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Analgesic and anti-inflammatory activities of *Acacia nilotica* (L.) Willd. Ex Delile, used in the traditional treatment of liver diseases in Mali

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Abstract
In Mali, *Acacia nilotica* is widely used in traditional medicine to treat numerous diseases, including liver disorders. The objective was to assess the toxicity and analgesic and anti-inflammatory effects of infusions of the leafy branches, stem bark, and fruits of this plant. Toxicity was assessed according to OECD guidelines. Analgesic activity of the extracts was evaluated on pain induced in mice or rats by acetic acid, formalin and hot water. Anti-inflammatory effect was determined on edema induced by carrageenan in the paws of rats. The oral infusions at 5000 mg/kg did not cause mortality in rats. The infusion of the stem bark gave the best activity in the different tests carried out. Percentage of inhibition of torsions of this extract was 71.43%, comparable to that of paracetamol at 100 mg/kg. In the late phase of the formalin test, the same extract gave a pain inhibition percentage of 68.14% higher than 66.56% for Acetyl Salicylic Acid at 100 mg/kg. For heat-induced pain, there was a 20.7% reduction in tail withdrawal time from hot water compared to the negative control group. The inflammation inhibition percentages were 58.57; 61.41 and 67.28% respectively at 1 hour, 3 hours and 5 hours after carrageenan injection. Analgesic and anti-inflammatory properties of aqueous extracts of *A. nilotica*, particularly from the stem bark, can contribute to the management of painful and inflammatory symptoms associated with liver diseases.

Keywords: Mali, *Acacia nilotica*, aqueous extracts, analgesic and anti-inflammatory activity

Introduction
Liver disease or hepatopathy is the generic term for liver damage [1]. Liver diseases are numerous and varied (hepatitis, cirrhosis, cholestasis, steatosis, tumors, abscesses). They constitute a major health problem because of their morbidity and mortality. All liver diseases evolve into chronicity and give rise to cirrhosis when they are not treated normally. Cirrhosis is one of the leading causes of death worldwide due to diseases [2]. Hepatitis, which is the most common form of liver disease, is an inflammation of the liver that can have several causes, including viruses [3, 4]. Viral hepatitis caused 1.34 million deaths in 2015. New data reported to WHO by 187 countries shows that the estimated number of deaths from viral hepatitis has increased from 1.1 million in 2019 to 1.3 million in 2022: 83% for hepatitis B and 17% for hepatitis C. Every day, hepatitis B or C kills 3,500 people worldwide [5]. In 2020, the African region accounted for more than 26% of the global disease burden from hepatitis B and C, with 125,000 associated deaths [6]. According to the WHO Hepatitis Scorecard 2019, the prevalence rate of HBV in Mali is estimated at 8.5% in the general population. This rate is 3.1% for HCV [7]. Liver diseases are mostly characterized by inflammation and/or pain [8, 9]. In Mali, a large number of people living with liver diseases resort to traditional medicine. A survey conducted at the hepato-gastroenterology department of Gabriel Touré Hospital revealed that 62.3% of patients with liver diseases use medicinal plants, particularly in the treatment of cirrhosis [10]. Among the plants used in the management of liver diseases, there is *Accacia nilotica* (L.) Willd. Ex Delile [11]. These fruits, in infusion, are used in the treatment of hepatitis in Senegal [12]. These seeds, in infusion, treat jaundice and in decoction, are used for the treatment of hepatitis in Togo [13] and liver diseases in Nigeria [14]. Previous studies conducted on extracts of this plant have demonstrated numerous properties, notably hepatoprotective [15,16], anti-inflammatory,

analgesic [17-20], anticancer [21-23], antioxidant [16, 24, 25] and antiviral [26, 27]. The goal of this study was to contribute to the valorization of this plant in the management of liver diseases. Its objective was to evaluate the analgesic and anti-inflammatory properties of infusions of its leafy branches, its stem bark and its fruits harvested in Mali.

Materials and Methods

1. Plant material

Samples of leafy branches, trunk bark and fruits of *Acacia nilotica* were collected in November 2020 in Kati (a locality located 15 km from Bamako). Samples were identified by Mr. Seydou M. Dembélé, water and forest engineer, head of the ethnobotany and raw materials department of the National Institute for Research on Traditional Medicine and Pharmacopoeia (NIRTMP). A specimen of the plant is available at the NIRTMP herbarium under number 3077/DMT. The collected samples were then dried in the shade for 3 weeks before being pulverized and kept for extraction.

2. Animal material

The animals used were Wistar rats weighing between 155-210 g and male and female Swiss Albino mice weighing between 24-32 g. The animals were kept under standard laboratory conditions (25 °C and a light/dark cycle, i.e. 12/12) and fed standard NIRTMP-prepared chow and tap water. Animal welfare requirements were strictly taken into account during these experiments. An authorization (No. 2021/273/CE/USTTB) from the ethics committee of the Faculties of Medicine and Odontostomatology (FMOS) and Pharmacy (FAPH) dated November 11, 2021 was obtained.

3. Extracts Preparation

One hundred grams of powder from each sample were infused in 1000 mL of boiling distilled water for 15 minutes. After filtration through cotton, the resulting infusions were concentrated using a rotary evaporator at 50 °C, then frozen and freeze-dried.

4. Acute toxicity

It was assessed using the sequential method reported by the Organization for Economic Cooperation and Development [28]. Female rats were weighed and randomly assigned to groups of three. They were then deprived of food but given free access to water for 14 hours. Infusions of leafy twigs, trunk bark, and fruits were administered by gavage sequentially at doses of 5, 50, 300, 2000 mg/kg, and 500 mg/kg. After administration, the rats were again deprived of food for 3 to 4 hours. The rats were observed for the first four hours after administration and daily for 14 days. Observations included changes in the skin, hair, eyes, mucous membranes, respiratory system, autonomic and central nervous system activity, somatomotor activity, and behavior. Tremors, convulsions, diarrhea, lethargy, and sleep were also noted.

5. Analgesic activity test

5.1 Acetic acid-induced writhing inhibition test

The mice were randomly divided into 11 groups of 5 mice and fasted for 16 hours before the start of the test. Infusions of the leafy branches, stem barks and fruits of *A. nilotica* were each administered at single doses of 400, 200 and 100 mg/kg. Distilled water (10 mL/kg) and paracetamol (100 mg/kg) were used respectively as negative control and reference analgesic drug. One hour after administration of the treatments, the animals received intraperitoneally 10 mL/kg of a 0.6% solution of acetic acid in physiological saline. Five minutes after the injection of acetic acid, the number of writhing movements was counted in each mouse for twenty minutes [29]. The analgesic effect was evaluated according to the following formula:

$$PI = \frac{Wb - Wt}{Wt} \times 100$$

- PI: Percentage of pain inhibition
- Wb: Mean number of writhing movements in mice from the negative control group
- Wt: Mean number of writhing movements in mice from groups treated with extracts and paracetamol.

5.2 Formalin test

Male and female rats were randomly divided into groups of 5 and fasted from food (with free access to water) for 16 hours before the start of the test. The groups receiving the infusions and the negative control group were treated as in the previous tests. Acetyl salicylic acid (100 mg/kg per os) and morphine (10 mg/kg intraperitoneally) were used as reference products. One hour after treatment administration (30 minutes for morphine), 20 µl of 5% formalin was injected into the sole of the right hind paw of the rats. Then the animals' reaction to pain (licking and biting of the injected paw) was counted for 30 min in two phases: 0 to 5 minutes (early phase), 15 to 30 minutes (late phase). The percentage of pain inhibition was calculated for each phase with the following formula [30]:

$$PI = \frac{M1 - M2}{M1} \times 100$$

PI: Percentage of pain inhibition
M1: Mean pain response time of the negative control group
M2: Mean pain response time of the group treated with the extracts and the reference products

5.3 Tail flick test

This test was performed according to the method used by Ramabadran *et al*. [31] and modified by Gawel *et al*. [32]. The rats were fasted before the start of the test as before. Before the administration (T = 0) of the extracts, 3 centimeters of the tail of each rat was immersed in water maintained at 55 °C and the retraction time was noted. The infusions, distilled water and morphine were then also administered as in the previous test. The time between immersion and tail retraction was recorded at 30; 60; and 90 minutes after the administration of the treatments. A cut-off time of 20 seconds was maintained to avoid tissue damage to the tail. The percentages of pain inhibition were calculated by applying the following formula:

$$PEM = \frac{Tb - Ta}{Tc - Ta} \times 100$$

MEP: Percentage of Maximum Possible Effect
Tb: Retraction time after administration
Ta: Retraction time before administration
Tc: Cutoff time

6. Evaluation of anti-inflammatory activity

The extracts were administered under the same conditions and at the same doses as previously. The reference drug used was Acetyl Salicylic Acid at 100 mg/kg. One hour after administration of the treatments, edema (inflammation) was induced by administering 50 µL of a 1% solution of carrageenan in physiological saline under the plantar fascia of the right hind paw of the rats. Then the volume of the right hind paw of each rat was measured 1 hour, 3 hours and 5 hours after the injection of carrageenan [33]. Anti-inflammatory activity was assessed as the percentage reduction in edema in treated rats compared to white controls according to the following formula:

$$PI = \frac{(A - B)}{B} \times 100$$

PI: Percentage of inhibition of inflammation
A: Mean increase in paw volume of rats in the negative control group
B: Mean increase in paw volume of rats in the treated groups

7. Statistical analysis

The obtained data were analyzed using GraphPad socket 5 software. The results were expressed as means±SEM (Standard Error of the Mean). Comparisons were performed by One-way ANOVA followed by multiple comparison tests. The difference was considered significant if $p<0.05$.

Resultats

1. Acute toxicity

Infusions orally at 5000 mg/kg did not cause mortality or major behavioral changes in rats.

2. Analgesic activity

2.1 Acetic acid-induced writhing inhibition test

The effect of the infusions on writhing induced by acetic acid is presented in Table 1. The infusions significantly reduced the number of writhing induced by acetic acid in mice. The best inhibitory activity (71.43%) was obtained with the infusion of stem barks at a dose of 400 mg/kg per os (see Table 1).

Table 1: Effect of *Acacia nilotica* extracts on acetic acid-induced writhing in mice

Treatments	Dose (mg/kg)	Numbers of writhing	Percentage of inhibition
Negative control	-	86,8	0
Paracetamol	100	24±4.74***	72.35
leafy branches	400	65.20±7.46*	24.88
	200	73.20±10.62	15.67
	100	67.60±8.88	22.12
Stem barks	400	24.80±4.27 ***	71.43
	200	57.60±9.18**	33.64
	100	53.40±7.37***	38.48
Fruits	400	62.60±5.37*	27.88
	200	75.20±17.25	13.36
	100	79.00±7.48	8.99

*** $p<0.001$ treatments vs negative control; ** $p<0.01$ treatments vs negative control; * $p<0.05$ treatments vs negative control.

2.2 Formalin test

The results of the formalin test show that only the stem bark infusion at 200 mg/kg exhibits significant activity ($p<0.05$) compared to the negative control group with a percentage reduction in pain of 21.88% during the early phase. The infusions of leaves, stem bark and fruits significantly reduced the pain induced by formalin during the late phase. The best activity was obtained with the stem bark infusion at a dose of 400 mg/kg per os with a percentage inhibition of 68.14% (See Table 2). Morphine was 100% effective during both phases while aspirin acted significantly only in the late phase (66.56%).

Table 2: Effect of *Acacia nilotica* extracts on formalin-induced pain in rats

Treatments	Dose (mg/kg)	Early phase		Late phase	
		Times (second)	%	Time (second)	%
Negative control	-	65.8±7,5	0	190.2±11,5	0
Morphine	10	0***	100	0***	100
Aspirin	100	56.4±5.59	14.29	63.6±12.9***	66.56
Leafy branches	400	64.8±7,01	1.53	124.2±12.52***	34.70
	200	57±7.04	13.37	163.4±11,48***	14.02
	100	58.8±1.64	10.64	160.4±12.58***	15.67
Stem barks	400	53.4±7.89	18.84	60,6±8,11***	68.14
	200	51.4±5.9*	21.88	92,2±9,63***	51.52
	100	65.4±10	0.61	154±16.9***	19.03
Fruits	400	65±8	1.22	143±11.77***	24.82
	200	65.25±6,18	0.84	170.2±11.90*	10.52
	100	61±6.83	7.60	180±15.60	5.36

*** $p<0.001$ treatments vs negative control; ** $p<0.01$ treatments vs negative control; * $p<0.05$ treatments vs negative control

2.3 Tail flick test

Table 3 represent the data obtained with the tail immersion test. The extract from stem bark at 400 mg/kg significantly reduced the tail withdrawal time from hot water compared to the negative control batch with respective activity percentages of 20.7 ($p<0.001$) and 9.06% ($p<0.05$) at the

60th and 90th minutes. The morphine used as a reference was significantly active (p<0.001) during the three times of measurement of the tail withdrawal time (Table3).

Table 3: Effect of *Acacia nilotica* extracts on pain induced by immersion of rats' tails in hot water

Treatments	Dose (mg/kg)	T_0	T_1		T_2		T_3	
			Time (second)	%	Time (second)	%	Time (second)	%
Negative control		3.74±0,61	3.90±0.68	0.98	3.85±0.86	0.66	3.54±0.66	-1.25
Morphine	10	3.96±0.87	13.57±1.47***	59.93	16.178±1.72***	76.17	11.83±1.33***	49.09
Leafy branches	400	3.36±0.93	3.65±0.47	1.77	4.01±0.85	3.93	3.72±0.65	2.18
	200	3.35±0.45	4.56±0.63	7.28	4.34±0.77	5.94	3.36±0.76	0.07
	100	2.81±0.59	3.30±0.81	2.83	4.43±0.91*	9.45	3.08±0.44	1.59
Stem barks	400	2.86±0.57	3.60±0.8	4.35	6.40±0.45***	**20.70**	4.41±0.35*	9.06
	200	4.31±0.84	5.52±0.85	7.69	5.1±0.76	5.03	5.33±0,97	6.48
	100	3.13±0.53	3.77±0.41	3.84	3.21±0.39	0.52	3.28±0.70	0.91
Fruits	400	2.88±0,5	3.26±0.39	2.21	3.88±0.55	5.86	3.35±0.49	2.73
	200	4.46±0.73	3.96±0.69	-3.22	5.43±0.70	6.25	4.31±0.37	-0.94
	100	3.01±0,78	3.47±0.49	2.67	3.77±0,51	4.43	3.52±0.76	3.00

T_0 = Time before administration of treatments; T_1 = 30 minutes after administration of treatments; T_2 = 60 minutes after administration of treatments; T_3= 90 minutes after administration of treatments. *** p<0.001 treatments vs negative control; ** p<0.01 treatments vs negative control; * p<0.05 treatments vs negative control.

3. Anti-inflammatory Activity

Most extracts significantly reduced (p<0.001) carrageenan-induced inflammation, as shown in Table 4. The extract from stem barks exhibited the highest activity percentages at all hours, at 58.57, 61.41, and 67.28%, respectively, at 1 hour, 3 hours, and 5 hours after carrageenan injection. Under the same conditions, aspirin yielded activity percentages of 42.55, 77.59, and 82.10% (see table 4).

Table 4: Effect of *Acacia nilotica* extracts on carrageenan-induced paw edema in rat

Extraits	Doses(mg/kg)	1H		2Heures		5H	
		Numbers	% inhibition	Numbers	% inhibition	Numbers	% inhibition
Negative control	-	2.46±0.38	0	2.41±0.2	0	1.62±0.09	0
Aspirin	100	1.44±0.02***	42.55	0.54±0.02***	77.59	1.51±0.03***	82.10
Leafy branches	400	2.46±0.21	1.99	1.6±0.02***	33.61	0.98±0.11***	39.51
	200	2.02±0.31***	19.52	1.57±0.17***	34.85	0.99±0.09***	38.89
	100	2.1±0.15**	16.33	2.13±0.25	11.62	0.79±0.05***	51.23
Ecorce de tronc	400	1.04±0.1***	58.57	0.93±0,05***	51.47	0.53±0.06***	67.28
	200	1.55±0.24***	38.27	1.09±0.17***	54.77	0.56±0.04***	65.43
	100	1.76±0.1***	29.88	1.31±0.08***	45.64	0.86±0.05***	46.91
Fruit	400	1.75±0.11***	30.28	1.63±0.07***	32.37	0.89±0,1***	45.06
	200	1.83±0.11**	27.02	1.67±0.16***	30.71	0.99±0.09***	38.89
	100	2.46±0.06	1.99	1.7±0.12***	29.46	1.04±0.04***	35.80

*** p<0.001 treatments vs negative control; ** p<0.01 treatments vs negative control; * p<0.05 treatments vs negative control

Discussion

The aim of this study was to evaluate the analgesic and anti-inflammatory activity of infusions of leafy twigs, stem barks, and fruit of *A. nilotica*. Prior acute toxicity assessment of the extracts showed that they are not toxic up to 5000 mg/kg. Therefore, according to the OECD's globally harmonized classification system, these extracts can be classified as category 5 and considered to have low oral toxicity. These results are consistent with those reported in the literature [34, 35]. These data support the safety of using infusions of leafy branches, stem barks and fruits of *A. nilotica* per os. The extracts showed analgesic activity by inhibiting acetic acid-induced writhing. The decrease in the number of writhing's by the extracts suggests that they possess peripheral analgesic effects. This analgesic action of the extracts could be through the inhibition of prostaglandin synthesis by action on cyclooxygenases (COX). Indeed, pain induced by acetic acid is sensitive to NSAIDs such as aspirin [36] and paracetamol [37, 38] which are peripheral analgesics with COX inhibition as their mechanism of action. Extracts from stem barks significantly inhibited formalin-induced pain during the early phase. Early-phase formalin-induced pain is neurogenic in origin and is thought to result from direct stimulation of nociceptors. This suggests that these extracts exhibit central analgesic activity. All extracts protected against formalin-induced pain during the late phase with dose-dependent activity in stem barks. This protection suggests that all extracts exhibit peripheral analgesic properties because during this late phase the pain is of peripheral origin during which inflammatory phenomena would occur [39]. In the tail flick test, none of the extracts showed significant activity at the 30th minute. At the 60th and 90th minutes, the stem barks significantly reduced the pain induced by immersing the rats' tails in hot water. This suggests that these extracts also exhibit central analgesic activity in this test. This activity, which was manifested from the 60th minute after the administration of the extracts, confirms the central analgesic activity exhibited by the stem barks in the early phase of the formalin test. Carrageenan administration induced inflammation in rats as seen in the increased paw volume of rats in the negative control group. All extracts significantly reduced edema in rats with the best activity for trunk bark. This suggests that the extracts exhibit anti-inflammatory properties. The anti-inflammatory activity of the extracts was more pronounced at 3 hours and 5 hours. A publication made by our team [40]

had demonstrated that the leafy branches, stem barks and fruits of *A. nilotica* possess antiradical properties. The polyunsaturated fatty acids of membrane phospholipids are targets of certain free radicals, thus initiating lipid peroxidation chains [41]. This phenomenon will result in the blocking of the anti-inflammatory process and partially elucidates the involvement of free radicals in the inflammatory phenomenon. The anti-radical activity of *A. nilotica* extracts could therefore also contribute to their analgesic and anti-inflammatory effects. The results obtained during our study are similar to those reported by many other authors who have also shown the analgesic and anti-inflammatory activity of extracts and isolated molecules of *Acacia nilotica*. Methanolic extracts of stem barks and its different fractions significantly inhibited acetic acid-induced pain in mice [42]. Methanolic extract of trunk bark was also effective against formalin-induced inflammation in rats [19]. Nilotican, a diterpene isolated from the ethyl acetate extract of A nilotica trunk bark, showed strong prostaglandin inhibition activity (percentage inhibition >75% on COX 1 and<40% on COX 2) [18]. Aqueous maceration of the seeds at 500 mg/kg caused a 20% reduction in carrageenan-induced inflammation in the paws of rats. The same extract also produced a reduction in the latency time (hot plate reaction) [43]. Since many liver conditions manifest with pain and inflammation [8, 9, 44], these analgesic and anti-inflammatory properties demonstrated by extracts of *A. nilotica* can significantly reduce these symptoms during liver diseases.

Conclusion

Infusions of leafy twigs, stem barks, and fruits of *A. nilotica* are not acutely toxic when taken orally and possess analgesic and anti-inflammatory properties. These analgesic and anti-inflammatory properties of aqueous extracts of *A. nilotica*, particularly from the stem barks, may contribute to the management of painful and inflammatory symptoms associated with liver diseases.

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