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EFFECT OF THE AQUEOUS EXTRACT OF *JUSTICIA FLAVA* ON PROTEIN DENATURATION AND ON SOME SERUM BIOCHEMICAL PARAMETERS DURING FORMALDEHYDE-INDUCED ARTHRITIS

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ABSTRACT

Justicia flava is a plant species widely used in Côte d'Ivoire and recommended in traditional medicine. This plant is frequently used to treat joint pain. Therefore, the objective of this study was to evaluate the effect of an aqueous extract of *Justicia flava* on protein denaturation and several serum biochemical parameters in an anti-arthritic test. For the protein denaturation test, 0.2 mL of fresh egg albumin was added to 2.8 mL of phosphate-buffered saline (pH 6.4) and 2 mL of distilled water for the control tube. The mixture was incubated at 37 ± 2 °C for 15 min, heated to 70 °C for 5 min, and the absorbance was measured at 660 nm. For the anti-arthritic test, 36 rats were divided into 6 groups of 6 rats each. Two injections of 0.1 ml of freshly prepared 2.5% formaldehyde were administered to the right hind leg on days 1 and 3 to indurate the arthritis. Blood samples were taken for biochemical analysis. The aqueous extract of *Justicia flava* at concentrations ranging from 0.04 to 1.25 mm/ml inhibited protein denaturation by 13.06% to 43.71% compared to the control. It also significantly increased ($p<0.05$ and $p<0.01$) the mean total protein and albumin levels by 16.76% and 36.32%, respectively, compared to

arthritic rats. However, it significantly reduced ($p<0.05$, $p<0.01$) the levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase by 25.97%, 48.09%, and 30.16%, respectively, compared to arthritic rats. Therefore, the aqueous extract of *Justicia flava* inhibited protein denaturation and restored serum levels of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.

KEYWORDS: Denaturation, proteins, arthritis, *Justicia flava*, formaldehyde**.**

INTRODUCTION

Protein denaturation due to various tissue or metabolic stresses plays a crucial role in inflammatory diseases such as rheumatoid arthritis. Thus, inflammation is a natural protective response of the body to tissue damage caused by physical trauma, chemical agents, or infections. It is characterized by pain, redness, heat, swelling, and disruption of physiological functions.[1] In most cases, this reaction is beneficial to the injured host, but excessive activation can cause significant alterations, including the denaturation of certain proteins. These proteins, having lost their three-dimensional structure, can lead to the appearance of autoantigens, thereby transforming an inflammatory reaction into an autoimmune reaction. This autoimmune reaction produces new autoantigens that trigger and exacerbate the inflammatory cascade and joint destruction.[2] Furthermore, the daily and excessive use of anti-inflammatory drugs, which are very harsh on humans, can present risks of gastrointestinal toxicity, cardiovascular disease, and in some cases, serious hemorrhages.[3] In addition, in modern medicine, steroidal and non-steroidal anti-inflammatory drugs are used to treat inflammation. Thus, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) can lead to gastrointestinal disorders, kidney and skin toxicity.[4] Therefore, to limit or avoid the harmful effects of these molecules, some populations use traditional medicine for their health needs. It is in this context that *Justicia flava* (Forsk) Vahl, a plant used as a hemostatic agent, against convulsions, and for feverish aches and pains[5], has been used. Thus, this study was conducted on the denaturation of proteins contained in *Justicia flava* (Forsk) Vahl, and on some serum biochemical parameters determined during formaldehyde-induced arthritis in rats.

1. MATERIALS AND METHODS

1.1 Materials

1.1.1 Plant Material

The plant material used consisted of the entire plant without the roots (leaves, flowers,

inflorescences, and stem) of *Justicia flava* collected in Pétit Yapo, in the Agboville department (Côte d'Ivoire) in September 2016. The species was identified at the Botany Laboratory of Nangui Abrogoua University (Côte d'Ivoire), and subsequently confirmed at the National Floristic Center of Félix Houphouët-Boigny University, where a herbarium specimen is kept under number 17511 dated July 29, 1986.

1.1.2 Animal Material

The animal material consisted of male and female albino rats (Rattus norvegicus), of the Wistar strain, aged 8 to 12 weeks and with a body mass between 164 g and 240 g. They were used to evaluate the anti-inflammatory effect. These animals had free access to food and water under a 12-hour light/dark cycle. They were treated according to Good Laboratory Practices.[6] The various experimental protocols were followed in accordance with the European Council's guidelines on the protection of laboratory animals under Legislation.[7]

1.1.3 Technical Equipment

The technical equipment consisted of a magnetic stirrer (OVAN, USA) for homogenizing the different substances, an electronic balance (Neo-Tech SA, Belgium) for weighing, an oven (Heto, CD 52-I, France) for drying the extract, a water bath, and glass tubes.

1.1.4 Reagents and Pharmacodynamic Substances

The substances used in this study were aspirin® (Ivory Coast), methotrexate, and, as reference products, fresh egg albumin, formaldehyde for arthritis induction, phosphate-buffered saline, and LABKIT reagents (AST, ALT, Total Protein, Albumin, Alkaline Phosphatase, etc.).

1.2 Methods

1.2.1 Preparation of the Aqueous Extract of *Justicia flava*

Whole Justicia flava plants, excluding the roots, were washed with distilled water and dried at room temperature (22–24°C). They were then finely ground using an electric grinder (SM 100, Germany). One hundred grams of *Justicia flava* powder was decocted for 15 minutes in 1L of distilled water. The aqueous solution The resulting 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 minutes. This solution was also filtered. The filtrates were mixed and dried in an oven (Selecta, Belgium) at 45°C for 48 hours. A dark green powder of 14.37 g was obtained, corresponding to the aqueous extract of *Justicia flava* with a yield of

14.37%.[8]

1.2.2 Evaluation of the antiarthritic effect of the aqueous extract of *Justicia flava* in vitro by the protein denaturation method

The denaturation method for fresh egg albumin was performed as described in the work of.[9] Reaction mixtures were prepared for the control tube, aspirin, methotrexate, and for the tubes containing the extracts. aqueous extract of *Justicia flava*. A 5 mL reaction mixture tube was prepared with 0.2 mL of egg albumin, 2.8 mL of phosphate-buffered saline (pH 6.4), and 2 mL of distilled water for the control tube. 5 mL reaction mixtures per tube were prepared with 0.2 mL of egg albumin, 2.8 mL of phosphate-buffered saline (pH 6.4), and 2 mL of varying concentrations (0.078, 0.156, 0.312, 0.625, 1.25, 2.5, 5, and 10 mg/mL) of the aqueous extract of *Justicia flava*. Two reaction mixture tubes were prepared, each with 0.2 mL of egg albumin, 2.8 mL of phosphate-buffered saline (pH 6.4), and 2 mL of distilled water. ml of aspirin or methotrexate solution. The mixtures were then incubated at 37 ± 2 °C in an incubator for 15 min, and then heated to 70 °C for 5 min. After cooling, the absorbance was measured at 660 nm, taking into account the dilutions performed. Each experiment was carried out in triplicate, and the average was taken. The percentage of protein denaturation inhibition was calculated using the following formula:

$$\% \text{ INH } (\%) = \frac{\text{At}}{\text{Ac} - 1} \times 100$$

A t = absorbance of the tested lots,

A c = absorbance of the control lot.

1.2.3 Formaldehyde-Induced Arthritis 2.5%

The non-immunologically induced arthritis model described by[10] was used. The experiments lasted 14 days. A curative model was used. Six groups of 6 rats received various treatments. Arthritis was induced by injecting 0.1 mL of freshly prepared 2.5% formaldehyde into the right hind leg of rats in all groups except group 1 (healthy control) on days 1 and 3. Subsequently, rats in group 1 (healthy control) and group 2 (arthritic control) received 10 mL/kg body weight of 0.9% NaCl by gavage. Rats in groups 3, 4, and 5 were gavaged with aqueous extract of *Justicia flava* at doses of 125 mL/kg body weight, respectively. 250 and 500 mg/kg body weight. Finally, the rats in group 6 received aspirin by gavage at a dose of 100 mg/kg body weight. These different administrations were given daily for 10 days to each rat. To assess the progression of arthritis, blood samples were taken for the measurement of biochemical parameters.

Blood Sampling and Biochemical Parameter Measurements

During this study, three blood samples were taken on days 0, 3, and 14 of the experiment. The blood collected in dry tubes was centrifuged at a speed of 3000 rpm for 10 minutes to obtain the serum. This serum was used for the analysis of biochemical parameters using a semi-automated analyzer (ROBINIK, India). The serum collected in dry tubes was used to measure alkaline phosphatase, transaminases, total protein, and albumin. The various assays were performed using the LABKIT reagent according to the methods (kinetic, enzymatic, and colorimetric) described by.[11] and[12]

1.3 Statistical Analysis

The results are presented as the mean followed by the standard error of the mean (M ± SEM). Statistical analysis was performed using GraphPad Prism 5.01 software (San Diego, California, USA). One-way analysis of variance (ANOVA) followed by Dunnett's test was used to identify differences between the treatment and control groups. Differences were considered significant for $p < 0.05$.

2. RESULTS

2.1. Effect of the aqueous extract of *Justicia flava* on protein denaturation

EAJf, at concentrations between 0.04 and 1.25 mm/ml, inhibits heat-induced protein denaturation in fresh egg white. These inhibitions range from 13.06% to 43.71%. Aspirin and methotrexate have inhibition percentages of 15.57% and 21.60%, respectively (Table 1).

Table 1: Variation in inhibition percentages of protein denaturation in fresh egg white.

Extract	Concentration (mg/ml)	Absorbance (660 nm)	Percentage of Inhibition (%)
Control		0,79 ± 0,00	-
EAJf	0.004	0.44± 0.00	44.30
	0.009	0.45± 0.00	43.03
	0.019	0.46± 0.00	41.77
	0.039	0.55± 0.00	30.37
	0.078	0.58± 0.00	26.58
	0.156	0.60± 0.00	24.05
	0.312	0.64± 0.00	18.98
	0.625	0.66 ± 0.00	16.45
	1.25	0.69 ± 0.00	12.65
Aspirin	0.937	0.67 ± 0.00	15.18
Methotrexate	0.093	0.63 ± 0.00	20.25

n = 3, m ± esm

2.2. Effect on serum total protein levels in rats

The total protein levels recorded at the beginning of this study in all groups of rats ranged from 72.4 ± 2.16 to 76.1 ± 1.51 g/dL, with no significant differences between them. After 3 days of arthritis induction, the total protein level of rats treated with 2.5% formaldehyde was significantly reduced ($p < 0.05$) from 55 ± 1.33 to 64.5 ± 1.83 g/dL compared to healthy control rats with a total protein level of 72.0 ± 2.13 g/dL. An increase in total protein levels was observed after 10 days of treatment with EAJf at doses of 125, 250, and 500 mg/kg bw, ranging from 7.34% to 16.76% compared to the arthritis control. This increase was significant ($p < 0.05$) at the 500 mg/kg bw dose. The total protein level of rats treated with aspirin increased by 13.37% compared to the arthritis control (Table 2).

Table 2: Change in serum total protein concentration during formaldehyde-2,5-induced arthritis in rats treated with aqueous extract of *Justicia flava.*

Treatment mg/kg de pc	Total protein (g/dL) / percentage increase or decrease in parentheses (%)		
	Day 0	Day 3	Day 14
Healthy control NaCl 9 ‰ (mL/kg de pc)	72.4 ± 2.16	72.0 ± 2.13	71.54 ± 2.13
Arthritic control NaCl 9 ‰ (mL/kg de pc)	73.0 ± 2.90	55.0 ± 1.33$^{###}$ (23,61)	53.1 ± 2.29
EAJf 125	73.3 ± 2.27	63.0 ± 1.70$^{##}$ (12.5)	57.3 ± 2.33 (7.34)
EAJf 250	75.5 ± 0.75	61.8 ± 2.01$^{###}$ (14.16)	59.5 ± 1.99 (12.05)
EAJf 500	74.1 ± 1.24	64.5 ± 1.83$^{##}$ (10.41)	62.0 ± 0.38* (16.76)
Aspirin 100	76.1 ± 1,51	58.5 ± 2.37$^{###}$ (18.75)	60.2 ± 2.66 (13.37)

##p < 0.01; ###p < 0.001; significant difference between rats in the healthy control group (9‰ NaCl) and those in the other groups on day 3. *p < 0.05: significant difference between the arthritic control group and the respective treated groups (EAJf and aspirin) on day 14. EAJf: Aqueous extract of *Justicia flava*; n = 6, m ± esm.

2.3. Effect on serum albumin levels in rats

The serum albumin level at the beginning of this experiment in all rats ranged from 2.79 ± 0.04 to 2.87 ± 0.12 g/dL. After 3 days of arthritis induction, albumin levels were significantly reduced ($p < 0.05$), ranging from 2.01 ± 0.05 to 2.27 ± 0.16 g/dL. An increase in albumin was observed after 10 days of treatment with EAJf at doses of 125, 250, and 500 mg/kg body

weight, ranging from 14.52% to 36.32% compared to the arthritis control. This increase was significant ($p < 0.05$) at both 250 and 500 mg/kg body weight. Albumin levels in rats treated with aspirin were increased by 14.52% compared to the arthritis control (Table 3).

Table 3: Variation in serum albumin concentration during formaldehyde-2.5-induced arthritis in rats treated with aqueous extract of *Justicia flava.*

Treatment mg/kg de pc	Albumin (g/dL) / percentage increase or decrease in parentheses (%)		
	Day 0	Day 3	Day 14
Healthy control NaCl 9 ‰ (mL/kg de pc)	2.81 ± 0.21	2.80 ± 1.12	2.83 ± 0.28
Arthritic control NaCl 9 ‰ (mL/kg de pc)	2.83 ± 0.10	2.01 ± 0.09# (28,21)	2.34 ± 0.16
EAJf 125	2.79 ± 0.04	2.27 ± 0.16# (18.92)	2.69 ± 0.17 (14.95)
EAJf 250	2.87 ± 0.12	2.11 ± 0.05# (24.64)	3.19 ± 0.19** (36.32)
EAJf 500	2.84 ± 1.03	2.06 ± 0.23# (26.42)	2.96 ± 0.03* (26.49)
Aspirin 100	2.82 ± 1.17	2.04 ± 0.22# (27.14)	2.68 ± 0.06 (14.52)

#$p < 0.05$; significant difference between rats in the healthy control group (9‰ NaCl) and those in the other groups on day 3. *$p < 0.05$; **$p < 0.01$: significant difference between the arthritic control group and the respective treated groups (EAJf and aspirin) on day 14. EAJf: Aqueous extract of Justicia flava; n = 6, m ± esm.

2.4. Effect on serum aspartate aminotransferase levels in rats

Serum AST levels in all rats at the start of the experiment ranged from 148 ± 9.10 to 162 ± 9.36 IU/L. After 3 days of arthritis induction, serum AST levels increased from 214 ± 21.1 to 263 ± 15.9 IU/L. Serum AST levels decreased by 17.74% to 25.97% compared to arthritis controls after 10 days of treatment with aspirin and EAJf at different doses (Table 4).

Table 4: Change in serum aspartate aminotransferase concentration during formaldehyde-2,5-induced arthritis in rats treated with aqueous extract of *Justicia flava.*

Traitement mg/kg de pc	Aspartate aminotransferase (UI/L) / pourcentage d'augmentation ou de réduction entre parenthèse (%)		
	Day 0	Day 3	Day 14
Healthy control NaCl 9 ‰ (mL/kg de pc)	152 ± 9.92	169 ± 16.30	160 ± 15.34
Arthritic control NaCl 9 ‰ (mL/kg de pc)	158 ± 11.4	214 ± 21.1# (26.62)	231 ± 19.4
EAJf 125	148 ± 4.35	249 ± 15.1# (47.33)	190 ± 17.4 (17.74)
EAJf 250	164 ± 9.10	214 ± 19.4# (26.62)	184 ± 5.74 (20.34)
EAJf 500	162 ± 9.36	263 ± 15.9# (55.62)	171 ± 13.5* (25.97)
Aspirin 100	156 ± 11.8	251 ± 27.4# (48.50)	174 ± 18.3 (24.67)

#p < 0,05; différence significative entre les rats du lot témoin sain (NaCl 9 ‰) et ceux des autres au jour 3. *p < 0,05: différence significative entre groupe témoin arthritique et groupes traités (EAJf et aspirine) respectifs au jour 14. **EAJf:** Extrait aqueux de *Justicia flava;* n = 6, m ± esm.

2.5. Effect on Serum Alanine Aminotransferase Levels in Rats

The ALT level in all rats before the experiment varied non-significantly at the start of the experiment from 31.9 ± 3.71 to 39.2 ± 4.12 IU/L. Three (3) days after the induction of arthritis, the serum ALT level increased significantly ($p < 0.05$) from 43.2 ± 2.93 to 51.9 ± 9.7 IU/L. After 10 days of treatment with aspirin and EAJf at different doses, a decrease ranging from 27.4% to 48.09% was observed compared to the arthritis controls (Table 5).

2.6. Effect on serum alkaline phosphatase levels in rats

Serum alkaline phosphatase (ALP) levels in all rats at baseline ranged from 256 ± 18.2 to 283 ± 28.6 IU/L. Three (3) days after arthritis induction, serum ALP levels increased significantly ($p < 0.05$), from 296 ± 15.6 to 367 ± 18.1 IU/L. ALP levels in rats treated with EAJf decreased by 20.32% to 30.16% compared to arthritis controls. This decrease was significant at 500 mg/kg body weight ($p < 0.05$). The amount of ALP in rats treated with aspirin was reduced by 27.54% compared to arthritis controls (Table 6).

Table 5: Change in serum alanine aminotransferase concentration during formaldehyde-2,5-induced arthritis in rats treated with aqueous extract of *Justicia flava.*

Treatment mg/kg de pc	Alanine aminotransferase (UI/L) / percentage increase or decrease in parentheses (%)		
	Day 0	Day 3	Day 14
Healthy control NaCl 9 ‰ (mL/kg de pc)	39.2 ± 4.12	33.4 ± 6.25	30.9 ± 5.13
Arthritic control NaCl 9 ‰ (mL/kg de pc)	34.4 ± 5.38	46.5 ± 5.86$^{\#\#}$ (39,22)	55.1 ± 7.17
EAJf 125	36.8 ± 2.25	44.1 ± 6.46$^{\#}$ (32.05)	40.0 ± 3.35 (27.40)
EAJf 250	31.9 ± 3.71	43.2 ± 2.93$^{\#\#}$ (29.34)	31.5 ± 2.29** (42.83)
EAJf 500	38.5 ± 1.87	48.9 ± 11.7$^{\#}$ (46.40)	28.6 ± 3.78** (48.09)
Aspirin 100	35.1 ± 4.06	51.9 ± 9.7$^{\#\#}$ (55.38)	30.6 ± 5.34** (44.46)

#p < 0.05; ##p < 0.01; ###p < 0.001: Significant difference between rats in the healthy control group (NaCl 9‰) and those in the other group on day 3. *p < 0.05; **p < 0.01: Significant difference between the arthritis control group and the respective treated groups (EAJf and aspirin) on day 14. EAJf: Aqueous extract of Justicia flava; n = 6, m ± esm.

Table 6: Change in serum alkaline phosphatase concentration during formaldehyde-2.5-induced arthritis in rats treated with aqueous extract of *Justicia flava.*

Treatment mg/kg de pc	Alkaline phosphatase (UI/L) / percentage increase or decrease in parentheses (%)		
	Day 0	Day 3	Day 14
Témoin sain NaCl 9 ‰ (mL/kg de pc)	267 ± 22.3	279 ± 30.5	270 ± 29.1
Témoin arthritique NaCl 9 ‰ (mL/kg de pc)	260 ± 32.3	309 ± 19.4$^{\#}$ (10,75)	305 ± 28.2
EAJf 125	273 ± 25.3	328 ± 15.2$^{\#\#}$ (17.56)	243 ± 26.1 (20.32)
EAJf 250	263 ± 21.2	314 ± 17.3$^{\#\#}$ (12.54)	233 ± 18.9 (23.60)
EAJf 500	283 ± 28.6	367 ± 18.1$^{\#}$ (31.54)	213 ± 25.5* (30.16)
Aspirine 100	256 ± 18.2	296 ± 15.6 (06.09)	221 ± 16.1 (27.54)

#p < 0.05; ##p < 0.01; significant difference between rats in the healthy control group (NaCl 9‰) and those in the others on day 3. *p < 0.05: significant difference between the arthritic control group and the respective treated groups (EAJf and aspirin) on day 14. EAJf: Aqueous extract of Justicia flava; n = 6, m ± esm.

3. DISCUSSION

In this study, the protein denaturation method was used to evaluate the in vitro anti-arthritic properties of EAJf. In arthritic control rats, the production of autoantigens in certain arthritic diseases can be attributed to protein denaturation. Indeed, CFA injection into the rat's leg caused changes in hematological and biochemical parameters, as well as protein degradation.[13] In contrast, after treatment of the rats with EAJf, an inhibition of protein denaturation was observed. This could be explained by the restoration of total protein and albumin levels. EAJf at concentrations ranging from 1.25 to 0.004 mg/ml induced inhibition of egg white albumin protein denaturation ranging from 13.06% to 43.71%. These results corroborate those of[14], who showed that *Rhizophora mucronata* leaves at 400 mg inhibited egg protein denaturation by 97.56% in a dose-dependent manner.

Total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels were restored in rats treated with EAJf. Formaldehyde induces arthritis by denaturing proteins involved in the immune response.[15] This explains the decrease in total serum protein. Furthermore, other studies have reported that protein denaturation is also a major cause of arthritic diseases. This protein denaturation is primarily characterized by alterations in hydrophobicity, electrostatics, hydrogen bonds, and disulfide bridges that stabilize the molecule.[16],[17] This phenomenon demonstrates the decrease in albumin and total protein levels following the induction of arthritis by formaldehyde. However, after 10 days of treatment with EAJf, a restoration of total protein and albumin levels is observed. Furthermore, repeated formalin injections caused an increase in AST, ALT, and ALP levels. Indeed, this increase in these parameters could be due to increased liver activity and bone erosion.[18],[19] The increase in ALP in arthritic rats following formaldehyde-induced arthritis led to bone remodeling and resorption.[18] These results corroborate those of.[20] These authors showed that the anti-arthritic activity of *Murraya exotica* at doses of 50, 200, and 400 mg/kg bw restored AST, ALT, ALP, total protein, and albumin levels.

CONCLUSION

The aqueous extract of *Justicia flava* decreased the mean number of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, but increased the mean number of total protein and albumin. The aqueous extract of *Justicia flava* inhibited protein denaturation.

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