

Effect of the Fractions of Hydro-ethanolic Extract of *Strychnos Camptoneura* (Loganiaceae) Leaves on Acute and Chronic Inflammation in Wistar Rats

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Abstract: *S. camptoneura* is a plant of the traditional Congolese pharmacopoeia known for its anti-inflammatory properties. This work is a comparative study of the effect of the hydro-ethanolic extract of *S. camptoneura* (Loganiaceae) leaves and its different fractions in order to identify the most effective fraction against acute and chronic inflammation. The fractions (F1, F2, F3 and F4) were obtained after fractionation of the hydro-ethanolic extract by open column chromatography. The acute and chronic anti-inflammatory effect was evaluated by injection of 2.5% formaldehyde, at the level of the plantar fascia in the Wistar rat 1 hour after administration of the extract and fractions at doses of 100 and 200mg /Kg, Diclofenac (10mg/Kg) and distilled water (1mL/100g). Edema volume (mm) was measured using an electronic caliper at 1/2, 1, 2, 3, 4 and 24 h after induction of inflammation. The obtained results showed that at doses of 100 and 200 mg/kg the extract, fractions and Diclofenac significantly inhibit ($p < 0.001$) acute inflammation at 82.80 and 83.45% for F4; 81.64% for Diclofenac. Similarly, a significant inhibition ($p < 0.001$) was observed with F4, F3 at 200 mg/Kg and Diclofenac at 83.02; 71.82 and 77.94% respectively. At J9, the inhibition was non-significant with the extract, F1 and F2 against a significant inhibition ($p < 0.05$) with Diclofenac, F3 and F4 compared to distilled water (negative control). The inhibitions went from 77.94 to 35.60%; 71.82 to 65.45% and from 83.02 to 62.16% from J3 to J9 respectively for Diclofenac, F3 and F4. The maximum anti-inflammatory effect was obtained with the F4 fraction. These results show that the use of fractions in the care of inflammation would be a good alternative.

Keywords: *S. camptoneura*, Diclofenac, fraction, inflammation, formaldehyde

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1. Introduction

Inflammation is a defense mechanism of the body against physical, chemical, biological or infectious attacks, essential to its integrity [1]. It is also a normal reaction of the body to injuries and infections involved in the appearance of a large number of pathologies such as arthritis, diabetes, asthma, allergies and cancer [2]. Increasingly, inflammation and its associated pathologies constitute a major health problem both in terms of the number of patients and its different forms of manifestations. Treatment is often based on the intake of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. However, these molecules have harmful side effects on the body, especially in the case of long-term use, particularly in the treatment of chronic

inflammation [3]. Taking anti-inflammatory drugs often presents gastrointestinal risks (gastroduodenal ulcers, perforation, stenosis), acute renal risks and sometimes cardiac complications [4]. The high cost of modern treatments, their availability and patient care currently lead to the use of treatments based on plant extracts [5]. Nowadays, about 80% of the populations living in developing countries use medicinal plants in primary health care [6]. Plant extracts offer structurally different substances, with several biological activities but, their identification and isolation remains difficult due to the complexity of the plant matrix [7]. Also, fractionation being one of its isolation and separation processes can be done by several methods including chromatographies. Bio-guided fractionation of plant extracts allows to identify promising bioactive extracts and to isolate the compounds responsible for their biological effects. The anti-inflammatory effect of a plant extract could be due to

a phenolic compound whose use of the water-ethanol mixture would allow a better extraction (substances soluble in water and/or in ethanol) contained in plant species [8]. According to Quy Diem Do et al, (2014), ethanol which is less polar extracts the apolar compounds present in the recipes of the leaves. The extraction yield of phenolic compounds is better with an ethanolic solvent in combination with water [10,11]. A previous study carried out with the aqueous extract of the leaves of *S. camptoneura* showed an immunomodulatory effect in the Wistar rat with stimulation of the secretion of the anti-inflammatory cytokines IL-10 and IL-4 [12]. Another phytochemical study with the ethanolic extract of the leaves of the same species already had richness in phenolic compounds [13]. We were interested in this work in carrying out a comparative study of the anti-inflammatory effect of the hydro-ethanolic extract of the leaves of *S. camptoneura* (Loganiaceae) and its fractions in order to highlight the most effective fraction.

2. Material and Methods

Plant material and preparation of the extract

The plant material consists of the leaves of *S. camptoneura* harvested in July 2022 (drought period) in the forest of Village M'voola located approximately 740 km from Brazzaville (Cuvette-Ouest Department) in the Republic of Congo. The sample is authenticated at the Institute for Research in Exact and Natural Sciences (IRSEN) in comparison with the reference specimen registered under No. 271. The leaves are cleaned with distilled water and dried in the laboratory for 14 days at $25 \pm 1^\circ\text{C}$ then reduced to powder. The extract is prepared by maceration with stirring for 48 hours of 100 g of powder in 1000 mL of solvent (distilled water/Ethanol 90°, V/V). The maceration is filtered and the filtrate concentrated using a rotary evaporator at 70°C brand RE-201 D Heating power 100W until obtaining approximately 22g of pasty maceration for fractionation.

Fractionation of the hydro-ethanolic extract

The fractionation of the hydro-ethanolic extract of the leaves of *S. camptoneura* is done by open column chromatography. The stationary phase is made of polyamide 6' (SIGMA ALDRICH) and the mobile phase of a hydro-ethanolic solvent with decreasing polarity : 100% distilled water, 70% water + 30% ethanol 90°, 30% water + 70% ethanol 90° and finally 100% ethanol 90°. The separation is done according to the polarity gradient, the fractions obtained are concentrated with a rotary evaporator then preserved for pharmacological tests.

Animal material

This study was conducted in Wistar albino rats with a body weight between 100 and 150g. The animals were provided by the animal facility of the National Institute for Research in Health Sciences (IRSA). They were acclimatized for one week before the experiment, housed in standard conditions and fed with ordinary food with

free access to water. The rats were divided into 12 batches of 3 mice each.

Evaluation of anti-inflammatory activity

Inflammation was studied using two (2) methods, namely : acute and chronic. Inflammation was induced with 2.5% formaldehyde in the plantar fascia of the rat. The animals divided into twelve (12) batches of 3 rats each were treated per os one hour before the injection of formaldehyde with the different test molecules : distilled water (1mL for 100g bw), diclofenac (10mg/kg), hydro-ethanolic extract and its different fractions at doses of 100 and 200mg/kg.

Acute inflammation

Acute inflammation is induced following the method used by Elion Itou et al. (2017) slightly modified. Formaldehyde at 2.5% or 0.2mL is injected into the right hind leg of the animals one hour after the above-mentioned treatments. Edema is measured at 1/2, 1, 2, 3, 4 and 24h after formaldehyde administration using the Blywoo 0-150mm Digital Caliper electronic caliper and the percentage of inhibition of inflammation is calculated using the relationship.

$$\%PI = \frac{(vt - vo)_{\text{témoin}} - (vt - vo)_{\text{test}}}{(vt - vo)_{\text{témoin}}} \times 100$$

Chronic inflammation

The method reported by Mendoza et al. (2013) slightly modified is used. On day J0, the animals receive one hour later, an injection of 0.2 ml of 2.5% formaldehyde in the right hind paw followed by treatment with the test products for 9 days. The injection of formaldehyde is repeated every three days (J4 and J8) in all animals. The volume of the edema is measured using the caliper, on J0 before induction of inflammation and every 3 days after and the percentage of inhibition calculated.

Statistical analysis

Excel software (office, 2016) was used to process the results, specifically the Student test, the calculation of means and standard errors. The results presented are expressed as means plus or minus standard error ($M \pm \text{ESM}$). The significance threshold (p) was set at $p < 0.05$.

3. Results

Acute inflammation

Table 1 presents the effect of fractions and hydro-ethanolic extract of *S. camptoneura* leaves on acute inflammation in rats at doses of 100 and 200 mg/kg, Diclofenac (10 mg/kg) and distilled water (1 mL/100g). At 100 mg/kg of extract and fractions F1, F2, F3 and F4, the edemas volumes decreased significantly from 1.97 ± 0.04 to $2.71 \pm 0.14\text{mm}$ with Diclofenac (10 mg/kg) ;

from 1.90 ± 0.03 to 3.24 ± 0.04 mm with the extract ; from 1.85 ± 0.05 to 3.31 ± 0.03 mm with F1 ; from 1.92 ± 0.07 to 3.56 ± 0.09 mm with F2; from 1.90 ± 0.03 to 3.36 ± 0.06 mm with F3 and with F4, this volume goes from 1.76 ± 0.01 to 2.66 ± 0.03 mm against 2.06 ± 0.11 to 6.65 ± 0.08 mm with distilled water (1mL/100g) respectively from T0 to T24. The same trend is observed with the dose of 200 mg/Kg. These values indicate a very significant inhibition

($p < 0.001$) of edema over time and particularly after 24h for the extract and fractions at the doses studied. The calculation of the percentage of inhibition of edema over time (Table 2), shows that the inhibitory effect is dose dependent with however the highest percentages of inhibition : 82.80 and 83.45% with the fraction F4 100 and 200 mg/kg respectively.

Table 1. In vivo effect of the hydro-ethanolic extract of *S. camptoneura* leaves and its fractions on acute inflammation induced by 2.5% formaldehyde in Wistar rats

treatments	Concentrations mg/mL	Diameter of edema as a function of time (mm)						
		T ₀	T _{1/2h}	T _{1h}	T _{2h}	T _{3h}	T _{4h}	T _{24h}
Distilled water	1mL/100g p.c	2.06 ± 0.11	4.91 ± 0.18	6.10 ± 0.41	6.53 ± 0.39	7.03 ± 0.29	7.16 ± 0.19	6.65 ± 0.08
Diclofenac	10mg/kg	1.97 ± 0.04	$2.40 \pm 0.04^{***}$	$2.54 \pm 0.05^{**}$	$2.75 \pm 0.05^{**}$	$2.63 \pm 0.06^{***}$	$2.47 \pm 0.08^{***}$	$2.71 \pm 0.14^{***}$
Extract H.E	100 mg/kg	1.90 ± 0.03	$3.21 \pm 0.21^*$	$3.40 \pm 0.16^*$	$3.33 \pm 0.10^{**}$	$3.53 \pm 0.13^{**}$	$3.52 \pm 0.11^{***}$	$3.46 \pm 0.07^{***}$
	200mg/kg	2.02 ± 0.11	$2.7 \pm 0.04^{**}$	$2.62 \pm 0.26^{**}$	$2.89 \pm 0.03^{**}$	$3.10 \pm 0.12^{***}$	$2.99 \pm 0.08^{***}$	$3.01 \pm 0.09^{***}$
F1	100 mg/kg	1.85 ± 0.05	$3.32 \pm 0.10^{**}$	$3.38 \pm 0.13^*$	$3.32 \pm 0.02^{**}$	$3.40 \pm 0.07^{**}$	$3.55 \pm 0.10^{***}$	$3.31 \pm 0.03^{***}$
	200mg/kg	1.88 ± 0.02	$2.85 \pm 0.19^{**}$	$2.99 \pm 0.16^{**}$	$2.96 \pm 0.24^{**}$	$2.86 \pm 0.07^{***}$	$2.99 \pm 0.31^{**}$	$3.07 \pm 0.20^{***}$
F2	100 mg/kg	1.92 ± 0.07	$3.46 \pm 0.20^*$	$3.47 \pm 0.11^*$	$3.61 \pm 0.09^{**}$	$3.47 \pm 0.12^{**}$	$3.55 \pm 0.07^{***}$	$3.56 \pm 0.09^{***}$
	200mg/kg	1.79 ± 0.06	$2.60 \pm 0.09^*$	$2.73 \pm 0.06^*$	$2.62 \pm 0.06^{**}$	$2.65 \pm 0.09^{**}$	$2.64 \pm 0.04^{**}$	$2.65 \pm 0.07^{**}$
F3	100 mg/kg	1.90 ± 0.03	$3.2 \pm 0.06^{**}$	$3.27 \pm 0.04^*$	$3.25 \pm 0.08^{**}$	$3.52 \pm 0.12^{**}$	$3.52 \pm 0.12^{***}$	$3.36 \pm 0.06^{***}$
	200mg/kg	1.83 ± 0.02	$2.47 \pm 0.08^{**}$	$2.58 \pm 0.00^{**}$	$2.96 \pm 0.24^{**}$	$2.65 \pm 0.08^{***}$	$2.71 \pm 0.12^{***}$	$2.72 \pm 0.05^{***}$
F4	100 mg/kg	1.76 ± 0.01	$2.22 \pm 0.09^{***}$	$2.66 \pm 0.09^{**}$	$2.61 \pm 0.02^{**}$	$2.42 \pm 0.05^{***}$	$2.50 \pm 0.06^{***}$	$2.66 \pm 0.03^{***}$
	200mg/kg	1.8 ± 0.01	$2.19 \pm 0.05^{***}$	$2.48 \pm 0.01^{**}$	$2.50 \pm 0.07^{**}$	$2.63 \pm 0.10^{***}$	$2.64 \pm 0.19^{***}$	$2.63 \pm 0.12^{***}$

Each value represents the mean of the edema diameter (M) plus or minus standard error (M $\pm$ ESM) nsp>0.05 ; **p>0.01 and ***p>0.001 Student's test significant compared to the control group treated with distilled water

Extract H.E: Hydro-ethanolic extract, F1: Fraction 1, F2: Fraction 2, F3: Fraction 3, F4: Fraction 4

Table 2. In vivo effect of the hydro-ethanolic extract of *S. camptoneura* leaves and its fractions on acute inflammation induced by 2.5% formaldehyde in Wistar rats

Treatments	Concentrations (mg/mL)	Percentage inhibition of edema (%)					
		T _{1/2h}	T _{1h}	T _{2h}	T _{3h}	T _{4h}	T _{24h}
Diclofenac	10mg/kg	85.04	85.94	82.61	86.72	88.88	81.64
Extract H.E	100 mg/kg	53.97	62.47	67.83	68.14	68.14	65.89
	200mg/kg	76.16	79.95	80.44	80.96	80.96	78.30
F1	100 mg/kg	54.20	62.89	67.76	68.47	68.47	68.65
	200mg/kg	53.50	61.73	63.58	67.16	67.16	68.79
F2	100 mg/kg	44.39	60.14	61.11	67.10	67.10	63.13
	200mg/kg	71.14	75.45	81.19	82.14	82.14	81.13
F3	100 mg/kg	57.94	65.64	69.02	70.76	70.76	71.04
	200mg/kg	54.55	81.69	81.56	81.16	81.16	79.60
F4	100 mg/kg	84.11	77.78	81.04	85.54	85.54	82.80
	200mg/kg	88.66	84.69	85.74	84.76	84.76	83.45

Each value represents the percentage of inhibition of edema (%)

Extract H.E: Hydro-ethanolic extract, F1 : Fraction 1, F2 : Fraction 2, F3 : Fraction 3, F4 : Fraction 4

Chronic inflammation

Table 3 shows the effect of the extract and fractions (100 and 200 mg/kg) on chronic inflammation induced by 2.5% formaldehyde in Wistar rats every 3 days followed by a 9-day continuous treatment. The measurement of the volume of the edema was carried out every 3 days using the electronic caliper. A very significant inhibition ($p < 0.001$) of the volume of the edema was observed at the dose of 200 mg/kg with fractions F4 and F3 as well as Diclofenac compared to distilled water (negative control) after the third day. The volumes increased from 1.80 ± 0.01 on day J0 to 2.33 ± 0.03 mm on day J3 for F4 ; from

1.83 ± 0.02 on day J1 to 2.62 ± 0.04 mm on day J3 for F3 and from 1.97 ± 0.04 on day J0 to 2.61 ± 0.14 mm on day J3 for Diclofenac compared to distilled water or, the volumes go from 2.06 ± 0.11 on day J0 to 4.95 ± 0.13 mm on day J3. While with the fractions F1, F2 and the extract the significances are respectively $p < 0.01$ and $p < 0.05$. The calculation of the percentage of inhibition shows that the fraction F4 on day J3 presents the highest value compared to F3 and diclofenac: 83.02; 71.82 and 77.94 respectively. From the second induction, with the extract, the fraction F1 and F2 the inhibition of the edema is not significant compared to distilled water while, with Diclofenac, the fraction F3 and F4 we observe a significant inhibition

($p < 0.05$) on day J9. The volumes of the edemas go from 2.61 ± 0.14 on J3 to 2.83 ± 0.35 mm on J9 ; from 2.62 ± 0.04 on J3 to 2.79 ± 0.22 mm on J9 and from 2.33 ± 0.03 on J3 to 2.91 ± 0.29 on J9 respectively against volumes of 4.95 ± 0.13 on J3 to 4.90 ± 0.35 on J9 for distilled water (negative control). These results give inhibition percentages which go from 77.94 to 35.60% ; 71.82 to 65.45% and from 83.02 to 62.16% from day J3 to day J9 respectively for Diclofenac, F3 and F4.

4. Discussion

This work compared the effect of the hydro-ethanolic extract of *S. camptoneura* leaves and its fractions on acute and chronic inflammation in Wistar rats. From our experiment on acute inflammation after 24 hours, it appears that the extract and fractions significantly inhibit the volume of edema in rats, just like Diclofenac compared to distilled water. This result suggested an anti-inflammatory effect of the extract and fractions which would certainly involve the inhibition of the cyclooxygenase pathway by interfering with the synthesis of pro-inflammatory molecules. Our results are consistent with those of Ndiaye Sy et al. (2016) where an anti-inflammatory effect of subfractions of *Moringa oleifera* leaves was obtained [16].

In order to evaluate the long-term effect of the extract and its fractions, chronic inflammation is induced in the Wistar rat with 2.5% formaldehyde for 9 days. It appears that the extract and the fractions significantly reduce ($p < 0.001$) the volume of edema in the rat's paw on the third day. From the second injection, the inhibition of edema becomes less significant until day J9 of treatment. This could be explained by the fact that repeated injection of formaldehyde would cause chronic inflammation of the rat's paw which involves the proliferation phase of inflammation caused by cyclooxygenase mediators [15]. Also, it would manifest itself by the activation of monocytes, macrophages and the secretion of

inflammatory mediators such as nitric oxide (NO). This, having as consequences, with each episode of tissue destructions less and less well repaired causing a decrease in the effect of the extract and fractions. Also, this injection of formaldehyde would lead to the secretion of pro-inflammatory cytokines : $\text{TNF-}\alpha$, $\text{IL-1}\beta$, prostaglandins and many others. This analysis suggests that the anti-inflammatory effect of the H.E extract and fractions would pass through the inhibition of the cyclooxygenase pathway. Researchers have worked on the immunomodulatory effect of the aqueous extract of the leaves of this plant [12], as well as on the healing activity of the ethanolic extract of the seeds of the same species have demonstrated an inhibition of the production of the cytokines $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ for a secretion of IL-4 and IL-10 [17]. Our results are consistent with those obtained by Mendoza et al. on the effect of D-002 on formaldehyde-induced osteoarthritis in rats [15]. This study showed appreciable anti-inflammatory activity in the short and long term for all fractions and the extract used. A thorough analysis of our results for acute and chronic inflammation suggests that the F4 fraction would have shown more effective inhibition than Diclofenac (reference molecule). In acute, the F4 fraction inhibits the volume of edema by 82.80 and 83.45% respectively at 100 and 200 mg/Kg compared to 81.64% for Diclofenac and, in chronic, F4 inhibits by 62.63 and 62.16% at 100 and 200 mg/Kg compared to 35.60 for Diclofenac. According to a study, the anti-inflammatory activity of flavonoids was initially reported in 1980 by Baumann's team [18]. Indeed, flavonoids are capable of modulating the enzymatic activity of arachidonic acid (AA), a fatty acid produced in the context of inflammation. Polyphenols are also said to have an anti-inflammatory effect [8]. The phytochemical study of *S. camptoneura* showed the presence of polyphenols and flavonoids [13], which would therefore be responsible for the observed anti-inflammatory effect.

Table 3. Effect of hydro-ethanolic extract of *S. camptoneura* leaves and fractions on chronic inflammation induced by 2.5% formaldehyde in Wistar rats

Traitements	Concentrations mg/mL	Diameter of edema as a function of time (mm)				Percentage inhibition of edema (%)		
		J ₀	J ₃	J ₆	J ₉	J ₃	J ₆	J ₉
Distilled water	1mL/100g p.c	2.06 ± 0.11	4.95 ± 0.13	5.8 ± 0.18	4.9 ± 0.35	/	/	/
Diclofenac	10mg/kg	1.97 ± 0.04	$2.61 \pm 0.14^{**}$	$3.2 \pm 0.26^{**}$	$2.83 \pm 0.35^*$	77.94	60.91	35.60
Extract H.E	100 mg/kg	1.9 ± 0.03	$3.18 \pm 0.14^{**}$	$3.37 \pm 0.06^{**}$	3.83 ± 0.11^{ns}	55.65	52.92	31.72
	200mg/kg	2.02 ± 0.11	$3.18 \pm 0.25^*$	$3.41 \pm 0.43^*$	3.19 ± 0.33^{ns}	59.93	55.48	44.06
F1	100 mg/kg	1.85 ± 0.05	$3.28 \pm 0.19^{**}$	$3.36 \pm 0.1^{**}$	3.64 ± 0.07^{ns}	51.27	52.27	37.72
	200mg/kg	1.88 ± 0.02	$2.91 \pm 0.14^{**}$	$3.65 \pm 0.07^{**}$	3.92 ± 0.15^{ns}	69.97	38.33	28.08
F2	100 mg/kg	1.92 ± 0.07	$3.18 \pm 0.07^{**}$	$3.24 \pm 0.13^{**}$	$3.3 \pm 0.16^*$	56.46	58.04	51.58
	200mg/kg	1.79 ± 0.06	$2.65 \pm 0.11^*$	$3.11 \pm 0.24^*$	3.43 ± 0.28^{ns}	70.43	58.04	42.30
F3	100 mg/kg	1.90 ± 0.03	$3.09 \pm 0.16^{**}$	$3.19 \pm 0.22^{**}$	$3.23 \pm 0.14^*$	62.93	63.04	57.69
	200mg/kg	1.83 ± 0.02	$2.62 \pm 0.04^{***}$	$3.00 \pm 0.19^{**}$	$2.79 \pm 0.22^*$	71.82	61.87	65.45
F4	100 mg/kg	1.76 ± 0.01	$2.53 \pm 0.14^{**}$	$2.82 \pm 0.05^{**}$	$3.05 \pm 0.21^*$	73.44	66.13	62.63
	200mg/kg	1.8 ± 0.01	$2.33 \pm 0.03^{***}$	$2.66 \pm 0.09^{**}$	$2.91 \pm 0.29^*$	83.02	73.37	62.16

Each value represents the mean of the edema diameter (M) plus or minus standard error (M $\pm$ ESM) and the percentage of inhibition of edema $ns > 0.05$;

$^{**}p > 0.01$ and $^{***}p > 0.001$ Student's test significant compared to the control group treated with distilled water

Extract H.E: Hydroethanolic extract, F1 : Fraction 1, F2 : Fraction 2, F3 : Fraction 3, F4 : Fraction 4

5. Conclusion

The results of this study show that the hydro-ethanolic extract of *S. camptoneura* leaves and its fractions would have an anti-inflammatory effect in vivo in the short and long term that would be more effective than Diclofenac (reference molecule). They would act by inhibiting the cyclo-oxygenase pathway by inhibiting pro-inflammatory cytokines and probably increasing the anti-inflammatory molecules that should be sought.

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