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Effect of Aqueous Leaf Extract of *Anogeissus leiocarpus* against Experimental Models of Pain and Pyrexia

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Abstract

This study was undertaken to investigate the anti-nociceptive and anti-pyretic activities of the aqueous leaf extract of *Anogeissus leiocarpus* (ALAE) in Wistar rats and mice. The anti-nociceptive activities of ALAE were studied using acetic acid- induced writhing and tail immersion models while antipyretic activities were examined using Dinitrophenol and Brewer's yeast-induced pyrexia in Wistar rats. Oral Median lethal dose (LD_{50}) of ALAE was also estimated to determine its safety. Twenty- four (24) rats/mice were randomized into 4 groups of 6 animals for each experiment. Groups 1 and 4 (controls) received 5 ml/kg of 0.9% normal saline and150 mg/kg of aspirin and 10 mg/kg of morphine (tail immersion study) respectively; while groups 2 and 3 received 200 and 400 mg/kg of ALAE respectively. ALAE at doses of 200 and 400 mg/kg significantly ($p<0.05$) reduced/ abolished the induced pain and pyrexia, in a manner comparable to the respective positive controls. The study clearly shown that the aqueous leaf extract of *Anogeissus leiocarpus* possess anti-nociceptive and anti- pyretic activities. The plant extract therefore could be used as an alternative or adjunct therapy in the management of pain and pyrexia.

Keywords: Pyrexia, Pain, *Anogeissus leiocarpus*, Experimental, Rats

1.0 Introduction

Pain is an unpleasant sensation associated with potential or actual tissue damage (Cole, 2002). Pain is not only a symptom used to diagnose several diseases and conditions but also has a protective function. The organism's ability to detect noxious stimuli and engage in appropriate protective behaviours against these stimuli is essential for its survival and wellbeing. Unrelieved pain may cause suffering and inability to perform daily activities hence imposing high health costs and economic losses to the victim and society (Ezeja *et al.*, 2011; Prystupa *et al.*, 2013).

Fever or pyrexia is a common medical symptom that involves increase in body temperature outside the normal range which is usually from 36.0°C to 37.5°C (97.0°F to 99.5°F). The elevated temperature creates an environment where infectious agents or damaged tissues cannot survive. Fever is caused or induced by substances called pyrogens such as microbial infections, trauma, drugs and chemicals. These pyrogens trigger the formation of cytokines like interleukins, tumor necrosis factor and interferon. These cytokines enhance the synthesis of prostaglandin E2 (PGE2) next to the pre-optic hypothalamus region hence elevating the body temperature through promoting heat generation mechanism and decreasing heat loss. Fever is usually accompanied by symptoms, such as sweating, chills and sensation of cold. It is exhibited in many illnesses for example; malaria, typhoid and arthritis (Kumar *et al.*, 2012; Anochie & Ifesinachi, 2013).

Non-steroidal anti-inflammatory drugs (NSAIDs) besides analgesics, antipyretic and anti-inflammatory drugs are used throughout the world to treat and manage inflammation, pain and fever. However most of these drugs are associated with side effects such as nausea, respiratory depression, gastrointestinal bleeding and addictive potential. Moreover, they are toxic to the brain cortex, hepatocytes, cardiac muscles and glomeruli. Therefore, there is need for new anti-inflammatory, analgesics and antipyretic drugs with improved efficacy and safety (Paschapur *et al.*, 2009; Deghrigue *et al.*, 2015; Almgeer *et al.*, 2015).

The use of plants for medicinal remedies is an integral part of the African cultural life, and this is unlikely to change in the years to come. Over the past decade, herbal medicine has become a topic of global importance, making an impact on both world health and international trade. Medicinal plants continue to play a central role in the healthcare system of large proportions of the world's population. This is particularly true in developing countries, where herbal medicine has a long and uninterrupted history of use. Continuous usage of herbal medicine by a large proportion of the population in developing countries is largely due to the high cost of Western pharmaceuticals and healthcare. In addition, medicinal plants posses numerous phyto-compounds that might become leads for the discovery of new drugs which may be used in the prevention and management of diseases (Lahlou, 2013). One such plant with various medicinal uses is *Anogeissus leiocarpus*.

Anogeissus leiocarpus is a fodder tree occurring in most of savanna areas from the driest region to the borders of forest zones (Ibrahim *et al.*, 2005). It belongs to the family combrataceae. The plant is very common in central and western Africa where it has a wide range of use (Burkill, 1985). I t is commonly called the African Birch. In Nigeria, it is known as Otra in Idoma, Marke (or kwankila) in Hausa, Atara in Ibo and Orin-odan in Yoruba (Agaie and Amali, 2007). It has numerous medicinal applications all over Africa (Adigun *et al.*, 2000). In traditional medicine its infusion and decoction is used as cough medicine, the powdered root is applied to wounds and ulcers while powdered bark is rubbed on gums to reduce toothache (Ibrahim *et al.*, 2005). The decoction is used as vermifuge and for fumigation while leprotic, laxative and antihelmintic properties of the leaf extract have also been reported in man and animals (Burkill, 1985). This study evaluated the effects of the aqueous leaf extract of the plant against experimental models of pain and pyrexia.

2.0 Materials and Methods

2.1 Materials

2.1.1 Chemicals and drugs

Acetic acid, 2, 4-Dinitrophenol, Brewers' yeast and Methyl-cellulose (Sigma Chemical Co. Ltd (USA), Clinical thermometer (Boots, Birmingham, England) and Aspirin (Healthseal® Pharmacy Ltd., Lokoja).

2.1.2 Animals

Healthy adult Wistar rats (150-200 g) and mice (18-22 g) were used for this study. They were kept in stainless steel cages under standard laboratory conditions. They were maintained on clean water and standard rodent feed.

2.2 Methods

2.2.1 Plant collection and identification

The leaves of *Anogeissus leiocarpus* were collected from a natural habitat in Agbeji area of Kogi State, Nigeria. The plants were identified at the Herbarium Unit of the Department of Biological Sciences, Federal University, Lokoja.

2.2.2 Preparation of extract

The leaves of *Anogeissus leiocarpus* were shade- dried for seven (7) days and pulverized using an electric blender. One thousand- five hundred (1500) gram of the pulverized leaves was soaked in distilled water separately for 72- hours. The resulting mixture was filtered using Whatmann filter paper (Size No1) and the extract was concentrated using freeze- dryer. The extract of *Anogeissus leiocarpus* shall henceforth be referred to as ALAE.

2.2.3 Acute toxicity study/ LD_{50} determination

The oral median lethal dose (LD50) of the extract was determined in rats according to the method of Lorke, (1983).

2.2.4 Acetic acid-induced writhing test:

Twenty- four (24) randomly selected adult albino mice of both sexes were used for this analgesic study. They were subjected to 24 h fast but had free access to water and later, were divided into 4 groups of 6 mice per cage. According to procedure described by Singh and Majumbar (1995) and Akuodor *et al*. (2011), control groups 1 and 4 received orally, 20 ml/kg of distilled water and 150 mg/kg of aspirin respectively; while group 2 and 3 received orally 200 and 400 mg/kg of ALAE respectively. Thirty minutes following above treatment, each mouse in all groups received intraperitoneally, 20 ml/kg of 0.7% acetic acid to induce pain sensation. Each mouse was then placed in a transparent observation chamber. Five minutes post acetic acid administration, the number of abdominal constrictions or writhing behavior for each mouse was noted, counted and recorded for a period of 30 min.

2.2.5 Tail immersion test:

The method described by Ramabadran *et al*. (1989) and Akuodor *et al*. (2015) was used for this study. Twenty-four randomly selected adult albino mice of both sexes were divided into 4 groups of 6 mice in each cage and were subjected to 24 h fast, but free access to water. Control groups 1 and 4 were treated orally with 5 ml/kg of distilled water and subcutaneously, with 10 mg/kg of morphine, respectively; While groups 2 and 3 received orally, 200 and 400 mg/kg ALAE respectively. Thirty minutes after above treatment, each mouse was placed in the restrainer cage, leaving the tail hung out and freely exposed to be dipped in a hot water bath that was maintained thermo-statistically at 51 ± 1°C. The duration of stay (latency) of the tail in the hot-water bath before the animal withdrew its tail out of the water was recorded. The latency was evaluated at 30, 60, 90 and 120 min (Akuodor *et al*., 2015)

2.2.6 Yeast-induced pyrexia:

The modified method by Mukherjee *et al*. (2002), Akuodor *et al*. (2011) and Essien *et al*. (2015) was used for this study. Twenty-four (24) Wistar rats were randomly selected and divided into 4 groups of 6 rats per cage. Clinical thermometer was used in measuring their initial basal rectal temperature. Thereafter, pyrexia was induced in rats by injecting subcutaneously 20 ml/kg of 15% brewer's yeast, China) suspended in 0.5% methylcellulose solution. After 24 h, rectal temperature was again measured and any rat(s) without elevated temperature above by 0.5°C was disregarded for the study. Thereafter, 200 and 300 mg/kg ALAE were administered orally to groups 3 and 4 respectively; while control groups 1and 4 received distilled water (5 ml/kg) and aspirin (150 mg/kg) respectively. Their rectal temperature was again recorded at 1h interval and for 6 h after drug administration.

2.2.7 4-Dinitrophenol (DNP)-induced pyrexia:

The modified method by Okokon and Nwafor (2010) and Essien *et al*. (2015) was adopted. After 24 hour-fast with free access to water, twenty-four (24) rats were divided into 4 groups of 6 rats per cage. Their basal rectal temperature was recorded before inducing pyrexia intraperitoneally, with 10 mg/kg of DNP. Thirty minutes post DNP administration, rectal temperature was measured to confirm the state of pyrexia and to disregard rats without temperature elevation above 0.5°C. Thereafter, 200 and 400 mg/kg ALAE were administered orally to groups 2 and 3 respectively; while control groups 1 and 4 received distilled water (5 ml/kg) and aspirin (150 mg/kg) respectively. Thereafter, the rectal temperature was measured and recorded at 1 h interval and for 6 h.

2.3 Statistical Analysis

Results were expressed as mean ± S.E.M. These data were analyzed using one-way ANOVA followed by Neuman-Keuls post hoc test and their differences between means of treated and control groups were considered significant at $p<0.05$.

3.0 Results

The results of acute toxicity studies showed no mortality or signs of toxicity up to a dose of 5000 mg/kg of aqueous leaf extract of *Anogeissus leiocarpus*. The oral LD_{50} of the extract was then taken to be > 5000 mg/kg.

Table 1: Observations from the Acute Toxicity Study of the Aqueous Leaf Extract of *Anogeissus leiocarpus* in Rats

Phase	Group	Treatment (mg/kg)	D/T	Observed Sign of Toxicity
I	1	ALAE (10)	0/3	-
	2	ALAE (100)	0/3	-
	3	ALAE(1000)	0/3	-
II	1	ALAE(1600)	0/1	-
	2	ALAE(2900)	0/1	-
	3	ALAE(5000)	0/1	-

D=death, T= No of animals treated

3.2 Acetic Acid-induced Writhing/Abdominal Constriction

Table 2 shows the effect of aqueous leaf extract of *Anogeissus leiocarpus* on acetic-acid- induced abdominal constriction in mice. The extract at both doses used, significantly ($p<0.05$) produced reduction of abdominal constrictions in mice. The 400 mg/kg dose of the extract produced an effect (84.5%) which is comparable to that of the standard drug used- aspirin (85.9%)

Table 2: Effect of the Administration of Aqueous Leaf Extract of *Anogeissus leiocarpus* (ALAE) on Acetic acid-induced Writhing in Mice

Treatment	Abdominal Constrictions	% Inhibition
Control (5ml/kg NS)	30.31 ± 0.77	0.00
ALAE (200 mg/kg)	6.48± 0.43*	78.6*
ALAE (400 mg/kg)	4.71 ± 0.58*	84.5*
Aspirin (20 mg/kg)	4.26 ± 0.62*	85.9*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at $p<0.05$

3.3 Tail Immersion

The aqueous leaf extract of *Anogeissus leiocarpus* at 200 and 400 mg/kg significantly ($p<0.05$) protected the animals from the heat stimuli of the hot-bath. The dose of 400 mg/kg of the extract produced an effect that is comparable to that of 10 mg/kg of morphine; while mice receiving distilled water had no protection at all (**Table 3**).

Table 3: Effect of the Administration of Aqueous Leaf Extract of *Anogeissus leiocarpus* (ALAE) on Mouse-tail Immersion in 51 ± 1°C hot bath

Treatment/Duration of stay	0 min	30 min	60min	90 min	120 min
Control (5ml/kg NS)	6.24 ± 0.21	6.73 ± 0.23	6.91 ± 0.15	6.67 ± 0.11	6.55 ± 0.28
ALAE (200 mg/kg)	6.33 ± 0.13	6.64 ± 0.44	10.47 ± 0.72*	12.13 ± 0.56*	13.91 ± 0.31*
ALAE (400 mg/kg)	5.90 ± 0.28	6.99 ± 0.32	17.38 ± 0.81*	20.23 ± 0.77*	20.57 ± 0.75*
Morphine (10 mg/kg)	6.17 ± 0.17	7.06 ± 0.18	18.12 ± 0.69*	20.48 ± 0.61*	21.43 ± 0.45*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at $p<0.05$

3.4 Brewer's Yeast- induced Pyrexia

Table 4 shows the effect of the administeration of aqueous leaf extract of *Anogeissus leiocarpus* on brewer's yeast- induced pyrexia in rats. The extract at 200 and 400 mg/kg significantly ($p<0.05$) suppressed the pyrexia induced by brewer's yeast. Both doses of the extract administered produced reduction in temperature after 1hr and this was sustained up to 6hr. The anti-pyretic activity of the extract was comparable to that of the standard drug- aspirin.

Table 4: Effect of the Administration of Aqueous Leaf Extract of *Anogeissus leiocarpus* (ALAE) on Brewer's yeast- induced pyrexia in Rats

Treatment	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Control (5ml/kg NS)	37.39±0.04	37.57±0.13	37.61±0.08	37.88±0.14	37.96±0.09	37.51±0.13	37.88±0.12
ALAE (200 mg/kg)	37.43±0.05	36.48±0.08*	36.59±0.06*	36.69±0.09*	36.57±0.11*	36.56±0.06*	35.34±0.09*
ALAE (400 mg/kg)	37.47±0.05	36.51±0.07*	36.61±0.01*	36.56±0.05*	36.81±0.08*	35.48±0.08*	35.57±0.10*
Aspirin (150 mg/kg)	37.51±0.04	36.50±0.05*	36.43±0.06*	36.38±0.08*	36.45±0.11*	35.67±0.34*	35.48±0.08*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at $p<0.05$

3.5 Dinitrophenol- induced Pyrexia

The aqueous leaf extract of *Anogeissus leiocarpus* at 200 and 400 mg/kg significantly ($p<0.05$) reduced DNP-induced pyrexia (**Table 5**). Similarly, both doses of the extract administered produced reduction in temperature after 1hr and this was sustained up to 6hr. The anti-pyretic activity of the extract was comparable to that of the standard drug- aspirin.

Table 5: Effect of the Administration of Aqueous Leaf Extract of *Anogeissus leiocarpus* (ALAE) on Dinitrophenol- induced Pyrexia in Rats

Treatment	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Control (5ml/kg NS)	37.55±0.06	37.61±0.09	37.42±0.08	37.43±0.03	37.76±0.04	37.85±0.09	37.70±0.05
ALAE (200 mg/kg)	37.61±0.08	36.34±0.07*	36.43±0.10*	36.89±0.09*	36.56±0.11*	35.71±0.04*	35.49±0.04*
ALAE (400 mg/kg)	37.42±0.04	36.23±0.01*	35.58±0.05*	35.26±0.08*	35.77±0.09*	35.82±0.11*	35.91±0.08*
Aspirin (150 mg/kg)	37.73±0.01	35.66±0.02*	35.61±0.06*	35.45±0.11*	35.45±0.10*	35.60±0.08*	35.55±0.11*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at $p<0.05$

4.0 Discussion

The results of acute toxicity studies showed no mortality or signs of toxicity up to a dose of 5000 mg/kg of aqueous leaf extract of *Anogeissus leiocarpus*. The oral LD_{50} of the extract was then taken to be > 5000 mg/kg. Therefore, the plant extract can be said to be free of toxic effects when consumed acutely. This acute safety profile of the plant is very important as many conventional drugs available for the management of pain and fever are associated with a host of side effects.

The data presented here suggests that the leaf extract of *Anogeissus leiocarpus* possesses anti-nociceptive and antipyretic activities. The extract at the doses tested was shown to possess anti-nociceptive activity evident in both the nociceptive models, signifying it possesses both central and peripherally mediated activities. The abdominal constriction response induced by acetic acid is a sensitive procedure to evaluate peripherally acting analgesics (Gene *et al.*, 1998). In general, acetic acid causes pain by liberating endogenous substances such as serotonin, histamine,

prostaglandins (PGs), bradykinins and substance P which stimulate nerve endings. Local peritoneal receptors are postulated to be involved in the abdominal constrictions response (Bentley *et al.*, 1983). The method has also been associated with prostanoids in general, that is, increased levels of PGE2 and PGF2 in peritoneal fluids (Dredt *et al.*, 1980), as well as lipoxygenase products (Insel, 1996). The significant reduction in acetic acid-induced writhes by the leaf extract of *Anogeissus leiocarpus* suggests that the analgesic effect may be peripherally mediated via the inhibition of synthesis and release of PGs (Koster *et al.*, 1959) and other endogenous substances. Tail immersion test further proved that the leaf extract of *Anogeissus leiocarpus* possesses potent analgesic action by significantly protecting mice from heat stimuli from the hot-bath. Morphine acts by inhibiting central nociceptive neurons (Laurence and Bennett, 1994) and nociceptive spinal reflexes, thereby, blocking the transmission of nociceptive impulses through the dorsal horn (Fields and Basbaum, 1994; Oluwatoyin *et al*., 2008). This effect is similar to that produced by Morphine, thereby, suggesting that the extract could possess similar central mechanism of action.

The aqueous leaf extract of *Anogeissus leiocarpus* also exhibited significant antipyretic activity against induced pyrexia in the two models-Brewer's yeast and 4-Dinitrophenol). Pyrexia begins whenever exogenous or/and endogenous stimuli which may include pyrogens are exposed to host cells-monocytes and macrophages (Arai *et al*., 1990). Formation of cascade of other pyrogenic cytokines like interleukin-1, TNF-α, interleukin-6 etc. follows. As a result of an interaction of cytokines and their receptors in the preoptic region of the anterior hypothalamus, phospholipase A is activated to catalyze arachidonate (substrate for COX), leading to synthesis of prostaglandins, that could further trigger the temperature to be elevated (Dinarello, 1997; Vane and O'Grady, 1993 The regulation of body temperature requires a subtle equilibrium between the production and loss of heat. As the temperature regulating structure is administrated by a nervous feedback mechanism, whenever the body temperature becomes very high, it dilates the blood vessels and increase sweating to reduce the temperature; but when the body temperature becomes very low, hypothalamus protect the internal temperature by 'vasoconstriction'. Under the influence of fever, this set point is elevated and a drug like paracetamol does not influence body temperature when it is elevated by factors such as exercise or an increase in ambient temperature22. Drugs or agents that would inhibit activity on prostaglandin biosynthesis possess antipyretic effect. The NSAIDs, such as aspirin and others exhibit their suppression of fever mainly by inhibiting Prostaglandin E (PGE) synthesis in the hypothalamus (Rang *et al*., 1999). Hence, aqueous leaf extract of *Anogeissus leiocarpus* showing high efficacy similar to aspirin in inhibiting the elevated temperature in the yeast and Dinitrophenol-induced fever models suggests similar possible mechanism of action.

5.0 Conclusion

This study has clearly shown that the aqueous leaf extract of *Anogeissus leiocarpus* significantly reduced pain and pyrexia in rats used in all the experimental models. The plant extract therefore could be used as an alternative or adjunct therapy in the management of pain and pyrexia.

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