscular Hemoglobin Concentration (MCHC), are major indices for assessing circulatory erythrocytes which are important in the diagnosis of anemia and serve as a useful indicator of bone marrow's capacity to produce red blood cells in mammals [25]. The effect of the investigated plants did not show a significant increase ($P >0.05$) in CCMH and TCMH while MCV and hemoglobin (Hb) level did not decrease significantly ($P >0.05$) in treated rats compared to control group. This also suggests that since immune producers are suppressed, animals may be at risk of developing a disease such as anemia. Biochemical indices monitored in serum such as electrolytes and other secretory substances from the liver and kidney can be used as markers to assess the functional capacities of organs [26,27].

5. CONCLUSION

Medicinal plants remain the population's primary care option, not only due to the inaccessibility of synthetic products for to their high cost, but also necessary for therapeutic failure caused by the resistance of certain microorganisms. The toxicity test conducted on Wistar rats showed no effect on the variation of biochemical parameters of vital organs over the 14-day observation period. The various variations observed in the results obtained during acute toxicity tests on Wistar rats were not significant.

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