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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)

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Abstract

Background: Several classical antipyretics are used to treat fever. But their harmful sides effects have led to the research of the others alternative based on medicine herbals. Rarely, studies are focused on the onset of action and assess the effects of Drugs Herbal interaction *in vivo* using experimental models. The main objective of this work is to assess potential antipyretic activities of two African plants (*Ceiba pentandra* and *Pseudocedrela kotschyi* concerning the onset of action and evaluate the effects of their association to the combination based on artemisinin (CTA).

Methods: Turpentine 2 ml/kg, yeast brewers 20%, boiled milk 1 ml/kg were used to induce fever in young rats. The crudes of the extract of *Ceiba pentandra* 200 mg/kg; 400 mg/kg and *Pseudocedrela kotschyi* 100 and 150 mg/kg were administered orally and the temperatures (°C) were taken each 10 minutes. The Drugs-Herbal medicine interactions were also assessed (Extracts of our plants plus CTA). GraphPad Prism software version 7 was used to analyse the data. The difference was considered significant when $P<0.05$.

Results: Aqueous extract of the *Ceiba pentandra* and *Pseudocedrela kotschyi* quickly reduce the fever by reducing the onset time of action (10-30 minutes). P-value<0.001 but our study has shown pharmacodynamics interaction between CTA and *Pseudocedrela*. There may have some interaction between CTA and the natural compounds contained in these medicine plants that reduce their efficacy.

Conclusion: This present study showed the onset action of our two plants is between 10-30 minutes. Their association with CTA reduce the efficacy of extracts aqueous of leaves of *Pseudocedrela kotschyi* 150 mg/kg but no *Ceiba pendantra* 400 mg. They may be used as an alternative to classical drugs as antipyretics especially in children. But others studies may be done to assess the pharmacokinetic pharmacodynamics interactions with association based on artemisinin.

Keywords: *Pseudocedrela kotschyi*; *Ceiba pentandra*; Antipyretic; Onset of action; Plants

Introduction

Fever or pyrexia is one of the most causes of hospitalisation in Africa due to infectious diseases, especially in children. Unfortunately, conventional antipyretic therapeutic (Non-Steroid Anti-inflammatory Drugs) are harmful, expensive and possess several sides effects (Haemorrhage, gastric ulcer, hepatic toxicity, renal failure) [1]. Moreover, Fever normally results from the auxiliary effect of contamination, tissue harm, and aggravation; unite dismissal, threat or other unhealthy states, so it is for the most part connected with disorderly conduct, for example, depression, anorexia, tiredness, sleepiness, failure to think and hyperalgesia [1]. In children, because of their physiological vulnerability fevers can cause dramatic situations ranging from convulsions to loss of consciousness and even death.

Traditional drugs and herbal medicinal products can be defined as dietary supplements containing medicinal herbs or the herbal medicines traditionally used in phytotherapy for treating or preventing diseases [2]. According to the World Health Organization (WHO), more than 80% of the African population use plants for their health [3]. It is necessary because of public health to valorise this medicine plants that used for many Africans.

Several Africans plants are widely used as comestible and medicinal plants, such as *Ceiba pentandra* (Malvaceae) [4]; There are described for the treatment of many diseases, e.g., antidiabetic [5], antimicrobial [6], hypolipemiants [7] and *Pseudocedrela kotschyi* (Meliaceae); antiparasitary [8-10] antidiabetic [11] and others pathologies [12]. But, also, *Ceiba pentandra* and *Pseudocedrela kotschyi* are used to treat fever [13-15].

However, all the studies that assess potential antipyretic of medicinal herbs were focused on the effect between one to 6 hours

generally in adult experimental models. Indeed, rapid delay of action may have contributed to the efficacy and quickly decrease the fewer particularly relieved temperature in children where high pyrexia my caused convulsion, seizure and tissues damage. Also, for the moral and ethical reasons, most of the time, studies in clinical and experimental are focused on adults and outcome parameters found are extrapolated to the young subjects. That cannot be always justified; because of young organs immaturities and their sensibility to drugs response. Pharmacokinetic parameters may be different between adults and young. Indeed, absorption is modified by age. Also, pharmacodynamics interactions have been less studied. However, the drugs can act by potentiation, antagonist, or synergy, i.e. the herbal medicines potentiate the pharmacological/toxicological action of synthetic drugs, or antagonistic, i.e. the herbal medicines reduce the efficacy of synthetic drugs further by complexations, enzymatic inhibitions [16]. So, as you all know absorption plays an important role in drug efficacy and treatment outcome.

Artemisinin-based combination (CAT) or especially Lumefantrine/Artemether is widely used, in association with an antipyretic drug in the treatment of malaria in African especially in children, that it is one of the most cause of death of children.

The main objective of this work is to perform an antipyretic potential activity of two plants based on onset of action on rat young weight under 100 grams and assess pharmacodynamics interaction between Artemisinin-based combination and our medicinal herbal.

Materials and Methods

Plant material

Our Leaves of *Ceiba pentandra* (Malvaceae) and *Pseudocedrela kotschyi* (Meliaceae) were collected from Pakouabo (Bouaflé, Côte d'Ivoire). The plants were identified and authenticated by National Floristic Center (NFC) of University of Felix Houphouet Boigny of Abidjan.

Chemical compounds and reagents

Cow milk was purchased locally shepherd, Artemisinin-based combination (Coartem® dispersible, Novartis Lumefantrin/Artemether); paracetamol (Doliprane 500 mg®) and yeast brewers (Arkopharma Laboratories) were by at the prived pharmacy. Turpentine bought from essential oils store.

Laboratory animals used

All experiments performed on the laboratory animals in this study followed the standard operating procedures. Hundred (100) Wistar rats (Rattus norgevicus) (<100 g) were used for the study of antipyretic activity. All the animals were bred in the laboratory of Pharmacology of UFR Pharmaceutical and Biological Sciences of Felix Houphouet-Boigny University. The rats were acclimated under standard conditions of temperature 24°C ± 1°C with 75% humidity and light (approximately 12/24 light-dark cycle). All the animals were fasted for 24 hours but allowed water ad libitum were used for the experiment.

Preparation of *Ceiba pentandra* and *Pseudocedrela kotschyi* leaves aqueous extracts

Leaves of *Ceiba pentandra* and *Pseudocedrela* were dried in a dark ventilated room for 10 days. These parts were ground to fine powder using Restsch GM 300™ grinder mill. Extraction was carried out by cold maceration of 100 g of fine powder with 1000 ml of distilled water for 24 hours. The macerate was successively filtered through the fabric, hydrophilic cotton, and finally Whatman paper. Subsequently, the filtrate was evaporated dried in a Memmert™ brand oven at 45°C for 3 days and the dark brown dried solids were stored in a refrigerator at 4°C for the pharmacological study.

Hypothermic effect

Before experimentation, rectal temperature of the rat was recorded by inserting a well-lubricated bulb of a thermometer in the rectum. Care was taken to insert it to the same depth each time (about 3 cm). Effect of *Ceiba pentandra* 400 mg/kg and *Pseudocedrela kotschyi* 150 mg/kg leaves aqueous extracts on the basal temperature of rats was assessed. The basal temperature was taken and extracts were given after, one-hour, rectal temperature was taken each hour until six.

Evaluation of antipyretic activity

Fever induced by essential oil of turpentine: Before fever induction, rats were weighed and their basal rectal temperature measured and recorded. The animal was fasted for 12 hours during the entire experimental period but was allowed access to water ad libitium. Steam distilled turpentine solution was used to induce fever. Rats were immediately administered subcutaneously turpentine 2 ml/kg in the dorsolateral region and the animal left for three hours [17]. After 3 hours, the T° was again taken and a rise in rectal temperature of Wistar albino rats by 0.5°C after one hour was termed pyretic and proceeded to be used in the assay.

Fever induced by cow milk boiled: Before fever induction, rats were weighed and their basal rectal temperature measured and recorded. Milk was collected from local cow had been boiled. When the temperature of the boiled milk equilibrates to room temperature then rats were injected boiled milk at the dose of 0.5 ml/kg body weight, to induce pyrexia. Induction of fever was taken about six hours [18]. 8 groups of 6 rats each homogeneous in temperature: Group 1: Aqueous extract of *Ceiba pentandra* 200 mg/kg; Group 2: Aqueous extract of *Ceiba pentandra* 400 mg/kg, Group 3: Aqueous extract of *Pseudocedrela kotschyi* 100 mg/kg group 4: Aqueous extract of *Pseudocedrela kotschyi* 150 mg/kg Group 6 control group received 0.9% NaCl. Group 7 received paracetamol 100 mg/kg. The rectal temperatures were then noted at 10 minutes (T10), 20 (T20), 30 (T30), 40(T40), 50 (T50), 60 (T60) using a digital thermometer TMP 812 RS ™ (Panlab) [15].

All the doses used were no toxic for the animal and literature data are shown that *Ceiba pentandra* is not toxic at the doses of 2 g/kg [19] and for *Pseudocedrela kotschyi* DL50 by oral route is 1750 g/kg [20].

We performed all experiments on the laboratory animals in this study followed the standard operating procedures.

Pharmacodynamics and drugs herbal interactions

To assess Drug-Herbal interactions, we used combination based on artemisinin (CTA) 5 mg/kg in distilled water orally in association with

our extracts. Others groups of animals were used in the same conditions using suspension of 20% brewer's yeast at 1 ml per 100 g body weight. Then, the rats fasted for food (free access to water). Seven (07) homogeneous groups of 6 rats each were made with the rats which showed an increase of at least 0.5°C in their rectal temperature. Homogeneity was obtained using the level of variation of hyperthermia.Group 8: *Ceiba pentandra* 400 mg/kg; Group 9: CTA 5 mg/kg; Group 9: *Ceiba pentandra*+CTA 5 mg/kg group 10: *Pseudocedrela kotschyi* 150 mg/kg. Group 11: *Pseudocedrela kotschyi* 150 mg/kg+CTA 5 mg/kg; Group 12: control group received 0.9% NaCl group received paracetamol 100 mg/kg. The rectal temperatures were then noted at 10 minutes (T10), 20 (T20), 30 (T30), 40 (T40), 50 (T50), 60 (T60) using a digital thermometer TMP 812 RS™ (Panlab) [15].

The research protocols were in accordance with the ethical rules and recommendation of the University of Felix Houphouet Boigny committee on the use and handling of laboratory animals. These principles are also in accordance with the National Research Council Guide for Care and Use of Laboratory Animals [21].

Statistical analysis

The rectal temperatures were recorded in GraphPad Prism software version 7 for statistical analysis. Descriptive statistics were expressed as the mean ± standard error of the mean. One-way Analysis of Variance (ANOVA) was used to determine the significant difference between the means of different treatment groups followed by Dunnett post hoc tests for pairwise comparison among the various treatment groups. The mean activity of the two extracts was compared using unpaired student t-test. The values of $p \leq 0.05$ were considered significant. The data were presented in tables (Tables 1-7) and graphs/ figures (Figures 1-6).

Results

Hypothermic activity

Ceiba pentandra 400 mg/kg and *Pseudocedrela kotschyi* 150 mg/kg had not any impact on the normal temperature (Table 1). Extracts seem to have no action on the basal temperature at the doses used (Figure 1).

Plants	Temperature (°C)	Time (Hours)						
		0	1	2	3	4	5	6
Ceiba pentandra 400 mg/kg	Mean ± SD	36.23 ± 0.51	36.17 ± 0.40	36.42 ± 0.28	36.38 ± 0.36	36.18 ± 0.46	36.5 ± 0.56	36.37 ± 0.34
Pseudocedrela kotschyi 150 mg/kg	Mean ± SD	36.23 ± 0.51	36.17 ± 0.44	36.42 ± 0.28	36.38 ± 0.36	36.18 ± 0.46	36.15 ± 0.56	36.37 ± 0.34

Table 1: Effect of two extracts on the basal temperature.

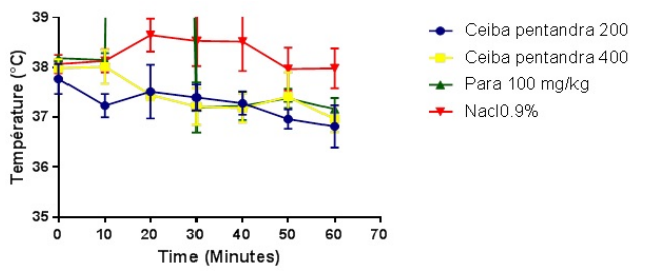

Figure 1: Onset action of Antipyretic activities of *Ceiba pentandra*.

Onset of action of potential antipyretic activities of *Ceiba pentandra* fever induced by turpentine (Table 2).

The antipyretic effect of our aqueous extracts has started between 20 and 30 minutes (Figure 2). So onset of action *Ceiba pentandra* comparatively to NaCl 0.9% at doses 200 mg and 400 mg are the same (Table 3).

	0	10	20	30	40	50	60
NaCl 0.9% *vs Ceiba pentandra* 200 mg/kg	*	****	ns	***	****	***	****
NaCl 0.9% *vs Ceiba pentandra* 400 mg/kg	ns	ns	ns	****	****	*	***
NaCl 0.9% *vs* Para 100 mg/kg	ns	ns	ns	****	****	*	**

Table 2: Onset of action of *Ceiba pentandra* comparatively to NaCl 0.9% at doses 200 mg and 400 mg. *P<0.05; **<0.01; ***<0.001; ns=no significance.

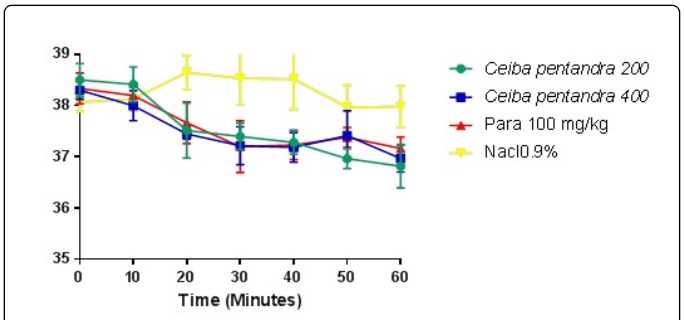

Figure 2: Onset action activities of potential antipyretic fever induced by boiled milk.

	0	10	20	30	40	50	60
NaCl 0.9% *vs Ceiba pentandra* 200 mg/kg	*	ns	***	***	****	***	***

NaCl 0.9% *vs Ceiba pentandra* 400 mg/kg	ns	ns	***	****	****	*	***
NaCl 0.9% *vs* Para 100 mg/kg	ns	ns	***	****	****	*	**

Table 3: Onset of action of *Ceiba Pentandra* comparatively to NaCl 0.9% at doses 200 mg and 400 mg. *P<0.05; **<0.01; ***<0.001; ns=no significance.

The antipyretic effect of our aqueous extracts has started between 10 and 20 minutes (Figure 3). So Onset of action of *Ceiba Pentandra* comparatively to NaCl 0.9% at doses 200 mg and 400 mg are the same (Table 4).

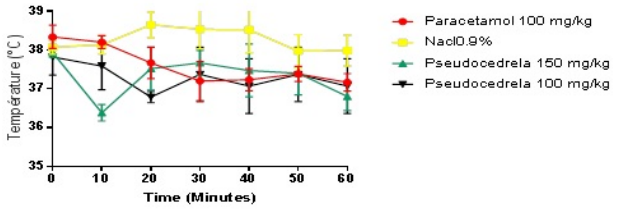

Figure 3: Onset of action potential antipyretic activities of aqueous extracts of *Pseudocedrela Kotschyi*.

Time (min)	0	10	20	30	40	50	60
NaCl 0.9% *vs* Paracetamol 100 mg/kg	ns	ns	***	***	**	ns	*
NaCl 0.9% *vs Pseudocedrela* 150 mg/kg	ns	***	***	*	*	ns	***
NaCl 0.9% *vs Pseudocedrela* 100 mg/kg	ns	*	****	**	**	ns	**

Table 4: Onset of action potential antipyretic activities of aqueous extracts of *Pseudocedrela Kotschyi*. *P<0.05; **<0.01; ***<0.001; ns=no significance.

Time to have antipyretic action start at 10 minutes for the leaves of aqueous extracts at 150 mg/kg better than paracetamol 100 mg/kg (Figure 4 & Table 5).

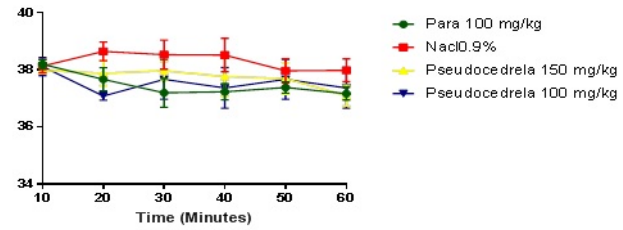

Figure 4: Onset of action of aqueous extracts of *Pseudocedrela kotschyi* fever induced by boiled milk.

Drug-drug interaction induction due to yeast brewers

Time to have antipyretic action start at 10-20 minutes for the leaves of aqueous extracts at 150 mg/kg fever induced by cow boiled milk (Figure 5 & Table 6).

	0	10	20	30	40	50	60
NaCl 0.9% *vs* Paracetamol 100 mg/kg	ns	ns	***	***	**	ns	*
NaCl 0.9% *vs Pseudocedrela* 150 mg/kg	ns	ns	**	ns	ns	ns	**
NaCl 0.9% *vs Pseudocedrela* 100 mg/kg	ns	ns	***	*	**	ns	ns

Table 5: Onset of action of aqueous extracts of *Pseudocedrela Kotschyi* fever induced by boiled milk. *P<0.05; **<0.01; ***<0.001; ns=no significance.

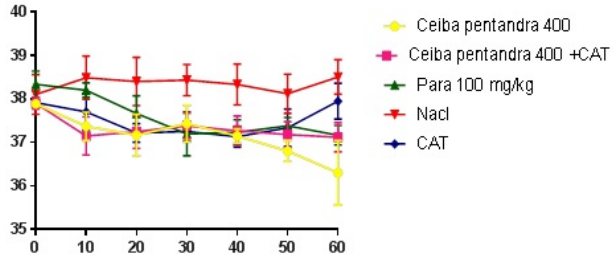

Figure 5: Interaction between Lumefantrine/Artemether 30/5 mg/kg and *Ceiba petendra* 400 mg/kg.

	0	10	20	30	40	50	60
Ceiba pentandra 400 *vs Ceiba pentandra* 400+CAT	ns	ns	ns	ns	ns	ns	*
Ceiba pentandra 400 *vs* Paracetamol 150 mg/kg	*	**	ns	ns	ns	*	*
Ceiba pentandra 400 *vs* NaCl	ns	***	***	***	***	***	***
Ceiba pentandra 400 *vs* CAT	ns	ns	ns	ns	ns	ns	***
Ceiba pentandra 400+CAT *vs* Paracetamol 150 mg/kg	ns	***	ns	ns	ns	ns	ns
Ceiba pentandra 400+CAT *vs* NaCl	ns	***	***	***	***	***	***
Ceiba pentandra 400+CAT *vs* CAT	ns	ns	ns	ns	ns	ns	*
Paracetamol 150 mg/kg *vs* NaCl	ns	ns	*	***	***	**	***
Paracetamol 150 mg/kg *vs* CAT	ns	ns	ns	ns	ns	ns	*
NaCl *vs* CAT	ns	*	***	***	***	**	ns

Table 6: *Ceiba pentandra* absorption. *P<0.05; **<0.01; ***<0.001; ns=no significance.

CAT does not affect *Ceiba pentandra* absorption. There is no difference between *Ceiba pentandra* 400 *vs Ceiba pentandra* 400+CAT. Also, *Ceiba pentandra* 400 *vs.* NaCl shows a significative difference in the fever. It seems that CAT does not affect *Ceiba pentandra* absorption (Figure 6 & Table 7).

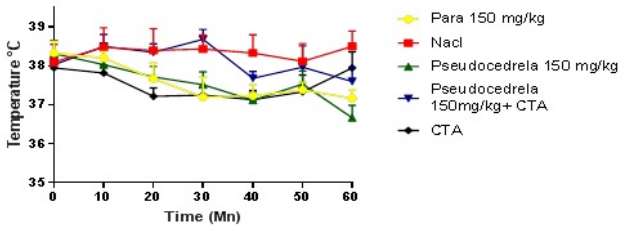

Figure 6: Interaction of Lumefantrine/Artemether 30/5 mg/kg with *Pseudocedrela* 150 mg/kg.

	0	10	20	30	40	50	60
Paracetamol 150 mg/kg *vs* NaCl	ns	ns	*	****	****	*	***
Paracetamol 150 mg/kg *vs* *Pseudocedrela* 150 mg/kg	ns	ns	ns	ns	ns	ns	ns
Paracetamol 150 mg/kg *vs* *Pseudocedrela* 150 mg/kg+CTA	ns	ns	*	****	ns	ns	ns
Paracetamol 150 mg/kg *vs* CTA	ns	ns	ns	ns	ns	ns	**
Nacl *vs* *Pseudocedrela* 150 mg/kg	ns	ns	*	**	****	ns	***
Nacl *vs* *Pseudocedrela* 150 mg/kg +CTA	ns	ns	ns	ns	**	ns	**
Nacl *vs* CTA	ns	*	****	****	****	*	ns
Pseudocedrela 150 mg/kg *vs* *Pseudocedrela* 150 mg/kg +CTA	ns	ns	*	****	*	ns	***
Pseudocedrela 150 mg/kg *vs* CTA	ns	ns	ns	ns	ns	ns	***
Pseudocedrela 150 mg/kg+CTA *vs* CTA	ns	*	****	****	*	ns	ns

Table 7: Interaction of Lumefantrine/Artemether 30/5 mg/kg with *Pseudocedrela* 150 mg/kg. (P<0.05) *P<0.05; **<0.01; ***<0.001; ns=no significance.

The comparison of NaCl *vs. Pseudocedrela kotschyi* 150 mg/kg +CTA doesn't show any different, by NaCl *vs. Pseudocedrela kotschyi* 150 mg/kg gives a difference starting at 10 minutes. So, CTA leads the inhibition of the absorption of *Pseudocedrela kotschyi.*

Discussion

The harmful effects on the various organs of the body of antipyretic drugs of modern medicine such as paracetamol, aspirin, ibuprofen etc., have led recently to search herbal remedies with potent antipyretic activity [22]. So, this present study should have shown the interest of medicine plants against fever. Otherwise, the results of previous toxicity study have revealed that these plants might be considered as a broad non-toxic one. Indeed, traditional used and toxicological studies have revealed the safety and security of these two plants (Comestible and natural remedies) [7,20,23].

First of all, our two extracts did not show any activity on the normal temperature of the rats. The extracts are not hypothermic (Table 1). These results confirm that these extracts act only on the endogenous mediators of fever. The aqueous extracts of these two plants could be used in the manufacture of drugs without the risk of lowering the temperature below normal values.

The antipyretic activity exhibited that both aqueous extracts of leaves possess a significant antipyretic effect in maintaining normal body temperature and reducing boiled milk induced and turpentine.

The Non-Steroidal Anti-inflammatory Drugs (NSAIDs) acts their antipyretic action mainly by inhibiting Prostaglandin E (PGE) production in the hypothalamus [24]. The hypothalamus works like a thermostat in many situations [25,26]. The febrile response involves innate immune system activation *via* Toll-like receptor 4 (TLR-4) leading to the production of pyrogenic cytokines such as; (IL)-1ß, IL-6, and tumour necrosis factor (TNF-α). These pyrogenic cytokines act on an area of the brain known as the Organum vasculum of the laminae terminalis (OVLT) and eventually leading to the release of PGE2 *via* activation of cyclo-oxygenase 2 enzyme (COX-2) [25,27].

The study was designed to evaluate the antipyretic activity of aqueous extract of *Ceiba pentandra* and *Pseudocedrela kotschyi* on hyperthermia induced by turpentine, milk boiled and yeast brewers on experimental models. Several exogenous pyrogens can be used to induce fever in laboratory animals (lipopolysaccharides (LPS), *E. coli,* amphetamines, sulphur, brewer's yeast, and turpentine. [17,28]. Turpentine is a clear flammable liquid with a pungent odour and bitter taste, refined from resin pine. It is a mixture of organic compounds especially terpenes. Subcutaneous administration of turpentine is a well-established model for sterile inflammation. Turpentine causes tissue damage and induces acute phase response as well as fever [29]. However, Fever induced by boiled milk and yeast Brewers is like fever leads to infectious diseases [30,31].

Total aqueous extract of *Pseudocedrela kotschyi* and *Ceiba pentandra* have reduced the elevated rectal temperature in rats and their effect are comparable to that of standard antipyretic drug paracetamol and more than NaCl 0.9% (Figures 2 and 3). The onsets of action of our two water extract between 10 to 30 minutes and are similar to the standard antipyretic drug. That reduction of rectal temperature of tested animals by both plants appears to be due to the presence of a single bioactive principle or mixture of compounds in them. Thus, herbal medicines contain a combination of pharmacologically active plant constituents that are claimed to work synergistically to produce an effect greater than the sum of the effects of the single constituents [32].

Pseudocedrela kotschyi and *Ceiba pentandra* demonstrated effective antipyretic activity as evident in the blocking of temperature elevation in the yeast, boiled milk, turpentine models. The antipyretic action of the extract may possibly be through inhibition of prostaglandin production, leading to suppression of elevated plasma levels [33]. The antipyretic activity observed can be attributed to the presence of steroids, tannins, alkaloids flavonoids, and polyphenols [32]. The present study, therefore, supports the claims of traditional medicine practitioners as an antipyretic remedy. However, to know the exact mechanism of action of our plants leaves extract further study with purified fractions/bioactive compounds are warranted. Those compounds act only on the endogen mediators of pyrexia.

Several factors influence the efficacy of drug therapy and it depends on related to a drug's pharmacokinetic and pharmacodynamic properties, which can be altered by differences in genetic polymorphisms, age, gender, circadian rhythms, intestinal bacteria, pathophysiological conditions, pharmaceutical dosage form, and

xenobiotic. The co-administration of traditional drugs and herbal medicinal products may cause unexpected interactions. Drugs-herbal interactions may affect the efficacy of the medicinal plants. We assessed co-administration of CTA and our two plants on fever (Figures 4 and 5). In our study, it seems that there is not physicochemical complexation of the aqueous extracts of the leaves of *Ceiba pentandra* at 400 mg/kg and Lumefantrine/Artemether (Figure 4). The association between CAT and *Ceiba pentandra* decreased the fever. So we can say that CAT doesn't affect *Ceiba pentandra* effect on fever. The bioactive composition of their constituents may interact with others drugs took similarly Herb-drug pharmacodynamics interactions involve changes in the pharmacological effects of the drug through additive, synergistic or antagonistic actions. Indeed, any single herbal preparation contains several components, many of them having unknown biological activities; therefore, a herbal medicine can potentially mimic, increase, or reduce the effects of co-administered drugs through simultaneous effects on the same drug targets. Toxicity may occur if the effect of the drug in combination with the herbal medicine is enhanced synergistically or by additive effects [34].

Drugs-herbal interactions may affect the efficacy of the medicinal plants in many cases. In this work Assessment of co-administration of CTA and Aqueous extracts of leaves *Pseudocedrela kotschyi* at 150 mg/kg on fever (Figure 5) has shown decreasing of activity of *Pseudocedrela kotschyi*. That means CTA may inhibit absorption of our plant in the conditions of the analysis by enhancing their onset of action. Because of his pharmacokinetic modification, *Pseudocedrela kotschyi* should not be associated with CAT. In the previous studies plants have reduced the efficacy of synthetic substances, indeed, Asphilia Africana, when used along with artemisinin, or chloroquine for malaria, has been reported to antagonize their effects [35]. Toxicity may occur if the effect of the drug in combination with the herbal medicine is enhanced synergistically or by additive effects. Also, many different side effects to herbs have been reported and recently reviewed including adverse events caused by herb-to-drug interactions [36]. Since all herbal medicines are mixtures of more than one active ingredient, such combinations of many substances obviously increase the likelihood of interactions taking place. Hence, theoretically, the likelihood of herb-to-drug interactions is higher than drug-to-drug interactions, if only because synthetic drugs usually contain single chemical entities.

Conclusion

In conclusion, *Ceiba pentandra* and *Pseudocedrela kotschyi* do not have effects on the basal temperature. At the doses of 400 mg and 150 mg extracts aqueous of the leaves respectively *Ceiba pentandra* and *Pseudocedrela kotschyi.* Their onset of action is between 10-30 minutes. Many others studies must be done to assess the pharmacokinetic interactions with association based on artemisinin.

Conflicts of Interest

The authors declare no conflicts of interest regarding this manuscript. The authors alone are responsible for the content and writing of the manuscript.

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