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Anti-nociceptive Potential of Ethanol Extract of *Terminalia macroptera* Guill&Perr (Combretaceae) Stem Bark in Mice

S. A. ATUNWA[*1 A-F], M. O. AMALI[1D-F], S. O. LAWAL[1B-D,F], S. O. USMAN,[2C,E,F]; A.I. OLAPADE[1B,F]

Department of Pharmacology and Toxicology, [2]Department of Pharmacognosy and Drug Development, Faculty of Pharmaceutical Sciences, University of Ilorin, P.M.B. 1515, Ilorin, 240213, Kwara State, Nigeria

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: *Terminalia macroptera* Guill. &Perr. (Combretaceae) is a flowering plant with several ethno-medicinal claims. However, the dearth of information on its analgesic property has necessitated this study.

Objectives: to evaluate the anti-nociceptive potential of ethanol extract of *Terminalia macroptera* stem bark (TMSB) in mice.

Materials and Methods: Male and female mice of weight range 22 – 25g were randomly allotted into seven groups (n= 5) and treated as follows: Group I received 0.5 mL distilled water orally (negative control), Groups II-V were orally administered ethanol extract of *T. macroptera* stem bark (TMSB) at 50, 100, 200, and 400 mg/kg respectively while groups VI-VII received piroxicam 10 mg/kg and pentazocine 2 mg/kg intraperitoneally respectively as standards. The same treatment pattern was adopted for both pain models: tail immersion and acetic acid-induced writhing assays. Data were expressed as mean ± standard error of mean (SEM) using two-way analysis of variance (ANOVA) followed by Tukey's and Bonferroni's multiple comparisons tests with $p < 0.05$ taken as significance.

Results: The ethanolic extract of *Terminalia macroptera* stem bark showed significant dose-dependent anti-nociceptive activity at 100 and 400 mg/kg (2.95±0.41 and 2.9±0.31 respectively) 60 min post-treatment compared to the negative control group in the tail immersion test. Significant inhibition of nociception (0.20±0.20) was obtained at 400 mg/kg compared to the negative control group in the acetic acid-induced writhing test.

Conclusions: The ethanol extract of *Terminalia macroptera* stem bark exhibited dose-dependent anti-nociceptive potential in both tail immersion and acetic acid-induced writhing assays in mice.

Keywords: *Terminalia macroptera*; Combretaceae; Anti-nociceptive potential; Tail immersion; Acetic acid-induced writhing assay

INTRODUCTION

The use of medicinal plants and plant products to prevent, diagnose, manage, treat and cure a myriad of ailments (Nwabuise, 2002) especially those associated with pain is well known throughout history (Almeida *et al*., 2008). In fact, medicinal plants are the singular most important component of many medicinal preparations as over 60% of medicines (both crude and refined) are obtained from plant sources either directly or otherwise (Amin *et al*., 2004; Kinghorn and Balunas, 2005; Aiello *et al*., 2018). Plant-derived substances have, and will certainly continue to have, a relevant place in the process of drug discovery (Suba *et al*., 2005), particularly in the development of new analgesic drugs (Elisabetsky *et al*., 1995 and Wirth *et al*., 2005). Thus, plants still remain the novel source of structurally important compounds that could lead to the development of innovative drugs, thereby,

reducing the present challenges of huge cost and devastating adverse drug reactions associated with orthodox medicines (Atta and Alkofahi, 1998).

Terminalia macroptera Guill & Perr (Combretaceae) is a flowering plant most common to West African, some parts of Sudan (Akpovona *et al*., 2015), and Nigeria (Sultan *et al*., 2013 and Pham *et al*., 2014). It is widespread in deciduous open woodland and bushy grassland up to 1400 m altitude and thrives well by the tropical climate of Sub-Saharan Africa (Kaey *et al*., 1994). It often occurs near rivers on poorly drained clay soils, however, could also be found on black cotton soil, rocky slopes and termite mounds. The thick, corky bark makes the tree quite fire-resistant. It is locally called "Kwandari" and "Orin idi odan" by the Hausas and Yorubas respectively (Ibrahim, 2005). Ethnomedicinally, ***T. macroptera*** is used in combination with *Anogeissus leiocarpa* for colouring cotton fabric yellow or ochre and then used for treatment of newly circumcised children due to its putative antimicrobial effect (Jansen and Cardon, 2005). The roots of the plant are regarded as an efficient anti-bacterial (Traore *et al*., 2015a) and as antimicrobial remedy which is sold in markets in Guinea-Bissau (Silva *et al*., 1997). In Burkina Faso, Guinea, and Mali, the plant is employed against malaria (Sanon *et al*., 2003; Traore *et al*., 2013; Pham *et al*., 2011; Haidara *et al*., 2018). The bark is reported to be used against gonorrhoea (Silva *et al*., 2002 and Traore *et al*., 2015b), diarrhoea and dysentery in Nigeria (Gill, 1992), inflammation (Usman *et al*., 2017). A decoction of the leaves is indicated in the management of obesity, and treatment of hepatitis, ringworm and skin diseases (Pham *et al*., 2014). The root extract was reported to be useful in treating gastritis and ulcer caused by *Helicobacter pylori* (Silva *et al*., 2012), colic and hypertension, fever, lepra and tuberculosis (Arbonnier, 2004 and Malterud *et al*., 2011), anti-HIV (Dwevedi *et al*., 2016).

In spite of the progress that has taken place in recent years in the development of pain therapy, the medical community still urgently needs effective and potent analgesics (Musa *et al*., 2008). Many patients with intense and unrelenting pain, especially chronic pain such as those resulting from cancer, neuropathies or trauma, have to depend on morphine, despite its well-known side effects (Atunwa *et al*., 2017). At the same time, non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) which are indicated in acute pain management are bedevilled with serious undesirable effects (Cazacu *et al*., 2013; Lawal, 2013 and Olaleye 2013)). This has renewed the interest of pharmaceutical industry in higher plant-derived secondary metabolites as part of the search for new clinically useful drugs. Despite, most research activities into natural products are still limited to the inventory of folkloric information and utilization of various plants and trees. Therefore, evaluating the ethnomedicinal claims is critically and timely necessitated. More so, the result of an ethnobotanical survey that was conducted among some traditional medicinal practitioners and local inhabitants recorded the efficacy of the use of *Terminalia macroptera* in pain management (Atunwa *et al*., 2019). However, the dearth of scientific information on the analgesic property of *Terminalia macroptera* Guill & Perr (Combretaceae) thus necessitated this study. The objective of this present study was therefore to investigate the antinociceptive potential of ethanol extract of *Terminalia macroptera* stem bark (TMSB) on tail immersion and acetic acid-induced writhing assays in mice.

Figure 1: Stem Bark of *Terminalia macroptera* Guill &Perr (Combretaceae)

METHODOLOGY

Collection and identification of plant material

The stem barks of *Terminalia macroptera* were collected, identified and authenticated as reported by Usman *et al*., 2017. A voucher specimen with number: UILH/001/1230 was thereafter deposited at the Herbarium Unit of the Department of Plant Biology, University of Ilorin, Ilorin, Nigeria.

Preparation and extraction of plant materials

The preparation and ethanol extraction of stem bark of *Terminalia macroptera* was as reported by Usman *et al*., 2017. The extract (dry powder) was thereafter stored in a clean, dry, enclosed container and kept at a room temperature until use.

Experimental animals

Male and female mice of weights 22 – 25g were obtained from the animal house of the Department of Biochemistry, University of Ilorin, Ilorin. They were transferred to the animal holding of the Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Ilorin, Ilorin and kept for a week to get acclimatized before the experimental procedures. They were fed with standard diet, provided water *ad libitum* and maintained at room temperature under natural 12 h daylight/night conditions. The principles of responsible laboratory animal care, guidelines and procedures were followed accordingly in this study (NIH, 1985).

Drugs and reagents

Normal saline solution, acetic acid solution (100 %^{v}/v), distilled water, piroxicam and pentazocine injection were used in this study.

Experimental procedures

Tail immersion assay

The central analgesic effect of *T. macroptera* stem bark (TMSB) was assessed using tail immersion assay (Akanmu *et al.*, 2011). Thirty-five mice were randomly grouped into seven clusters (*n*= 5) and treated as follows: Each mouse in Group I was administered 0.5 mL distilled water orally (negative control). Groups II-V were orally treated respectively with 50, 100, 200, and 400 mg/kg ethanol extract of *T. macroptera* stem bark (TMSB). Groups VI-VII were administered piroxicam 10 mg/kg and pentazocine 2 mg/kg intraperitoneally as positive controls. After 30 minutes of administrations of either the controls or plant extracts, each mouse was restricted in a suitable container with the lower two-third of its tail (distal portion) extending out. Then, about 2-3 cm in length of its tail from the tip was marked and immersed in a beaker containing hot water (50 ± 1 ºC) and observed for the pain threshold (reaction time) to the thermal stimulus. The duration of placing tail in water until mouse withdraws or recoils its tail from the hot water was measured (reaction time) and considered as acute pain threshold. The initial scores were taken immediately before administration of the reference drugs and different doses of the extract. Mice with reaction times of not more than 4 seconds were selected for the assay. Then, reaction times was measured at 30, 60, 90, 120, 150, and 180 minutes (T_0, T_{30}, … and T_{180}) (Ogbeche *et al*., 2003). The cut-off time was set as 12 seconds in order to avoid tissue damage in mice (Almeida *et al*., 2008)

$$(\%)\ \text{MPE} = \frac{\text{Post-treatment Latency - Pre-treatment Latency X 100}}{\text{Cut-off Time - Pre-treatment Latency}}$$

Acetic acid-induced writhing for peripheral analgesic assay

The peripheral analgesic activity of the samples was evaluated in mice using acetic acid-induced writhing assay (Rahman *et al*., 2014). Another set of thirty-five mice were randomly allotted into seven groups (n = 5) and treated similar to the tail immersion procedure: Group I received 0.5 mL distilled water orally (negative control), while Groups II-V were orally administered ethanol extract of *T. macroptera* stem bark (TMSB) at 50, 100, 200, and 400 mg/kg respectively. Then, Groups VI-VII received piroxicam 10 mg/kg and pentazocine 2 mg/kg intraperitoneally respectively as positive controls.

After 30 minutes of administration of the control (oral), standards (intraperitoneal) and the extracts of *T. macroptera* stem bark (oral), 0.3 ml of 0.7 %^{v}/$_{v}$ acetic acid solution was injected into each of the test mice intraperitoneally (Rahman *et al*., 2014). Then, the animals were placed on an observation table and the number of abdominal contractions (writhing response) that occurred within the next 30 minutes following active acetic acid injection was counted and recorded over 5 minutes intervals. The acetic acid administered intraperitoneally into the mice produces pain which causes successive writhing thereby analgesic agent administered earlier is expected to reduce the writhing (Le Bars *et al*., 2001). The response was thus observed as contractions of abdominal muscles followed by opening of the back feet or stretching of the whole body in the animal. A significant reduction in the number of acetic-acid induced abdominal contractions of the treated mice, compared to the contractions in the untreated control mice was taken as an indication of analgesic activity (Ishola *et al*., 2016).

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM) using two-way analysis of variance (ANOVA) followed by Tukey's and Bonferroni's multiple comparisons tests with $p < 0.05$ taken as significance.

$$\text{Inhibition (\%)} = \frac{\text{Number of writhes}_{(\text{control})} - \text{Number of writhes}_{(\text{treatment})} \text{ X } 100}{\text{Number of writhes (control)}}$$

RESULTS AND DISCUSSION

Tail immersion assay

In the tail immersion test, ethanolic extract of *T. macroptera* showed significant inhibition of nociception at 100 mg/kg (2.95±0.41) and 400 mg/kg (2.9±0.31) 60 minutes post-treatment whereas allodynic effect was observed at 200 mg/kg (2.20±0.12) 150 minutes post-treatment as shown in Table 1.

Table 1: Anti-nociceptive Activity of Ethanolic Extract of Terminalia macroptera Using Tail immersion test

	LATENCY (REACTION) TIMES (minutes)						
GROUP	**0**	**30**	**60**	**90**	**120**	**150**	**180**
A	1.15±0.11	1.66±0.30	1.63±0.21	2.64±0.26	2.44±0.16	2.53±0.31	1.91±0.15
B	1.74±0.33	2.87±0.60	2.56±0.45	3.17±0.42	3.2±0.38	2.70±0.33	2.13±0.31
C	1.79±0.46	1.89±0.42	2.95±0.41*	2.94±0.34	2.72±0.09	2.74±0.17	2.15±0.10
D	1.68±0.35	1.92±0.24	2.19±0.17	3.10±0.41	2.67±0.32	2.20±0.12*	2.04±0.12
E	1.44±0.20	2.22±0.26	2.9±0.31*	3.15±0.16	3.39±0.11	2.74±0.49	2.51±0.14
F	1.42±0.21	2.03±0.22	2.97±0.26*	2.21±0.24	2.33±0.21	2.65±0.27	2.63±0.21
G	0.95±0.12	2.79±0.10	2.91±0.30*	3.17±0.24	3.19±0.20	3.73±0.82	2.95±0.15

** p < 0.05 vs negative control (distilled water 10 mL/kg) (Tukey's multiple comparison)*

Legend:
***A** = Distilled water (10 mL/kg), **B** = T. macroptera stem bark ethanol extract (50 mg/kg)*
***C** = T. macroptera stem bark ethanol extract (100 mg/kg), **D** = T. macroptera stem bark ethanol extract (200 mg/kg),*
***E**= T. macroptera stem bark ethanol extract (400 mg/kg), **F**= Piroxicam (10 mg/kg), **G** = Pentazocine (2 mg/kg)*

Acetic acid-induced writhing assay

The outcome of experimental investigation in the acetic acid-induced writhing test showed inhibition of nociception at 50 mg/kg of ethanolic extract of *T. macroptera* stem bark (TMSB) after 10 - 15 minutes (0.00±0.00) following post-induction with acetic acid intra-peritoneally. Similarly, 400 mg/kg of ethanolic extract of *T. macroptera* stem bark after 10 - 15 minutes (0.20±0.20) and 15 - 20 minutes (0.60±0.40) post-induction of intraperitoneal administration of acetic acid respectively as shown in Table 2.

Table 2: Anti-nociceptive Activity of Ethanolic Extract of Terminalia macroptera Using Acetic acid-induced Writhing Test

	DURATION OF WRITHES (minutes)					
Groups	**0-5**	**5-10**	**10-15**	**15-20**	**20-25**	**25-30**
A	3.00±0.89	2.60±1.77	3.80±2.07	4.60±0.60	3.20±1.16	3.20±1.02
B	1.40±0.60	0.60±0.40	2.00±0.95	0.00±0.00*	1.60±0.51	0.80±0.58
C	1.40±1.40	2.00±1.54	1.40±0.87	1.20±1.20	0.80±0.58	0.40±0.40
D	0.00±0.00	0.40±0.40	1.20±0.80	2.00±1.26	0.60±0.60	0.80±0.80
E	0.40±0.40	0.60±0.60	0.20±0.20*	0.60±0.40*	0.40±0.24	1.40±0.87
F	0.00±0.00	0.40±0.40	0.00±0.00*	0.40±0.40*	0.20±0.20	0.20±0.20
G	0.00±0.00	0.00±0.00	0.20±0.20*	1.00±0.63*	1.80±1.20	1.20±0.80

**p<0.05 vs negative control (distilled water 10 mL/kg) (Bonferroni's multiple comparisons test)*

Legend:
***A** = Distilled water (10 mL/kg), **B** = T. macroptera stem bark ethanol extract (50 mg/kg)*
***C** = T. macroptera stem bark ethanol extract (100 mg/kg), **D** = T. macroptera stem bark ethanol extract (200 mg/kg),*
***E**= T. macroptera stem bark ethanol extract (400 mg/kg), **F**= Piroxicam (10 mg/kg), **G** = Pentazocine (2 mg/kg)*

DISCUSSION

Nociception is defined as the neural processes of encoding and processing noxious stimuli (Cohen *et al*., 2018). Nociceptive pain involves the normal neural processing of pain that occurs when free nerve endings are activated by tissue damage or inflammation (Treede, 2001 and Daniel *et al*., 2009). Nociception involves four processes, viz: transduction, transmission, perception, and modulation (Sulaiman *et al*., 2004; Bannon and Malmberg, 2007). However, improved understanding of nociception has promoted the development of new treatment options and enabled the use of various medications and interventions to target nociceptive processes (Fitzgerald, 2005 and Schaible, 2007). A strong intertwine in the pathophysiology of nociception and inflammation exists, and often times, drugs (including plant extracts) which show anti-inflammatory activities also elicit anti-nociceptive activities (Suba *et al.*, 2005; Orhan *et al*., 2007 and Sowemimo *et al.*, 2015). This study was therefore carried out to evaluate the anti-nociceptive potential of ethanol extract of *Terminalia macroptera* stem bark in mice following its report of anti-inflammatory activity by Usman *et al*., 2017 and ethnomedicinal claim of its analgesic effect (Atunwa *et al*., 2019).

Nociceptive tests use thermal, mechanical, or chemical stimuli (Le Bars *et al*., 2001). Some of them rely on the latency of appearance of avoidance behaviour, usually a withdrawal reflex of the paw or tail (Le Bars *et al*., 2001). The tail immersion assay which is interchangeably used for tail flick assay is a well-used model for the determination of centrally acting agents that modulate the transmission of acute nociceptive pain. It is a variant of tail flick test using radiant heat (Le Bars *et al.*, 2001). The immersion of the animal's tail in hot water (50±1°C) induces the transmission of nociceptive stimuli through the spinal cord and causes the animal to swiftly retract its tail from the water. Significant protraction of the time taken for the animal to retract its tail from the water is taken as an indication of anti-nociceptive activity (Njan *et al.*, 2015). Although, the tail flick is a spinal reflex, it could be influenced by supraspinal processes. Nonetheless, as a setback of this model, tail flick is prone to habituation; which is described as a reduction in the response with repetitive stimulation (Le Bars *et al.*, 2001). However, in order

to avoid this shortcoming, it is preferred to choose high baselines values (lower heat intensity) to favour the detection of faster responses rather than choice of low baseline values (higher heat intensity) to favour the detection of delayed response. This therefore justified our preference for high baseline values (lower heat intensity) by considering 50±1 ºC as the temperature of hot water. Thus, the highest mean latency time recorded in this study is 3.73±0.82 at 150 minutes post-treatment with pentazocine as observed in Table 1.

The result obtained in tail immersion test showed that groups administered 100 mg/kg (2.95±0.41) and 400 mg/kg (2.9±0.31) ethanol extract of *T. macroptera* stem bark (TMSB) significantly inhibited nociception at 60 minutes post-treatment as compared to the group administered distilled water. Expectedly, the anti-nociceptive effects observed are similar to those recorded for the standards; pentazocine 2 mg/kg and piroxicam 10 mg/kg at 60 minutes post-treatment. Paradoxically, the group administered 200 mg/kg of TMSB showed significant hyperalgesia (habituation) at 150 minutes post-treatment when compared to the negative control as depicted in Table 1. This could be explained by the fact that though thermal experimental nociceptive models often allow repeated measures, they are sensitive to stress and stress-induced analgesia (Le Bars *et al*., 2001). Thus, it is always required to set a cut-off time in order to avoid or limit the risk of burn experienced by the animal. This therefore gives scientific explanation to the cut-off time set at 12 seconds as observed in this study.

The writhing test sometimes called abdominal contortion test, abdominal constriction response, or stretching test is one of the most commonly utilized models for evaluating chemical-induced nociception and its prevention (Le Bars *et al.,* 2001). Different irritating chemical agents can be used as nociceptive stimuli to assess pain and preclinically evaluate analgesic drugs (Negus *et al*., 2006). In the writhing test, irritating agents are administered intraperitoneally, inducing a stereotyped behaviour. These behaviours are considered to be reflexes and characterized by abdominal contractions, which are quantified (Le Bars *et al*., 2001). They induce a tonic pain state that is evaluated by behavioural scoring which includes contractions of abdominal muscles followed by opening of back feet or stretching of the whole body in the animal. A significant reduction in the number of acetic acid-induced abdominal contractions of the treated animals, compared to the contractions in the untreated control mice is taken as an indication of analgesic activity (Ishola *et al*., 2016). Acetic acid is a common choice in nociceptive studies as it is easy to handle and prepare in the laboratory. A shortfall of this model is the fact that it could not be used to measure the duration of action of any agent being tested. This was conspicuously observed from the result obtained in this assay since no significant time-dependent disparity in the number of writhing across the treated groups was recorded. More so, this model lacks specificity but however very useful for sifting moieties with unknown pharmacodynamic properties since it is a known fact that all analgesics inhibit abdominal cramps (Le Bars *et al.,* 2001). In other words, this model can be said to have poor specificity but very sensitive and predictive advantage especially when several agents are due for evaluation over a relatively short period of time.

In acetic acid-induced writhing assay, the ethanol extract of *T. macroptera* stem bark showed significant inhibition of nociception with 50 mg/kg (0.00±0.00) at 15-20 minutes post-induction of intraperitoneal administration of acetic acid. Similarly, group administered 400 mg/kg ethanol extract of *T. macroptera* stem bark respectively showed significant inhibition of nociception at 10–15 minutes (0.20±0.20) and 15-20 minutes (0.60±0.40) post-induction with i.p. administration of acetic acid as presented in Table 2. As expected, both the piroxicam and pentazocine significantly attenuated nociceptive responses to chemical stimuli in the writing test similar to the extract-treated groups. This observation corroborates the postulation that acetic acid induces pain through indirect stimulation of the release of endogenous mediators which consequently causes sensitization of nociceptive neurons (Boyce-Rustay *et al*., 2010).

Several phytochemicals present in the leaves, stem, root, flowers and other parts of *T. macroptera* have been reported among which are: flavonoids, tannins, terpenoids (Conrad *et al*., 1998 and 2001; Akpovona *et al*., 2016; Usman *et al*., 2017; Omotugba *et al*., 2019), saponins, resins, anthraquinones, quercetin, terminolic, chlorogenic and ellagic acids (Innalegwu *et al*., 2017). Similarly, proximate analyses have reported the presence of cutin, mucilage, polysaccharides (Zou *et al*., 2014), fibre, fixed oils, calcium oxalate, and alkaloids among others (Akpovona *et al*., 2016; Usman *et al*., 2017). Hence, the presence of these secondary metabolites could possibly be responsible for the anti-nociceptive activity observed. However, further studies to verify the findings using other *in vivo* and some selective *in vitro* models; understand its pharmacodynamics; and conduct structural elucidation studies in order to establish the mechanism of action of *T. macroptera* in analgesia, and characterize the phytochemical(s) responsible for the antinociceptive activity are thus recommended.

CONCLUSION

Preliminary findings from this study suggest that the ethanol extract of stem bark of *Terminalia macroptera* Guill & Perr (Combretaceae) may possess dose-dependent anti-nociceptive activity in both tail immersion and acetic acid-induced writhing assays in mice. Thus, its folkloric use in the management of pain associated ailments could be justified.

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*Address for correspondence: Soliu Abiola Atunwa

Department of Pharmacology and Toxicology,
Faculty of Pharmaceutical Sciences,
University of Ilorin,
P.M.B. 1515, Ilorin,
Kwara State, Nigeria

Telephone: 08068652938
E-mails: atunwa.sa@unilorin.edu.ng

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