Available online on 15.08.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Antipyretic Activity and Acute Toxicity Evaluation of *Ceiba pentandra* (Malvaceae) and *Ipomoea pes-caprae* (Convolvulaceae) Extracts

Gnienèfèrètien Nounaféri Awa SILUE *[a], Lenoir Thierry Ayoman DJADJI [a], Mohamed Bonewendé BELEMLILGA [b], Jean Noël KOUSSE [b], Gisèle KOUAKOU-SIRANSY [a]

[a] *Unité pédagogique Pharmacologie, Physiologie humaine, Anatomie, Sémiologie et Pharmacie Hospitalière, UFR Sciences Pharmaceutiques et Biologiques, Université Félix Houphouët-Boigny, 01 BP V34 Abidjan 01, Côte d'Ivoire*

[b] *Laboratoire de Recherche-Développement de Phytomédicaments et Médicaments (LR-D/PM), Institut de Recherche en Sciences de la Santé (IRSS), Centre National de la Recherche Scientifique et Technologique (CNRST) BP 7047 Ouagadougou 03, Burkina Faso*

Article Info:

Article History:

Received 17 May 2025
Reviewed 26 June 2025
Accepted 19 July 2025
Published 15 August 2025

Cite this article as:

Silue GNA, Djadji LTA, Belemlilga MB, Kousse JN, Kouakou-Siransy G, Antipyretic Activity and Acute Toxicity Evaluation of *Ceiba pentandra* (Malvaceae) and *Ipomoea pes-caprae* (Convolvulaceae) Extracts, Journal of Drug Delivery and Therapeutics. 2025; 15(8):50-59
DOI: http://dx.doi.org/10.22270/jddt.v15i8.7274

*For Correspondence:

Gnienèfèrètien Nounaféri Awa SILUE, *Unité pédagogique Pharmacologie, Physiologie humaine, Anatomie, Sémiologie et Pharmacie Hospitalière, UFR Sciences Pharmaceutiques et Biologiques, Université Félix Houphouët-Boigny, 01 BP V34 Abidjan 01, Côte d'Ivoire*

Abstract

The management of fever using synthetic antipyretics is associated with significant adverse effects, including hepatotoxicity and gastrointestinal complications. This study aimed to evaluate the antipyretic activity of combined extracts of *Ceiba pentandra* (Malvaceae) and *Ipomoea pes-caprae* (Convolvulaceae), two medicinal plants that are traditionally used in African phytotherapy to treat fever. Aqueous extracts were prepared by decoction. Antipyretic activity was evaluated using a brewer's yeast-induced fever model in Wistar rats. The animals were divided into groups that received either a saline control, *Ceiba pentandra* alone at doses of 125 or 200 mg/kg, a combination of *Ceiba pentandra* and *Ipomoea pes-caprae*, or the acetaminophen reference. Rectal temperatures were recorded for four hours. Acute oral toxicity was assessed according to OECD guideline 423. *Ceiba pentandra* demonstrated dose-dependent antipyretic activity, with a rapid onset of action within 30 minutes. Combinations showed markedly improved efficacy compared to *Ceiba pentandra* alone, improving by 5.17–47.37 percentage points. The combination of 200 mg/kg of *Ceiba pentandra* and 25 mg/kg of *Ipomoea pes-caprae* achieved superior effects to acetaminophen during the first two hours, with 100% inhibition compared to 82.11% for acetaminophen. No significant toxicity was observed, with an LD_{50} greater than 2000 mg/kg. The combination of *Ceiba pentandra* and *Ipomoea pes-caprae* extracts demonstrated enhanced antipyretic activity and an excellent safety profile. This validates traditional African medicinal practices and suggests promising therapeutic potential.

Keywords: Antipyretic, brewer's yeast, potentiation, *Ceiba pentandra*, *Ipomoea pes-caprae*

1. INTRODUCTION

A fever is defined as a temperature of 38.0°C or higher[1, 2]. It may indicate a bacterial or viral infection, or an inflammatory process[3]. The most common and widespread conventional antipyretics are synthetic molecules, particularly acetaminophen, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)[4]. While they have proven their effectiveness, they are now known to cause many serious adverse effects. Acetaminophen is the most widely used analgesic-antipyretic in the world, and although it is considered safe with few adverse effects, it is the active substance most commonly involved in cases of drug poisoning, whether voluntary or involuntary[5]. It also poses a significant risk of hepatotoxicity[6]; in England and the United States, acetaminophen is the leading cause of acute hepatitis, ahead of viral and other iatrogenic causes[7]. Other active substances with antipyretic activity, particularly NSAIDs, are not exempt from this issue. Indeed, despite being widely prescribed, these drugs can cause adverse effects such as gastric irritation and ulceration, prolonged bleeding, kidney failure and itchiness[8, 9]. Similarly, a large number of hospitalisations are drug-related and attributable to NSAIDs[10]. Exploring natural antipyretic substances, particularly plant-derived active principles, could provide alternative therapeutic options.

The *Ceiba pentandra* (Malvaceae) tree, commonly known as the kapok tree, is native to tropical regions of the Americas. This giant of the plant kingdom occupies a significant cultural place in tropical Africa, where many communities revere it as a "palaver tree" and "fetish tree"[11, 12]. It is now widely cultivated in all tropical regions and is particularly prevalent in West and Central Africa, from Cape Verde to Chad and down to Angola. It is also found in East Africa and Southeast Asia, notably in Indonesia and Thailand, where intensive cultivation

takes place[13]. Different parts of the plant have traditionally been used to treat various conditions[6]. The bark and leaves of *Ceiba pentandra* are traditionally used as a febrifuge. Bark infusion is recognised for its antipyretic properties[14], while macerated leaves, particularly in combination with Ananas comosus leaves, are used as an external or oral antipyretic[15].

Ipomoea pes-caprae (Convolvulaceae) is a prostrate, perennial, herbaceous plant with stems up to 30 m long that contain latex and root at the nodes[16]. It establishes and develops on tropical and subtropical beach dunes. It has a pantropical distribution and has been observed on the coasts of North and South America, Asia, Africa (the central, eastern and western coasts) and Australia. There are numerous well-documented traditional uses for *Ipomoea pes-caprae*, including the treatment of lumbar muscle tension, rheumatic joint pain, fatigue, weakness, and pain and inflammation resulting from bites, arthritis, and rheumatism. It is also used to treat various intestinal disorders, such as ulcers, dysentery and cramps; skin conditions, such as boils, bedsores and dermatitis; and diabetes. Traditional preparation methods include infusions, decoctions, plant-based poultices and vegetable oils, which are primarily administered orally or topically according to the therapeutic indications targeted[16, 17]. Pharmacologically, *Ipomoea pes-caprae's* anti-inflammatory activity is one of its main documented biological effects[18]. In some regions of Africa, particularly Burkina Faso, the leaves of these two species are traditionally combined to make decoctions for treating fever[19].

Although the antipyretic properties of *Ceiba pentandra* have been scientifically documented[20–22], the effectiveness of its combination with *Ipomoea pes-caprae* has not been evaluated according to the literature reviewed.

This study aimed to evaluate the antipyretic activity of a *Ceiba pentandra* and *Ipomoea pes-caprae* extract mixture on a brewer's yeast-induced fever model in rats.

2. MATERIAL AND METHODS

2.1. Plant material

The plant material consisted of *Ceiba pentandra* leaves and leafy *Ipomoea pes-caprae* branches. The *Ceiba pentandra* leaves were collected in *Nabélékaha*, a village in the *Komodorougou* department in northern Côte d'Ivoire, while the *Ipomoea pes-caprae* leafy branches were collected in *Toukoro-Sambla*, a village in the *Karangasso-Sambla* department in the Bobo-Dioulasso province of Burkina Faso. Specimens of these plants were identified and authenticated by the National Centre for Floristics (CNF) in the Botany Department at Félix Houphouët-Boigny University in Abidjan. The *Ceiba pentandra* leaves were washed and dried in the shade before being pulverised using a *RETSCH® SM 100* knife mill. The fine powder was stored in a clean, dry jar.

2.2. Extraction

Aqueous extraction by decoction was performed on fresh aerial parts of *Ipomoea pes-caprae* and dried *Ceiba pentandra* leaf powder separately. Five litres of distilled water were added to 500 g of the fresh aerial parts of *Ipomoea pes-caprae* and two litres to 50 g of the dried *Ceiba pentandra* leaf powder. Each mixture was boiled for 30 minutes. The resulting decoctions were successively filtered through hydrophilic cotton, followed by Whatman No. 1 filter paper. The extracts were then evaporated to dryness in an oven at 50 °C for 72 hours. The resulting anhydrous material was scraped off, ground up, and the dry extracts obtained were stored in a refrigerator at 4°C for subsequent antipyretic activity studies.

2.3. Animal material

Experiments were performed on Wistar rats (*Rattus norvegicus*) weighing between 125 and 170 g and NMRI mice weighing between 25 and 36 g. These animals were sourced from the animal facilities of the Pharmacology, Clinical Pharmacy and Therapeutics Laboratory at the Faculty of Pharmaceutical and Biological Sciences at Félix Houphouët-Boigny University in Abidjan and the Institute of Health Sciences Research (IRSS). The animals were kept in a controlled environment at a temperature of 24 ± 1 °C, with a 12-hour light/dark cycle. They had free access to water and food. All experiments were conducted in accordance with international animal welfare standards, as recommended by the European Union (EEC 86/609 and EU 2010/63 directives).

2.4. Chemical substances

The following substances and reagents of a pharmacological nature were used in the study: sodium chloride solution (NaCl 0.09%, exp: 27/11/2021, lot: 18 332 A 03), brewer's yeast (Saccharomyces cerevisiae, *Arkopharma*® laboratories, exp: 03/2021, lot H01615A), and acetaminophen (*Doliprane*® 100 mg sachet, exp: 09/2019, lot: 2691). All pharmaceutical products were purchased from retail pharmacies.

2.5. Evaluation of antipyretic activity

The antipyretic effect of *Ceiba pentandra* and *Ipomoea pes-caprae* extracts was studied in accordance with the protocol outlined by Wang et al.[23]. The rats were fasted for 12 hours prior to experimentation, after which their baseline rectal temperatures were recorded. Hyperthermia was then induced by the subcutaneous administration of a 20% saline suspension of brewer's yeast at a rate of 10 mL/kg body weight in the dorso-lumbar region. Sixteen hours after administration, the rectal temperature of each rat was measured again, and those showing hyperthermia (a thermal variation of more than 0.5°C) were selected and divided into homogeneous groups of six according to the level of hyperthermia reached. These groups then received a 0.09% NaCl solution (negative control), *Ceiba pentandra* leaf extract (125 and 200 mg/kg), mixtures of *Ceiba pentandra* and *Ipomoea pes-caprae* extracts (125+3.125, 125+12.5, and 200+25 mg/kg) or the reference substance acetaminophen (100 mg/kg) by gavage. Rectal

temperatures were measured by inserting a lubricated 12-probe digital thermometer (TMP 812 RS™) approximately 2 cm into the rats' rectums. This thermometer displays temperatures with 0.1°C precision. Measurements were taken 30 minutes after substance administration, then every hour for four hours, and the recorded values were noted down.

Inhibition percentages were calculated relative to the control (NaCl 0.9%) according to the following formula:

%Inhibition = [(T° n - T°-16) Control - (T° n - T°-16) Treated] /(T° n - T°-16) Control ×100

T°n = temperature measured post-treatment; T°-16 = baseline temperature.

2.6. Evaluation of acute oral toxicity

Acute general toxicity was evaluated according to OECD guideline 423[24]. Aqueous decoctions of *Ceiba pentandra* and *Ipomoea pes-caprae* leaves were administered orally to male mice that had undergone a four-hour fasting period beforehand. A limit test was conducted at a dose of 2000 mg/kg body weight: the extract was administered by gavage to three mice via a gastric tube, and the mice were then observed individually for two hours before being refed. The mice were then monitored daily for 14 days to note any mortality or signs of intoxication, including cutaneous and hair modifications, ocular and mucosal changes, and the possible presence of convulsions, salivation, diarrhoea, lethargy, somnolence and coma. Water consumption was monitored daily throughout the study. Food consumption, as well as the individual weight of each animal, was determined once per week. At the end of the test, the surviving animals were weighed, anaesthetised with ketamine (50 mg/kg), and then subjected to macroscopic autopsy. Vital organs, such as the heart, kidneys, liver, lungs and spleen, were isolated, cleaned and examined macroscopically for any abnormalities in shape, size or colour. All organs were weighed on a precision scale (*Sartorius*®) to determine their relative weight and all macroscopic pathological alterations were recorded.

The relative weight of organs of each rat was calculated according to the following formula:

Relative organ weight (%) = [organ weight (g) ÷ animal weight (g)] × 100

2.7. Statistical analysis

The results were processed using Excel and GraphPad Prism version 7.0 software. The results are presented as the mean ± standard error of the mean (SEM). Data comparisons between groups were performed using analysis of variance (ANOVA), followed by a Tukey–Kramer post-test. Differences were considered statistically significant at $p < 0.05$. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3. RESULTS

3.1. Antipyretic activity of *Ceiba pentandra*

Figure 1 illustrates the effect of the aqueous extract of *Ceiba pentandra* on brewer's yeast-induced hyperthermia. Table 1 shows the percentage inhibition of fever by the *Ceiba pentandra* extract over a 4-hour period.

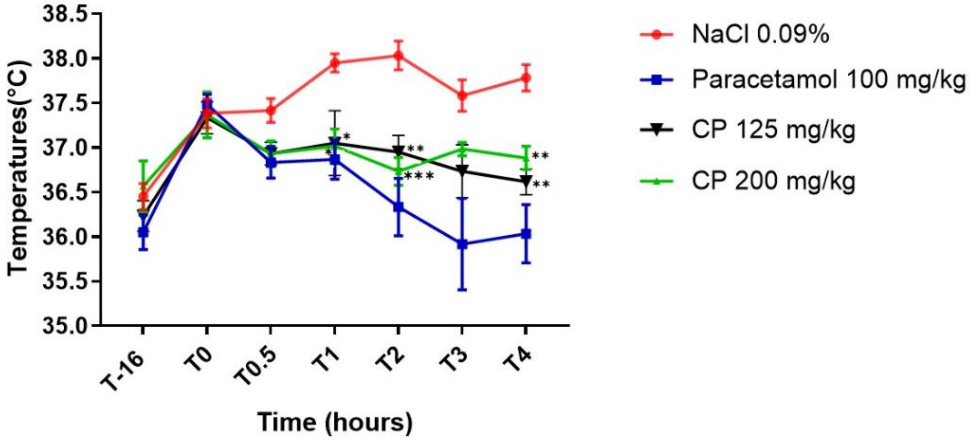

Figure 1: antipyretic activity of *Ceiba pentandra* at doses of 125 mg/kg and 200 mg/kg after fever induction by brewer's yeast (n=6).

Table 1: Inhibition percentages of *Ceiba pentandra*

Treatments (mg/kg)	Time(hours)				
	T0.5h	T1h	T2h	T3h	T4h
CP 125	27.59	45.56	54.74	55.88	71.25
CP 200	62.07	70.00	89.47	63.24	76.25
Acetaminophen 100	18.97	45.56	82.11	111.76	101.25

Administering *Ceiba pentandra* at doses of 125 mg/kg and 200 mg/kg caused a significant decrease in the body temperature of rats compared to the control group. This antipyretic effect was observed between the first and fourth hours after administration. Furthermore, the extract administered at 200 mg/kg demonstrated a superior hypothermic effect to that of the reference drug acetaminophen during the first two hours of observation.

3.2. Antipyretic activity of the mixture of *Ceiba pentandra* and *Ipomoea pes-caprae* extracts after brewer's yeast-induced fever

3.2.1. Effects of the mixture of *Ceiba pentandra* 125 mg/kg and *Ipomoea pes-caprae* at doses of 3.125 and 12.5 mg/kg on brewer's yeast-induced fever

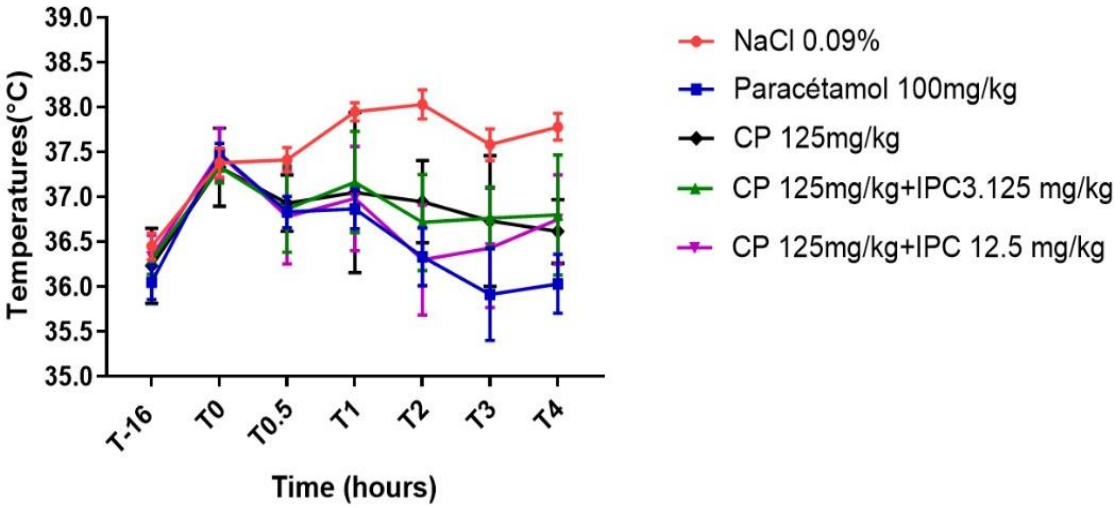

Figure 2: Antipyretic activity of the mixture of *Ceiba pentandra* 125 mg/kg and *Ipomoea pes-caprae* extracts at doses of 3.125 and 12.5 mg/kg after fever induction by brewer's yeast. (n=6).

Table 2: Inhibition percentages of *Ceiba pentandra* at 125 mg/kg dose in association with *Ipomoea pes-caprae*

Treatments (mg/kg)	Time (hours)				
	T0.5h	T1h	T2h	T3h	T4h
CP 125 + IPC 3.125	41.38	42.22	73.68	58.82	62.50
CP 125 + IPC 12.5	53.45	56.67	102.11	91.18	68.75

Figure 2 shows the antipyretic activity of the 125 mg/kg dosage of the aqueous *Ceiba pentandra* extract in combination with the 3.125 and 12.5 mg/kg doses of *Ipomoea pes-caprae* extract. These combinations produced an antipyretic effect similar to that observed with a single 125 mg/kg administration of *Ceiba pentandra*. However, the therapeutic efficacy of the combinations was superior to treatment with *Ceiba pentandra* alone. The *Ceiba pentandra* (125 mg/kg) and *Ipomoea pes-caprae* (12.5 mg/kg) combination demonstrated more pronounced antipyretic activity than the combination with *Ipomoea pes-caprae* (3.125 mg/kg).

Hyperthermia inhibition percentages induced by the *Ceiba pentandra* 125 mg/kg + *Ipomoea pes-caprae* 3.125 mg/kg association, evaluated from the 30th minute to the 4th hour post-administration, were significantly lower than those measured with the *Ceiba pentandra* 125 mg/kg + *Ipomoea pes-caprae* 12.5 mg/kg combination (Figure 2 and Table 2).

3.2.2. Effect of the mixture of *Ceiba pentandra* 200 mg/kg and *Ipomoea pes-caprae* 25 mg/kg extracts on brewer's yeast-induced fever

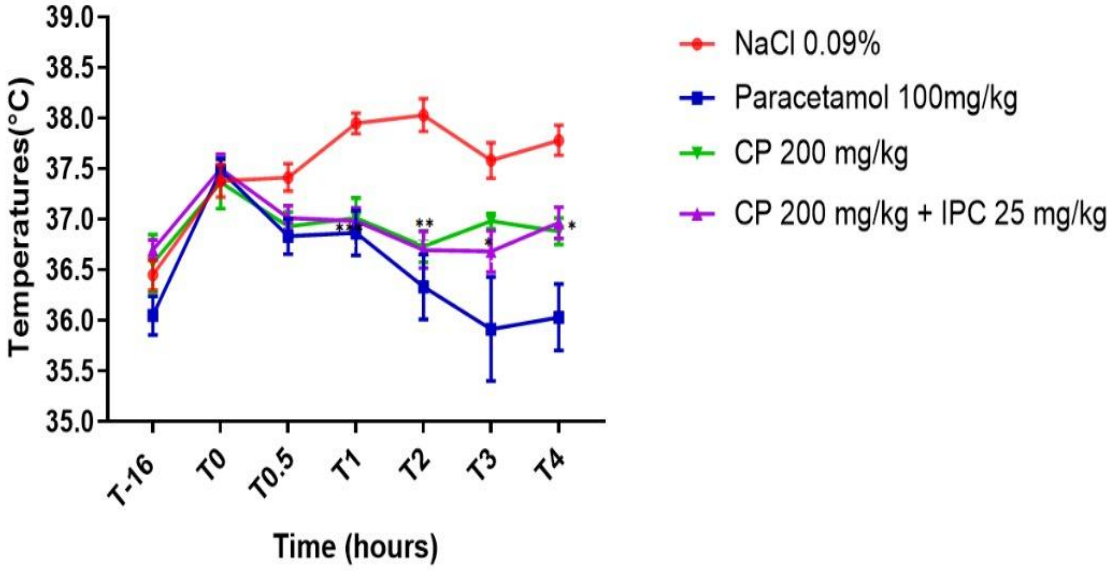

Figure 3: Antipyretic activity of the mixture of *Ceiba pentandra* 200 mg/kg and *Ipomoea pes-caprae* extracts at 25 mg/kg dose after fever induction by brewer's yeast (n=6).

Table 3: Inhibition percentages of *Ceiba pentandra* at 200 mg/kg dose in association with *Ipomoea pes-caprae*

Treatments (mg/kg)	Time(hours)				
	T0.5h	T1h	T2h	T3h	T4h
CP 200 + IPC 25	67.24	81.11	100.00	101.47	80.00

Figure 3 shows the antipyretic activity of a combination of 200 mg/kg of aqueous *Ceiba pentandra* extract and 25 mg/kg of aqueous *Ipomoea pes-caprae* extract. The experimental results demonstrate that the combination of *Ceiba pentandra* (200 mg/kg) and *Ipomoea pes-caprae* (25 mg/kg) has a significantly greater antipyretic effect than *Ceiba pentandra* (200 mg/kg) administered alone. Furthermore, the percentages of inhibition of induced hyperthermia, measured with this combination from the 30th minute to the 2nd hour post-administration, are superior to those obtained with acetaminophen at 100 mg/kg, which was used as the therapeutic reference (Figures 3 and Table 3).

3.3. Variations in inhibition percentages: interest of the mixture of *Ceiba pentandra* and *Ipomoea pes-caprae* extracts

3.3.1. Effect of the mixture of *Ceiba pentandra* 125 mg/kg and *Ipomoea pes-caprae* extracts at doses of 3.125 and 12.5 mg/kg compared to the activity of *Ceiba pentandra* 125 mg/kg alone

Table 4 summarizes the difference in inhibition percentages between the mixture and *Ceiba pentandra* 125 mg/kg extract alone.

Table 4: Variations in inhibition percentages: mixture of *Ceiba pentandra* 125 mg/kg and *Ipomoea pes-caprae* at doses of 3.125 and 12.5 mg/kg

Treatments (mg/kg)	Time (hours)				
	T0.5h	T1h	T2h	T3h	T4h
(CP 125 + IPC 3.125) - CP 125	+13.79	-3 .33	+18.95	+2.94	-8.75
(CP 125 + IPC 12.5) - CP 125	+25.86	+11.11	+47.87	+35.29	-2.50

This table illustrates the improvement in antipyretic efficacy that occurs with increasing doses of *Ceiba pentandra* and *Ipomoea pes-caprae* when used in combination. A comparative analysis of the differences in inhibition percentages reveals that adding a 12.5 mg/kg dose of *Ipomoea pes-caprae* considerably increases the activity of a 125 mg/kg dose of *Ceiba pentandra*, particularly in the initial phases of treatment. This

potentiation of the antipyretic effect is evident at T1h (+11.11% vs. -3.33%) and is further accentuated at T2h (+47.87% vs. +18.95%), thus confirming the optimisation of antipyretic efficacy through an increased concentration of *Ipomoea pes-caprae* in the combination. However, the negative values observed at later time points (T3h and T4h) for the high-dose combination suggest a potential decrease in this enhancement beyond two hours.

3.3.2. Effect of the mixture of *Ceiba pentandra* 200 mg/kg and *Ipomoea pes-caprae* 25 mg/kg Extracts compared to the activity of *Ceiba pentandra* 200 mg/kg alone

Table 5 summarizes the difference in inhibition percentages between the mixture and *Ceiba pentandra* 200 mg/kg extract alone.

Table 5: Difference in inhibition percentages: mixture of *Ceiba pentandra* 200 mg/kg and *Ipomoea pes-caprae* at 25 mg/kg dose

Treatments (mg/kg)	Time (hours)				
	T0.5h	T1h	T2h	T3h	T4h
(CP 200 + IPC 25) - CP 200	+5.17	+11.11	+10.53	+38.24	+3.75

These data reveal constant improvement in the antipyretic efficacy of *Ceiba pentandra* (200 mg/kg) when combined with *Ipomoea pes-caprae* (25 mg/kg). The inhibition gains observed were +5.17% at T0.5h, +11.11% at T1h and +10.53% at T2h, reaching a maximum of +38.24% at T3h before decreasing to +3.75% at T4h. Therefore, the combination exhibits a potentiating effect, reaching peak activity at the third hour post-administration.

3.4. Acute oral toxicity

Effect of *Ceiba pentandra* and *Ipomoea pes-caprae* on behavior, physiology, and mortality

Table 6: Effect of aqueous extracts of *Ceiba pentandra* (CP) and *Ipomoea pes-caprae* (IP) in single administration on some physiological parameters in mice.

Parameters	Groups		
	Control	CP (2000mg/kg)	IP (2000 mg/kg)
Hair	N	N	N
Eyes	N	N	N
Convulsions	A	A	A
Salivation	A	A	A
Diarrhea	A	A	A
Lethargy	A	A	A
Somnolence	A	A	A
Coma	A	A	A
Mortality	A	A	A

N : normal ; A : absent ; P : present

Table 6 summarises the effects of *Ceiba pentandra* (CP) and *Ipomoea pes-caprae* (IP) on mouse physiology during the evaluation of acute toxicity. No deaths were recorded in the control group or the treated groups within 14 days of a single 2000 mg/kg dose being administered. According to OECD guidelines, the median lethal dose (LD_{50}) is therefore estimated to be greater than 2000 mg/kg body weight.

Effect of *Ceiba pentandra* (CP) and *Ipomoea pes-caprae* (IP) on weight and relative organ Weight

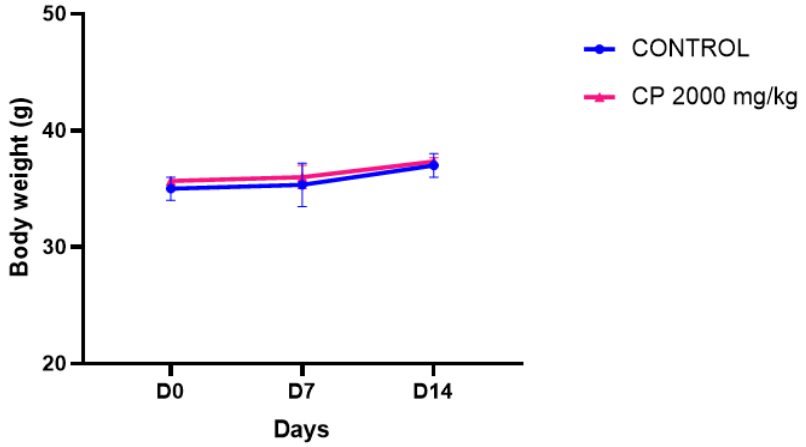

Figure 4: Effect of a single dose of *Ceiba pentandra* (CP) on mouse weight evolution

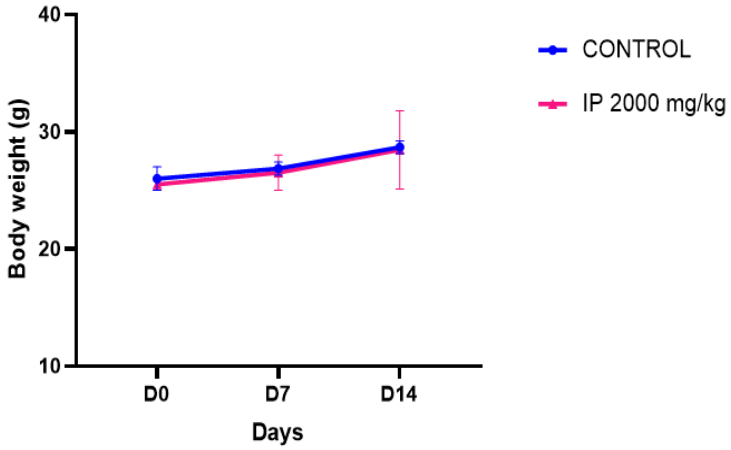

Figure 5: Effect of a single dose of *Ipomoea pes-caprae* (IP) on mouse weight evolution

Figures 4 and 5 show how the weight of mice subjected to acute toxicity testing changed over time. It can be seen that the weight curve increases in a similar way for all the mice during the treatment period, regardless of whether they are given *Ceiba pentandra* or *Ipomoea pes-caprae* extracts. Statistical analysis of these results shows that there is no significant difference in average weight between treated mice and those in the control group.

Table 7: effect of *Ceiba pentandra* (CP) in single administration on relative organ weight in mice.

Organs	Groups	
	Control	CP (2000 mg/Kg)
Liver	4.84 ± 0.25	4.93 ± 0.50
Kidney	1.51 ± 0.24	1.26 ± 0.07
Lungs	0.49 ± 0.09	0.59 ± 0.21
Heart	0.59 ± 0.09	0.54 ± 0.01
Spleen	0.37 ± 0.03	0.38 ± 0.09

Values are presented as mean ± standard deviation (SD).

Table 8: Effect of *Ipomoea pes-caprae* in single administration on relative organ weight in mice.

Organs	Groups	
	Control	IP (2000 mg/Kg)
Liver	4.37 ± 0.41	4.89 ± 0.48
Kidney	1.02 ± 0.33	0.92 ± 0.10
Lungs	0.56 ± 0.12	0.55 ± 0.04
Heart	0.69 ± 0.06	0.62 ± 0.08
Spleen	0.51 ± 0.04	0.46 ± 0.19

Values are presented as mean ± standard deviation (SD).

Tables 4 and 5 illustrate the relative weight of the organs of control mice and mice treated with aqueous extracts of *Ceiba pentandra* or *Ipomoea pes-caprae*. The data obtained revealed no significant differences in the relative weight of the liver, heart, lungs, kidneys and spleen between the treated mice and the control group.

4. DISCUSSION

This study aimed to evaluate the antipyretic activity of *Ceiba pentandra* and *Ipomoea pes-caprae* extract combinations on a brewer's yeast-induced fever model in rats.

The aqueous extract of *Ceiba pentandra* leaves was found to effectively lower the body temperature of febrile rats, exhibiting significant and early antipyretic activity from the thirtieth minute post-treatment. This finding corroborates the work of Saptarini et al., who demonstrated the antipyretic activity of *Ceiba pentandra* leaf extract in mice at doses of 189, 378, and 756 mg/kg[21]. This confirms the superiority of *Ceiba pentandra* leaf extract over Gossypium arboreum, which belongs to the same family (Malvaceae). These results also align with the observations of Djadji et al.[20], who evaluated the curative activity of the extracts on brewer's yeast-induced fever and the onset of action of the extracts on turpentine-induced fever.

The antipyretic effect was significantly increased when the *Ceiba pentandra* decoction was associated with *Ipomoea pes-caprae* extracts. Indeed, the fever inhibition percentages obtained with *Ceiba pentandra* extract alone improved by between 5.17 and 47.37 percentage points in the presence of *Ipomoea pes-caprae*.

The improvement in the antipyretic effect observed with *Ipomoea pes-caprae* extracts is based on the documented biological properties of this plant, particularly its well-established anti-inflammatory properties[25, 26]. These properties could complement the antipyretic properties of aqueous *Ceiba pentandra* decoction, thereby explaining the increased efficacy observed when the two are combined. Indeed, it has been demonstrated that *Ipomoea pes-caprae* exhibits anti-inflammatory effects at doses of 200 and 400 mg/kg in rats[27]. The anti-inflammatory effect involves the inhibition of COX-1 and COX-2; therefore, the antipyretic activity would operate through the same mechanism. Thus, *Ipomoea pes-caprae* would reduce PGE2 synthesis induced by pro-inflammatory cytokines (IL-1β, IL-6, TNF-α and IFN-γ), which are produced following the injection of brewer's yeast, by inhibiting COX.

Furthermore, the presence of compounds such as 3,4-dihydro-8-hydroxy-3-methylisocoumarin, eugenol, 4,4,7-trimethyl-1,4-dihydro-2-hydroxy-1-naphthalenone and 4-vinyl-guaiacol gives *Ipomoea pes-caprae* the ability to inhibit prostaglandin synthesis, thereby opposing inflammatory processes and fever[28]. Similarly, the presence of secondary metabolites, particularly flavonoids[29, 30], in the aerial parts of the plant would contribute to its antipyretic activity by suppressing TNF-α [31].

This improvement in efficacy demonstrates the potential advantages of combining different plant substances in phytotherapy, where they can work together to optimise the therapeutic effect[32]. This approach improves pharmacological efficacy by acting on multiple targets simultaneously while reducing the required dosage of individual components and minimising side effects[33]. Possible mechanisms include the enzymatic facilitation of bioactive compounds in *Ipomoea pes-caprae*, which could enhance the effect of *Ceiba pentandra* decoction; improved absorption of water-soluble active principles; and complementary action on different pathways of thermoregulation and inflammation. These results scientifically validate the traditional combination of *Ceiba pentandra* and *Ipomoea pes-caprae* for treating fever, demonstrating the rationale behind local phytotherapeutic practices.

An evaluation of the acute oral toxicity of a single 2000 mg/kg dose of aqueous extracts of *Ceiba pentandra* and *Ipomoea pes-caprae* administered to NMRI mice revealed no mortality or severe morbidity within 14 days. Therefore, the LD_{50} for each plant extract is greater than 2000 mg/kg. Therefore, the aqueous extracts of *Ceiba pentandra* leaves and the aerial parts of *Ipomoea pes-caprae* can be classified as category 5 substances under the Globally Harmonized System of Classification[24], i.e. substances without acute toxic effects.

Also, the relative weight of vital organs such as the heart, liver, kidneys, lungs and spleen should be considered. Evaluating organ weight variation is one of the most reliable ways of detecting the toxicity of an experimental substance[34, 35]. This approach has the advantage of revealing significant changes in the weight of target organs in exposed animals compared to the control group, even when there are no observable morphological alterations[34].

Thus, determining vital organ weight constitutes an early and sensitive biomarker, enabling the identification of potential harmful effects of a tested substance before any detectable anatomical changes appear.

The maintenance of the physical integrity of vital organs suggests a favourable safety profile for aqueous extracts of *Ceiba pentandra* and *Ipomoea pes-caprae*. This safety profile is a major asset when it comes to developing a phytomedicine for use as an antipyretic.

5. CONCLUSION

This study scientifically validates the traditional use of the *Ceiba pentandra–Ipomoea pes-caprae* combination as an antipyretic by demonstrating that its therapeutic efficacy is superior to that of *Ceiba pentandra* alone. An LD_{50} greater than 2000 mg/kg indicates an acceptable safety profile for this combination. These results confirm the ethnopharmacological approach and traditional phytotherapeutic practices based on the combination of multiple plant species. However, elucidation of the molecular mechanisms of action and evaluation of subacute toxicity are still necessary to characterize the interactions between the bioactive compounds and establish the potential for pharmaceutical development of this combination.

Acknowledgments: The authors would like to express their sincere appreciation to the Health Sciences Research Institute (Ouagadougou, Burkina Faso) and the Faculty of Pharmaceutical and Biological Sciences (Abidjan, Côte d'ivoire), whose exemplary collaboration made this work a reality.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Authors' contributions: Study conception, data analysis, and manuscript writing were performed by GNAS. Experimental supervision and resource acquisition were conducted by GKS. Experiments were carried out by GNAS and JNK. Data analysis, manuscript revision, study conception, and study implementation were undertaken by LTAD and MBB.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethical approval: All experiments were conducted in accordance with international animal welfare standards, as recommended by the European Union (EEC 86/609 and EU 2010/63 directives).

REFERENCES

1. Cross JH. Fever and fever-related epilepsies. Epilepsia . 2012;53(Suppl 4):3-8. https://doi.org/10.1111/j.1528-1167.2012.03608.x

2. Graaf S, Keuning MW, Pajkrt D, Plötz FB. Fever without a source in children: international comparison of guidelines. World J Pediatr . 2023;19(2):120-8. https://doi.org/10.1007/s12519-022-00611-8

3. DeWitt S, Chavez SA, Perkins J, Long B, Koyfman A. Evaluation of fever in the emergency department. Am J Emerg Med . 2017;35(11):1755-8. https://doi.org/10.1016/j.ajem.2017.08.030

4. Doyle JF, Schortgen F. Should we treat pyrexia? And how do we do it? Crit Care . 2016;20(1):1-10. https://doi.org/10.1186/s13054-016-1467-2

5. Cipolat L, Loeb O, Latarche C, Pape E, Gillet P, Petitpain N. Le paracétamol : connaissance, usage et risque de surdosage en patientèle urbaine de médecine générale. Étude prospective descriptive transversale. Therapie . 2017;72(4):453-63. https://doi.org/10.1016/j.therap.2016.12.012

6. Perkins JD. Etiology and prognosis of fulminant hepatitis in adults. Liver Transpl . 2008;13(5):67-79. https://doi.org/10.1002/lt.21612

7. Jaeschke H, Ramachandran A. Acetaminophen hepatotoxicity: paradigm for understanding mechanisms of drug-induced liver injury. Annu Rev Pathol Mech Dis . 2024;19:453-478. https://doi.org/10.1146/annurev-pathmechdis-051122-094016

8. Sonsupap C, Pokhakul P, Kariya T, Suzuki Y, Hamajima N, Yamamoto E. Characteristics of adverse drug reactions due to nonsteroidal anti-inflammatory drugs: a cross-sectional study. Nagoya J Med Sci . 2023;85(4):668-681.

9. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci . 2013;16(5):821-847. https://doi.org/10.18433/J3VW2F

10. Wirth T, Lafforgue P, Pham T. NSAID: current limits to prescription. Joint Bone Spine . 2024;91(4):105685. https://doi.org/10.1016/j.jbspin.2023.105685

11. Dick CW, Bermingham E, Lemes MR, Gribel R. Extreme long-distance dispersal of the lowland tropical rainforest tree *Ceiba pentandra* L. (Malvaceae) in Africa and the Neotropics. Mol Ecol . 2007;16(14):3039-49. https://doi.org/10.1111/j.1365-294X.2007.03341.x

12. Gómez-Maqueo X, Gamboa-Debuen A. The Biology of the Genus Ceiba, a Potential Source for Sustainable Production of Natural Fiber. Plants . 2022;11(4). https://doi.org/10.3390/plants11040521

13. PROTA4U. *Ceiba pentandra* (L.) Gaertn [Internet]. [cité 2025 juin 27]. Available from : https://prota.prota4u.org/protav8.asp?g=pe&p=Ceiba+pentandra

14. Burkill HM. The useful plants of West Tropical Africa II. Kew (UK): Royal Botanic Gardens ; 2000. p. 481.

15. Grosvenor PW, Gothard PK, Mcwdham NC, Suprlono A, Gray DO. Medicinal plants from Riau Province, Sumatra, Indonesia. Part 1: Uses. J Ethnopharmacol . 1995;45:75-95. https://doi.org/10.1016/0378-8741(94)01209-I

16. Akinniyi G, Lee J, Kim H, Lee JG, Yang I. A Medicinal Halophyte *Ipomoea pes-caprae* (Linn.) R. Br.: A Review of Its Botany, Traditional Uses, Phytochemistry, and Bioactivity. Mar Drugs . 2022;20(5). https://doi.org/10.3390/md20050329

17. Manigauha A, Kharya MD, Ganesh N. In vivo antitumor potential of *Ipomoea pes-caprae* on melanoma cancer. Pharmacogn Mag . 2015;11(42):426-33. https://doi.org/10.4103/0973-1296.153099

18. Zhu J, Zou Y, Wu Y, Deng X, Huang Y, Yuan E, et al. Exploring the Mechanism of Action of Honeybran-Fried Cimicifuga Rhizoma in the Treatment of IBS-D Based on Metabolomics and Network Pharmacology. Biomed Chromatogr . 2025;39(5). https://doi.org/10.1002/bmc.70026

19. Silué GNA. Évaluation de l'activité antipyrétique des feuilles de *Ceiba pentandra* L. Gaertn (Bombacaceae) et essais de formulation d'un phytomédicament [Pharmacy thesis]. Abidjan (Côte d'Ivoire): Université Félix Houphouët-Boigny ; 2019. 237 p.

20. Djadji ATL, Ke E, S AGA, Sl K, G ING, G KS. The Onset of Action of Aqueous Extracts of *Ceiba pentandra* (Malvaceae) and *Pseudocedrela kotschyi* (Meliaceae) Plants with Potential Antipyretic Activity on Young Rats and their Interactions with Antimalaria Drugs (Artemisinin-based Combination). J Clin Exp Pharmacol . 2018;8(6):6-12.

21. Saptarini NM, Deswati DA. The antipyretic activity of leaves extract of *Ceiba pentandra* better than Gossypium arboreum . J Appl Pharm Sci . 2015;5(7):118-21. https://doi.org/10.7324/JAPS.2015.50718

22. Silué ANG, Djadji LTA, Kouakou LS, Siransy-Kouakou GN. Preclinical research and development of a herbal antipyretic drug based on leaves of *Ceiba pentandra* (Malvaceae). Int J Basic Clin Pharmacol . 2020;9(12):1778. https://doi.org/10.18203/2319-2003.ijbcp20205113

23. Wang XM, Xu WJ, Xu LK, Song S, Xing XF, Luo JB. Antipyretic Effect of Herba Ephedrae-Ramulus Cinnamomi Herb Pair on Yeast-Induced Pyrexia Rats: A Metabolomics Study. Chin J Integr Med . 2018;24(9):676-82. https://doi.org/10.1007/s11655-017-2778-0

24. OCDE. Ligne directrice de l'OCDE pour les essais de produits chimiques 423 - Toxicité orale aiguë - méthodes par classe de toxicité aiguë . Paris: Organisation de Coopération et de Développement Économiques ; 2001. 14 p.

25. Pongprayoon U, Bohlin L, Soonthornsaratune P, Wasuwat S. Antiinflammatory activity of *Ipomoea pes-caprae* (L.) R. Br. Phytother Res . 1991;5(2):63-6. https://doi.org/10.1002/ptr.2650050205

26. Eijaz S, Mirza A, Khan M, Perveen A, Mansuri S, Nadir M, et al. In vitro anti-inflammatory and antifungal activity of stem and roots extracts of *Ipomoea pes-caprae* (Linn.) R. Br. Int J Biol Res . 2018;6(2):73-84.

27. Venkataraman ND, Atleeb WC, Prabhuc TP, Kannana R. Anti-inflammatory potential of ethanolic extracts from aerial parts of *Ipomoea pes-caprae* (L.) R.Br using cotton pellet induced granuloma model. J Appl Pharm Sci . 2013;3(7):61-3.

28. Meira M, da Silva EP, David JM, David JP. Review of the genus Ipomoea : traditional uses, chemistry and biological activities. Rev Bras Farmacogn . 2012;22(3):682-713. https://doi.org/10.1590/S0102-695X2012005000025

29. Nilam R, Jyoti P, Sumitra C. Pharmacognostic and phytochemical studies of ***baker's***

pes-caprae , an halophyte from Gujarat. J Pharmacogn Phytochem . 2018;7(1):11-8.

30. Manigaunha A, Ganesh N, Kharya MD. Morning glory: a new thirst in-search of de-novo therapeutic approach. Int J Phytomedicine . 2010;2(1):18-21.

31. Adesokan AA, Yakubu TM, Owoyele VB, et al. Effect of administration of aqueous and ethanolic extracts of Enantia chlorantha stem bark on brewer's yeast-induced pyresis in rats. Afr J Biochem Res . 2008;2(7):165-9.

32. Williamson EM. Synergy and other interactions in phytomedicines. Phytomedicine . 2001;8(5):401-9. https://doi.org/10.1078/0944-7113-00060

33. Donkor MN, Donkor AM, Mosobil R. Combination therapy: synergism among three plant extracts against selected pathogens. BMC Res Notes . 2023;16(1):83. https://doi.org/10.1186/s13104-023-06354-7

34. Zainal Z, Ong A, May CY, Chang SK, Rahim AA, Khaza'ai H. Acute and subchronic oral toxicity of oil palm puree in Sprague-Dawley rats. Int J Environ Res Public Health . 2020;17(10). https://doi.org/10.3390/ijerph17103404

35. Nirogi R, Goyal VK, Jana S, Pandey SK, Gothi A. What suits best for organ weight analysis: review of relationship between organ weight and body/brain weight for rodent toxicity studies. Int J Pharm Sci Res . 2014;5(4):1525-32.