**ACUTE TOXICITY AND ANTIPYRETIC ACTIVITY OF TALINUM TRIANGULARE COMPOUNDS**

**Abstract**

*Talinum triangulare* is a food plant renowned for its nutritional properties and anti-malarial virtues. Malaria is a disease that manifests as inflammation, fever and pain. Thus, this study on the safety and antipyretic activity of certain compounds derived from *Talinum triangulare* was carried out with a view to expanding the scientific data in favor of this plant's antiplasmodial attributes. To this end, an acute toxicity study was carried out in accordance with OECD 423 protocol using these compounds. To evaluate the toxicity of these compounds; they were orally administered to nulliparous, non-pregnant rats at a dose of 2000 mg/Kg body weight and observed for any clinical signs of toxicity. In addition, the antipyretic potential of plant extracts at doses of 100 mg/Kg, 200 mg/Kg and 400 mg/Kg of MC and of paracetamol (reference molecule) at a dose of 150 mg/Kg of MC were determined on rats whose hyperthermia was induced by 20% brewer's yeast. The results of the acute toxicity tests showed that no morbidity or mortality was observed in the animals. As for induced hyperthermia, it revealed a highly significant difference (p< 0.0001) between the temperature evolution of treated feverish rats compared to untreated feverish rats. In addition, there was a no significant difference (p˃ 0.05) between the temperature evolution of feverish rats treated with the different *Talinum triangulare* solutions and that of paracetamol.

**Key words**: *Talinum triangulare*, safety, antipyretic activity, paracetamol

**INTRODUCTION**

Over recent years, the understanding of the effects of plant utilization has expanded significantly, garnering increasing attention from researchers globally.(**Nyah *et al*., 2005)**. Phytotherapy, the use of plant-based treatments, is increasingly recognized for its significance and is garnering substantial interest within the field of biomedical research. **(Fetni & Bertella, 2021)**. In Africa, particularly in Côte d'Ivoire, plants are also used for nutritional and therapeutic purposes **(Effoe *et al*., 2020; Ouro-Djeri *et al*., 2022)**. However, plants are traditionally known for their therapeutic properties, but are yet to be scientificaly validated (**Zhou *et al*., 2009**; **Kamenan, 2024**). Traditional plants are very rich in bioactive chemical compounds and are easily accessible (**Ngbolua *et al*., 2019**). Moreover, according to **Koffi *et al*. (2024**), they are more biodegradable and are suspected of having resistance-reversing properties. As a result, plants are undoubtedly a promising alternative and complementary option for preventing and treating diseases in humans and animals. Moreover, they are a therapeutic remedy frequently used in sub-Saharan Africa in the treatment of numerous diseases. However, more research is needed to enable the widespread use of molecules derived from medicinal plants in modern therapy (**Alaoui *et al.*, 2007**; **Fetni & Bertella, 2021**). Despite their proven pharmacological properties, herbal remedies are associated with numerous side effects (**Bohui, 2020)**. This study will enable us to seek scientific validation of the efficacy of plants, and determine their tolerance limits for proper use.

From the big range of plants used in Côte d'Ivoire, *Talinum triangulare*, a food plant with little-known antimalarial properties, was chosen for this study. Previous studies have shown that acqeous and 70 % hydroethanol extracts have antimalarial activity (**Okou *et al*., 2019**)**.** As malaria is most often followed by fever, we also conducted further studies on *Talinum triangulare* compounds that have shown very good antimalarial profiles in order to establish the scientific basis for their uses. The aim of this work is to evaluate the biological tolerance of certain *Talinum triangulare* compounds, and then to test their efficacy in Wistar rats.

More specifically:

* To test the acute toxicity of *Talinum triangulare* compounds on Wistar rats;
* To determine the antipyretic activity of these compounds in Wistar rats.

**MATERIALS AND METHODS**

1. **Hardware**
	1. **Plant material**

The plant material used in this study consists of *Talinum triangulare* leaves belonging to the Talinaceae family. These leaves were collected in July and August 2021 in the early morning (6:30 am) at Koffikro, a camp located 12 km from Daloa and within the UEESO-CI housing estate near the COPRO college in Daloa (Haut-Sassandra Region, Côte d'Ivoire). This plant was identified by Professor AKE Assi, at the national floristic center located in Abidjan, Campus Universitaire de Cocody, under specimen UCJ014548.

**1-2 Animal materials**

Wistar rats of the species *Rattus norvegicus*, 8 to 10 weeks old, were supplied by the animal house of the UFR des Sciences Pharmaceutiques et Biologiques laboratory of the Université Félix Houphouët Boigny (Côte d'Ivoire). These animals were housed in plastic cages and reared at the animal house of the Ecole Nationale Supérieur d'Abidjan (ENS), (Abidjan, Côte d'Ivoire) under standard temperature conditions (25 ºC ± 2 ºC), relative humidity (70% ± 5%) with alternating 12 hours of light, 12 hours of darkness and fed with pellets supplied by FACI (Société de Fabrication d'Aliments Composés Ivoiriens). Bottles containing tap water were used as their daily watering source. The bedding, made of sawdust, is changed twice a week to ensure optimum hygiene conditions for the animals.

1. **Methods**

**2-1 Harvesting, drying and spraying *Talinum triangulare* leaves**

*Talinum triangulare* leaves were harvested, cleaned, sun-dried for ten weeks and then ground to a fine powder using an electric grinder. The fine powder obtained was stored at room temperature in glass jars to prevent mould.

**2-2 Preparation of *Talinum*** triangulare **hydroethanol extract and leaf fractions**

The active ingredients were extracted by cold maceration in specific solvents.

**2-2-1 Preparation of hydroethanol extract**

Fine *Talinum triangulare* leaf powder was macerated in 70% ethanol using the method of **Zirihi *et al*. (2003)**. One hundred grams of the plant powder was cold-macerated in an ethanol-water mixture (70/30 : v/v) using a blender. After three minutes of homogenization, the resulting homogenate was collected in a clean, white cloth square, then squeezed by hand. The collected solution was filtered twice on absorbent cotton and once on Whatman filter paper (3 mm). The 70% hydroethanol extract (HOH) was obtained after drying the filtrate in an oven at 60°C for 72 hours.

**2-2-2 Fractionation of hydroethanol extract**

In order to optimize the activity of the crude extract (HOH) recognized for its anti-plasmodial efficacy, partition chromatography was carried out using solvents of increasing polarity that were immiscible with each other: hexane, dichloromethane, ethyl acetate and butanol. The technique, inspired by **Bolou *et al* (2011)**, involved dissolving 100 g of HOH extract in 500 mL of distilled water, then transferring the resulting solution to a 1000 mL separatory funnel. Each extraction solvent (Hex, DCM, Ace and But) was then added in three 250 mL fractions. The different phases obtained were evaporated separately to isolate their respective fractions. Finally, the residual hydroalcoholic phase (Faq), obtained after treatment with the organic solvents, was also concentrated and evaporated.

**2-3 Acute toxicity test**

Acute toxicity is defined as the totality of adverse effects, which may be morphological and functional lesions in a living organism, caused by a substance introduced at a single relatively high dose, or at small doses repeated over a long period of time (**Hodgson, 2004**). It was carried out in accordance with OECD 423 (Organisation for Economic Co-operation and Development) protocol **(OECD, 2008)**. Four batches of 3 nulliparous, non-pregnant 10-11 week-old rats weighing between 100 and 150 g were formed and fasted 24 h before the start of the test. After this period, the animals were weighed and marked for identification. Test batches were then created. Of these, batch 1 represented the control, while batches 2 to 4 were the experimental batches. Animals in batch 1 were given 10 mL distilled water/Kg MC via an intubation cannula. While those in experimental batches (2, 3 and 4) were respectively given 2000 mg/Kg MC of HOH extract, DCM fraction and Faq (the three *Talinum triangulare* compounds most active on *Plasmodium*). After this stage, the animals were observed every 30 min for the first three hours of the day, then daily until the 14th day of experimentation. All observations were systematically recorded in order to note any clinical signs of intoxication, including symptomatological disorders identifiable with the naked eye, such as tremors, convulsions, salivation, diarrhea, lethargy, sleep, changes in skin, hair, eyes and mucous membranes, and coma. During this experiment, animal masses were recorded every two days.

**2-4 Assessment of antipyretic activity**

The antipyretic activity of HOH extract, DCM and Faq fractions (*Talinum triangulare* compounds of interest) was assessed by the brewer's yeast-induced hyperthermia method as described by **Bhowmick *et al*. (2014)** in healthy rats, ranging in weight from 150 to 200 g**.** To this end, the initial rectal temperature (basal temperature) of each rat was determined using a digital thermometer well before the induction of pyrexia. Pyrexia was then induced by subcutaneous injection of 20% of an aqueous suspension of brewer's yeast (*Sacchararomyces cerevisiae*) at a rate of 10 mL/Kg into the dorsal region of each rat. The animals were then fasted for 16 hours, after which their rectal temperature was again determined. Pyrexia was confirmed when there was a 0.5°C increase in basal temperature. Rats meeting these pyrexia conditions were retained for the study **(Muhammad *et al.,* 2012).** After this stage, the different batches of rats were randomly constituted (homogeneous batches). In practice, sixty-six (66) rats were selected and divided into 11 batches of 6 rats. With two control batches and nine experimental batches. The negative control (batch 1) received distilled water at a rate of 10 mL/Kg of MC. While the positive control (batch 2) was treated orally with 150 mg/Kg MC of paracetamol (reference antipyretic). Rats in batches 3, 4 and 5 received oral doses of 100 mg/Kg, 200 mg/Kg and 400 mg/Kg of HOH extract MC respectively. Rats in batches 6, 7 and 8 were treated with 100 mg/Kg, 200 mg/Kg and 400 mg/Kg MC of the DCM fraction respectively. Rats in batches 9, 10 and 11 were administered doses of 100 mg/Kg, 200 mg/Kg and 400 mg/Kg of MC from the Faq fraction respectively. All these experiments were carried out by gavage with 10 mL/Kg of MC of each substance immediately after taking the pyrexia temperature (16 hours after brewer's yeast injection). Finally, the rectal temperature of all animals was determined every hour for four hours. At the end of the test, all animals were given paracetamol to prevent any resurgence of fever after the study. The percentage reduction in pyrexia was calculated according to the following formula:

**PIF = [(MF-MT) / MF] x 100**

***(PIF):*** *Percentage of fever inhibition;* ***MF:*** *Average temperature of fever control batches;* ***MT****: Average temperature of* ***treated*** *batches.*

**2-5 Statistical analysis**

Statistical analyses and graphical representations were performed using Graph Pad Prism software version 8.0.2 (263). Analysis of variance (ANOVA ONE WAY) and values were expressed as means with standard errors on the mean (mean ± SEM). All data were normally distributed. Differences between means were determined using Dunnet's comparison test.

**RESULTS AND DISCUSSION**

**1- Results**

**Acute toxicity result**

Oral administration of the 2000 mg/Kg MC dose of hydroethanol extract (HOH), dichloromethane (DCM) and total aqueous (Faq) fractions of *T*. *triangularis* to rats from the batches made up did not result in symptomatological disorders such as tremors, convulsions, salivation, diarrhoea, lethargy, sleep, changes in skin, hair, eyes and mucous membranes, and coma. However, it was noted that after the experimental tests, there was a slight stimulation of appetite and drinking in the animals. On the other hand, there was no morbidity or mortality during the experimental period. As for the determination of body mass, there was a non-significant difference between the mass of the test animals and that of the controls (**figure 1)**.



Figure 1: Effect of *T*. *triangulaire* compounds on rat body mass compared to control

**Antipyretic results**

Basal temperatures in experimental rats ranged from 37.5± 0.14 to 37.1± 0.17 ºC. After subcutaneous injection of 20% of an aqueous suspension of brewer's yeast (*Saccharomyces cerevisiae*), they ranged globally from 38.52± 0.1 to 39.8± 0.04 ºC. Thus, this injection induced a highly significant rise (p< 0.0001) in the temperature of these rats. On the other hand, untreated feverish rats achieved overall temperatures of 39.82± 0.04°C and 39.1± 0.2°C. This demonstrates a non-significant (p > 0.05) decrease in temperature in untreated feverish rats. At 4thhour and at a dose of 400 mg/Kg MC of *T*. *triangulare* extract and fractions, there was a highly significant difference (p< 0.001) between the temperature evolution of feverish rats treated with the different *T*. *triangulare* solutions and that of untreated feverish rats. However, a highly significant difference (p< 0.0001) was observed between the temperature evolution of untreated feverish rats and that of rats treated with the reference molecule at a dose of 150 mg/Kg MC. Indeed, the body temperature of untreated feverish rats was 39.1± 0.2°C, whereas that of feverish rats treated with the different solutions was 36.6± 0.1°C (paracetamol), 37.2± 0.3°C (Faq), 37.6± 0.46°C (HOH) and 37.9± 0.2°C (DCM). Nevertheless, comparison of the body temperature of feverish rats treated with the extract and fractions of *T*. *triangulare*, and the reference molecule at 4thhour revealed a non-significant difference (p˃ 0.05) between the temperature evolution of feverish rats treated with the different *T*. *triangulare* solutions and that treated with the reference molecule. However, the body temperature of feverish rats treated with the DCM fraction at a dose of 400 mg/Kg MC, at 4thhour showed a marginally significant difference (p˂ 0.05) compared with the temperature of rats treated with paracetamol. In fact, the body temperature of fever-treated rats was 36.6± 0.1°C (paracetamol), while that of fever-treated rats treated with the various *T*. *triangulare* solutions was 37.2± 0.3°C (Faq), 37.6± 0.46°C (HOH) and 37.9± 0.2°C (DCM).

Antipyretic activity result

Table I: Variation in rectal temperatures of animals treated with the different solutions as a function of time

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  TM NEG | TM POSITIVE | FAQ 100 | DCM 100 | HOH 100 | FAQ 200 | DCM 200 | HOH 200 | FAQ 400 | DCM 400  | HOH 400 |
| TB 37.24±0.1 | 37,4±0,07 | 37,2±0,11 | 37,3±0,09 | 37,5±0,14 | 37,1±0,17 | 37,2±0,09 | 37,15±0,09 | 37,17±0,16 | 37,25±0,14 | 37,2±0,11 |
| T0 39,8±0,04 | 39,35±0,13 | 39,3±0,13 | 39,3±0,13 | 39,05±0,08 | 38,85±0,3 | 39,45±0,08 | 38,97±0,12 | 38,7±0,22 | 39,37±0,17 | 38,52±0,1 |
| T1 39,5±0,1 | 37,17±0,5a3 | 38,7±0,1b2 | 38,8±0,04b2 | 38,7±0,09b2 | 38,2±0,1a2 | 38,4±0,27a1 | 38,2±0,2a1 | 38,05±0,3a2 | 37,7±0,2a3 | 38,05±0,13a2 |
| T2 39,4±0,1 | 36,5±0,3a4 | 38,5±0,15b3 | 38,4±0,08b3 | 38,6±0,07b3 | 38±0.1a2 b2 | 38.3±0.2a1b3 | 38.3±0.2a1b3 | 37.8±0.2a4b1 | 37.6±0.2a4b1 | 37.7±0.3a4 b1 |
| T3 39,1±0,1 | 36,2±0,1a4 | 38,5±0,1b3 | 38,3±0,1b3 | 38,2±0,09b3 | 38,1±0,15b3 | 38±0.06a2b3 | 38,22±0,1b3 | 37.4±0.3a3b1 | 37.7±0.3a3b2 | 37.8±0.45a3 3 |
| T4 39,1±0,2 | 36.6±0.1a4 | 38,5±0,19b3 | 38,2±0,16b2  | 38,1±0,06b3 | 38,2±0,17b2  | 38,15±0,3b2 | 38,25±0,2b2  | 37,2±0,3 a3 | 37.9±0.2a3b1 | 37,6±0,46 a3 |

a: significant difference compared with negative control batches (untreated rats with fever) ;

b: significant difference compared with positive control batches (feverish rats treated with the reference molecule);

The exponents in figures are the number of stars: 1, 2, 3 and 4 correspond respectively to \* p˂0.05; \*\* p˂0.01; \*\*\* p˂0.001; \*\*\*\* p˂0.0001.

Notations: not significant ( ): p > 0.05; insignificant (\*): p < 0.05; significant (\*\*): p < 0.01; highly significant (\*\*\*): p < 0.001; highly significant (\*\*\*\*): p < 0.0001.

**2- Discussion**

This study is part of a project to develop medicinal plants and, above all, to find new molecules from plant extracts. In the course of this work, the acute toxicity test carried out in accordance with OECD 423 protocol confirmed that the hydroethanol extract (HOH), dichloromethane (DCM) and total aqueous (Faq) fractions of *T*. *triangularis* are non-toxic by the oral route at a dose of 2000 mg/Kg MC. In fact, the results obtained revealed no particular signs of toxicity in rats during the 14 days of observation. These results are similar to those obtained by **Soro (2023**) who, in his thesis work, demonstrated that animals treated with decoctate of the aerial parts of *Olax subscorpioïdea* (DOSA) and decoctate of *Rhynchospora corymbosa* (DRC) at a dose of 2000 mg/Kg/PC showed no change in behavior or signs of intoxication during the 14 days of experimentation. The slight, non-significant difference between the body mass of animals treated with *T*. *triangularis* solutions and that of the control batch corroborates the results obtained by some authors. These report that, in addition to their therapeutic properties, medicinal plants can positively influence animal nutrition (**Kahiya *et al*., 2003; Tano, 2016**). Insofar as the results of this study did not highlight the death of animals throughout the experimental tests, it is possible to say that there is no immediate toxicity of these test substances by the oral route at the dose of 2000 mg/Kg MC. Thus, according to the **OECD's** Globally Harmonized System (GHS) of classification **(2001)**, the hydroethanol extract and fractions (dichloromethane and total aqueous) of *T. triangular* belong to category 5 or non-toxic (LD50 ˃ 2000). However, according to **Kim *et al*. (2011)**, these results are not sufficient to definitively conclude that *T. triangular* leaf solutions are absolutely safe. In fact, assessing the toxicity of a substance by the repeated-dose method (subacute toxicity) is a fundamental test advocated for assessing the safety of that substance.

Subcutaneous administration of a 20% suspension of sarcomycetous brewer's yeast to the dorsolateral region of rats induced hyperthermia in these animals. This was due to the release of cytokines that stimulate prostaglandin biosynthesis **(Morabandza *et al*., 2016)**. Indeed, the prostaglandins released cause a rise in the thermostat at the hypothalamic center, resulting in pathogenic fever. According to **Muhammad *et al* (2012)**, this test is used to investigate the antipyretic properties of plants or synthetic drugs. As such, this rise in temperature would indicate that any reduction in fever during the 4 hours of experimentation would be due to the effects of the products administered. On the other hand, the plant solutions and paracetamol had antipyretic effects throughout the experiment. Plant extracts had the best effects at high doses of 400 mg/Kg of MC. These results are in line with those of **Saptarini and Deswati (2015)**. For these authors, the higher the dose to be administered, the higher the antipyretic activity. Thus, this observed antipyretic activity is dose-dependent. However, the reference molecule at a dose of 150 mg/Kg of MC caused a decrease (36.6± 0.1 (o) C) in the normal rectal temperature of rats (37.2 ± 0.11 - 37.5 ± 0.14 (o) C), in contrast to the different fractions and extract of *Talinum triangulare* at doses of 400 mg/Kg of MC. This higher activity of the reference molecule at a dose of 150 mg/Kg of MC compared with *Talinum triangulare* solutions at doses of 400 mg/Kg of MC could be explained by the fact that paracetamol (the reference molecule) is a pure molecule as opposed to *Talinum triangulare* solutions, which are still aggregates of molecules. However, this observation is also justified by the fact that the various solutions of *Talinum triangulare* fractions and extracts do not behave like hypotonic substances such as *Kaya senegalensis* extracts (**Lompo *et al*., 1998)**. *Talinum triangulare*'s antipyretic effect may be linked to prostaglandin inhibition **(Sakande *et al*., 2004)**. Furthermore, according to **Vasundra *et al*. (2013)** and **Safari *et al.* (2016**), the presence of flavonoids and alkaloids may inhibit prostaglandin synthesis. Similarly, **Gepdiremen *et al.* (2004)** revealed that phenolic compounds and saponins are potent prostaglandin inhibitors. All the above compounds are secondary metabolites. As a result, the antipyretic properties of *Talinum triangulare* fractions and extracts can be attributed to their high levels of secondary metabolites.

**CONCLUSION**

This study demonstrated the safety of *Talinum triangulare* hydroethanol extract and fractions (dichloromethane and total aqueous) after oral administration at a dose of 2000 mg/Kg of MC, suggesting an LD50 is strictly greater than 2000 mg/Kg of MC. These results confirm their classification in OECD GHS category 5, defining them as non-toxic. Hyperthermia induced in rats by subcutaneous injection of a 20% suspension of sarcomycetous brewer's yeast revealed that solutions of *T*. *triangularis* had a dose-dependent antipyretic activity. This activity was highly significant at doses of 400 mg/Kg of MC, close to that of the reference molecule, paracetamol (150 mg/Kg of MC). These antipyretic effects could be attributed to the presence of secondary metabolites in *Talinum triangulare* fractions and extract, opening up prospects for further therapeutic exploitation.

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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