

Evaluation of Antipyretic and Analgesic Effects of *Alchornea cordifolia* Schum. & Thonn. (Euphorbiaceae) and *Quassia africana* Baill (Simaroubaceae)

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Abstract: *Alchornea cordifolia* (Euphorbiaceae) is widely used in Africa for the treatment of malaria, fever, tooth decay, leprosy, amoebic dysentery, hemorrhoids, headaches, venereal diseases and inflammation. It is also used as emmenagogue and oxytocic. *Quassia africana* (Simaroubaceae) is also widely used in Africa for the treatment of malaria, gastritis, intestinal worms, rheumatism, bronchopneumonia, gonorrhoea, headache, tooth decay and tonsillitis. The present study aims to highlight the analgesic and antipyretic effects of both plants. Fever was induced by oral administration of 20 ml / kg of 20% beer yeast in rats 24 hours before treatment. The rectal temperature was measured 1h, 2h and 3h after treatment. The pain was induced by intraperitoneal injection of 0.1 ml / 10 g of 0.6% acetic acid in rats 1 hour after oral treatment. The analgesic activity was assessed for 10 minutes by counting the number of cramps. The aqueous, ethanolic and dichloromethane extracts of the leaves and fruits of *Alchornea cordifolia* at 400 and 800 mg / kg per os showed a very significant antipyretic effect identical to paracetamol at 100 mg / kg per os. The aqueous extracts of the leaves and fruits of *Alchornea cordifolia* as well as barks of *Quassia africana* at 400 and 800 mg / kg per os showed a very significant analgesic effect. These effects are related to the presence of alkaloids and terpenes for *Alchornea cordifolia* and Quassinoides for *Quassia africana*.

Keywords: *Alchornea Cordifolia*, *Quassia Africana*, Extracts, Analgesic, Antipyretic

Résumé: *Alchornea cordifolia* (Euphorbiaceae) est très utilisée en Afrique dans les traitements du paludisme, de la fièvre, de la carie dentaire, de la lèpre, de la dysenterie amibienne, des hémorroïdes, des céphalées, des maladies vénériennes et de l'inflammation. Elle est aussi utilisée comme emménagogue et ocytocique. *Quassia africana* (Simaroubaceae) est aussi une espèce largement utilisée en Afrique dans le traitement du paludisme, de la gastrite, des vers intestinaux, de rhumatisme, de la bronchopneumonie, de la blennorragie, des céphalées, de la carie dentaire et des angines. La présente étude vise à mettre en évidence des effets antalgique et antipyrétique de ses deux plantes. La fièvre a été induite par administration orale de 20 ml/kg de levure de bière à 20% chez le rat, 24 h avant le traitement. La température rectale a été mesurée 1h, 2h et 3h après traitement. La douleur a été induite par injection de 0,1 ml/10 g de l'acide acétique à 0,6% par voie IP chez le rat 1h après traitement oral. L'activité antalgique a été appréciée pendant 10 minutes en comptant le nombre de crampes. Les extraits aqueux, éthanolique et au dichlorométhane des feuilles et des fruits de *Alchornea cordifolia* à 400 et 800 mg/kg per os ont montré un effet antipyrétique très significatif et comparable au paracétamol à 100 mg/kg per os. Les extraits aqueux des feuilles et des fruits de *Alchornea cordifolia* ainsi que des écorces de *Quassia africana* à 400 et 800 mg/kg per os ont montré un effet antalgique très significatif. Ces effets seraient liés à la présence des alcaloïdes et des terpènes pour *Alchornea cordifolia* et aux quassinoides pour *Quassia africana*.

Mots-clés: *Alchornea cordifolia*, *Quassia africana*, Extracts, Antalgique, Antipyrétique



Introduction

Leaves, barks, roots and fruits of *Alchornea cordifolia* (Euphorbiaceae) are widely used in traditional medicine. This plant is used in Africa in several treatments: malaria, fever, tooth decay, leprosy, amoebic dysentery, hemorrhoids, personal hygiene, headaches, venereal diseases and inflammation (OMS, 1978; Bouquet, 1969; Adjanohoun et al., 1994). Pharmacologically, *Alchornea cordifolia* is known for its effects against malaria, trypanosomiasis (Mesia et al., 2008), bacterial and fungal infections (Gatsing et al., 2010; Mambe et al., 2016; Akpo et al., 2016; Noundou et al., 2016; Ebenyi et al., 2017), inflammation (Mavar-manga et al., 2008; Adejuwon et al., 2014), antioxidant activity (Olaleye et al., 2007), diarrhoeal (Agbor et al., 2004; Emudainohwo et al., 2015), nervous system (Umukoro et al., 2010; Kamenan et al., 2013; Ishola et al., 2014), diabetic (Mohammed et al., 2012; Thomford et al., 2015), HIV-1 (Noundou et al., 2019), hepatotoxicity. Phytochemical investigations revealed flavonoids, tannins, saponins, glycosides, terpenoids, carbohydrate and imidazopyrimidine alkaloids, alchorneine, alchornidine and several guanidine alkaloids as chemical groups present in all parts. As molecules, leaves contain a range of hydroxybenzoic acid, namely, gallic acid, anthralinic acid, protocatechuic acid and ellagic acid, stigmasterol, stigmasta - 4, 22-dien-3-one, friedelin, friedelane, 3-O-acetyl-aleuritic acid, 3-O-acetyl-erythrodiol and methyl-3, 4, 5-trihydroxybenzoate (methyl gallate); the seed oil contains alchornoic (Ngaha et al., 2016; Noundou et al., 2016).

Quassia africana (Simaroubaceae) is also widely used in Africa for the treatment of malaria, gastritis, intestinal worms, rheumatism, bronchopneumonia, gonorrhoea, headache, tooth decay and angina (Adjanohoun et al., 1988; Bouquet, 1969). Pharmacologically, antimalarial (Kirby et al., 1989; Mbatchi et al., 2006), amoebicide (Wright et al., 1988), pediculosis (Jensen et al., 1978), insecticid, antiviral (Apers et al., 2002; Diehl et al., 2016), antiinflammatory (Toma et al., 2003; Guo et al., 2005), antitumor, anti-ulcer (Toma et al., 2002; Yinsua et al., 2012), antifertility properties have been notified in *Quassia* genus. In the Simaroubaceae family, numerous compounds have been isolated and their structure has been elucidated; among these, quassinoids, alkaloids, triterpenes, steroids, coumarins, anthraquinones, and flavonoids and other metabolites (Barbosa et al., 2011). The present study aims to evaluate the analgesic and antipyretic effects of these plants.

II. Material and methods

1. Animal material

Wistar rats, both sexes, weighing between 150 and 200 g were used. Animals are raised in the animalerie of Laboratoire de Physiologie et Physiopathologie animales of the Faculty of Science and Technology

(FST) under standard conditions ($25 \pm 5^\circ \text{C}$, 40-70 HR, cycle light / dark 12h), they were regularly fed and had free access to water. The ethical rules of animal experiments published by the International Association for the Study of Pain was respected (Canadian Council 1980; Zimmermann, 1983).

2. Plants material

The roots and leaves of *Quassia Africana*, and leaves and fruits of *Alchornea cordifolia* collected at Makana village in the Department of the Pool-Congo, were used. These samples were identified in the Congo National Herbarium by botanists from the Botany Laboratory of the Institut National de Recherche en Sciences de la Santé (IRSSSEN) of Brazzaville-Congo. A specimen voucher from each sample was deposited and registered under the number QAS003 (*Quassia africana*) and ACE005 (*Alchornea cordifolia*).

3. Preparations of plants extracts

We made a decoction in water and macerations with ethanol and dichloromethane. The decoction was prepared by boiling 25 g of plant material in 250 ml of water at 100°C for 30 min. The macerate was prepared by placing 25 g of plant material (leaves and fruit) in 250 ml of organic solvents (ethanol or dichloromethane). The mixture was stirred for 24 h, before being filtered successively with a cotton wool and a filter paper (wattman). The filtrates were concentrated. For experimentation, organic extracts were dissolved in 10% of Tween 80.

4. Treatments of rats

Rats of the same age, were divided into seven (7) lots of 5 rats each and fasted 24 hours before the experiment. These rats were orally treated as follows:

4.1. Treatment of antipyretic effect evaluation

- Lot 1 received the distilled water at a dose of 1ml / 100g of rat body weight;
- Lot 1' received the Tween 80 (10%) at a dose of 1ml / 100g of rat body weight;
- Lot 2 received the paracetamol at a dose of 100 mg / kg of rat body weight;
- Lot 3 received the aqueous leaf extract of *Alchornea cordifolia* at a dose of 400 mg / kg of rat body weight;
- Lot 4 received the aqueous extract of leaves of *Alchornea cordifolia* at a dose of 800 mg / kg of rat body weight;
- Lot 5 received the aqueous extract of the fruit of *Alchornea cordifolia* at the dose of 400 mg / kg of rat body weight;
- Lot 6 received the aqueous extract of the fruit of *Alchornea cordifolia* at a dose of 800 mg / kg of rat body weight;
- Lot 7 received the aqueous root extract of *Quassia africana* at a dose of 800 mg / kg of rat body weight;
- Lot 8 received the aqueous root extract of *Quassia africana* at a dose of 400 mg / kg of rat body weight;

- Lot 9 received the ethanolic extract of leaves of *Alchornea cordifolia* at a dose of 400 mg / kg of rat body weight;
- Lot 10 received the dichloromethane extract from leaves of *Alchornea cordifolia* at a dose of 400 mg / kg of rat body weight;
- Lot 11 received the ethanolic extract of the fruit of *Alchornea cordifolia* at a dose of 400 mg / kg of rat body weight;
- Lot 12 received the dichloromethane extract from the fruit of *Alchornea cordifolia* at a dose of 400 mg / kg of rat body weight.

4.2. Treatment of analgesic effect evaluation

- Lot 1 received distilled water at a dose of 1ml / 100g of rat body weight;
- Lot 2 received paracetamol at a dose of 100 mg / kg of rat body weight;
- Lot 3 received the aqueous leaf extract of *Alchornea cordifolia* at a dose of 400 mg / kg of rat body weight;
- Lot 4 received the aqueous extract of leaves of *Alchornea cordifolia* at a dose of 800 mg / kg of rat body weight;
- Lot 5 received the aqueous extract of the fruit of *Alchornea cordifolia* at the dose of 400 mg / kg of rat body weight;
- Lot 6 received the aqueous extract of the fruit of *Alchornea cordifolia* at a dose of 800 mg / kg of rat body weight;
- Lot 7 received the aqueous root extract of *Quassia africana* at a dose of 800 mg / kg of rat body weight;
- Lot 8 received the aqueous root extract of *Quassia africana* at a dose of 400 mg / kg of rat body weight.

5. Evaluation of the antipyretic effect

To each animal fasting for 24 hours, the rectal temperature is measured and orally 20 ml / kg of 20% yeast beer is administered (Nsonde Ntandou et al., 2016) 24 h later, a new rectal temperature is measured (T24h). Animals showing a rise in rectal temperature ≥ 0.5 ° C were selected for study and

then treated. After administration of the products, the rectal temperature was further measured after one (1) hour, two (2) hours, and three (3) hours.

6. Evaluation of the analgesic effect

One hour after administration of the test products, each rat is treated with 0.1 ml / 10 g of 0.6% acetic acid IP and placed in a cage (Nsonde Ntandou et al., 2018). The analgesic activity is appreciated for 10 minutes by counting the number of cramps (stretching of the legs and dorso-abdominal torsion of the muscles). The result was expressed as percent inhibition calculated according to the formula:

% inhibition = $100 \times (\text{Number of cramps in the control group} - \text{number of cramps in the treated batch}) / \text{Average cramps}$

7. Statistical analyzes

The results are expressed on average \pm SD for a number of n = 5 rats per lot using the Microsoft Excel Windows 7 software. The results obtained in the test groups were compared to the control lot using the Student's t test. Significances were established at * p <0.5, ** p <0.01 and *** p <0.001.

III. Results

1. Antipyretic effect

1.1. Antipyretic effect in rats treated with aqueous extracts of both plants

The administration of 20% brewer's yeast caused an increase in the rectal temperature of 1.2 ± 0.05 of the lots of the rats used in the antipyretic effect evaluation. The figure 1 shows the effect of *Alchornea cordifolia* aqueous extracts of leaves and fruits, *Quassia africana* roots at the doses 400 and 800 mg / kg, distilled water (10 ml / kg), and paracetamol (100 mg / kg) on the yeast induced hyperthermia following oral administration. It shows that the 400 and 800 mg / kg of *Alchornea cordifolia* aqueous extracts of leaves and fruits as well as the reference drug significantly (p <0.01) lowered the rectal body temperature.

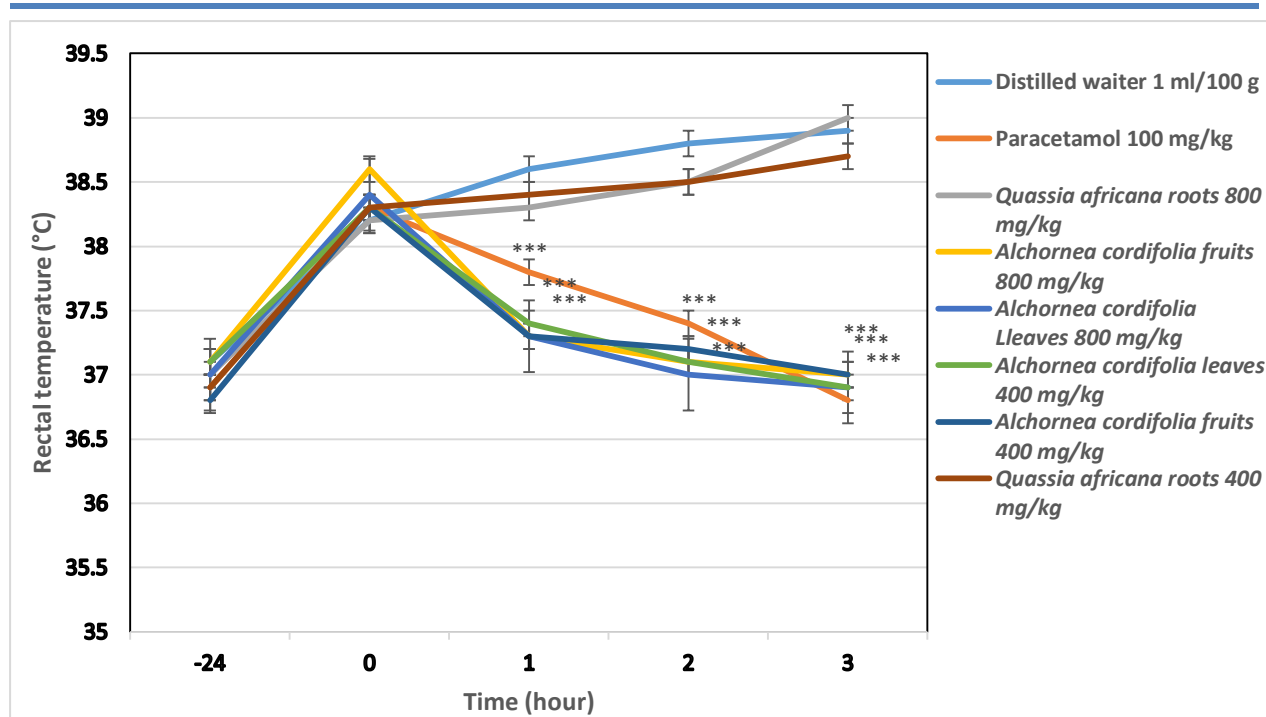


Figure 1. Effect of aqueous extracts of leaves and fruits of *Alchornea cordifolia* and roots of *Quassia africana* on the hyperthermia induced by brewer's yeast, results expressed as mean \pm SD, n = 5, *** p < 0.001 compared to controls.

1.2. Antipyretic effect in rats treated with ethanol and dichloromethane extracts of *Alchornea cordifolia*

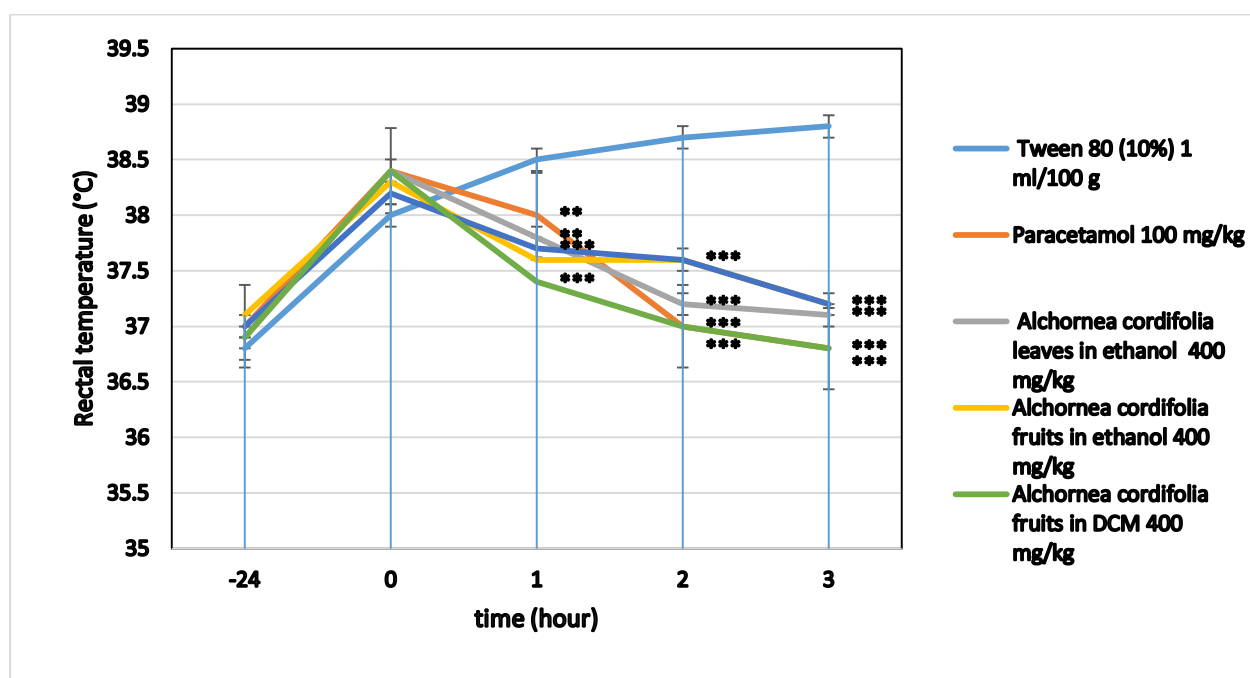


Figure 2. Effect of the ethanolic and dichloromethane extracts of leaves and fruits of *Alchornea cordifolia* at the dose of 400 mg / kg, following hyperthermia induced by brewer's yeast, results expressed on average \pm DS, n = 5, *** p < 0.001 compared to the control.

2. Analgesic effect

Figures 3 and 4 show the effect of products on the acetic acid abdominal cramps. The rats received distilled water, the number of contortions is

significantly very pronounced compared with those which were treated with paracetamol at 100 mg/kg and the different aqueous extracts at the doses of 400 and 800 mg/kg.

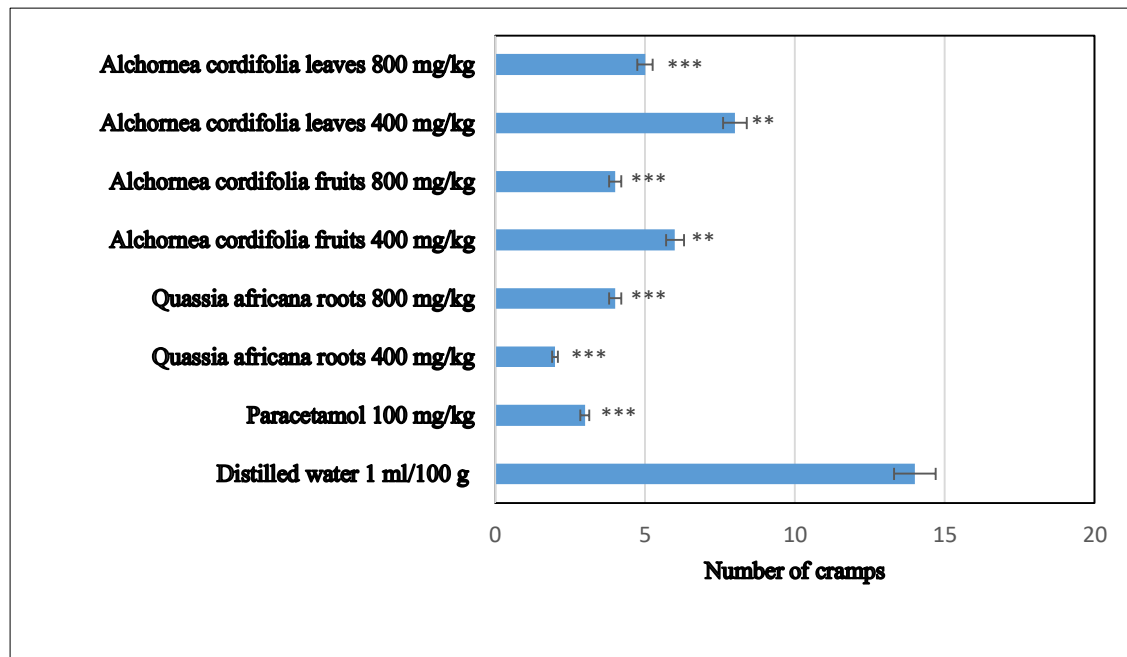


Figure 3. Effect of *Quassia africana* roots and *Alchornea cordifolia* fruits and leaves aqueous on abdominal cramps induced by acid acetic n= 5, **p < 0.01, ***p < 0.001 significant difference compared to control.

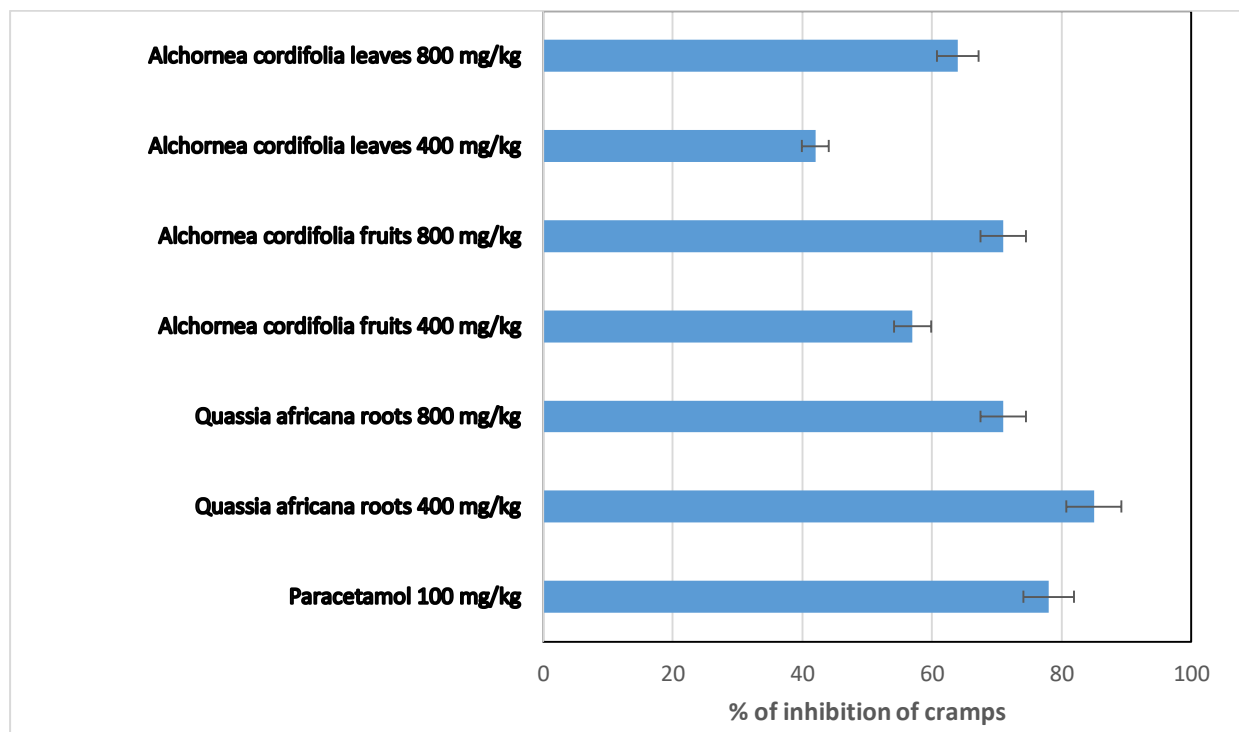


Figure 4. % inhibitions of abdominal cramps induced by acid acetic of *Quassia africana* roots and *Alchornea cordifolia* fruits and leaves aqueous extracts n= 5

IV. Discussion

Fever is a result of the secondary impact of infection, tissue damage, inflammation, graft rejection, malignancy or other diseased. Brewer's yeast is commonly used to induce pyrexia in rats (Nsonde Ntandou et al., 2016). Brewer's yeast induces pyrexia by increasing the synthesis of prostaglandins (PGE₂). From the work carried out in the rats, we could demonstrate the antipyretic effect of plants extracts. However, these plants have interesting pharmacological properties and have been studied in order to confirm or deny the therapeutic virtues cited by traditional healers in Congo. *Alchornea cordifolia* has good pharmacological activities and is not toxic. In this work, aqueous and organic leaves and fruits extracts of *Alchornea cordifolia* have presented more good results. *Alchornea cordifolia* extracts at different doses has significant antipyretic effects. The effect at the dose of 400 mg / kg is equal to that of paracetamol. However, Effo et al. (2013) have already shown antipyretic effect of *Alchornea cordifolia* methanol leaves extract with Ivory Coast sample (Okokon et al., 2017); our study confirms this antipyretic effect with congolese sample and have particularity to demonstrated this effect using water, ethanol and DCM extract and using fruits as other organ samples.

These results confirm the traditional use of *Alchornea cordifolia* as antipyretic. This effect is due to the presence of alkaloids, terpenes since these chemical families possess antipyretic properties.

From the work done in rats, we could check the analgesic effect of plants extracts. IP injection of 0.6% acetic acid in rats caused a painful effect which was manifested by stretching movements of the hind legs and the dorso-ventral musculature. These cramps which occur after injection of acetic acid are produced by prostaglandin PGE₂ and PGF alpha synthesized in the presence of cyclooxygenase-2. Plants extracts expressed their antalgic power by inhibiting the synthesis of prostaglandins. The disadvantage with the chemical method is that the pain can be induced by the injury caused by the needle. *Quassia Africana* and *Alchornea cordifolia* extracts, and paracetamol significantly reduce abdominal cramps caused by injection of acetic acid to 0.6%. This reduction of cramps number reveals significant analgesic activity mediated peripherally. Both plants have antalgic effect. However, at a dose of 400 mg/kg, roots extract of *Quassia Africana* has most interesting antalgic effect than *Alchornea cordifolia* extracts (400 and 800 mg/kg) and paracetamol (100 mg/kg). The extract from *Quassia africana* shows that it is more significant at the dose of 400mg / kg than at the dose of 800 mg / kg. This effect is similar with those found with *Quassia amara* another simaroubaceae (Toma et al., 2003). In our study we exhibited the antalgic effect of *Alchorean cordifolia* in leaves and fruits extracts. This finding is in accordance with Ismaila et al. (2010) which

demonstrated antinociceptif activity of the aqueous root extract of *Alchornea cordifolia*. In species of Simaroubaceae and Euphorbiaceae families it was demonstrated anti-inflammatory effect (Adejuwon et al., 2014; Mavar-Manga et al., 2018). We know that antiinflammatory drugs are for the most part analgesic. The pharmacological effect of *Quassia africana* is related to the presence of quassinoids (Wright et al., 1988; Apers et al., 2002; Alvesa et al., 2014; Guo et al., 2005).

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