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Effect of an Aqueous Extract of *Justicia Flava* (Forsk) Vahl (Acanthaceae) in Subacute Administration on Some Lipid and Protein Blood Parameters and on Cardiac Tissue

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Abstract

Justicia flava (Forsk) Vahl is one of the many medicinal plants widely used in the daily lives of Ivorian and African populations. Rats were divided into seven groups of 10 animals, each consisting of five males and five females. A control group received distilled water orally at 10 mL/kg bw. Groups 2 to 5 received EAJf orally at doses of 125, 250, 500, and 1000 mg/kg bw, respectively. Groups 6 (distilled water at 10 mL/kg bw) and 7 (EAJf at 1000 mg/kg bw) were the satellite groups for this experiment. Oral administration of EAJf during the subacute toxicity study showed that the extract is nontoxic. Blood samples were collected at D0, D28 and a third sample was taken 14 days after D28 and the animals' hearts were weighed and the relative weights were then determined. Approximately 3 mL of blood was collected in dry serum tubes for biochemical analysis using the Culter (RAYTO-RT 7600S; China). The method used for the histochemical test is the paraffin embedding technique. EAJf at doses of pc showed that the relative heart weight of rats did not undergo any significant variation compared to that of rats in the control group. Administration of EAJf did not cause any significant variation in serum levels of total protein (TP), albumin (ALB), triglycerides (Trigly) and total cholesterol (Chol T) compared to those of the control group during the entire period of the experiment. Regarding rat heart histology, no damage was observed at the end of the experiment. Finally, subacute oral administration of EAJf was nontoxic to cardiac tissue and some lipid parameters.

Keywords: *Justicia flava;* Toxicity; Subacute; Histology; Heart; Lipid; Protein.

1. Introduction

In Africa, traditional medicine abounds with numerous herbal remedies held by herbalists for several generations [1]. Interest in plants also stems from the fact that modern medicine does not always provide effective solutions for many pathologies such as liver disorders, heart disease, and certain chronic conditions [2]. Furthermore, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroidal anti-inflammatory drugs (SAIDs) used to relieve pain, fever, and reduce inflammation, when used for prolonged periods, can cause gastrointestinal disorders, kidney toxicity, and skin toxicity [3, 4]. Thus, public interest in herbal medicine has grown steadily over the years. This so-called traditional herbal medicine is highly diverse, versatile, and available in many parts of the world. Furthermore, herbal medicine is low cost and very accessible for very poor populations living in villages and camps [5]. *Justicia flava* (Forsk) Vahl is one of the many plants used in the daily lives of Ivorian and African populations. It is renowned for its hemostatic properties, whether for cuts, vaginal hemorrhage or hemoptysis. The leaf pulp is used to rub babies who have convulsions or suffer from feverish aches and pains [6]. *Justicia flava* also has analgesic and anti-inflammatory properties according to the work of Kouamé, *et al.* [7] ; Kouamé, *et al.* [8]. In Ghana, this plant is used to treat upsets and feverish pain in babies, as well as lurching and diarrhea in children [9]. However, the lack of scientific report regarding the safety of this plant on some lipid and protein blood parameters and on cardiac tissue is essential. According to Ng [3], prolonged use of certain drugs such as anti-inflammatory drugs, analgesics and

painkillers can cause disorders in the gastrointestinal tract, toxicity in the kidney and liver. This study is therefore part of the verification of the safety of an aqueous extract of *Justicia flava* through the sub-acute toxicity test.

2. Material and Methods

2.1. Plant Material

The plant material consists of leaves, flowers, inflorescences, and stems of *Justicia flava* collected in the Agboville department (Côte d'Ivoire) in September 2016. The identification of this species was carried out at the Botanical Laboratory of NANGUI ABROGOUA University (Côte d'Ivoire), and was then confirmed with a herbarium preserved under number 17511 dated July 29, 1986, at the National Floristic Center of Félix Houphouët Boigny University.

2.2. Animal Material

The animal material consists of male and female albino rats (Rattus norvegicus) of the Wistar strain, aged 6 to 8 weeks and with a body mass between 75 g and 100 g. In accordance with Good Laboratory Practice [10], these animals were given free access to water and food with a 12-hour light/dark cycle. The various experimental protocols were followed in accordance with the European Council's protocols for the protection of experimental animals under Regulation 2012/707[11].

2.3. Technical Equipment

The technical equipment consisted of a feeding cannula, a magnetic stirrer (OVAN, USA), a binocular optical microscope (CYAN, Belgium), a microtome, a camera (TECNO, China), an electronic balance (Neo-Tech SA, Belgium), and an incubator (Heto, CD 52-I, France).

2.4. Reagents and Pharmacodynamic Substances

In this study, the aqueous extract of *Justicia flava*, distilled water, formalin solution, dyes (hematoxylin, eosin), and alcohol were used.

3. Method

3.1. Preparation of the Aqueous Extract of *Justicia Flava*

The leaves, flowers, inflorescences, and stems of *Justicia flava* were dried at room temperature (22-24°C). After drying, they were pulverized using an electric grinder (SM 100, Germany). 100 g of Justicia flava powder was infused for 15 min in 1 L of distilled water. The resulting aqueous solution was filtered through absorbent cotton and Whatman No. 3 filter paper. Half a liter of distilled water was added to the residue and boiled for 10 min. This solution was also filtered. The filtrates were mixed and dried in an oven (Selecta, Belgium) at 45°C for 48 h. A dark green powder weighing 14.37 g was obtained, corresponding to the aqueous extract of *Justicia flava* with a yield of 14.37%.

3.2. Subacute Toxicity Assessment

This subacute toxicity study was conducted following OECD 407 guidelines [12]. Seventy (70) rats were divided into seven groups of 10 animals, each consisting of five males and five females. Group 1 (control) received distilled water at 10 mL/kg bw orally. Groups 2 to 5 were gavaged with EAJf at doses of 125, 250, 500, and 1000 mg/kg bw, respectively. Two satellite groups (group 6 and group 7) consisting of five male rats and five female rats per group were added. Group 6, the satellite control group, received distilled water at 10 mL/kg bw orally. Group 7 was orally treated with EAJf at 1000 mg/kg bw. These daily treatments lasted 28 days for groups 1 to 5. Those in the satellite groups continued for two weeks after the 28-day mark to observe the reversibility, persistence, or delayed onset of toxic effects.

3.3. Blood and Heart Collection from the Rats

Three (3) blood samples were taken on Days 0 and 28, and a third sample was taken 14 days after Day 28. The samples taken on Days 0 and 28 were taken from rats in the test groups (treated groups and control group), while the sample taken 14 days after Day 28 was taken from rats in the satellite groups. Approximately 3 mL of blood was collected in dry serum tubes for biochemical analysis using the Culter (RAYTO-RT 7600S; China). These samples were taken during the experiment from rats previously fasted for 15 hours and anesthetized with diethyl ether, by puncture at the level of the retro orbital sinus of the eye. The hearts were collected after the 28th day (treated and control groups) and on the 14th day after the 28 days of treatment (satellite groups). These hearts were weighed and the relative weights were then determined as described in the work of Kharchoufa, *et al.* [13]:

$$\text{Relative weight}\ (\%) = \frac{\text{Organ weight(g)}}{\text{animal weight (g)}} \times 100$$

Biochemical parameters were analyzed using a semi-automatic centrifuge (ROBINIK, India). Total protein, albumin, total cholesterol, and triglycerides were determined using LABKIT reagent according to the kinetic, enzymatic, and colorimetric methods described by Tietz [14] and Young [15].

3.4. Histochemical Tests

The method used for the histochemical test was the paraffin embedding technique [16]. Preserved in 10% formalin, longitudinal sections were cut through the hearts. Histological sections were observed under a binocular optical microscope (CYAN, CM001CYANS cope, Belgium) and photographs were taken using a camera

Table-1.

	Relative heart weights (%)
Groups	**Heart**
Control (Distilled water 10 mL/kg pc)	0,33 ± 0,22
EAJf 125 mg/kg pc	0,32 ± 0,02
EAJf 250 mg/kg pc	0,33 ± 0,01
EAJf 500 mg/kg pc	0,31 ± 0,09
EAJf 1000 mg/kg pc	0,34 ± 0,04

(TECNO, Camon 12, China) mounted on the microscope.

4. Statistical Analysis

The results obtained are given as the mean followed by the standard error of the mean (SEM ± MSE). Statistical analysis was performed using Graph Pad Prism 5.01 software (San Diego, California, USA). The Student t-test and ANOVA (One-Way Analysis of Variance) followed by Dunett's comparison test were used to identify differences between treated and control groups. Differences were considered significant at $p < 0.05$.

5. Results

5.1. Effect on Changes in Relative Organ Weights

Oral administration of EAJf at doses of 125; 250, 500, and 1000 mg/kg bw showed that the relative heart weight of the treated rats did not undergo any significant change compared to that of the control rats (Table 1).

5.2. Effect of the Aqueous Extract of *Justicia Flava* on some Lipid and Protein Profile Parameters

5.3. Effect of EAJf on triglyceride concentration

After 28 days of oral administration of EAJf, a decrease in triglyceride concentration was recorded compared to the control rats. The triglyceride concentration of the control rats was 116 ± 7.60 mg/dL. The cholesterol concentration of rats treated with EAJf at doses of 125, 250, and 500 mg/kg bw decreased from 114 ± 11.5 mg/dL (EAJ 125 mg/kg bw) to 94.7 ± 7.46 mg/dL (EAJ 250 mg/kg bw). This decrease was significant ($p < 0.05$) at the dose of 1000 mg/kg bw, with an estimated triglyceride concentration of 83.5 ± 1.95 mg/dL (Table 2).

5.4. Effect of EAJf on Cholesterol Concentration

Cholesterol concentration decreased nonsignificantly ($p > 0.05$) compared to that of control rats after administration of EAJf. Cholesterol concentrations in rats treated with EAJf decreased from 127 ± 11.6 mg/dL (500 mg/kg bw) to 116 ± 6.65 mg/dL (1000 mg/kg bw), while those in the control group were 135 ± 4.32 mg/dL (Table 2).

5.5. Effect of EAJf Administration on Total Protein Concentrations

Total protein concentrations increased after the use of EAJf at all doses. This increase was significant at the 1000 mg/kg bw dose compared to the control group. Total protein concentrations in rats in the control group were 9.60 ± 0.40 mg/dL, while they reached 17.1 ± 1.57 mg/dL in rats in the 1000 mg/kg bw group (Table 2).

Table 1: Effect of *Justicia flava* aqueous extract on relative heart weight

$p > 0.05$ non-significant difference compared to the control group for the heart. EAJf: *Justicia flava* aqueous extract; n = 10, m ± esm.

Table-2. Variation of some parameters of the lipid and protein profile following repeated oral administration of the aqueous extract of *Justicia flava* in rats

		Doses de EAJf (mg/kg)			
Paramètres	**Témoin (Eau distillée 10 mL/kg pc)**	**125**	**250**	**500**	**1000**
Trigly (mg/dL)	116 ± 7,60	114 ± 11,5	94,7 ± 7,46	99,2 ± 4,39	83,5 ±1,95
Chol T (mg/dL)	135 ± 4,32	120 ± 5,50	123 ± 5,69	127 ± 11,6	116 ± 6,65
PT (mg/dl)	9,60 ± 0,40	10,7 ± 0,38	14,5 ± 1,86	14,4 ± 2,28	17,1 ± 1,57**
ALB (g/dl)	3,55 ± 0,19	2,95 ± 0,24	3,08 ± 0,20	3,22 ± 0,26	3,18 ± 0,28

p < 0,01: significant difference between rats in groups t treated with EAJf compared to rats in the control group. **Chol T: Total cholesterol**; Trigly:** Triglycerides**; PT:** Total protein, **ALB** : Albumin, **EAJf:** Justicia flava aqueous extract. n=10, m ± esm.

5.6. Effect of EAJf Administration on Albumin Concentration

Albumin concentration during the experiment underwent a non-significant change after 28 days of EAJf administration (125, 250, 500, and 1000 mg/kg bw). The albumin concentration of rats in the control group was 3.55 ± 0.19 g/dl. This albumin concentration fluctuates between 2.95 ± 0.24 and 3.22 ± 0.26 g/dl in the presence of EAJf (125-1000 mg/kg bw (Table 2).

5.7. Effects of the Aqueous Extract of Justicia Flava on Biochemical Parameters Two Weeks after Treatment Cessation

On day 28, significant differences were recorded in total protein levels in treated rats compared to the control. This significant difference appeared in this experiment at the level of this parameter in most rats pretreated with EAJf at a dose of 1000 mg/kg bw. Fourteen (14) days after the end of the experiment, no significant variation in the values of this parameter in the groups treated with EAJf was recorded compared to those of the different control groups. Thus, the potential toxic effects of EAJf are reversible. No delayed effects appeared after treatment discontinuation (Table 3).

6. Histological examination of the Rat heart.

6.1. Effect of Aqueous Extract of Justicia Flava on Heart Histology

Histological analysis performed on the hearts of rats treated with EAJf (125, 250, 500, and 1000 mg/kg bw) revealed no abnormalities. The hearts had a normal appearance and showed no major histological differences from those of the control group (Figure 1).

6.2. Effect of Administration of Aqueous Extract of Justicia Flava on Organ Histology (Liver, Kidney, Heart) Two Weeks after Discontinuation of the Various Treatments

Fourteen (14) days after discontinuation of the various treatments, the histology of the heart still presented a normal appearance, and no delayed toxic effects were observed (Figure 2).

Table-3. Effect of the aqueous extract of Justicia flava on biochemical markers two weeks after stopping the different treatments

Settings	Day 28		Two weeks after stopping treatment	
	Control (Distilled water)	EAJf (1000 mg/kg de bw)	Control (Distilled water)	EAJf (1000 mg/kg de bw)
PT (mg/dl)	9,60 ± 0,40	17,1 ± 1,57**	9,28 ± 0,38	9,87 ± 0,45
ALB (g/dl)	3,55 ± 0,19	3,18 ± 0,28	3,11 ± 0,14	3,36 ± 0,11
Trigly (g/l)	116 ± 7,60	83,5 ±1,95	71,1 ± 23,8	73,2 ± 20,3
Chol T (g/l)	135 ± 4,32	116 ± 6,65	125,7 ± 4,11	123,2 ± 7,28

p < 0,01: significant difference between rats in groups t treated with EAJf compared to rats in the control group. **PT: Total protein; **ALB**: Albumin; **Chol T:** total Cholesterol**; Trigly**: Triglycerides. **EAJf** : Aqueous extract of Justicia flava; n = 10, m ± esm.

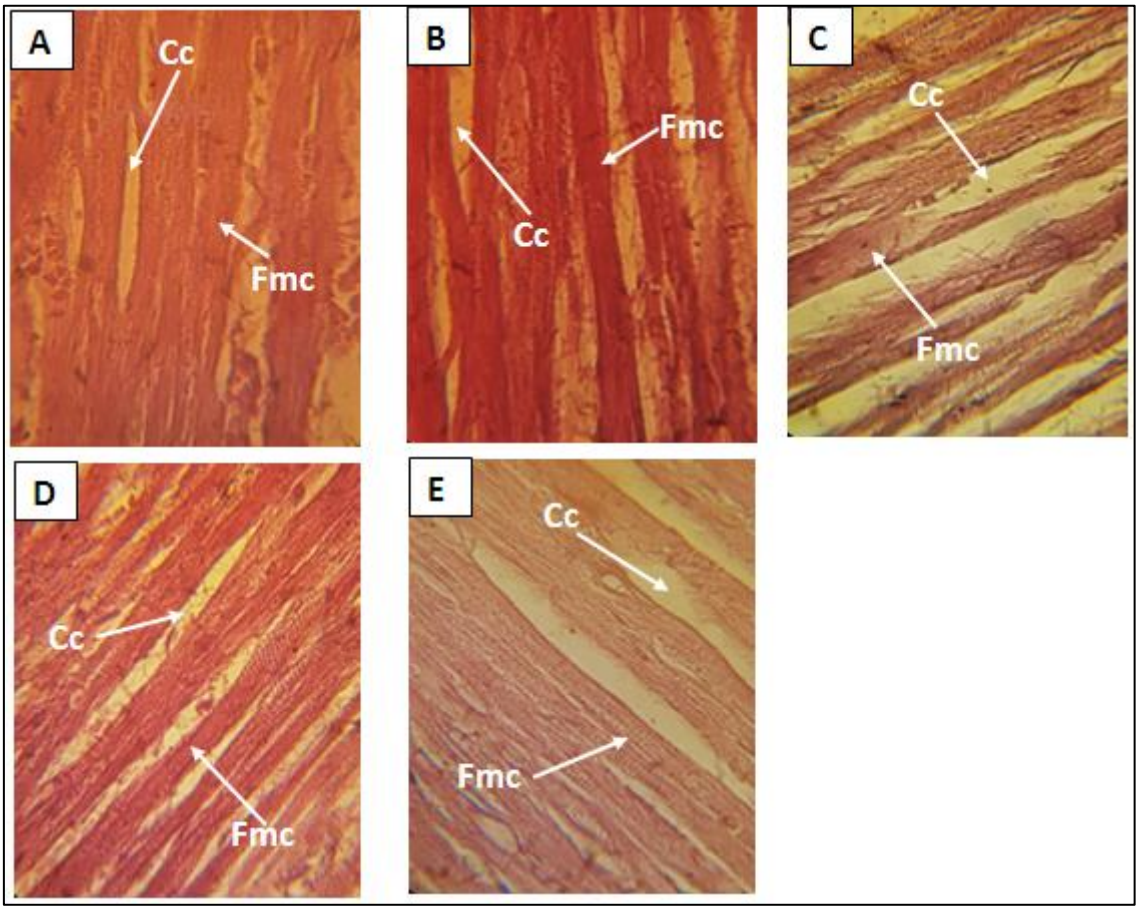

Figure-1. Photomicrograph of rat heart tissue after 28 days of treatment with Justicia flava aqueous extract

A: Control rat heart tissue; B: Rat heart tissue treated with 125 mg/kg bw; C: Rat heart tissue treated with 250 mg/kg bw; D: Rat heart tissue treated with 500 mg/kg bw; E: Rat heart tissue treated with 1000 mg/kg bw; Fmc: Cardiac muscle fibers; Cc: Heart cavity. Hematoxylin-eosin staining; (G X 1000)

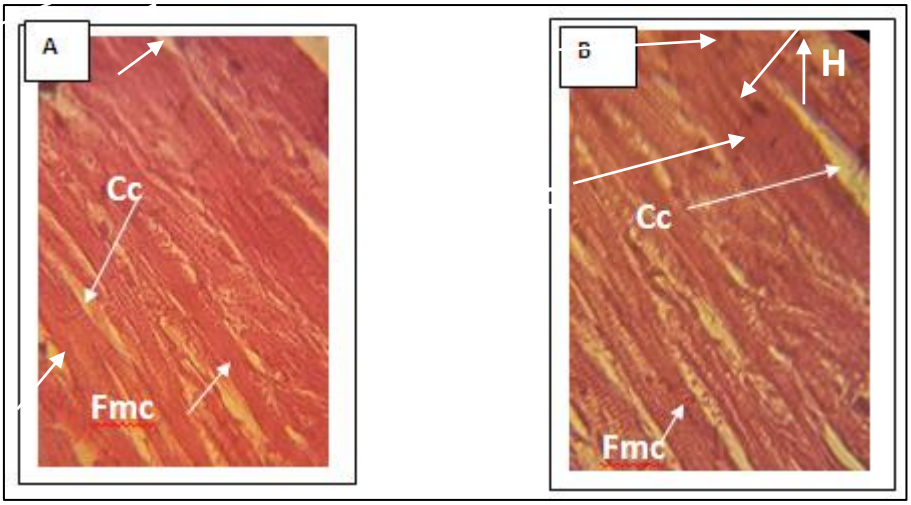

Figure-2. Photomicrograph of rat (cardiac) tissues 14 days after treatment cessation

A: Heart tissue of a control rat; B: Heart tissue of a rat treated with 1000 mg/kg bw; Fmc: cardiac muscle fibers; Cc: cardiac cavity. Hematoxylin-eosin staining; (G X 1000)

7. Discussion

General observations made during the subacute toxicity study showed that the extract did not cause death. No significant changes in the relative weights of the hearts collected at the end of the experiment were recorded. This result is similar to those of Koné, *et al.* [17]. These researchers showed that no significant changes in body weight and vital organ weights were recorded in animals treated with Secamone afzelii (200, 300, and 400 mg/kg) compared to controls. Repeated administration of EAJf at doses of 125, 250, and 500 mg/kg bw caused a significant increase ($p<0.01$) in total protein at a dose of 1000 mg/kg bw. Furthermore, exposure of the body to natural products can cause dysfunction in organs such as the heart (regulatory organ). Thus, certain biochemical markers such as total protein (TP), albumin (ALB), triglycerides (Trigly) and total cholesterol (Chol T) make it possible to evaluate the functioning of certain cells in the body [18]. The elevation of these markers in the serum indicates lesions, dysfunction and as indicators of the destruction of cells of the heart, skeletal muscles, lungs and kidneys [19]. However, repeated administration of the aqueous extract of Justicia flava (125 to 500 mg/kg bw) did not cause any significant variation in the serum levels of these parameters compared to those of the control group. Furthermore, the increase in total proteins after repeated administration of EAJf at 1000 mg/kg bw shows that dysfunction could occur at the level of metabolic or purification organs. Two weeks after treatment discontinuation, no significant changes in total protein were recorded. This suggests that this extract does not cause damage to cardiac tissue. These results are similar to those of Koné, *et al.* [20]. These authors showed that the total aqueous extract of Sacoglottis gabonensis has no effect on plasma biochemical parameters. Similarly, the work of Kushwaha, *et al.* [21] showed that aqueous and ethanolic extracts of Ipomoea carnea administered at doses of 250, 500, and 1000 mg/kg bw for 28 days of treatment showed no abnormalities in biochemical parameters.

8. Conclusion

Histologically, the rat hearts suffered no damage. This suggests that EAJf would not have a significant toxic effect on the hearts after repeated use for 28 days. Two weeks after stopping treatment, no delayed or reversible effects were observed on heart structure. Furthermore, the aqueous extract of Justicia flava acted by decreasing lipid profile parameters. Indeed, the decrease in lipid profile parameters is an important property in reducing the incidence of cardiovascular diseases [22]. This observation suggests that the aqueous extract of Justicia flava could have a protective action on the cardiovascular system. These results are similar to those of Gome, *et al.* [23]. They showed that the aqueous extract of Passiflora foetida at a dose of 800 mg/kg bw could have a protective action on the cardiovascular system. Furthermore, the work of Gnahoué, *et al.* [24] showed that the total aqueous extract of Alchornea cordifolia does not affect heart function. 3- Partial Conclusion

Subacute oral administration of the aqueous extract of Justicia flava is non-toxic. It does not cause any significant changes in some blood lipid (triglycerides and total cholesterol), protein (total protein and albumin), or cardiac tissue parameters.

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