



ANTI-INFLAMMATORY ACTIVITY OF THE FRACTIONS OF THE AQUEOUS EXTRACT OF *Ximenia americana* (LINNAEUS) (OLACACEAE)

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ABSTRACT

This study is a continuation of previous work during which we studied the effects of aqueous extract of *Ximenia americana* on inflammation induced by carrageenan on the rat paw. These studies have demonstrated the anti-inflammatory action of the aqueous extract of *Ximenia americana*, its effect seemed to be due to saponins and flavonoids contained in this total extract, so we started to fractionate the total extract of *Ximenia americana*, to verify the hypothesis that the anti-inflammatory effect of aqueous extract of *Ximenia americana* would be due to saponins and flavonoids. To do this we used the fractionation method developed by Wagner. This method gave us 6 fractions that we tested on rats in which, we injected, into the right hind paw the carrageenan, which causes inflammation in these animals. The study of this inflammation after administration of indomethacin, a reference anti-inflammatory, of the aqueous extract of *Ximenia americana*, and the fractions F2, F4 and F6 showed anti-inflammatory properties of these substances.

Key words: *Ximenia americana*, Indomethacin, Anti-inflammatory, Saponins, Flavonoids.

INTRODUCTION

Ximenia americana (Linnaeus) (Olacaceae) or sea lemon [1] is a shrub highly branched from the base, thorny, glabrous, slender twigs. It sometimes reaches 6 meters high. Leaves alternate, whole, elliptical, are thin, reaching a length of 4 to 10 cm and a width of 2 to 4 cm [2]. The flowers consist of axillary cymes. The fruits are drupes globose, fleshy, smooth, yellowish to orange, 3 cm long, they are edible [1].

Pantropical plant, native from Central and South America, *Ximenia americana* is widespread throughout tropical Africa. The popular African medicine of tropical areas of Senegal to Zimbabwe, through Nigeria and Tanzania holds for this plant essence a considerable place: - The roots, leaves, stem bark, treat various diseases including headaches, stomach, heart, sexual impotence, diarrhea, fever, toothache and mental illness.

Previous work has shown the anti-inflammatory effect of aqueous extract of *Ximenia Americana*. The phytochemical screening of the aqueous extract from *Ximenia americana* showed the presence of sterols

polyterpenes, polyphenols, flavonoids, alkaloids, saponins, and catechin tannin. The anti-inflammatory properties of *Ximenia americana* would be associated with the presence of flavonoids and saponins in the extract. Flavonoids are indeed, antioxidants, while the saponins are inhibitors of prostaglandins. To test this hypothesis, we began the fractionation of the aqueous extract of *Ximenia americana* and test the anti-inflammatory effect of different fractions.

MATERIAL AND METHODS

Ethical Considerations

Experimental procedures and protocols used in this study were approved by Ethics Committee of Félix Houphouët-Boigny University. These guidelines were in accordance with the internationally accepted principles for laboratory use and care [3]

MATERIAL

Vegetal material

It consists of a lyophilized aqueous infusion of

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stem bark of *Ximenia americana* (Olacaceae). The stem barks were harvested at Korhogo in northern of Cote d'Ivoire, and identified by the laboratory of Botanical of the Faculty of Biosciences of University Felix Houphouet Boigny Cocody, from a herbarium of the National Centre of Floristic. These barks are dried in the shade between 25 and 28 °C, then ground to a powder from which the aqueous extract was carried out.

Animal material

It consists of rats which have been used to study the anti-inflammatory activity.

The rats used belong to the species *Rattus norvegicus*. They are of Wistar strain, and weigh between 150 and 200 g. They were raised to the animal house of UFR Biosciences of University Felix Houphouet Boigny Cocody, where the average temperature is 28 ± 3 °C, with a relative humidity of 70%. The photoperiod is from 12/24 hours. The animals received food and water *ad libitum*.

Chemical product

The Indomethacin (INDOCID) : FROSST IBERICA SA, Madrid (Spain).

METHODOLOGY

Preparation of the aqueous extract of the stem bark of *Ximenia americana*

One hundred and fifty (150) grams of the powder of *Ximenia americana* stem bark are taken and placed in a beaker of 5 liters. There was added 3 liters of distilled water heated to 100 ° C. This mixture is stirred for 24 hours with a magnetic stirrer.

The solution is then filtered on the hydrophilic cotton and paper Wattman (3 mm). The resulting filtrate was freeze-dried using a freeze dryer (type SERIAL). The lyophilisate is a light-brown powder from 17.50% yield.

Fractionation method of the aqueous extract of bark stem of *Ximenia americana*

This fractionation method, developed by Wagner [4] and used by Zirihi [5], separates the main chemicals substances in the crude extract depending to their properties.

Two hundred (200) grams of lyophilisate is dissolved in one liter of 70% ethanol. The mixture was stirred for 6 hours and decanted into a flask to decant for 24 hours, two phases are obtained:

– Ethanolic phase (F1) which is the supernatant. It contains molecules of low molecular weight (terpenes, oils, alkaloids, flavonoids, cardiac glycosides and the saponins of small size);

– An aqueous phase (F2), which is deposited. It contains molecules of large molecular weight (glucosides, polysaccharides, proteins, glycoproteins, and the Big saponins) [5].

These two phases were collected separately. Then, they are evaporated using a rotary evaporator (type RCT basic Laborotechnik KIKA). The pellets obtained were dried in an oven at 50 ° C.

Part of the ethanolic phase is taken up by a mixture of cyclohexane - water (v / v). The resulting solution was stirred for 6 hours to fully homogenize. It is then decanted for 24 hours in a flask to decant.

Two phases are again obtained:

A cyclohexane phase (F3) which is the supernatant, it contains oils and terpenes;

An aqueous phase (F4), which settles to the bottom of the tank. It contains alkaloids, saponins, flavonoids, and cardiac glycosides [4].

The two phases are collected separately, evaporated in a rotary evaporator. The pellets obtained were dried in an oven at 50 ° C. Portions of the aqueous phase, the pellet is taken up by a mixture of ethyl acetate - water (v / v). The solution suffered the same treatment as other mixtures.

Two phases are also collected:

A supernatant which is the ethyl acetate phase (F5) contains alkaloids and small size flavonoids;

A pellet which is the aqueous phase (F6) contains saponins, flavonoids of large molecular weight, and cardiac glycosides [4].

The two phases are collected separately and evaporated in a rotary evaporator. The pellets were dried in an oven at 50 ° C.

At the end of these operations six different fractions of the aqueous extract stem bark of *Ximenia americana* are obtained, that are F1, F2, F3, F4, F5 and F6.

Method of studying the anti-inflammatory activity

The injection of carrageenan in the footpad of the right hind paw of rats causes an inflammatory reaction which can be reduced by the anti-inflammatory substances [6].

The vigil rats distributed in batches of 7, were fasted 16 hours prior to experimentation. For each rat, the circumference (Co) of the right hind paw is measured. Then, we administer, the various treatments by gavage at 1 ml per 100 g body weight. This injection is supplemented with distilled water to a total volume of 5 ml, which provides uniform hydration, in all rats and minimizes the response of individual variations.

The aqueous extract, and indomethacin have concentrations of 40 mg / ml and 1 mg / ml. Dilutions are made with distilled water.

The oral administration of the product is carried out using a rigid probe of olivary end.

- Distilled water (control)
- Vegetal extract
- Indomethacin (Reference substance)

An hour after feeding, we injected to each rat, 0.05 ml of carrageenan solution 1% in the footpad of the right hind leg, then animals are returned to the cage. The development of edema is determined at times 1, 2, 3, 4, 5, and 6 hours after injection.

To assess the anti-inflammatory activity, the transmetatarsien diameter of the ankle and the

circumference of the leg at the metatarsal level (yaw) are determined using of an electronic display caliper branded COGEX SENSEMAT (France) [7].

Then, the percentage of inhibition of edema was calculated [8].

$$\text{Percentage of inhibition (\%)} = \frac{C - C1}{C} \times 100$$

C = Percentage (%) of average increase in the circumference of the edematous leg of the control group (group 1 in a given time).

C1 = Percentage (%) of average increase in the circumference of the edematous leg of the test group at the same time.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 4.0 software (San Diego, Mo, Ca, USA). The comparing of averages of the measurements between batches was made using the Student t test ($p < 0.05$).

RESULTS

Table 1 shows the effect of indomethacin, of aqueous extract of *Ximenia americana* and its fractions on the evolution depending the time of the circumference of the edema

induced by carrageenan on the rat paw ($n = 7$).

After injection of carrageenan 1% into the right hind paw of the rat, the circumference of the leg increased from 14.5 ± 0.7 to 16.2 ± 0.8 mm after 1 hour and 19.8 ± 0.9 mm after 6 hours through a maximum diameter equal to 20.2 ± 0.9 mm measured after 4 hours. These values indicate the increase of the respective percentages of $11.3 \pm 0.5\%$; $36.6 \pm 1.7\%$ and $38.9 \pm 1.8\%$ for the maximum value.

After treatment of the paw with indomethacin (10 mg/kg bw), *Ximenia americana* (300 mg/kg bw) and fractions F1 to F6 of *Ximenia americana* (300 mg/kg bw), it is noted that the aqueous extract of *Ximenia americana* and the fractions F1, F4 and F6 reduce the circumference of the paw of the rat as indomethacin.

If the effects of indomethacin 10 mg / kg bw, are larger, the maximum circumference of the paw is measured after 4 hours as for the aqueous extract of *Ximenia americana*, and fractions F1, F4 and F6. This value is $24.4 \pm 1.2\%$ for the aqueous extract of *Ximenia americana*, $21.36 \pm 1.24\%$ for F1, $19.61 \pm 1.07\%$ for F4, $16.88 \pm 1.07\%$ to F6, versus $16.28 \pm 0.86\%$ for indomethacin (Table 2).

The fractions F2, F3 and F5 of *Ximenia Americana* have no significant effects on the paw edema of rat induced by the carrageenan (Figure 1).

Table 1. Effect of indomethacin, from aqueous extracts of *Ximenia americana* and fractions on the evolution with time of the circumference of the edema induced by carrageenan on the rat paw

| Treatment | Doses (mg/kg bw) | Evolution of the circumference of the paw(mm) | | | | | | |
|--------------------------|------------------|---|---------------|---------------|---------------|---------------|---------------|---------------|
| | | T 0 | 1 h | 2 h | 3 h | 4 h | 5 h | 6 h |
| Control (NaCl 9‰) | | 14,56 ± 0,72 | 16,21 ± 0,78 | 17,92 ± 0,83 | 18,4 ± 0,76 | 20,23 ± 0,97 | 20,07 ± 0,87 | 19,89 ± 0,95 |
| Indomethacin | 10 | 14,43 ± 0,70 | 15,23 ± 0,86* | 15,39 ± 0,92* | 15,52 ± 0,83* | 16,78 ± 0,89* | 16,55 ± 0,93* | 16,49 ± 0,90* |
| <i>Ximenia americana</i> | 300 | 14,59 ± 0,93 | 16,20 ± 0,84 | 17,62 ± 0,88* | 17,92 ± 0,86* | 18,15 ± 0,87* | 17,93 ± 0,89* | 17,85 ± 1,06* |
| F 1 | 300 | 14,60 ± 0,91 | 16,10 ± 0,97 | 17,20 ± 0,91* | 17,51 ± 0,96* | 17,72 ± 1,03* | 17,50 ± 0,87* | 17,41 ± 1* |
| F 2 | 300 | 14,47 ± 0,87 | 16,07 ± 0,89 | 17,79 ± 0,94 | 18,23 ± 0,88 | 20,09 ± 0,92 | 19,92 ± 0,98 | 19,71 ± 0,99 |
| F 3 | 300 | 14,44 ± 0,85 | 16,03 ± 0,87 | 17,66 ± 0,93 | 18,17 ± 0,82 | 20,04 ± 0,98 | 19,85 ± 1,05 | 19,66 ± 0,98 |
| F 4 | 300 | 14,53 ± 0,80 | 15,80 ± 0,92* | 16,21 ± 0,95* | 17,23 ± 0,94* | 17,38 ± 0,95* | 16,98 ± 0,91* | 16,87 ± 0,94* |
| F 5 | 300 | 14,55 ± 0,97 | 16,13 ± 0,91 | 17,75 ± 0,98 | 18,26 ± 0,90 | 20,11 ± 0,94 | 19,98 ± 0,94 | 19,81 ± 0,97 |
| F 6 | 300 | 14,39 ± 0,95 | 15,47 ± 0,98* | 15,79 ± 0,89* | 16,74 ± 0,92* | 16,82 ± 1,07* | 16,45 ± 0,97* | 16,41 ± 1,08* |

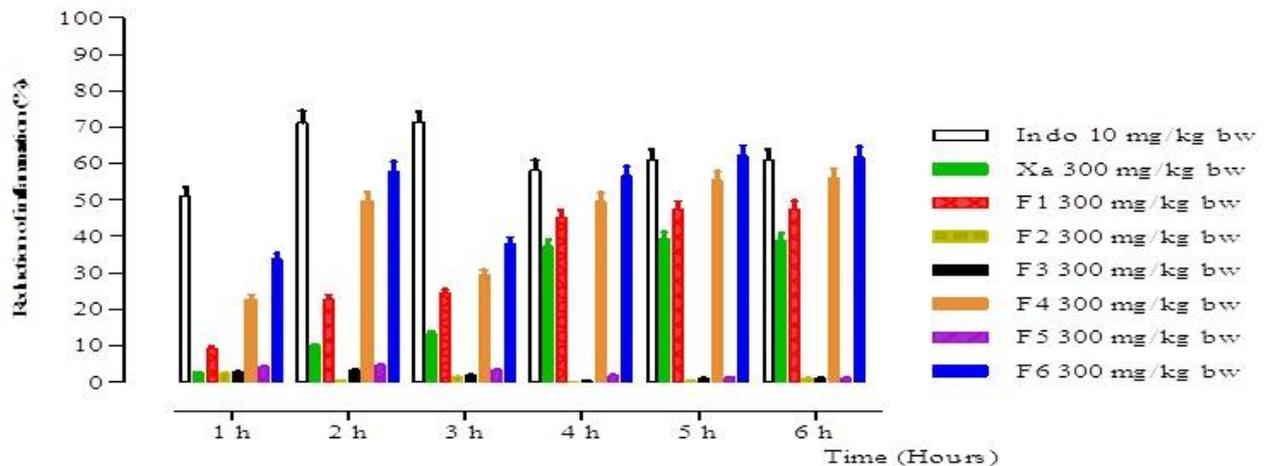
* $p < 0.05$ compared with the control group. Data indicate the mean circumference of the leg (mm). Values represent the mean (\pm SEM); $n = 7$ for each group.

Table 2. Effect of indomethacin, of aqueous extract of *Ximenia americana* and its fractions on the increase of the circumference of the edema of the rat foot induced by carrageenan

| Treatment | Doses (mg/kg bw) | Percent increase of the circumference of the paw induced by carrageenan | | | | | |
|--------------------------|------------------|---|---------------|---------------|---------------|---------------|---------------|
| | | 1 h | 2 h | 3 h | 4 h | 5 h | 6 h |
| Control (NaCl 9‰) | | 11,33 ± 0,54 | 23,07 ± 1,06 | 26,37 ± 1,08 | 38,94 ± 1,86 | 37,84 ± 1,64 | 36,6 ± 1,74 |
| Indomethacin | 10 | 5,54 ± 0,31* | 6,65 ± 0,39* | 7,55 ± 0,40* | 16,28 ± 0,86* | 14,69 ± 0,82* | 14,27 ± 0,78* |
| <i>Ximenia americana</i> | 300 | 11,03 ± 0,57 | 20,76 ± 1,03* | 22,82 ± 1,09* | 24,40 ± 1,16* | 22,89 ± 1,13* | 22,34 ± 1,32* |
| F 1 | 300 | 10,27 ± 0,61 | 17,80 ± 0,94* | 19,93 ± 1,07* | 21,36 ± 1,24* | 19,86 ± 0,98* | 19,24 ± 1,10* |
| F 2 | 300 | 11,05 ± 0,62 | 22,94 ± 1,21 | 25,98 ± 1,25 | 38,83 ± 1,77 | 37,66 ± 1,85 | 36,21 ± 1,81 |
| F 3 | 300 | 11,01 ± 0,59 | 22,29 ± 1,17 | 25,83 ± 1,16 | 38,78 ± 1,89 | 37,46 ± 1,98 | 36,14 ± 1,80 |
| F 4 | 300 | 8,75 ± 0,5* | 11,56 ± 0,67* | 18,58 ± 1,01* | 19,61 ± 1,07* | 16,86 ± 0,9* | 16,10 ± 0,89* |
| F 5 | 300 | 10,85 ± 0,61 | 21,99 ± 1,21 | 25,50 ± 1,25 | 38,21 ± 1,78 | 37,31 ± 1,75 | 36,15 ± 1,77 |
| F 6 | 300 | 7,50 ± 0,47* | 9,72 ± 0,54* | 16,33 ± 0,89* | 16,88 ± 1,07* | 14,31 ± 0,84* | 14,03 ± 0,92* |

* $p < 0.05$ compared with the control group. The data indicate the average percentage increase of the paw. Values represent the mean (\pm SEM); $n = 7$ for each group.

Fig 1. Reducing inflammation by indomethacin, the aqueous extract from *Ximenia americana* and fractions compared with the control



Values represent the average percentage \pm SEM of inhibition of edema induced by indomethacin at a dose of 10 mg / kg bw, the aqueous extract from *Ximenia americana* and the fractions at the dose of 300 mg / kg bw per compared to the control rats, n = 7 for each group. The edema was caused by carrageenan.

DISCUSSION

The objective of this work is to study the anti-inflammatory activity of the fractions of the aqueous extract of *Ximenia americana*. To do this, we used rats, in which we injected the carrageenan in the footpad of the right hind paw which causes an inflammatory response that may be reduced by the anti-inflammatory substances [6].

The aqueous extract of stem bark of *Ximenia americana* and its fractions F1, F4 and F6 have significant effects on edema of the rat paw induced by the carrageenan, one of the most effective phlogistic [9]. The effects of the aqueous extract from *Ximenia americana* and its fractions to 300mg/kg body weight being similar to those of indomethacin 10 mg/kg bw, these naturally occurring substances have anti-inflammatory properties.

If the anti-inflammatory properties of natural products are clearly lower than those of indomethacin especially during the three (3) hours of the experiment, which lasts six (6) hours, those of fractions F1, F4 and F6 are significantly larger than those of the extract of *Ximenia americana*.

Sulphated mucopolysaccharide from a Rhodophyceae, the carrageenan causes inflammation typically linked to the activation of the cyclooxygenase [10]. This inflammation is biphasic. Indeed, it is known that, in the living animal, carrageenan in a first phase causes the synthesis of chemical mediators such as histamine and serotonin which maintain inflammation [10]. In a second phase, said reference molecule induces prostaglandin synthesis mainly proteases and lysosomes. This last step is sensitive to antagonists of prostaglandin synthesis and natural anti-inflammatory or synthetic such as glucocorticoids [11-14].

The effects of aqueous extract of *Ximenia americana* and its fractions F1, F4 and F6 manifesting as those of indomethacin from the first hour of the

experiment, it is concluded that these natural substances contain anti-serotonin and antihistamines compounds.

The activity of *Ximenia americana* and fractions F1, F4 and F6 are observed at the third time of experimentation at the time of the release of prostaglandins in the inflammatory site, these substances also contain inhibitors of prostaglandins, such as indomethacin. However, unlike the naturally occurring substances, this reference molecule reaches at this time, a maximum effect. This maximum effect corresponding to $71.4 \pm 2.9\%$ of reduction of the inflammation induced by carrageenan, is greater than the maximum effects of the extract of *Ximenia americana* and its fractions recorded between the 5th and 6th hour of experimentation.

These results confirm those of ASONGALEM *et al* [15], which considers that indomethacin is the best prostaglandin inhibitor (SAKANDE *et al.*) [16].

At the sixth hour experiment, the percentages of inhibition of *Ximenia americana* and fractions F1, F4 and F6 are comparable to that of indomethacin on the circumference of the edema induced by carrageenan in the rat paw. This result indicates the existence of the compounds that oppose the formation of lysosomes, and proteases in inflammatory zone.

The aqueous extract from *Ximenia americana* 300 mg / kg body weight administered by gavage reduced the inflammation induced by carrageenan injection of $2.64 \pm 0.12\%$; $13.46 \pm 0.55\%$ and $38.96 \pm 1.85\%$ in the 1st, 3rd and 6th hour. These effects are lower than the results obtained with the aqueous decoction of leaves *Acanthus montanus* to 400 mg / kg body weight administered by gavage. This extract reduces inflammation caused by injection of carrageenan of 28.12%; 18, 64% and 16.98% in the 1st, 3rd and 6th hour [15]. It is the same for the inhibition of inflammation with the infused of *Moringa olcifera*. Indeed, this extract at 750 mg / kg bw reduced by

23.7 ± 1.7%; 37.7 ± 12.8% and 51.2 ± 11.6% in the 1st, 3rd and 6th hour of experimentation [17].

The greater effectiveness of the fractions F1, F4 and F6 of *Ximenia americana* could be related to chemical profile of these extracts, particularly to the presence of polyphenolic compounds thereof.

Among these compounds there are the flavonoids that are capable of inhibiting oxidants released by leukocytes and other phagocytes in inflammatory zone and maintaining inflammation [18-25].

In addition of flavonoids, saponins contained in the aqueous extract of *Ximenia americana* and probably into its fractions F1, F4 and F6 are the powerful anti-inflammatory. Indeed, crude extracts of saponins from *Hedera colchica* to 100 mg / kg bw cause a percentage of inhibition of 79.25%; 57.11% and 58.89% respectively in the 1st, 3rd and 6th hour after injection of carrageenan. These percentages are higher for the purified extract dosed at 100 mg / kg bw especially in the 3rd and 6th hour where they measure respectively 88.2% and 86.04% against

74.41% in the first hour, we conclude as saponins are inhibitors of prostaglandin [26-28].

The low content in flavonoids and saponins of the fractions F2, F3 and F5 OF *Ximenia americana* compared to fractions F1, F4 and F6 may explain their low anti-inflammatory property.

CONCLUSION

The aqueous extract from *Ximenia americana* and its fractions F1, F4 and F6 have anti-inflammatory properties. The effects, depending on the time of these natural substances on edema rat paw, induced by carrageenan allow concluding that they also have anti-serotonin and anti-histaminic properties.

The anti-inflammatory properties of *Ximenia americana* and its fractions F1, F4 and F6 are linked to the presence of flavonoids and saponins in the extracts. Indeed, the flavonoids are antioxidants while, saponins are inhibitors of prostaglandin.

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