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Safety of the Aqueous Extract of the Leaves of *Senna alata* (L.) Roxb. (Leguminosae-Caesalpinioideae), a Plant Used in Benin to Treat Infections

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Abstract

Description of the Subject: *Senna alata* (L.) was a plant in the Benin pharmacopoeia used to treat skin infections. **Objectives:** The aim of our work was to test its harmlessness *in vivo*. **Method:** *Wistar* rats received by gavage a single dose of 2000 mg/kg of *Senna alata* leaves aqueous extract for the Acute Oral Toxicity (AOT) test. For the sub-Chronic Oral Toxicity (SCT) test, rats force-fed the extract at a daily dose of 300 mg/Kg of body weight for 28 days. The weight of the rats was taken and the blood samples were collected on Day 0, then respectively day 14 for the AOT and Day 28 for the SCT. The renal balance was carried out by dosage of the creatinine, the liver balance by the transaminases AST and ALT and the blood balance by the hemogram. The liver, kidneys and spleen were removed for histological analysis. The results were analyzed using the Student test, with the significance level set at 5%. **Results:** The weight of the rats did not change significantly in the acute or subchronic oral toxicity tests suggesting an absence of physical disturbance in the rats. Serum creatinine did not vary significantly, suggesting preservation of renal function. That was the same for ASAT and ALAT transaminases, indicating an absence of hepatic cytolysis. In hema-

tology, the hemoglobin level and the number of blood platelets did not vary significantly, suggesting that the extract did not create anemia and did not influence blood coagulation. Hepatic, renal and splenic parenchyma showed no atypia. **Conclusion:** The aqueous extract of *Senna alata* (L.) leaves did not reveal any acute or subchronic toxicity and offered prospects for its use in the treatment of infections.

Keywords

Senna alata, Oral Toxicity, Liver, Kidneys and Spleen

1. Introduction

Skin infections in modern medicine were a frequent reason for consulting a general practitioner. These infections were potentially recurrent and responsible for severe complications by a locoregional extension (abscess) or hematogenous spread. Especially with the emergence of bacteria multi-resistant to conventional antibiotics, the problem became more worrying [1]. Moreover, the management of these infections was often difficult for the poor population; they turned to traditional medicine for treatment.

Indeed, the main therapeutic approach since prehistoric times was phytotherapy, which played an important role in the development of primary health care [2]. In fact, 80% of people in developing countries depend mainly on medicinal plants [3]. Recently, it was discovered that a third of commonly used medicines are obtained from natural sources, which has led to the documentation of around 40,000 to 70,000 species of medicinal plants with exceptional therapeutic potential [4]. Scientific evaluation of the pharmacological activities of medicinal plants revealed that approximately 200,000 phytochemicals contribute to the apparent medicinal activities of plants and invariably justify the involvement of natural products in the development of new drugs [5]. Despite these accomplishments, the use of herbal medicines was not universally accepted in contemporary medicine due to the lack of scientific evidence and proper documentation [6]. However, the importance of herbs in pharmacology has necessitated the provision of scientific facts on bioactive compounds and pharmacological dosages of plants [6]. Medicinal plants with immense biological applications were considered the main sources of therapeutic substances that could lead to new therapeutic compounds. The search for these compounds from medicinal plants usually resulted in the isolation of new compounds and, eventually, the development of drugs [7]. Several medicinal plants with various interesting pharmacophores were studied scientifically, and one of these plants was *Senna alata* (*S. alata*), also known as *Cassia alata* and was a widely distributed herb in the Leguminosae family. It was commonly called candle bush, craw-craw plant, acapulo, moth bush, or moth plant. The plant was commonly found in Asia and Africa and had many local names [8]. It had arrays of bioactive chemical com-

pounds. Some of the reported chemical constituents are phenolic compounds (rhein, chrysaphanol, kaempferol, aloemodin and glycosides), anthraquinones (alatinone and alatonal), fatty acids (oleic, palmitic and linoleic acids), steroids and terpenoids (sitosterol, stigmasterol and campesterol). These secondary metabolites appeared to have numerous biological activities [9]. It should be noted that the traditional use of any plant for therapeutic purposes did not guarantee its safety [10]. Although the pharmacological effects of many plants have been proven in various laboratories, their toxicity was generally unknown. Therefore, evaluating the toxicity of herbal preparations was important in determining the safety of these remedies [11]. Hence this work was undertaken to study the acute and subchronic toxicity of the aqueous extract of *Senna alata* leaves in *Wistar* rats.

2. Materials and Methods

2.1. Animal Material

The animal material consisted of albino *Wistar* rats with an average body weight of 130 to 157 g, having free access to water and food and acclimatized to the rearing conditions of the animal facility of the Laboratory of Experimental and Clinical Biology. from the National School of Biosciences and Applied Biotechnologies (ENSBBA) of the National University of Sciences, Technologies, Engineering and Mathematics (UNSTIM) of Abomey in the Republic of Benin. Rearing took place in a well-ventilated room, with a day-night rhythm of 12 hours. The animals were kept in wire cages with feeders and drinkers. Their daily diet consisted of a mixture of foods in the form of croquettes and marketed by Veto Services (Benin). The enclosure was regularly cleaned to ensure the optimal development of the animals and to avoid infections.

2.2. Identification and Preparation of Plant Material

Senna alata leaves were collected in Abomey-Calavi in Benin in December 2019. The samples collected were identified and authenticated at the National Herbarium of Benin (YH 512/HNB). The University of Abomey-Calavi. The leaves were dried at moderate temperatures (20˚C - 25˚C), protected from humidity for four weeks. They were then ground into powder and stored in suitable containers at room temperature.

50 g of *Senna alata* leaf powder was boiled in 500 ml of distilled water in a 1000 ml flask for 30 minutes. After cooling, the mixture is filtered through a Bushner. This operation was repeated six times for a total mass of 300 g.

2.3. Acute Oral Toxicity Tests

Acute oral toxicity tests were performed in accordance with the recommendations of the Organization for Economic Co-operation and Development Guideline 423 for the Testing of Chemicals [12]. The substance was tested in a sequential process in which three animals, including 8- to 12-week-old females and

non-pregnant multiparas, were used at each stage. The absence or manifestation of substance-related mortality in a single-step dosed group would determine the next step. The initial dose was chosen from the following four doses: 5, 50, 300 and 2000 mg/kg of weight. The animals were administered 2000 mg *Senna alata* extract/kg body weight by gavage. The animals were carefully observed for four (4) hours and then daily for 14 days. They were weighed and blood was taken by an orbital puncture at the start of the experiment and then after 14 days.

2.4. Subchronic Toxicity Tests

Five *Wistar* rats received *Senna alata* extract at 200 mg/kg body weight daily for 28 consecutive days by gavage [13]. They were weighed and blood was taken by an orbital puncture at the start of the experiment and then after 28 days.

2.5. Blood Tests

Serum creatinine was measured to explore renal function. AST and ALT transaminases were measured for liver function. White blood cell count, hemoglobin level and blood platelet count were measured as hematological parameters.

2.6. Histology

At the end of the experiment, the animals were dissected. The liver, kidneys and spleen were removed, fixed in Bouin's solution and embedded in paraffin. Sample sections (5 µm) were mounted on glass slides, deparaffinized and hydrated. For histological analysis, the sections were stained with hematoxylin and eosin (H&E) according to a standard protocol [14] (Sènou *et al*., 2009). The pictures were taken at 400× magnification.

2.7. Statistical Analysis

Means were compared using the Mann-Whitney test. The significance threshold was set at 5%.

3. Results

3.1. The Aqueous Extract of *Senna alata* Leaves Was Not Acutely Toxic

The acute oral toxicity of the aqueous extract of *Senna alata* leaves was evaluated by measuring the weight of rats as a physical parameter, transaminases AST and ALT as hepatic parameters, serum creatinine as a renal parameter, the number of white blood cells as an immune parameter, hemoglobin level to assess anemia and platelet count for hemostasis (**Table 1**).

On D0, the mean weight of the rats was 143 ± 7 g; Serum creatinine was 13.7 ± 0.9 mg/L; AST and ALT transaminases were respectively 170 ± 12 and 104 ± 6 U/L; blood leukocytes number was 12.6 ± 0.7 G/L; Hemoglobin level was 15.3 ± 0.7 g/dl; blood platelets number was 496 ± 23 G/L. These different values did not

Table 1. Acute oral toxicity of the aqueous extract of *Senna alata*.

Parameters	Mean on D0	Mean on D14	P value	Difference
Weight of rats (g)	143 ± 7	157 ± 9	0.4	not significant
Creatinine (mg/L)	13.7 ± 0.9	8.6 ± 0.4	0.1	not significant
Transaminase AST (U/L)	170 ± 12	147 ± 9	0.4	not significant
Transaminase ALT (U/L)	104 ± 6	99.0 ± 6	0.7	not significant
Number of blood leukocytes (G/L)	12.6 ± 0.7	13.0 ± 0.5	0.9	not significant
Hemoglobin level (g/dl)	15.3 ± 0.7	14.6 ± 0.4	0.7	not significant
Number of blood platelets (G/L)	496 ± 23	668 ± 17	0.1	not significant

change significantly at the end of the experiment on D14, which indicated an absence of acute oral toxicity of the aqueous extract of *Senna alata*.

3.2. The Aqueous Extract of *Senna alata* Leaves Was Not Toxic in the Subchronic State

Since no toxic effects were observed during the acute toxicity study, the sub-chronic toxicity of the aqueous extracts of *Senna alata* was evaluated during a 28-day experiment in *Wistar* rats. Subchronic oral toxicity was evaluated by the same parameters previously measured for acute oral toxicity, namely the weight of the rat as a physical parameter, transaminases AST and ALT as hepatic parameters, creatinine as renal parameters, and a number of white blood cells as an immune parameter, the hemoglobin level and the number of blood platelets as hematological parameters (Table 2).

On D0, the mean weight of the rats was 156 ± 4 g; Serum creatinine was 10.9 ± 2 mg/L; AST and ALT transaminases were respectively 147 ± 7 and 101 ± 2 U/L; blood leukocytes number was 11.1 ± 1.0 G/L; Hemoglobin level was 14.8 ± 0.1 g/dl; blood platelets number was 587 ± 40 G/L. These different values did not change significantly at the end of the experiment on D28; this indicates an absence of chronic oral toxicity of the aqueous extract of *Senna alata*. The absence of disturbance of the hemoglobin level and the number of platelets indicated that the extract did not create anemia, nor disturb the phenomenon of blood coagulation.

3.3. The Aqueous Extract of *Senna alata* Leaves Did Not Alter Hepatic Parenchyma

Figure 1 shows liver histology in acute and subchronic oral toxicity testing.

In acute (Figure 1(b)) and sub-chronic (Figure 1(c)) oral toxicity tests, the liver of rats fed with *Senna alata* leaves aqueous extract did not show any visible

Table 2. Subchronic oral toxicity of the aqueous extract of *Senna alata*.

Parameters	Mean on D0	Mean on D14	P value	Difference
Weight of rats (g)	156 ± 4	182 ± 3	0.1	not significant
Creatinine (mg/L)	10.9 ± 2	8.5 ± 0.9	0.2	not significant
Transaminase AST (U/L)	147 ± 7	144 ± 5	0.9	not significant
Transaminase ALT (U/L)	101 ± 2	80.7 ± 2	0.1	not significant
Number of blood leukocytes (G/L)	11.1 ± 1.0	9.0 ± 1.0	0.4	not significant
Hemoglobin level (g/dl)	14.8 ± 0.1	14.9 ± 0.1	0.9	not significant
Number of blood platelets (G/L)	587 ± 40	612 ± 32	0.9	not significant

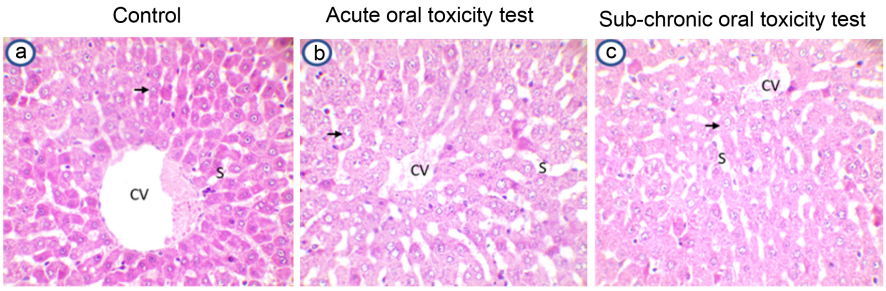

Figure 1. Hepatic paremchyma in the acute and subchronic oral toxicity test of *Senna alata* leaves aqueous extract (magnification 400×).

atypia. Hepatocytes (arrows) have normal appearances and are neatly arranged in radial cords around the central vein (CV). The venous sinusoids (S) are clearly visible as observed in the control rats (**Figure 1(a)**).

3.4. The Aqueous Extract of *Senna alata* Leaves Did Not Alter Renal Parenchyma

Figure 2 shows kidney histology in acute and subchronic oral toxicity testing.

In the acute oral toxicity tests (**Figure 2(b)**) and sub-chronic (**Figure 2(c)**), the renal parenchyma of the rats fed with *Senna alata* leaves aqueous extract kept its typical appearance as observed in the control rats (**Figure 2(a)**). The glomeruli (G), proximal and distal tubes (T) as well as collecting ducts (CD) did not exhibit any visible atypia.

3.5. The Aqueous Extract of *Senna alata* Leaves Did Not Alter Splenic Parenchyma

Figure 3 shows spleen histology in acute and subchronic oral toxicity testing.

In the acute oral toxicity tests (**Figure 3(b)**) and subchronic (**Figure 3(c)**), the

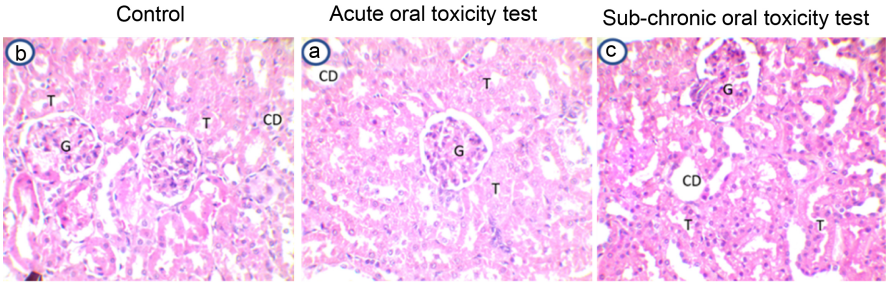

Figure 2. Renal paremchyma in the acute and subchronic oral toxicity test of *Senna alata* leaves aqueous extract (magnification 400×).

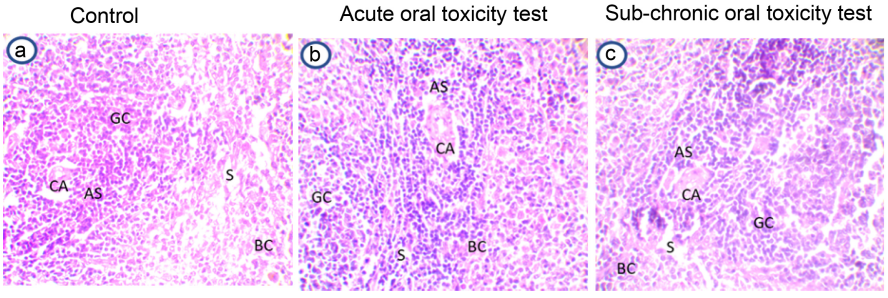

Figure 3. Splenic paremchyma in the acute and subchronic oral toxicity test of *Senna alata* leaves aqueous extract (magnification 400×).

splenic architecture of the rats force-fed with *Senna alata* leaves aqueous extract was not modified and was normal as in the control rats (**Figure 3(a)**). The central arteries (CA), the peri-arteriolar sleeves (AS) and the germinal centers of the white pulp appeared typical. It was the same for the venous sinusoids (S) and the Billroth cords (BC) of the red pulp which have kept the typical architecture.

4. Discussion

Although medicinal plants showed many biological activities, little was known about the toxic potential of their bioactive substances [15]. In this work, we investigated the safety of an aqueous extract of *Senna alata* leaves orally at acute and sub-chronic states as recommended by OECD [12]. The parameters analyzed were physical (rat weight), hepatic, renal, immune and hematological.

The aqueous extract of *Senna alata* leaves did not modify the behavior and body weight of rats in acute or subchronic oral toxicity tests. Subchronic administration of an aqueous extract of *Senna alata* at a dose of 200 mg/kg caused a non-significant decrease in ALT enzyme levels in the treated rats. These observations may suggest that the aqueous extract of *Senna alata* would have hepatoprotective effects. These observations corroborated those of [16], who explained in a similar study that a decrease in hepatic enzymes AST, ALT and Alkaline Phosphatase could indicate a hepatoprotective effect of the crude ethanolic extract of the roots of *Diospyros mespiliformis* hochst (ebenaceae). This result was confirmed by liver histology which remained normal.

Renal balance showed a non-significant decrease in blood creatinine on the

subchronic toxicity test, suggesting that the aqueous extract of *Senna alata* leaves was not nephrotoxic. The observation was confirmed by histology which showed renal parenchyma with glomeruli, proximal and distal tubules and collecting ducts apparently normal. These results were similar to those of [17] on the bark of *Psorospermum febrifugum*, an anti-anaemic plant. Carried out a study on *Senna alata* leaf extract and observed no significant variation in urea, bicarbonate, creatinine of the animals tested. An absence of subchronic oral toxicity of *Senna alata* flowers was also observed by [18], on the liver, kidneys and heart of *Wistar* rats.

Immune function as assessed by white blood cell count was not affected in acute or subchronic oral toxicity tests. The histology of the spleen, a peripheral immune organ, was not altered, confirming the non-toxic nature of the plant.

Similar observations were made with the aqueous extract of *Psorospermum febrifugum* bark and with the aqueous extract of *Cocos nucifera* root bark [19]. In addition, an anti-inflammatory effect was noted with the ethyl acetate extract of *Cocos nucifera* fiber following induction of inflammation in animal experiments by xylene.

This study showed no disturbance of the hemoglobin level and the number of platelets in the acute or subchronic state, indicating that the extract did not create anemia, nor disturb the phenomenon of blood coagulation. According to Mukinda *et al*. [20], the analysis of blood parameters was relevant because it gave information on hematopoietic function (evaluation of cells of the myeloid lineage), the occurrence of allergies (studies of white blood cells) and on intravascular effects such as hemolysis.

5. Conclusion

This study showed that the aqueous extract of *Senna alata* leaves has no acute and subchronic oral toxicity in *Wistar* rats at the doses studied. These results open up great prospects for its safe use. However, the study deserves to be continued with the chronic toxicity test to assess the toxicity of the extract in the longer term. This will make it possible to envisage its transformation into an improved traditional medicine accessible at a lower cost to the populations of poor regions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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