Anti-inflammatory and antipyretic effects of the stem bark aqueous extract of *Terminalia superba* Engl. & Diels (Combretaceae) in rats

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Date de réception : 06 Août 2021 ; Date de révision : 25 Août 2021 ; Date d'acceptation : 03 Septembre 2021

Abstract:
Terminalia superba is a plant commonly used in traditional medicine for several diseases treatment including abdominal pain. This study aims to assess the anti-inflammatory and antipyretic potentials of a total aqueous extract of *Terminalia superba* (Combretaceae) stem bark codified TAETs.
TAETs was prepared by infusing 100 g of *Terminalia superba* stem bark powder for 15 min. A weight between 100 to 120 g of albino rats *Rattus norvegicus* species *Wistar* strain of 8 to 2 weeks old were used. The anti-inflammatory and antipyretic effects of TAETs were evaluated respectively through the models of paw edema induced with 0.1 mL of fresh egg albumin or carrageenan and the model of hyperthermia induced with a subcutaneous injection of an aqueous suspension of brewer's yeast (20%) in the dorso-lateral region. Normal saline (NaCl, 9 ‰), TAETs (125, 250 and 500 mg/kg body weight (bw)) and aspirin® (100 mg/kg bw) were orally administered.
Results indicated that TAETs significantly reduced the plantar edema caused by the injection of fresh egg albumin compared to control (NaCl, 9 ‰) with an inhibition percentage of 39.80% on the 5th hour and 84.35% for carrageenan on the 3rd hour of experimentation. The dose of 500 mg/kg bw of TAETs decreased the hyperthermia caused by brewer's yeast solution from 37.52 ± 0.12 to 36.08 ± 0.30 °C on the 2nd hour of experimentation.
TAETs possesses anti-inflammatory and antipyretic properties similar to that of aspirin® when administered in rats by oral route.

Key words: *Terminalia superba*, anti-inflammatory, antipyretic, rat.

Effets anti-inflammatoire et antipyrétique d'un extrait total aqueux des écorces de tige de *Terminalia superba* Engl. & Diels (Combretaceae) chez des rats

Résumé :
Terminalia superba est utilisée en médecine traditionnelle pour le traitement de plusieurs maladies y compris les douleurs abdominales. Cette étude vise à évaluer les potentiels anti-inflammatoire et antipyrétique d'un extrait total aqueux d'écorces de tige de *T. superba* codifié ETATs.
ETATs a été préparé par infusion de 100 g de poudre d'écorces de tige de *T. superba* pendant 15 min. Des rats albinos (*Rattus norvegicus*), de souche Wistar (100-120 g), âgés de 8 à 12 semaines, ont été utilisés. Les effets anti-inflammatoire et antipyrétique de l'ETATs ont été évalués respectivement sur l'œdème de patte induit par 0,1 mL d'albumine d'œuf frais ou de carragénine et l'hyperthermie induite par l'injection sous-cutanée, dans la région dorso-latérale, d'une suspension aqueuse de levure de bière à 20 % à raison de 1 mL/100 g de pc. ETATs (125, 250 et 500 mg/kg de pc), l'aspirine® (100 mg/kg de pc) et la solution de NaCl 9 ‰ (10 mL/kg de pc) ont été administrés par voie orale.
Les résultats indiquent que l'ETATs a réduit de manière significative l'œdème plantaire provoqué par l'injection de l'albumine du blanc d'œuf par rapport au témoin, avec un pourcentage d'inhibition de 39,80 % à la 5^{ième} heure d'expérimentation et de 84,35 % pour la carragénine à la 3^{ième} heure. ETATs à 500 mg/kg de pc a baissé l'hyperthermie provoquée par la levure de bière de 37,52 ± 0,12 à 36,08 ± 0,30 °C à la 2ème heure d'expérimentation.
ETATs administré par voie orale possède des propriétés anti-inflammatoire et antipyrétique comparables à celle de l'aspirine® chez le rat.

Mots Clé : *Terminalia superba,* anti-inflammatoire, antipyrétique, rat.

Introduction

Inflammation is a protective strategy developed in organisms in response to harmful aggressions such as microbial infection, tissue damage and other harmful conditions. It is an essential immune response of the host whose goal is the elimination of harmful stimuli as well as the healing of damaged tissues. Acute inflammation was therefore considered to be part of innate immunity, the first line of defense of the host against foreign agents and dangerous molecules. Humanity has experienced the classic symptoms of inflammation that include redness, pain, swelling and heat (Medzhitov, 2008). The inflammation's treatments are various and

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depend on the disease. However, many synthetic drugs used in inflammatory diseases treatment such as steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive drugs have harmful side effects (Sokeng *et al*., 2020). These side and toxic effects lead people to use medicinal plants for the treatment of inflammation in certain inflammatory diseases. Therefore, this study was conducted on *Terminalia superba*, a plant used in traditional medicine for various ailments treatments (Adjanohoun *et al*., 1979; Aké Assi, 1984; Adjanohoun *et al*., 1991; Zirihi, 1991; Hutchings *et al*., 1996; Van Wyk *et al*., 1997) in order to provide scientific evidence for its traditional use. *Terminalia superba* has been studied for the antidiabetic properties of a methanol extract of stem bark associated with methylene chloride (Kamtchouing *et al*., 2005), analgesic activities of a butanolic extract (Dongmo *et al*., 2006), the antidiabetic and antioxidant properties of a mixture of *Aloe vera* and an aqueous extract of the bark and ethyl acetate extract of *T. superba* (Dzeufiet *et al*., 2009 ; Ngueguim *et al*., 2011), the anti-hypertensive effect of the aqueous extract of the bark *T. superba* (Tom *et al*., 2010 ; Tom *et al*., 2011), the antibacterial and anti-fungal potential of methanol, aqueous and hydroalcoholic extracts (Kuete *et al*., 2010), and finally the acute oral toxicity and anti-ulcer effects of the 70% ethanolic extract of the stem bark of *T. superba* (Goze *et al*., 2013 ; Kouakou *et al*., 2013). However, despite these multiple therapeutic properties of *T. superba*, no scientific study has been mentioned on anti-inflammatory and antipyretic activity yet to confirm the use of this plant in the treatment of peptic ulcers and abdominal pain in Côte d'Ivoire. That is why this study aims to evaluate the anti-inflammatory and antipyretic potentials of TAETs to complete the other scientific studies by reduction in plantar edema caused by the injection of fresh egg albumin or carrageenan solution in TAETs-treated rats.

Material and Methods

1. Material

1.1. Plant: The plant material consists of *Terminalia superba* stem bark. The plant was identified thanks to samples preserved respectively under the numbers 2456 of June 4th, 1954 and 416 of April 3rd, 1974 at the national herbarium of Côte d'Ivoire and authenticated by the National Floristic Center (CNF) of Félix Houphouët-Boigny University (Abidjan, Côte d'Ivoire).

1.2. Animals: Albino rats (*Rattus norvegicus*), wistar strain weighing between 100 g and 120 g were used. These animals were between 8 to 12 weeks old and had free access to water and pellet food (Ivograin® pellets). Good laboratory practices and the various experimental protocols were followed in accordance with the instructions for the protection of experimental animals of the European Legislation Council 87/609/EEC (OCDE, 1998).

1.3. Reagents: Reagents consisted of albumin contained in fresh egg white, carrageenan (Sigma aldrich, France), aspirin® (reference anti-inflammatory), brewer's yeast (Laboratoire Arkopharma, France) and normal saline (NaCl, 9 ‰) were used.

2. Methods

2.1. Preparation of TAETs: The TAETs was prepared according to the method described by Goze *et al*. (2013). The stem bark of *Terminalia superba* was washed with distilled water, cut into small pieces and dried in an oven (Heto, France) at 45 °C for 5 days and powdered using an electric grinder (Culati, France). A quantity of 100 g of *Terminalia superba* stem bark powder was infused for 15 min in 1 liter boiled distilled water. The aqueous solution obtained was filtered on hydrophilic cotton and on Whatman paper 3 mm. Half a liter of boiled distilled water was added to the residue for 10 minutes infusion again. This solution was also filtered. The filtrates were evaporated and dried in an oven at 45 °C, for 48 h to obtain 11.56 g of black brown powder to prepare the TAETs.

2.2. Anti-inflammatory activity study: The purpose of this test was to evaluate the reduction in plantar edema caused by the injection of fresh egg albumin or carrageenan solution in TAETs-treated rats. The method is based on that described by Winter *et al*. (1962). Thus, 5 homogeneous batches of 5 rats each were used. The rats were fasted 16 hours before the beginning of the experiment. The initial thickness (E_0) of the right hind paw of each rat was measured using a digital micrometer. The rats in Group 1 (Control group) were gavaged with normal saline (NaCl, 9 ‰) at 10 mL/kg bw. As for the rats in groups 2, 3 and 4, they received respectively by gavage the TAETs at doses of 125, 250 and 500 mg/kg bw as previously used in the work of Goze *et al*. (2013). Rats in group 5 or positive control group were orally administered

with acetylsalicylic acid (Aspirin®) at a dose of 100 mg/kg bw. One hour after the gavage of normal saline, extract doses and Aspirin® according to the group, each rat was injected with either 0.1 mL of fresh egg albumin or 0.1 mL of carrageenan (1%) solution under the rat's right hind paw. Thereafter, the thickness (E_t) of the right hind paw was measured 1 h, 2 h, 3 h, 4 h and 5 h (6 h for carrageenan) after the injection of fresh egg albumin or carrageenan solution. The anti-inflammatory activity was evaluated as an edema inhibition percentage in treated rats compared to control rats according to the formula used by Olajide *et al*., (2000).

$$\%I = [(E_t - E_0)_{Control} - (E_t - E_0)_{Treated})/(E_t - E_0)_{Control}] \times 100$$

With %I: inhibition percentage, E_t: thickness of the paw measured at time t, E_0: initial thickness of the paw before the injection of fresh egg albumin or carrageenan solution.

2.3. Antipyretic activity study: The purpose of this test was to measure the drop in the temperature of brewer's yeast hyperthermic rats treated with the TAETs. The test was performed according to the method of Tarkang *et al*. (2015). Rats were fasted for 24 hours. Normal rectal temperature of the animals was recorded using an electronic thermometer (Cooper, France). Then, the rats were subcutaneously injection with an aqueous suspension of brewer's yeast (20%) at 1 mL/100 g bw into the dorso-lateral region, to induce hyperthermia. The animal which temperature was increased by 0.7 °C and above, 18 hours after the injection of brewer's yeast, was selected for the test and 5 batches of 5 rats were formed. The rats received orally, either the normal saline (NaCl, 9 ‰) to 10 mL/kg bw (control group), or the TAETs at doses of 125, 250 and 500 mg/kg bw or the standard antipyretic drug (Aspirin®) at 100 mg/kg bw (positive control group). One hour after the administration of the substances, rectal temperature was measured again every hour for five hours. The percentage of reduction in rectal temperature is calculated using the formula described by Muhammad *et al*., (2012).

$$\%\ Reduction = [(B - Cn) / (B - A)] \times 100$$

A: Normal temperature.
B: Temperature after induction of hyperthermia.
Cn: Temperature after 1, 2, 3, 4 and 5 hours.

2.4. Statistical analysis: The statistical analysis was performed using Graph Pad Prism 5.01 software (San Diego, Californie, USA). The results obtained were shown as an average followed by the standard error on the mean (M ± SEM). The One-Factor Analysis of Variance (ANOVA1) followed by the Tukey comparison test were used to identify differences between treated and control groups. The significance threshold was set at $p < 0.05$.

Results

1. Effect of TAETs on fresh egg albumin -induced* edema*: The edema of the paw induced after the injection of fresh egg albumin was significantly reduced at doses of 125; 250 and 500 mg/kg bw. With an initial average paw thickness of 2.63 ± 0.14 mm in control rats, the injection of fresh egg albumin induced an average increase in the paw between 6.65 ± 0.19 mm and then 4.64 ± 0.10 mm during the 5 hours of experimentation. The edema induced with egg albumin in rats were inhibited by 23.32% to 31.84% and 23.38% to 39.80% compared to the control group, respectively by the doses of 250 and 500 mg/kg bw of the TAETs. The inhibitory effect of TAETs is dose-dependent. Aspirin®, the standard inflammatory drug used in this study, reduced egg white albumin-induced edema in rats from 29.1% to 55.72% compared to the control group. This inhibitory effect of aspirin® is higher than that induced by the TAETs at the different doses used (Table I).

2. Effect of TAETs on carrageenan-induced edema : The average thickness of the paw of rats before the injection of carrageenan was between 2.51 ± 0.06 and then 2.61 ± 0.05 mm. Carrageenan caused a maximum increase in the average paw thickness of rats from the control group ranging from 2.51 ± 0.06 mm (initial state) to 4.81 ± 0.17 mm (3^{rd} hour). The edema induced by carrageenan was significantly reduced by the TAETs from 2^{nd} hour of experimentation compared to the control group. The inhibition percentage of paw edema in rats pretreated with the TAETs ranged from 36.49% to 84.35% with a maximum reduction in edema at a dose of 500 mg/kg bw. For rats treated with aspirin®, the inhibition percentage of paw edema was between 56.76 and 77.33% compared to the control lot group (Table II).

Table I: Effect of the TAETs and Aspirin on fresh egg albumin-induced paw edema in rats.

Treatment and doses (mg/kg bw)	Paw thickness (mm) before the injection of egg white albumin	Paw thickness (mm) after egg white injection (Edema inhibition percentage)				
		1 h	2 h	3 h	4 h	5 h
Control group (mL/kg bw)	2.63 ± 0.14	6.65 ± 0.19	5.85 ± 0.19	5.16 ± 0.12	4.93 ± 0.14	4.64 ± 0.10
TAETs 125	2.67 ± 0.22	6.25 ± 0.21 (10.94)	5.69 ± 0.11 (6.21)	4.85 ± 0.12 (13.83)	4.69 ± 0.10 (13.91)	4.36 ± 0.12 (15.92)
TAETs 250	2.62 ± 0.13	5.70 ± 0.11* (23.38)	4.84 ± 0.20** (31.06)	4.56 ± 0.10* (23.32)	4.34 ± 0.11** (25.22)	3.99 ± 0.11*** (31.84)
TAETs 500	2.59 ± 0.07	5.67 ± 0.17** (23.38)	4.78 ± 0.13** (31.99)	4.40 ± 0.07** (28.46)	4.18 ± 0.08*** (30.87)	3.80 ± 0.03*** (39.80)
Aspirin® 100	2.60 ± 0.10	5.45 ± 0.22** (29.10)	4.54 ± 0.15*** (39.75)	4.39 ± 0.15** (29.25)	3.76 ± 0.11*** (49.56)	3.49 ± 0.08*** (55.72)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; n = 5: Differences were significant when values of treated groups were compared to that of control group, at the same corresponding time (same column).

Table II: Effect of the TAETs and Aspirin on carrageenan-induced paw edema in rats.

Treatment and doses (mg/kg bw)	Paw thickness (mm) before the injection of carrageenan	Paw thickness (mm) after carrageenan injection (Edema inhibition percentage)					
		1 h	2 h	3 h	4 h	5 h	6 h
Control group (mL/kg bw)	2.51 ± 0.06	2.97 ± 0.11	3.99 ± 0.11	4.81 ± 0.17	4.52 ± 0.20	4.33 ± 0.21	4.01 ± 0.17
TAETs 125	2.54 ± 0.04	3.06 ± 0.07 (-13.04)	3.32 ± 0.08** (47.30)	3.53 ± 0.15*** (56.96)	3.36 ± 0.12*** (59.20)	3.30 ± 0.19*** (56.04)	3.13 ± 0.22*** (60.67)
TAETs 250	2.55 ± 0.03	3.04 ± 0.08 (-6.52)	3.49 ± 0.17* (36.49)	3.91 ± 0,16** (84.35)	3.42 ± 0.14*** (56.72)	3.22 ± 0.14*** (63.19)	3.06 ± 0.08*** (66.00)
TAETs 500	2.61 ± 0.05	3.16 ± 0.04 (-19.57)	3.23 ± 0.05** (58.11)	3.39 ± 0.11*** (66.09)	3.16 ±0.12*** (72.64)	2.98 ± 0.06*** (79.67)	2.87 ±0.05*** (82.67)
Aspirin® 100	2.60 ± 0.09	3.07 ± 0.15 (-2.17)	3.24 ± 0.13** (56.76)	3.42 ± 0.10*** (64.35)	3.28 ±0.14*** (66.17)	3.17 ± 0.12*** (68.68)	2.94 ± 0.12*** (77.33)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; n = 5: Differences were significant when values of treated groups were compared to that of control group, at the same corresponding time (same column).

3. Effect of TAETs on brewer's yeast-induced hyperthermia: Table III shows the antipyretic effect of TAETs and aspirin® on brewer's yeast-induced hyperthermia. The injection of the brewer's yeast solution induced an increase in the rectal temperature of rats compared to their normal rectal temperature 18 hours later. In the control group, the initial temperature of 36.88 ± 0.13°C, increased to 37.88 ± 0.19°C and then remained relatively constant at 37.8 ± 0.19°C during this experiment. The administration of TAETs at doses of 125; 250; 500 mg/kg bw reduced this hyperthermia from 38.18 ± 0.24 to 37.38 ± 0.33 °C; 37.02 ± 0.33 to 36.02 ± 0.16 °C and 37.52 ± 0.12 to 36.44 ± 0.25 °C respectively, 1 hour after the induction of pyrexia. The hyperthermia reduced remained relatively constant after administration of TAETs during this study. The Aspirin® at 100 mg/kg bw has an antipyretic effect similar to that of the TAETs. The Aspirin® administration lowered hyperthermia from 37.54 ± 0.42 to 36.24 ± 0.37°C and this temperature was stabilized during this study. From 1 hour to 5 hours, the TAETs (250 and 500 mg/kg bw) and aspirin® significantly decreased the rectal temperature of treated rats compared to rats in the control group with a maximum reduction of 128.15 ± 29.1% at the 2nd hour. The TAETs at 125 mg/kg bw had no significant effect on rectal temperature in rats.

Table III: Antipyretic effect of TAETs and Aspirin on brewer's yeast induced hyperthermia in rats.

Treatment and doses (mg/kg bw)	Normal average temperature (°C)	Mean temperature (°C) after the brewer's yeast injection	Rectal temperature (°C) after TAETs or aspirin® administration / (Reduction percentage of rectal temperature)				
			1 h	2 h	3 h	4 h	5 h
NaCl control (mL/kg bw)	36.88 ± 0.13	37.88 ± 0.19	38.18 ± 0.28 (-29.10 ± 11.0)	37.98 ± 0.34 (-5.64 ± 17.8)	37.88 ± 0.27 (13.88 ± 17.1)	37.80 ± 0.31 (11.29 ± 16.4)	37.84 ± 0.24 (9.14 ± 18)
TAETs 125	37.07 ± 0.21	38.18 ± 0.24	37.38 ± 0.33 (79.12 ± 28.9)	37.28 ± 0.31 (91.21 ±31.2)	37.16 ± 0,39 (104.46 ± 38.7)	37.24 ± 0.37 (97.34 ±36.8)	37.24 ± 0.30 (94.61 ± 32.0)
TAETs 250	35.84 ± 0.23	37.02 ± 0.33	36.02 ± 0.16*** (84.22 ± 10.6)	36.14 ± 0.23** (71.99 ± 21.3)	36.14 ± 0.21** (76.89 ± 16.1)	35.78 ± 0.05*** (100.78 ± 17.9)	35.68 ± 0.25*** (114.99 ± 10.7)
ETATs 500	36.24 ± 0.15	37.52 ± 0.12	36.44 ± 0.25** (92.54 ± 19.60)	36.08 ± 0.30** (128.15±29.1)	36.02 ± 0.15*** (126.43 ± 16.8)	36.34 ± 0.26** (104.01 ± 22.6)	36.28 ± 0.17** (110.04 ± 21.4)
Aspirin® 100	36.20 ± 0.32	37.54 ± 0.42	36.24 ± 0.37*** (110.5 ± 12.1)	36.22 ± 0.39** (109.47 ± 24.0)	36.48 ± 0.36** (79.26 ± 7.56)	36.32 ± 0.34** (91.15 ± 7.18)	36.32 ± 0.38** (94.01 ± 5.54)

** p < 0.01; *** p < 0.001; n = 5: Differences were significant when values of treated groups were compared to that of control group, at the same corresponding time (same column).

Discussion

The anti-inflammatory potential of TAETs at doses of 125, 250 and 500 mg/kg bw was evaluated using the egg white albumin and carrageenan induced inflammation experimental models in rats. The injection of fresh egg albumin or carrageenan caused plantar edema which was reduced by the administration of TAETs. The TAETs has anti-inflammatory properties similar to that of aspirin®. However, these effects are lower than those of aspirin® on the edema of the rats paw induced by fresh egg albumin and substantially similar to that of aspirin® on carrageenan-induced edema in rats. The injection of phlogogenic substances (carrageenan, egg white albumin, dextran, etc.…) produces experimental inflammations (Pieri et Kirkiacharian, 1992). Indeed, the injection of egg albumin or carrageenan causes local inflammation which leads to the release of several chemical

mediators that are responsible for the inflammatory process. This inflammatory response has two phases. The initial phase lasts for about an hour and it is due to the release of histamine, serotonin and kinin. Bradykinin is released in the second phase between one and a half and three hours and the release of prostaglandins occurs beyond the third hour (Nwafor *et al*., 2007; Reanmongkol, *et al*., 2009). The TAETs inhibited plantar edema dose-dependently and in all phases with inhibitions ranging from 6.21% to 39.80% (egg white albumin) and from -19.57% to 84.35% (carrageenan). Thus, this extract could have an antagonistic action to pro-inflammatory substances such as histamine, serotonin, bradykinin, and prostaglandins biosynthesis. Strong inhibitions of edema were still observed beyond after the administration of the extract. This suggests that the TAETs would exert an inhibition action more on the cyclooxygenases that are responsible for the synthesis of prostaglandins. The results obtained with fresh egg albumin are similar to those obtained with methanol extracts of *Solanum aethiopicum* fruits (Anosike *et al*., 2012) and *Pupalia lappacea* leaves (Selvan *et al*., 2014). These authors showed that *Solanum aethiopicum* extract (100-400 mg/kg bw) and *Pupalia lappacea* extract (200 mg/kg bw) significantly reduced the edema induced by fresh egg albumin in rats by 56.67% after five hours (Anosike *et al*., 2012) and by 100% 60 minutes after the injection of fresh egg albumin (Selvan *et al*., 2014). Similarly, the results obtained with carrageenan are similar to those of Ashok and Upaghyaya (2013), Saravanan *et al.* (2018) and Sokeng *et al.* (2020). According to these authors, methanol extract from the aerial parts of *Artemesia vulgaris* (200-800 mg/kg bw) (Ashok et Upaghyaya, 2013) on the one hand, and the aqueous extract of Kabasura kudineer choornam (Indian drug formulation) at doses of 200 and 400 mg/kg bw (Saravanan *et al*., 2018) on the other hand, and finally, arachic acid ethyl ester isolated from Cameroonian propolis (12.5-50 mg/kg bw) (Sokeng *et al*., 2020) caused respectively significant inhibitions of edema caused experimentally by carrageenin of 93.9% and 59.72% after 4 hours, and finally 62.5% at the 5th hour of experimentation.

Hyperthermia induced by the injection of brewer's yeast (20%) allowed to study the antipyretic effect of the TAETs. Oral administration of the TAETs at doses of 125, 250 and 500 mg/kg bw significantly reduced the temperature rise induced by brewer's yeast. Indeed, hyperthermia induced by yeast injection is linked to the release of cytokines (TNFα, IL1β, IL6) that reached the blood vessels and stimulate the biosynthesis of prostaglandins (PGE2) around the thermoregulatory hypothalamic centre (Eschalier *et al*., 2000; Ribeiro *et al*., 2010). It is possible that the antipyretic effects of the TAETs and Aspirin® are due to the reduction of cytokine release and the biosynthesis of prostaglandins. This antipyretic property of the TAETs is similar to those obtained with the aqueous extracts of the leaves and roots of *Pterocarpus erinaceus* (Ouédraogo *et al*., 2012), alcoholic extracts of *Acacia hydaspica* (Afsar *et al*., 2015), the aqueous extract of *Vernonia amygdalina* leaves (400 and 800 mg/kg bw) (Elion *et al*., 2018) and the aqueous extract of *Argyreia nervosa* leaves at doses of 300, 400 and 500 mg/kg bw (Hassan *et al*., 2020).

Conclusion

This study showed that the total aqueous extract of *Terminalia superba* stem bark (TAETs) has remarkable anti-inflammatory and antipyretic properties. These results may justify the traditional use of this plant by herbalists in the treatment of abdominal pain, pain related to peptic ulcers and headaches.

Conflict of interest

The authors declare no conflict of interest.

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