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Evaluation of Analgesic and Antipyretic Effects of the Aqueous Extract of the Leaves of *Chenopodium ambrosioides* L. (Amaranthaceae)

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Abstract

C. ambrosioides is a Congolese medicinal plant used in the treatment of several pathologies. This work was initiated to evaluate the analgesic and antipyretic effect of the aqueous extract of leaves of *C. ambrosioides*. Analgesic effect was evaluated by using the acetic acid-induced writhing, the Tilk Flick test as well as the pain induced by formaldehyde. The results obtained showed that the aqueous extract significantly reduces the number of abdominal writhes ($p < 0.05$ and $p < 0.001$), significantly increased the immersion time of the tail ($p < 0.05$ and $p < 0.01$) and also significantly decreased the frequency of licking or biting the paw ($p < 0.001$). This result suggests an analgesic effect of aqueous extract. The fever was induced by subcutaneous administration of a solution of brewer's yeast. The results obtained showed a significant decrease ($p < 0.05$, $p < 0.01$ and $p < 0.001$) of the rectal temperature of the animals treated with the aqueous extract of leaves of *C. ambrosioides* (400 and 600 mg/kg) compared to control group (saline water). This result suggests an antipyretic effect. Chemical screening revealed the presence of alkaloids, flavones and mucilage. The presence of alkaloids and flavones could explain the analgesic and antipyretic effects attributed to this aqueous extract.

Keywords

Analgesic, Antipyretic, Medicinal Plant, *Chenopodium ambrosioides*

1. Introduction

Pain is an alarm signal that follows a lesion or trauma of a peripheral tissue of the body that generates an acute inflammatory defense reaction [1]. Pain studies show that it is the primary reason for clinical consultation. It is estimated that in three cases of consultation, two concern pain. Bassols *et al.* (1999) [2] think that, pain is a leading public health problem, as well as a source of personal and family suffering, and it constitutes a problem which goes beyond the individual and becomes a social illness. In the Republic of Congo, a study conducted on acute rheumatic pain gave a prevalence of 3.5% [3]. These joint rheumatic pains are often associated with fever. In developing countries, children frequently suffer from several forms of infections that present as fevers [4]. However, high fevers can denature enzymes and increase oxygen requirements and the speed of cellular metabolism. As a result, defense responses and the repair process are accelerated, leading to convulsions in certain predisposed individuals [5]. In view of these data, it is clear that pain and the fever are a public health problem that needs to be addressed. Pain and fever can be treated conventionally with analgesics and antipyretics. However, these conventional drugs have for the most part undesirable effects, this is the case of the narcotics which group together various molecules of the opioid family which are the most powerful and effective analgesics but also cause a lot of undesirable effects: drowsiness, nausea, vomiting, constipation, dry mouth and addiction. Paracetamol, which is both analgesic and antipyretic, can cause liver damage. In addition to this conventional treatment, man has always given himself the means to combat the pain and fever that are often provided by his natural environment. Thus, finding a simplified methodology for evaluating the pharmacological effects of medicinal plants is important. *C. ambrosioides* is a Congolese medicinal plant commonly used to cure or ameliorate a pathological process. In Ecuador province (of Congo), it is used to calm edema and local pain. The juice obtained by crushing the leaves between the fingers or the palms treats the most violent headaches [6]. Macerate leaves are used for the treatment of intestinal parasites [7]. Some scientific studies on *C. ambrosioides* have shown antiviral effects [8], anti-inflammatory [9], analgesic and antipyretic [10], antidiabetic [11], antimicrobial and antioxidant [12]. In this study, we aimed to evaluate the analgesic and antipyretic effects of the aqueous extract of leaves of *C. ambrosioides*.

2. Materials and Methods

2.1. Plant

The leaves of *C. ambrosioides* were collected in Brazzaville. Botanical identification of the plant material was done by Mousamboté, botanist systematistof Higher Normal School of Agronomy and Forestry (HNSAF) and confirmed at the Herbarium of the National Institute for Research in Exact and Natural Sciences (NIRENS) witch a collected sample was compared to a reference sample (no. 724). After identification, the plant material was dried and pulverized. 200 g

of powder of leaves were mixed with 2500 mL of distilled water in a heating balloon. The mixture was boiled for 15 min. After cooling and filtration, the filtrate obtained was concentrated on a double boiler (60˚C). The aqueous extract obtained was kept for experiments

2.2. Animals

Albino rats (150 - 200 g) and albino mices (20 - 30 g) of either sex obtained from the Faculty of Science and Technical of Marien NGOUABI-University were used. They were fed with a standard feed and water *ad libitum*. They were acclimatized during one week before experimentation and were housed under standard conditions (12 hours light and 12 hours dark) and at the temperature of 27˚C ± 1˚C. The rules of ethics published by the International Association for the Study of Pain [13] have been considered.

2.3. Evaluation of the Analgesic Activity of the Aqueous Extract of Leaves of *C. ambrosioides* Acetic Acid-Induced Abdominal Writhing in Mice

The administration of 0.6% acetic acid intraperitoneally to the mice causes a pain syndrome. The pain syndrome is characterized by stretching movements of the hind legs and torsion of the dorso-abdominal muscles. An analgesic would act by decreasing the number of abdominal writhing compared to the control group. The different doses of the aqueous extract of *C. ambrosioides* (400 and 800 mg/kg), physiological solution (control lot, 0.5 ml/100g) and paracetamol (standard group, 100 mg/kg) were administered orally, 1 hour before intraperitoneally administration of the acetic acid solution to the animals [14]. 5 minutes after the injection of acetic acid, the number of abdominal writhes developed by the animals was recorded during 20 min [15]. The analgesic effect is given by the percentage inhibition of abdominal cramps (PI) according to the following formula:

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

PI(%): percentage inhibition of abdominal writhing.

*M*1: Mean of abdominal writhing developed by the animals in the control group.

*M*2: Mean of abdominal writhing developed by the animals of the treated group.

2.4. Tail-Flick Test

This test involves inducing pain by immersion of the tail of the animal in a hot water bath at a temperature of 57˚C ± 1˚C. The pain sensation is characterized by the rapid withdrawal of the animal's tail. An analgesic would act by increasing the reaction time of the animal compared to the control group. Four groups of 5 rats each fasted for 24 hours were formed. The different doses of the aqueous extract of leaves of *C. ambrosioides* (400 and 800 mg/kg), physiological solution

(control group, 0.5 mL/100g) and tramadol (standard group, 10 mg/kg) were administered orally. 30, 60, 90 and 120 minutes after product administration, the rat was held upright to immerse its tail at a depth of 5 cm [16] in a hot water bath maintained at 57˚C ± 1˚C. The reaction time that the animal makes to remove its tail from the water has been noted. To prevent tissue damage, the threshold time that the animal's tail must spend in the hot water bath has been set at 30 seconds.

2.5. Formaldehyde-Induced Paw Liking

The formaldehyde-induced paw licking was studied in rat using the method reported by Elion Itou *et al.* (2017) [15]. Sub plantar administration of formaldehyde 2.5% induces neurogenic pain and inflammatory pain. The pain syndrome is characterized by licking or biting the paw. A central analgesic would inhibit the two phases equally, but a peripheral analgesic would only inhibit the second phase [16]. Four groups of 5 rats each fasted for 24 hours were formed. The different doses of the aqueous extract of the leaves of *C. ambrosioides* (400 and 800 mg/kg), physiological solution (control group, 0.5 ml/100g) and tramadol (standard group, 10 mg/kg) were administered orally to groups, 1 h prior to the local injection of formaldehyde subcutaneous tissue of the plantar surface of the right paw. Immediately, animals were placed in various cages to observe the noxious effects. The frequency that the animal licks or bites its paw was monitored over 0 to 10 min for neurogenic pain response and 10 to 30 min for inflammatory pain response.

2.6. Brewer's Yeast Pyrexia Test

The subcutaneous administration of the 20% brewer's yeast induces 24 hours after hyperthermia. An antipyretic would act by decreasing this hyperthermia. Before constituting the different groups to evaluate the antipyretic activity of the aqueous extract of leaves of *C. ambrosioides*, we proceeded to the selection of the animals. For this, the normal rectal temperature of each rat was measured using a digital thermometer. Fever was induced in all animals by subcutaneous administration of 20% solution of brewer's yeast (*Saccharomyces cerevisiae*) 10 ml/kg [17]. 24 hours later, the rectal temperature of the animals was measured again. All animals that did not show an increase in rectal temperature of 0.5˚C were excluded from the experiment [18]. The animals retained were divided into a groups of 5 rats each and treated orally with the different doses of the aqueous leaf extract of *C. ambrosioides* (400 and 800 mg/kg), the physiological solution (control group, 0.5 ml/100g) and paracetamol (standard group, 100 mg/kg). Rectal temperature was measured at 1, 2, 3, 4 and 5 hours after administration of the products.

2.7. Chemical Profile

The different secondary metabolites contained in the leaves of *C. ambrosioides*

was highlighted using the tube reaction method described by Cuilli, (1982) [19] and Sofowora, (1996) [20]. Thus the alkaloids, tannins, anthocyanins, flavonoids (flavones, flavanones and flavonols), free anthraquinones, sterols and triterpenes, saponosides and mucilages were sought.

2.8. Statistical Analysis

All values were expressed as mean ± standard error of mean (SEM). Analysis of variance followed by Student-Fischer t test "t" was performed. The significance level was set at $p < 0.05$.

3. Results

3.1. Effect of the Aqueous Extract of *C. ambrosioides* on Pain Induced by Acetic Acid

The administration of acetic acid induces abdominal writhes in animals of different groups (Table 1). Paracetamol (100 mg/kg) as well as the aqueous extract of *C.ambrosioides* at the doses used significantly reduce ($p < 0.05$ and $p < 0.001$) the number of abdominal writhes (physiological saline). The number of abdominal writhes performed by the control group is 51.6, and 39.4 ($p < 0.001$) for mice treated with paracetamol (standard drug); of 47.03 ($p < 0.001$) and 40.6 ($p < 0.001$) for the mice treated with the aqueous extract of the leaves of *C. ambrosioides* (400 and 800 mg/kg). The percentages of pain inhibition are 23.64% for the mice treated with paracetamol, 21.31% and 8.85% for the mice treated with the aqueous extract of the leaves of *C. ambrosioides* at the doses of 400 and 800 mg/kg (Table 1).

3.2. Effect of the Aqueous Extract of *C. ambrosioides* on the Pain Induced by the Hot Water Bath

Table 2 presents the results of the aqueous extract of *C. ambrosioides* leaves on the pain induced by the hot water bath in the rat. They show that up to 60 min after administration of the test products, none of the products used significantly increased ($p > 0.05$) the immersion time of the tailk in the hot water bath with compared to the control group (physiological saline). However, 90 min later,

Table 1. Effect of aqueous extract of *C. ambrosioides* on abdominal writhes induced by 0.6% acetic acid solution in mice.

Treatment	Doses	Number of Abdominal writhes	Inhibition (%)
Control group	(0.5 mL/100g)	51.6 ± 1.20	/
paracetamol	(100 mg/kg)	39.4 ± 1.28***	23.64
C. ambrosioides	(400 mg/kg)	47.03 ± 0.53*	8.85
	(800 mg/kg)	40.6 ± 0.87***	21.31

Each value represents the mean ± ESM. *$p < 0.01$; ***$p < 0.001$ Significant different (Student t-test) versus control group.

Table 2. Effect of aqueous extract of leaves of *C. ambrosioides* on tail-flick test in rat.

Treatment	Doses	Immersion time (sec)			
		30 mn	60 mn	90 mn	120 mn
Control group	(0.5 mL/100g)	2.19 ± 0.31	2.20 ± 0.34	2.14 ± 0.14	2.18 ± 0.20
Tramadol	(10 mg/kg)	2.37 ± 0.11 ns	2.72 ± 0.08 ns	2.92 ± 0.39***	3.61 ± 0.08***
C. ambrosioides	(400 mg/kg)	2.44 ± 0.23 ns	2.52 ± 0.19 ns	2.97 ± 0.14**	2.84 ± 0.28 ns
	(800 mg/kg)	2.75 ± 0.24 ns	2.96 ± 0.23 ns	3.11 ± 0.25**	3.08 ± 0.29*

Each value represents the mean ± ESM. *p < 0.05, **p < 0.01 et ***p < 0.001 ***p < 0.001 Significant different (Student t-test) versus control group, ns = No significant different versus control group.

tramadol (standard drug) and aqueous extract of *C. ambrosioides* (400 and 800 mg/kg) increased significantly ($p < 0.05$ and $p < 0.001$) immersion of the tailk in the hot water bath compared to the control group (physiological saline). This effect persists after 120 min with tramadol ($p < 0.001$) but decreases ($p < 0.05$) with the 800 mg/kg dose of the aqueous extract of *C. ambrosioides* and disappears completely ($p > 0.05$) with that 400 mg/kg.

3.3. Effect of Aqueous Extract of *C. ambrosioides* on the Pain Induced by Formaldehyde in Rat

Subplantar administration of formaldehyde induces neurogenic (Figure 1) and inflammatory (Figure 2) pain. The aqueous extract of leaves of *C. ambrosioides* (400 and 800 mg/kg) and tramadol (10 mg/kg) significantly decreased ($p < 0.001$) the frequency of licking and biting the paw during the neurogenic phase as well as during the inflammatory phase. The frequency of licking and biting the paw is 78.4; 52.6; 63.4 and 59.8 respectively for physiological saline (control), tramadol (standard drug) and aqueous leaf extract of *C. ambrosioides* (400 and 800 mg/kg) during the phase of neurogenic pain (Figure 1). For inflammatory pain (Figure 2), the frequency is 229.8; 142.4; 156.8 and 148.6 respectively for physiological saline (control), tramadol (standard drug) and aqueous extract of *C. ambrosioides* (400 and 800 mg/kg). These results also show that the inhibition percentages of tramadol and the aqueous extract of leaves of *C. ambrosioides* at doses of 400 and 800 mg/kg are respectively 32.39; 19.13% and 23.72% for neurogenic pain and 38.03; 31.85% and 35.33% for inflammatory pain (Figure 3 and Figure 4).

3.4. Antipyretic Effect of Aqueous Extract of Leaves of *C. ambrosioides*

The results of the effect of the aqueous extract of the leaves of *C. ambrosioides* (400 and 800 mg/kg) on the hyperthermia induced by the brewer's yeast are presented in Table 3. They show that the paracetamol, and the aqueous extract of *C. ambrosioides* leaves (400 and 800 mg/kg) significantly decreased ($p < 0.05$ and $p < 0.01$) hyperthermia from the second hour. The maximum decrease of

hyperthermia was observed at the third hour for paracetamol ($p < 0.001$) and the aqueous extract of *C. ambrosioides* leaves at a dose of 800 mg/kg ($p < 0.01$). For the aqueous extract at a dose of 400 mg/kg the maximum decrease of hyperthermia is observed at the fourth hour. However, no significant reduction (ns = $p > 0.05$) of hyperthermia was observed at 1 hour with paracetamol as well as with the aqueous extract of *C. ambrosioides* leaves (400 and 800 mg/kg.

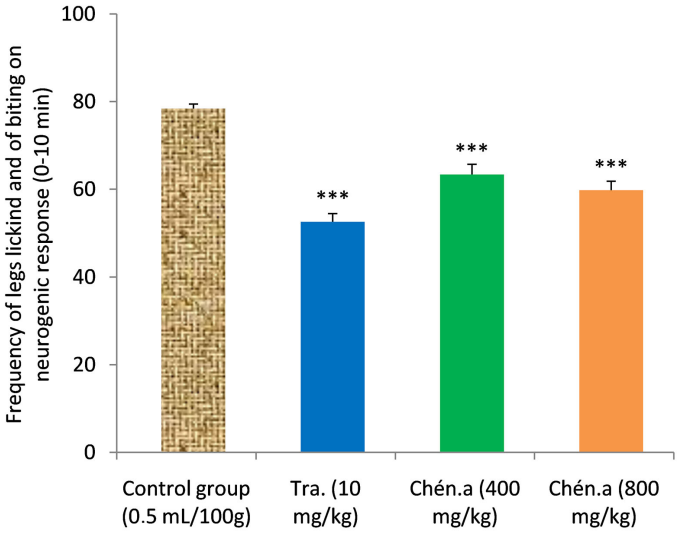

Figure 1. Effect of aqueous extract of leaves of *C. ambrosioides* (400 and 800 mg/kg) on neurogenic response. ***p < 0.001 Significant different (Student t-test) versus control group. Tra = tramadol; Chén.a = *Chénopodium ambrosioides*.

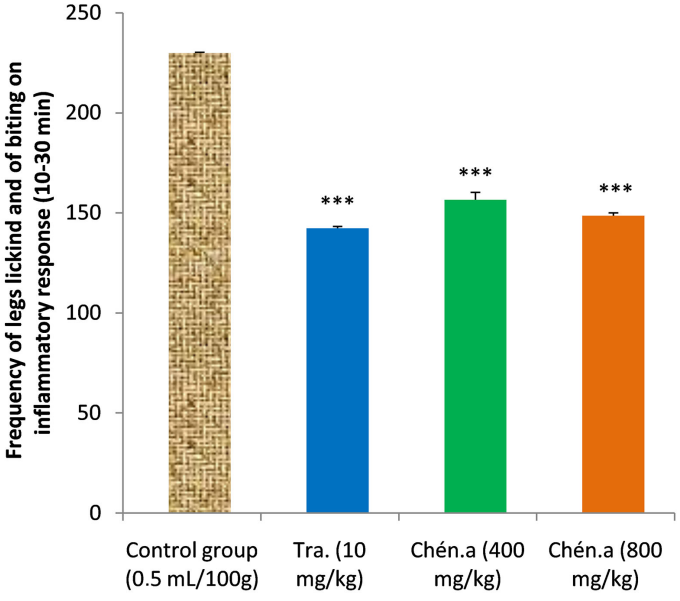

Figure 2. Effect of aqueous extract of leaves of *C. ambrosioides* (400 and 800 mg/kg) on inflammatory response. ***p < 0.001 Significant different (Student t-test) versus control group. Tra = tramadol; Chén.a = *Chénopodium ambrosioides*.

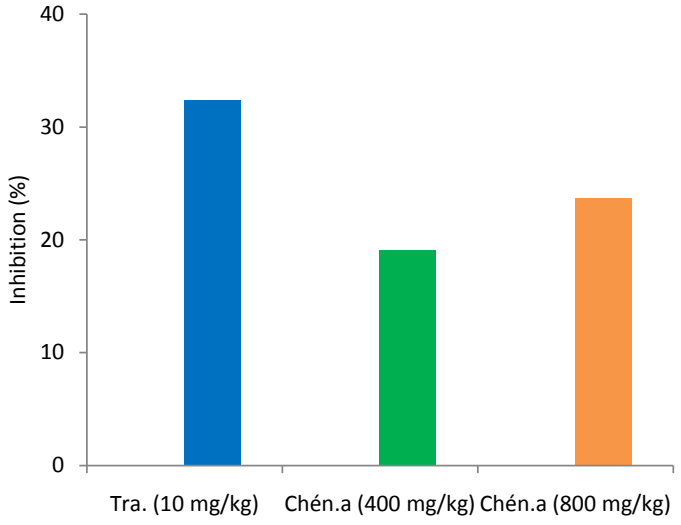

Figure 3. Inhibition by aqueous extract (400 and 800 mg/kg) of neurogenic response. Tra = tramadol; Chén.a = *Chénopodium ambrosioides*.

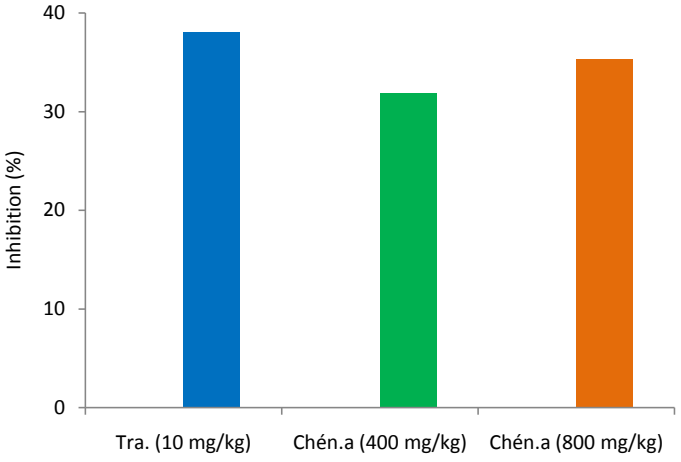

Figure 4. Inhibition by aqueous extract (400 and 800 mg/kg) of inflammatory response. Tra = tramadol; Chén.a = *Chénopodium ambrosioides*.

Table 3. Effect of aqueous leaf extract of *C. ambrosioides* on Brewer's yeast-induced hyperthermia in rats.

			Temperature (T°) after pyrexia induced					
Treatment	**Doses**	**T° normale**	**0 h**	**1 h**	**2 h**	**3 h**	**4 h**	**5 h**
Control group	(0.5 mL/100g)	35.58 ± 0.28	36.58 ± 0.17	37.02 ± 0.32	37.68 ± 0.07	37.11 ± 0.05	37.02 ± 0.08	37.02 ± 0.02
Paracetamol	(100 mg/kg)	35.96 ± 0.29	36.72 ± 0.43	36.46 ± 0.40ns	36.48 ± 0.32**	35.7 ± 0.19***	35.42 ± 0.15***	35.26 ± 0.14***
C. ambrosioides	(400 mg/kg)	35.78 ± 0.32	37.06 ± 0.24	36.58 ± 0.24ns	36.58 ± 0.27*	36.28 ± 0.24*	35.9 ± 0.22**	35.82 ± 0.22**
	(800 mg/kg)	35.96 ± 0.26	37.26 ± 0.14	36.96 ± 0.16ns	36.8 ± 0.17*	36.30 ± 0.15**	36.04 ± 0.16**	35.76 ± 0.24**

Each value represents the mean ± ESM. *$p < 0.05$, **$p < 0.01$ et ***$p < 0.001$ ***$p < 0.001$ Significant different (Student t-test) versus control group, Ns = no significant different versus control group.

3.5. Chemical Profile of the Aqueous Extract of Leaves of *C. ambrosioides*

The various reactions highlighted the different secondary metabolites contained in the aqueous extract of the leaves of *C. ambrosioides*. The results are reported in Table 4.

4. Discussion

The aim of this work was to promote the medicinal plants of the Congolese herbal with analgesic and antipyretic potentialities. The choice of this plant is justified by the fact that *C. ambrosioides* is cited by some authors as having analgesic and antipyretic properties ([6] [7]). Three methods were used in this study to evaluate the analgesic effect of the aqueous extract of *C. ambrosioides* leaves. These methods were chosen to highlight peripheral and central pain. Acetic acid induces abdominal writhing that translate visceral pain commonly used to assess the peripheral-type nociceptive effect, and the hot-water test (Tail immersion test) induces central-type pain, while the formaldehyde test induces both types of pain [21]. In addition, the Brewer's yeast test was used to induce pyrexia (hyperthermia). Intraperitoneal administration of acetic acid induced abdominal writhing in the mice. Indeed, acetic acid causes an increase in the release of prostaglandins (PGE2 and PGF2α), and also products of the lipooxygenase pathway involved in inflammatory pain by inducing the permeability of the capillaries. Indirectly acetic acid stimulates the release of endogenous mediators (histamine, serotonin) responsible for the stimulation of nociceptor neurons. In addition, it is well established that the nociceptive response caused by acetic acid also depends on the release of some cytokines, such as TNF-α, interleukin 1α and interleukin β via modulation of macrophages localized in the peritoneal cavity [21]. The aqueous extract of *C. ambrosioides* (400 and 800 mg/kg) significantly reduced ($p < 0.05$ and $p < 0.001$) the number of abdominal writhing induced by acetic acid compared to the control group (physiological saline) with a marked effect with the dose of 800 mg/kg. This result suggests a peripheral analgesic effect of the aqueous extract of the leaves of *C. ambrosioides* which could pass through an interference with one of the mechanisms of induction of abdominal pain by acetic acid. The Hot-water bath or Tail-flick induces central type pain by direct stimulation of Aδ fibers [22]. The aqueous extract of *C. ambrosioides* (400 and 800 mg/kg) increases significant ($p < 0.05$ and $p < 0.001$) 90 min after the immersion time of the beak in the hot water bath compared to the control group (physiological saline). This result, suggests a central analgesic effect of the Aqueous extract of *C. ambrosioides* leaves that could pass through interference with one of the central mechanisms of pain transmission.

The formaldehyde test is a very important model used to highlight not only the analgesic effect but also to clarify the mechanisms of analgesic action. Subplantar administration of formaldehyde to the rat caused neurogenic pain and inflammatory pain. Neurogenic pain is the result of direct stimulation of the C

Table 4. Secondary metabolites contained in the aqueous extract of the leaves of *C. ambrosioides*.

Secondary metabolites	**Results**
Alkaloids	++
Tannins	-
Anthocyans	-
Flavons	+
Flavanons	-
Flavanols	-
Free Anthraquinones	-
Carotenoids	-
Sterols and triterpenes	-
Saponosids	-
Mucilages	++

+ = presence; ++ = strong presence; - = absence.

and Aδ fibers, which reflects the central type of pain regulated by substance P release [23], while inflammatory pain is regulated by the release of the substances histamine, serotonin, bradikynins and prostaglandins that express peripheral-type pain. The aqueous extract of *C. ambrosioides* (400 and 800 mg/kg) significantly reduced ($p < 0.001$) the frequency of licking and biting the paw compared to the control group. This result suggests a peripheral and central analgesic effect of the aqueous extract of *C. ambrosioides* leaves. Other authors have also already demonstrated the analgesic effect of plant extracts [15].

Pain is often associated with fever therefore the evaluation of the antipyretic effect is necessary. Fever (hyperthermia) was induced by Brewer's yeast. The hyperthermia induced by the injection of Brewer's yeast is linked to the release of cytokines (TNFα, IL1β, and IL6) which have reached the blood vessels stimulate the biosynthesis of prostaglandins (PGE2) around the hypothalamic thermoregulatory center [24] [25]. The aqueous extract of the leaves of *C. ambrosioides* significantly reduced ($p < 0.05$, $p < 0.01$ and $p < 0.001$) the fever (hyperthermia) two hours after the onset of fever. This result suggests an antipyretic effect of the aqueous extract of the leaves of *C. ambrosioides* which could go through an interference with the mechanism of prostaglandin synthesis as would the paracetamol used by reference molecule. Our results are similar to those of [10] who already demonstrated the analgesic and antipyretic effects of the aqueous extract of *C. ambrosioides* leaves in mice. The chemical profile showed the presence of alkaloids and flavonoids. These same chemical families had already been identified by Hallal *et al.* (2010) [10]. However, in our study, tannins, terpenoidss and sterols are absents, unlike the work of Hallal *et al.* (2010) [10]. This difference could be explained by the reagents used where from the place of harvest. None less the presence of alkaloids and flavones in our study could ex-

plain the analgesic and antipyretic effects observed [26]. The antipyretic effect could be attributed by the presence of flavonoids [27].

5. Conclusion

C. ambrosioides is a Congolese medicinal plant used in the treatment of several pathologies. The aqueous extract of leaves has been used to evaluate the analgesic and antipyretic effects. The results obtained show that the aqueous extract of the leaves *C. ambrosioides* has analgesic and antipyretic effects that would be justified by the presence of flavonoids and alkaloids highlighted in this extract. These results could justify the use of this plant in traditional treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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