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Onset of action of aqueous extracts of *Ceiba Pentandra* and *Pseudocedrela Kotschyi* plants with potential antipyretic activity on young rats and their interactions with antimalarial drugs

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Abstract

Introduction: 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 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 P.* and *Pseudocedrela K.*) concerning the onset of action and evaluate the effects of their association to the combination based on artemisinin (CTA).

Materials and methods: Turpentine 2 mL/Kg, yeast Brewers 20%, Boiled Milk 1ml//kg were used to induce fever in the rats. The crudes of the extract of *Ceiba P.* 200mg/Kg; 400mg/Kg and *Pseudocedrela K.* 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 analyses the data. The difference was considered significative when $P<0.05$.

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

Conclusion: Our plants must be used as an alternative to the classical drugs as antipyretics. But others studies may be done to assess the pharmacokinetic pharmacodynamics interactions with association based on artemisinin.

Keywords: Acute toxicity, chemicals, herbal products, humans and safe dose.

1. 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 possessseveral sides effects (Heamorragea, gastric ulcer, hepatic toxicity, renal failure)[1]. Moreover, Fever normally results from auxiliary effect of contamination, tissue harm, 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 theirs 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 beacuase of public health to valorise this medicine plants that used for many africans people.

Several Africans plants are widely used as comestible and medicinal plants, such as *Ceiba Pentandra* (Malvaceae)[4]. There are described for the the treatment of many diseases, e.g., antidiabetic [5], antimicrobial [6], hypolipemiants [7] and *Pseudocedrela Kotschyi* (Meliaceae); antiparasitary[8,9,10] antidiabetic [11] and others pathologies [12]. But, also, *Ceiba P.* and *Pseudocedrela K.* are used to treat fever [13,14,15]. 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 [1].

Also, pharmacodynamics interactions have been less studied. However, the drugs can act by potentiating, 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 complications, enzymatic inhibitions [6]. So, as you all know absorption plays an important role in drug efficacy and treatment outcome.

Artemisinin based combination is widely used, in association with an antipyretic drug in the treatment of malaria in African specially in children, that it is one of most cause of death of children.

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

2. Materials and methods

2.1 Plant material collect

Leaves of *Ceiba Pentandra* (Malvaceae) and *Pseudocedrela Kotschyi* (Meliaceae) were collected from Pakouabo (Bouafle, Cote d'Ivoire). The plants were identified and authenticated by National Floristic Center (NFC) of university of Felix Houphouet Boingy of Abidjan.

2.2 Chemical compounds and reagents

Cow milk was purchasedlocally shepherd, Artemisinin based combination (Coartem ® dispersible, Norvartis); paracetamol (Doliprane 500 mg®) and yeast brewers (Arkopharma Laboratoires) were by at the prived pharmacy. Turpentine bought from essential oils store.

2.3 Animal

All experiments performed on the laboratory animals in this study followed the standard operation 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±1°C with 75% humidity and light (approximately 12/24 light-dark cycle). All the animals were fasted during 24 hours but allowed water *ad libitum* were used for the experiment.

2.3 Preparation of *Ceiba Pentandra* and *Pseudocedrela* 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 TM 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 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.

2.4 Effect of *Ceiba Pentandra* and *Pseudocedrela* leaves aqueous extracts on basal temperature of rats (Hypothermic effect)

Before experimentation rectal temperature of rat were 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).

Initial rectal temperatures of the rats were taken at the time T0h corresponding to the time after 16 hours of fasting. 4 groups of 6 rats each homogeneous in temperature: Group 1: Aqueous extract of *Ceiba P.* 400 mg/kg; Group 2: *Pseudocedrela. K.* 150 mg/Kg; Group 3: Control group received 0.09% NaCl. 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]

2.5 Evaluation of antipyretic activity

Before fever induction, rats were weighed and their basal rectal temperature measured and recorded. The animals were fasted for 12 hours during the entire experimental period, but were 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 raise in rectal temperature of Wistar albino rats by 0.8°C after one hour was termed pyretic and proceeded to be used in the assay.

Milk was collected from local cow had been boiled. When temperature of the boiled milk equilibrates to room temperature then rabbits 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]. 8groups of 6 rats each homogeneous in temperature: Group 1: Aqueous extract of *Ceiba P.* 200 mg/kg; Group 2: Aqueous extract of *Ceiba P.* 400 mg/kg; Group 3: Aqueous extract of *Pseudocedrela K.* 100 mg/Kg; Group 4: Aqueous extract of *Pseudocedrela K.* 150 mg/Kg; Group 6: Control group received 0.09% 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]

2.6 Pharmacodynamic and drugs herbal interactions

To assess Drug- Herbal interactions, we used combination based of artemisin (CTA) 5 mg/kg in distilled water orally in association to 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 were fasted for food (free access to water). Seven (07) homogenous groups of 6 rats each were made with the rats which showed an increase of at least 0.6°C in their rectal temperature. Homogeneity was obtained using the level of variation of hyperthermia. Group 8: *Ceiba P.* 400 mg/kg; Group 9: CTA 5mg/Kg; Group 9: *Ceiba P.* + CTA 5mg/Kg group 10: *Pseudocedrela K.* 150 mg/kg. Group 11: *Pseudocedrela K* 150mg/Kg. +CTA; Group 12: control group received 0.09% 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 to the National Research Council Guide for Care and Use of Laboratory Animals [19].

2.7 Statistical Analysis

The rectal temperatures were recorded in graphPad Prism software version for statistical analysis. Descriptive statistics was expressed as mean ± standard error of 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 pair wise 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 was presented in tables and graphs.

3. Results

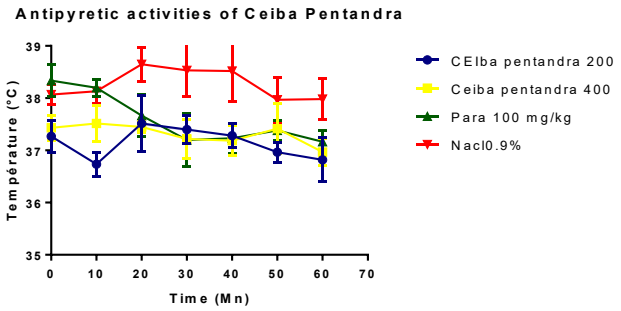
3.1 Hypothermic activity

Table 1: Hypothermic activity

Plants	Temp (°C)	Time (Minutes)						
Plants		**T0**	**10**	**20**	**30**	**40**	**50**	**60**
Ceiba P. 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 K. 150mg/Kg	Mean ±SD	36.23±0.51	36.17±0.44	36.42±0.28	36.38±0.36	36.18±0.46	36.5±0.56	36.37±0.34

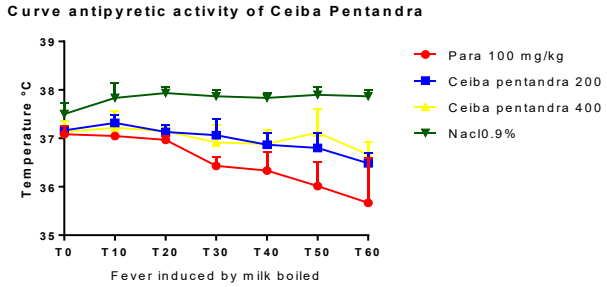
Ceiba P. 400 mg/Kg and *Pseudocedrela K.* 150 mg/Kg had not any impact on the normal temperature

Figure 1: Potential Antipyretic activities of *Ceiba Pentandra* Fever induced by turpentine



NaCl 0.9% vs. Ceiba pentandra 200;***P-value <0.001
NaCl0.9% vs. *Ceiba pentandra* 400; ***P-value <0.001

Figure 2: Potential Antipyretic activities of Ceiba Pentandra Fever induced by boiled milk



NaCl0.9% vs. Para 100 mg/kg: Test non parametric ANOVA P- Value <0.001 ***; NaCl 0.9% vs. *Ceiba pentandra* 200; Test non parametric ANOVA P- Value <0.001 ***; Nacl0.9% vs. *Ceiba pentandra* 400 Test non parametric ANOVA P- Value <0.001 ***

Figure 3: Fever induced by Turpentine M

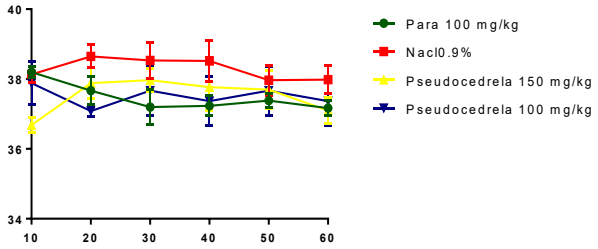


Figure 4: Fever induced by boiled milk

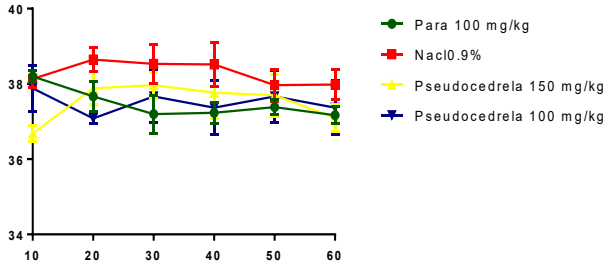
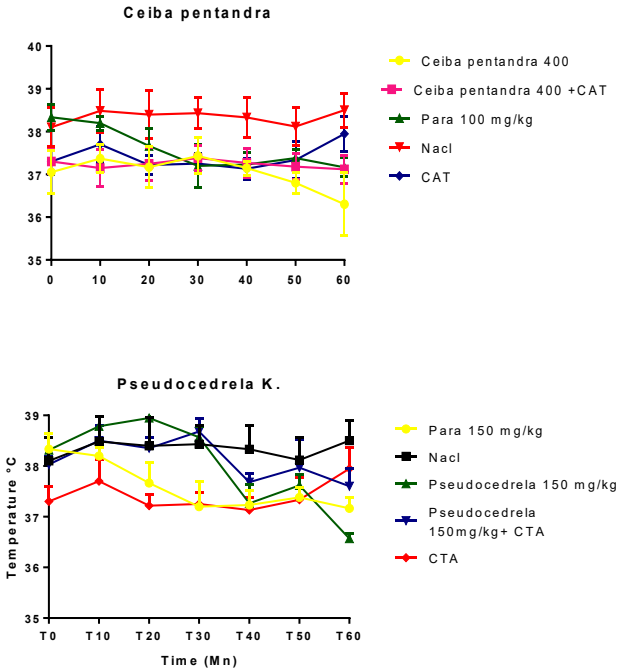


Figure 5: Dugs drugs interaction induction due to yeast brewers



Association of CTA and *Pseudocedrelaor Ceiba* decreased these absorptions and lead increasing of the fever without any significative difference. (P<0.05)

4. Discussions

The harmful effects on the various organs of the body of antipyretic drugs of modern medicine such as paracetamol, aspirin, ibuprofen… have led recently to search herbal remedies with potent antipyretic activity [20]. So, this present study should show 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)[7,21,22].

First of all, our two extracts did not show any activity on the normal temperature of the rats. The extracts are not hypothermic. 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 the 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 (NSAID) acts their antipyretic action mainly by inhibiting Prostaglandin E (PGE) production in the hypothalamus [23]. The hypothalamus works like a thermostat in many situations [24,25]. Febrile response involves innate immune system activation via Toll-like receptor 4 (TLR-4) leading to production of pyrogenic cytokines such as; (IL)-1β, IL-6, and tumor 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) [24,26].

The study was designed to evaluate the antipyretic activity of aqueous extract of *Ceiba P.* and *Pseudocedrela K.* 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 (lipopolysacharides (LPS), *E-coli*, amphetamines, sulphur, brewer's yeast and turpentine. [17,27]. Turpentine is a clear flammable liquid with 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 [28]. However, Fever induced by boiled milk and yeast Brewers is like fever leads to infectious diseases.[29,30]

Total aqueous extract of *Pseudocedrela* and *Ceiba P* have reduced the elevated rectal temperature in rats and their effect are comparable to that of standard antipyretic drug paracetamol. The onsets of action of our two water extract between T10 to T30 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 principles 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 [31].

Pseudocedrela K. 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 level [32]. The antipyretic activity observed can be attributed to the presence of steroids, tannins, alkaloids flavonoids, polyphenols [31]. 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 is depends on related to a drug's pharmacokinetic and pharmacodynamic properties, which can be alter by differences in genetic polymorphisms, age, gender, circadian rhythms, intestinal bacteria, pathophysiological conditions, pharmaceutical dosage form and xenobiotics. 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. Co-administration of CTA and our two plants don't affect the reduction of fever. The bioactive composition of their constituents may interact with others drugs took similarly. Pharmacodynamics interactions may be considered as antagonistic, i.e. the herbal medicines reduce the efficacy of synthetic drugs.

There is a general belief that herbal medicines are safe because they are natural. However, many different side effects to herbs have been reported and recently reviewed [33,34], including adverse events caused by herb-to-drug interactions [33]. 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.

5. Conclusion

Our plants must be used as an alternative to the classical drugs as antipyretics. But others studies may be done to assess the pharmacokinetic interactions with association based on artemisin.

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.

References

[1]. Sullivan JE, Farrar HC. Fever and Antipyretic Use in Children. *Pediatrics*. 2011;

[2]. Colalto C. Herbal interactions on absorption of drugs: Mechanisms of action and clinical risk assessment. *Pharmacol Res J*.

[3]. Oliveira FCS, Barros RFM, Moita Neto JM. Medicinal plants used in rural communities from Oeiras Municipality, in the semi-arid region of Piau{í} State (PI), Brazil. *Rev Bras Plantas Med.* 2010;

[4]. Friday ET, James O, Olusegun O, Gabriel A. Investigations on the nutritional and medicinal potentials of *Ceiba pentandra* leaf: a common vegetable in Nigeria. *Int J Plant Physiol Biochem*. 2011.

[5]. Dzeufiet PD, Ohandja DY TL al (. Antidiabetic effect of Ceiba pentandra extract on streptozo-tocin-induced non-insulin-dependent diabetic (NIDDM) rats. *African J Tradit.* 2007; 4(1): 47–54.

[6]. Doughari JALA. Antimicrobial activity of stem bark extracts of Ceiba pentandra. *Pharmacol online* 1. 2009;1333–40.

[7]. A. P, A. TP, S. P, K. S. Evaluation of ethanolic leaf extract of *Ceiba pentandra* for anti-obesity and hypolipidaemic activity in cafeteria diet (CD) treated wistar albino rats. *Int J Pharm Sci Res*. 2012.

[8]. Ahua KM, Ioset JR, Ioset KN, Diallo D, Mauël J, Hostettmann K. Antileishmanial activities associated with plants used in the Malian traditional medicine. *J Ethnopharmacol.* 2007.

[9]. Kone WM, Atindehou KK, Dossahoua T, Betschart B. Anthelmintic activity of medicinal plants used in northern Côte d'Ivoire against intestinal helminthiasis. *Pharmaceutical Biology*. 2005.

[10]. Sidjui LS, Nganso YOD, Toghueo RMK, Wakeu BNK, Dameue JT, Mkounga P, *et al*. Kostchyienones A and B, new antiplasmodial and cytotoxicity of limonoids from the roots of Pseudocedrela kotschyi (Schweinf.) Harms. *Zeitschrift fur Naturforsch - Sect C J Biosci.* 2018.

[11]. Bothon FT, Debiton E, Avlessi F, Forestier C, Teulade JC, Sohounhloue DK. *In vitro* biological effects of two anti-diabetic medicinal plants used in Benin as folk medicine. *BMC Complement Altern Med.* 2013.

[12]. Kassim OO, Copeland RL, Kenguele HM, Nekhai S, Ako-Nai KA, Kanaan YM. Antiproliferative activities of fagara xanthoxyloides and pseudocedrela kotschyi against prostate cancer cell lines. *Anticancer Res.* 2015.

[13]. 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.

[14]. Alagawadi Kallangouda R, Shah Amol S. Analgesic and antipyretic effects of Ceiba pentandra L. Seed extracts. *Int J Pharm Res.* 2012.

[15]. Essien GCAAD, Essiet GA, David-Oku E, Udoh JLA and FV. Evaluation of Antipyretic Potential of Pseudocedrela kotschyi Schweint. Harms (Meliaceae). *European J Med Plants*. 2013;3(1):105–13.

[16]. Thomford NE, Awortwe C, Dzobo K, Adu F, Chopera D, Wonkam A, *et al*. Inhibition of CYP2B6 by medicinal plant extracts: Implication for use of efavirenz and nevirapine based highly active anti-retroviral therapy (HAART) in resource-limited settings. *Molecules*. 2016.

[17]. Kuochung T, Haruko F, Yasuo Y YT. Effects of turpentine induced fever during the enamel formation of rat incisor. *Arch Oral Biol*. 2006;(51):464–70.

[18]. R Sankar Anand, V Subhadra Devi, B Arunprasath AS and CHA. Boiled milk induced pyrexia in rabbits-antipyretic activity *vernonia cinerea* roots. I*nt J Pharm an Pharm Res*. 2011; 2(1).

[19]. National Research Council (US) Committee. Guide for the Care and Use of Laboratory Animals, 8th Ed,. The National Academies Press, Washington, DC. 2011.

[20]. Hunter LJ, Wood DM, Dargan PI. The patterns of toxicity and management of acute nonsteroidal anti-inflammatory drug (NSAID) overdose. *Open Access Emergency Medicine.* 2011.

[21]. Sarkiyayi S, Ibrahim S, Abubakar MS. Toxicological studies of *Ceiba pentandra* Linn. *African J Biochem Res.* 2009;

[22]. Kabiru A, Muhammad DN, Bello MB, Akpojo AJ, Fei3 YM, Oricha BS, *et al*. A 28- Day Oral Toxicity Study of Pseudocedrela kotschyi Methanol Extract in Sprague-Dawley Rats. *European J Med Plants*. 2015;10(3): 1–11.

[23]. Aronoff DM NE. Antipyretic mechanism of action and clinical uses of in fever suppression. *Am J Med.* 2001; 111: 304–15.

[24]. Aronoff DM, Neilson EG. Antipyretics: Mechanisms of action and clinical use in fever suppression. American Journal of Medicine. 2001.

[25]. Boulant JA. Role of the Preoptic-Anterior Hypothalamus in Thermoregulation and Fever. *Clin Infect Dis*. 2000;

[26]. Dalal S ZD. Pathophysiology and management of fever. *J Support Oncol*. 2006; 4(1): 9–16.

[27]. Vasundra DP DP. Antipyretic Activity of Ethanol and Aqueous Extract of Root of Asparagus racemosus in Yeast Induced Pyrexia. *Asian J. J Pharm Clin Res* 6 190-119. 2013;6:190–119.

[28]. Wieslaw K, Mathew JK, Dariusz S, Carole C, Karin R *et al*. IL-6 and IL-1β in fever. Studies using cytokine-deficient (knockout) mice. *Annals of the New York Academy of Sciences*. 1998;(856):33–47.

[29]. Tarkang PA, Okalebo FA, Siminyu JD, Ngugi WN, Mwaura AM, Mugweru J, *et al*. Pharmacological evidence for the folk use of Nefang: Antipyretic, anti-inflammatory and antinociceptive activities of its constituent plants. *BMC Complement Altern Med*. 2015;

[30]. Effo KE, Kouakou-Siransy G, Irie NG, Sawadogo RW, Dally IL, Kamenan AB KL &Kablan B. Acute toxicity and antipyretic activities of a methanolic extract of Alchornea cordifolia leaves. *J Pharm Pharmacol.* 2013;4(7):1–6.

[31]. Ernst E, Pittler MH, Wider B BK. Oxford Handbook of Complementary Medicine. Oxford, Oxford University Press. 2008.

[32]. Ogbiti VM, Akindele AJ, Adeyemi OO. Analgesic, Anti-inflammatory, and Antipyretic Activities of Hydroethanolic Stem Bark Extract of Albizia glaberrima. *J Herbs, Spices Med Plants*. 2017;

[33]. Zhou SF, Zhou ZW, Li CG, Chen X, Yu X XC. Herington A: Identification of drugs that interact with herbs in drug development. *Drug Discov Today*. 2007; 12: 664–673.

[34]. Kennedy DA SD. Clinically based evidence of drug-herb interactions: a systematic review. *Expert Opin Drug Saf.* 2010;(9):79–124.