ORIGINAL ARTICLE

ISSN: 0331 - 670X

https://doi.org/10.51412/psnnjp.2024.31

The Nigerian Journal of PHARMACY

AS MEN OF HONOUR WE JOIN HANDS

THE OFFICIAL ORGAN OF THE PHARMACEUTICAL SOCIETY OF NIGERIA FOUNDED 1927

Anxiolytic and antiamnesic potentials of *Terminalia ivorensis* Chev (Combretaceae) stem and root bark methanol extracts in mice.

Lateef A. Akinpelu[1*], Muritala A. Adebayo[2], Oyeronke M. Aiyelero[1], Oluwasegun I. Eniaiyewu[3], Raymond T. Bobra[2], Somtochukwu O. Anyacho[2].

[1]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Ilorin, Kwara State, Nigeria

[2]Department of Pharmacognosy, College of Pharmacy, Igbinedion University, Okada, Edo State, Nigeria

[3]Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Ilorin, Kwara State, Nigeria

ARTICLE INFO

Article history:

Received 26th September 2024
Revised 10th October 2024
Accepted 11th October 2024
Online Published

Keywords:

Terminalia ivoriensis,

root bark,

stem bark,

anxiolytic,

antiamnesic effects.

**Corresponding Author:*
Lateef A. Akinpelu
Email: akinpelu.la@unilorin.edu.ng
Tel: +2348038590621

ABSTRACT

Background: *Terminalia ivorensis* (Chev) stem bark is used in combating mental illnesses in African traditional medicine. Previous studies demonstrated its antipsychotic properties but there are no documented reports on the anxiolytic and antiamnesic properties of *Terminalia ivorensis*. Hence, this study investigated the anxiolytic and antiamnesic potentials of methanol stem bark and root bark extracts of *T. ivorensis* in mice.

Methods: The anxiolytic potentials of stem and root bark methanol extracts at 100, 200 and 400 mg/kg b.w were investigated using mouse model of anxiety (elevated plus maze test), while the antiamnesic potentials were assessed using mouse model of short term memory assessment (Y-maze test).

Results: The stem and root bark methanol extracts at all the tested doses, significantly ($p \leq 0.05$) elongated the percentage number of entries into the open arm of the elevated plus maze, while the duration of stay on the open arm of the elevated plus maze was only significant ($p \leq 0.05$) at 100 mg/kg for stem bark extract. Stem and root bark extracts, at all the tested doses, significantly ($p \leq 0.05$) reduced the anxiety indices of mice indicative of antianxiety potentials. Both extracts showed significant ($p \leq 0.05$) dose-dependent decrease in percentage correct alternations compared to the scopolamine control group indicating antiamnesic effect.

Conclusion: This study revealed that stem and root bark extracts may possess anxiolytic and antiamnesic effects in mice which justify its use in treating mental illnesses in traditional medicine.

INTRODUCTION

Anxiety is a type of mental health condition characterized by intense, excessive and persistent worry and fear about everyday situations, it could also occur as a response to real or perceived threats[1]. Anxiety disorder is one of the most prevalent mental derangement with a very high co-morbidity with other psychiatric disorders[2] which negatively impacts on quality of life of the sufferers[3,4]. The symptoms of anxiety disorders could either be emotional or physical in nature[5,6]. The emotional symptoms include feelings of apprehension or dread, trouble in concentrating, feeling tense amongst others[7,8] while physical symptoms may include pounding heart, muscle tension, fatigue and insomnia, shortness of breath[9,10]. Recent studies have indicated the involvement of glutamatergic, GABAergic serotonergic, and noradrenergic transmission in the neurobiology and pathophysiology of anxiety disorders[11]. Hence, the involvement of these neurotransmitters

pathways have reflected in the use of benzodiazepines (e.g diazepam), as well as selective serotonin and noradrenaline reuptake inhibitors (e.g venlafaxine) in the management of anxiety disorders[12]. Besides these anxiolytic drugs, tricyclic antidepressants (e.g imipramine), beta-blockers (e.g propanalol), monoamine oxidase inhibitors (e.g tranylcypromine) and serotonergic anxiolytics (e.g buspirone) may also aggravate some symptoms of anxiety disorder[13].

Benzodiazepine drugs top the ranking of the mostly used synthetic antianxiety drugs by man, but can cause various side effects such as dependence, rebound anxiety, memory impairment, and discontinuation syndrome[14,15], thereby limiting their application particularly in patients that require long term therapy[16].

Amnesia is an intense memory loss, usually caused by physical injury or ingestion of toxic substances which damage the brain[17]. For instance, loss of appetite, nausea, vomiting and diarrhea are associated with the use of AChE inhibitors, while headache, hallucinations, mental confusion, insomnia and dizziness are associated with memantine[18]. Amnesia can be a symptom of several neurodegenerative diseases such as Alzheimer's disease (AD)[19]. Alzheimer's disease is the most common cause of dementia defined as loss of mental functions such as thinking, memory, and reasoning that is severe enough to interfere with a person's daily functioning[17]. The hallmark of AD appears to be decreased cholinergic neurotransmission, deposition of beta amyloid peptides in brain, formation of neurofibrillary tangles from tau proteins inside nerve cells and oxidative stress[20].

The therapeutic strategies for managing AD include inhibition of acetylcholinesterase enzyme (AChE) and blockade of glutamate via the N-methyl-D-aspartate (NMDA) receptors. Drugs that inhibit AChE such as donepezil and galantamine prevent the breakdown of ACh and enhance central cholinergic neurotransmission and transiently improve the symptoms of AD. The blockade of NMDA receptors by drug like memantine (NMDA receptor antagonist) protects the brain cells from the damaging effect of excessive release of glutamate in the brain20. Although, the conventional use of these drugs have proven beneficial against memory loss, they are limited due to attendant side effects associated with their use[18].

Terminalia ivorensis A. Chev (Combretaceae) is a deciduous tree growing up to 30 m found in the tropical and sub-tropical parts of the globe[21,22]. The stem bark is used in traditional medicine against yellow fever, general body pains, malaria, diuresis, wounds, haemorrhoids in the West Afriacan region of the world[5,23,24]. The stem is also reported to be used against psychosis, insomnia and epilepsy[25]. Phytochemical analysis of *T. ivorensis* stem bark revealed the presence of flavonoids, terpenoids, alkaloids, condensed tannins, saponins, cardiac glycosides, anthraquinones and steroids[26]. Two oleanane-type triterpenes named ivorengenin A and B together with arjungenin, arjunic acid, betulinic acid, sericic acid, and oleanolic acid, were isolated from stem barks of *T. ivorensis*[27].

Pharmacologically, the sedative[28], antiinflammatory, antinociceptive[29] and antipsychotic[30] properties of the plants have been reported. In spite of reported anxiolytic and antiamnesic effects of *T. chebula* and *T. belerica*[31-34], lack of literature information on similar activities in *T. ivorensis*, forms the basis of this present study.

MATERIALS AND METHODS

The *T. ivorensis* stem and root barks were collected in November 2019 from the Crown Estate of Igbinedion University, Okada. They were authenticated by Dr M. A, Adebayo of the Herbarium Unit of the College of Pharmacy, where the voucher number IUO/16/133 was obtained.

Preparation of Plant Materials

The stem barks and root barks were cut into smaller pieces and air-dried separately for three weeks at room temperature inside the laboratory. Dried plant materials were separately pulverized and 500 g of each sample was extracted with 2 liters of seventy percent (70 %) methanol for 72 hours. Each filtrate was separately concentrated in vacuo at a temperature of 40oC and freeze dried to yield 16.98 g (3.40 %) of crude root bark extract and 15.99 g (3.2 %) crude stem bark extract respectively.

Animals

The male mice (18-20 g) used in this experiment were purchased from the Central Animal House of the Igbinedion University, Okada, Edo State, Nigeria. They were housed in well-lit and aerated room and maintained under natural 12 hour light/12 hour dark condition to acclimatize for 2 weeks before the commencement of the experiment. The mice had free access to clean drinkable water and standard commercial diet (Guinea feeds brand, Bendel Feeds, Benin City, Edo State, Nigeria). The experimental protocols employed in this study were as

approved by the Igbinedion University Animal Ethical Committee vide the approval number IUO/ETHICS/053/24 which is in consonance with the United States National Institute of Health Guidelines for Care and Use of Laboratory Animals in Biomedical Research[35].

Drugs and Chemicals

Diazepam (Roche, Basel, Switzerland), Piracetam Scopolamine hydrobromide Dimethylsulfoxide (DMSO) (Sigma Aldrich, St. Louis, MO, USA) and normal saline (Unique Pharmaceutical Limited, Lagos, Nigeria) were employed in this study. Plant extracts were dissolved with 3% DMSO and made up to the required volume with normal saline. Drugs and plant extract were freshly prepared on each day of the experiments.

Evaluation of anxiolytic effect of extracts on elevated plus mazes (EPM)

The anxiolytic behavioural assays of stem and root bark extracts were investigated as previously described[36]. Briefly, adult male mice were randomised into 5 groups (n = 5). Negative control group I received normal saline (10 mL/kg, p.o.) only. Test groups II-IV received stem extract orally at doses of 100, 200 and 400 mg/kg respectively, while positive control group V received diazepam (1 mg/kg, i.p.). One hour after oral dosing of extract and 30 minutes following intraperitoneal administration of diazepam, each mouse was individually placed at the middle of the EPM, with the head facing one of the open arm of the EPM. Root extract was similarly assessed. The number of open arm entries and the duration of stay on the open arm of EPM were noted for 5 minutes. The percentage numbers of open arm entries and the percentage time spent in the open arm of the EPM were calculated using the formula below:

Percentage open arm entry (% OE) = [(number of open arm entries/ Total number of entries)] × 100

Percentage open arm time (% OT) = [(Time spent in open arm / Total time spent on EPM)] × 100

The open arm avoidance index (OAAI) interpreted as anxiety index was calculated as earlier done using the formula below[36].

Open arm avoidance index (OAAI) = 100 – [(% OE + % OT)] /2]

Evaluation of antiamnesic effect of extracts on Y-maze

The antiamnesic potential of extracts was investigated as previously carried out[36]. Briefly, adult male mice (18-20 g) were randomized into 6 groups (n = 5). The stembark and rootbark extracts were separately tested as follows: Group I: negative control group received normal saline (10 mL/kg, p.o.) only. Group II mice received scopolamine (1 mg/kg, i. p.) only, Group III mice received extract (100 mg/kg, p.o.), Group IV mice received extract (200 mg/kg, p.o.), Group V mice received extract (400 mg/kg, p.o.), while Group VI mice received piracetam (200 mg/kg, p.o.). Thirty minutes following oral ingestion in Groups III-VI, mice were singly injected scopolamine (1 mg/kg, i.p.). Thirty minutes post scopolamine treatment, each mouse was gently put on arm A (for consistency) of the Y-maze (40 × 3 × 12) with angles of 1200 between each of the three arms and the sequence of arms visited on consecutive choices in 8 minutes was recorded. The number of correct alternation, defined as visiting the three arms consecutively (triads), was recorded as 'percentage alternation' which is an assessment of short memory measurement[36]. An alternation is defined as an entry into all three arms on consecutive choices.

% Alternation = [(Number of alternations)/ (Total arm entries - 2)] × 100.

Data analysis

Results were expressed as mean ± S.E.M and analysed using One-way Analysis of Variance (ANOVA), followed by Dunnett's post hoc analysis. GraphPad InStat® Biostatistics software (GraphPad Software, Inc., La Jolla, USA). The level of statistical significance for all tests was set at $p \leq 0.05$.

RESULTS

Effect of extracts on percentage number of open arms entries on EPM in mice.

Oral administration of extracts at respective doses of 100, 200 and 400 mg/kg produced significant ($p \leq 0.05$) increase in the percentage number of open arm entries when compared to the control group. Root extract gave higher percentage number of the open arm entry at the lowest dose of 100 mg/kg while stem extract showed higher percentage number of open arm entries at the highest dose of 400 mg/kg. The stem bark extract showed dose-dependent increase in percentage number of open arm entries while no dose-dependency was observed with the root bark extract as its lowest dose showed the highest percentage number of open arm entries in mice [Figure 1].

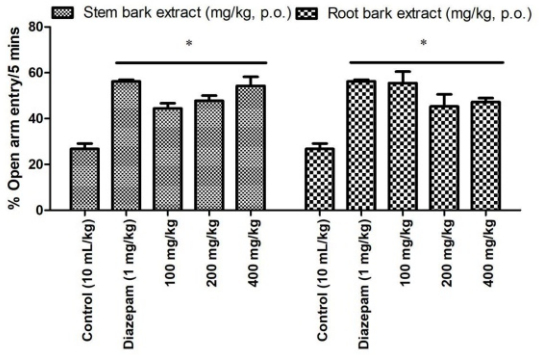

Figure 1: Effect of *Terminalia ivorensis* extracts on percentage open arm entry in mice.

Each bar represents Mean ± SEM, n=5, one-way ANOVA, Dunnett's post hoc test, *#p≤0.05 compared to respective control.

Effect of extracts on percentage time spent on the open arms of EPM in mice.

The oral administration of stem bark extract at the lowest dose of 100 mg/kg b.w, showed significant (p≤0.05) increase in the percentage time spent on the open arm of EPM when compared to the control treated group. The stem bark extract at all the tested doses showed dose-dependent decrease in the percentage time spent in the open arm while the root bark extract showed dose-dependent increase in the duration on the open arm but were not significant (p>0.05) from negative the control group [Figure 2].

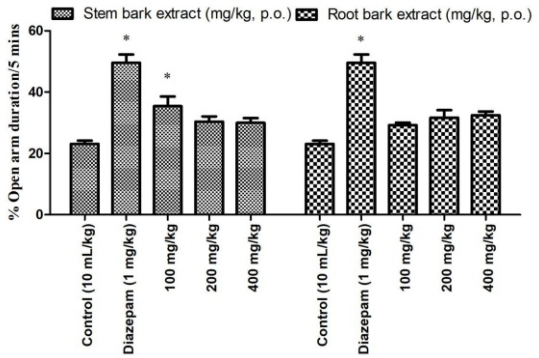

Figure 2: Effect of *Terminalia ivorensis* extracts on percentage open arm duration in mice.

Each bar represents Mean ± SEM, n=5, one-way ANOVA, Dunnett's post hoc test, *#p≤0.05 compared to the respective control group.

Effect of extracts on open arm avoidance index (anxiety index) in mice

The oral administration of each extract at 100, 200 and 400 mg/kg and diazepam at 1 mg/kg significantly (p≤0.05) reduced the anxiety indices of mice compared to the negative control group [Figure 3].

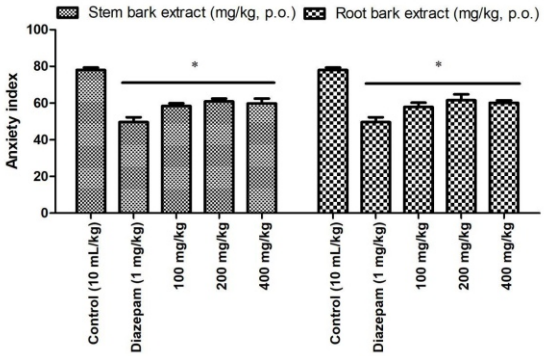

Figure 3: Effects of extracts on open arm avoidance index (anxiety index) in mice.

Each bar represents Mean ± SEM, n=5, one-way ANOVA, Dunnett's post hoc test, *#p≤0.05 compared to the respective control group.

Effect of *Terminalia ivorensis* extracts on percentage correct alternation.

Scopolamine (1 mg/kg, i.p.) significantly (p≤0.05) reduced the percentage correct alternation compared to the negative control group. However, oral ingestion of extracts at all the respective tested doses of 100, 200 and 400 mg/kg showed significant (p≤0.05) dose-dependent increase in percentage correct alternation compared to the scopolamine group [Figure 4].

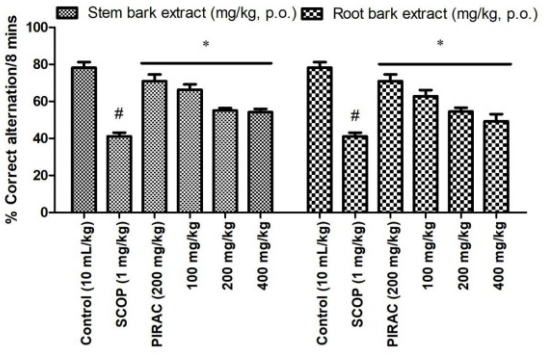

Figure 4: Effect of *Terminalia ivorensis* stem bark and root bark extracts on percentage correct alternation.

Each bar represents Mean ± SEM, n=5, one-way ANOVA, Dunnett's post hoc test, #p≤0.05 compared to the negative control group and *p≤0.05 compared to the scopolamine control group.

DISCUSSION

Terminalia species such as *Terminalia chebula* and *Terminalia belerica* have been evaluated for their anxiolytic and antiamnesic potentials[31-34]. Previously, *T. ivorensis* has been evaluated for its sedative, antipsychotic, antiinflammatory and antinociceptive effects[28-30]. However, there are scanty reports on the anxiolytic and antiamnesic potentials of its stem and root bark extracts. The doses of *T. ivorensis* extracts used in this study were as earlier reported by Avoseh et al.[29] in their investigations of the antiinflammatory and antinociceptive potentials of *T. ivorensis*.

The EPM has been previously employed to identify anxiolytic agents[37] based on the increase in the frequency of open arm entries and duration of stay in the open arm of the elevated plus maze[37], particularly anxiolytic potentials of benzodiazepine-like or GABA mediated agents in mice[36,38]. The increase in frequency of open arm entries, as well as the elongation of duration of stay in the open arm of the EPM by both extracts is a pointer to anxiolytic effects in mice. Reduction in anxiety indices of mice on EPM further lends credence to anxiolytic potential observed in other parameters of increase in percentage open arm entry and increase percentage time spent in the open arm of the elevated plus maze. This finding add to the existing literature of medicinal plants with anxiolytic effects such as *Vitex doniana* and *Bambusa vulgaris*[36,39.]

Although, the mechanism of anxiolytic action of the extracts were not determined in this study, it could probably be suggested that they acted via agonistic action on GABA receptor neurotransmission since EPM has been found to be sensitive to anxiolytic potentials of benzodiazepine-like or GABA mediated agents[36,39].

Scopolamine is an antimuscarinic agent used extensively to induce amnesia on Y-maze in mice[36]. The correct percentage alternation is an index of antiamnesic potentials of medicinal agents with ameliorative effects in mice35. Therefore, the reduction in the percentage alternation by scopolamine suggests the amnesic effect[36]. The reversal of the induced amnesia by *T. ivorensis* stem and root bark methanol extracts in this study may suggest the antiamnesic and restorative potentials for *T. ivorensis*. This finding is in consonance with earlier reports on some plants that mitigated scopolamine-induced amnesia and hence possess antiamnesic effects in mice[36]. The amnesic agent used in this study was a muscarinic cholinergic antagonist which possibly suggests that methanol extracts of *T. ivorensis* stem and root bark may be acting either via agonistic action on muscarinic acetylcholine receptor[35,39] or inhibition of the enzymatic activity of AChE or via both mechanisms.

CONCLUSION

This study revealed that the stem bark and the root bark methanol extracts of *T. ivorensis* may possess anxiolytic and antiamnesic effects, respectively. However, further study needs to be carried out on the antiamnesic potentials of these extracts on object recognition test in mice.

CONFLICT OF INTEREST

None declared

References

1. Saki K, Bahmani M, Rafieian-Kopaei M (2014) The effect of most important and medicinal plants on two important psychiatric disorders (anxiety and depression)—a review. *Asian Pacific Journal of Tropical Medicine* 7(1):34-42. https://doi.org/10.1016/S1995-7645(14)60201-7
2. Bandelow B, Michaelis S (2015) Epidemiology of anxiety disorders in the 21st century. *Dialogues in Clinical Neuroscience* 7(3):327–335. doi: 10.31887/DCNS.2015.17.3/bbandelow
3. Kessler RC, Berglund P, Dernier O, Jin R, Merikangas KR, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archive of General Psychiatry* 62(6):593–602. doi:10.1001/archpsyc.62.6.593
4. Grant BF, Hasin DS, Stinson FS, Dawson DA, June Ruan W, Goldstein RB, Smith SM, Saha TD, Huang B (2005) Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on alcohol and related conditions. *Psychological Medicine* 35: 1747–1759. doi:10.1017/S0033291705006069
5. Amali MO, Atunwa SA, Omotesho QA, Oyedotun EO, Olapade AI (2020) Assessment of anxiolytic potential and acute toxicity study of Combretum micranthum G. Don. leaves (Combretaceae). *Journal of Medicinal Plants for Economic Development* 4(1):97. doi: https://doi.org/10.4102/jomped.v4i1.97.
6. Ströhle A, Gensichen J, Domschke K (2018) The Diagnosis and Treatment of Anxiety Disorders. *Deutsches Arzteblatt International* 155(37):611-

620. doi: 10.3238/arztebl.2018.0611.
7. Onete OU (2020) Anxiety disorder and mental health of adolescents in contemporary Nigeria. *Journal of Science Engineering and Technology* 7(1):110-115
8. Stein MB, Stein DJ (2008) Social anxiety disorder. *Lancet* 371(9618):1115-1125. doi:10.1016/S0140-6736(08)60488-02
9. Moser DK (2007). The rust of life: Impact of anxiety on cardiac patients. *American Journal of Critical Care* 16(4): 361–369.
10. Koen N, Stein DJ (2011). Pharmacotherapy of anxiety disorders: A critical review. *Dialogues in Clinical Neuroscience* 13(4): 423-437. doi: 10.31887/DCNS.2011.13.4/nkoen
11. Nutt DJ, Ballenger JC, Sheehan D, Wittchen HU (2022) Generalized anxiety disorder: comorbidity, comparative biology and treatment. *International Journal of Neuropsychopharmacology* 5(4): 315-325. doi: 10.1017/S1461145702003048
12. Tyrer P, Baldwin D (2006). Generalised anxiety disorder. *Lancet* 368 (9553): 2156-2166. doi: 10.1016/S0140-6736(06)69865-6
13. Khan A, Akram M, Thiruvengadam M, Daniyal M, Zakki SA, Munir N, Zainab R, Heydari M, Mosavat SH, Rebezov M, Shariati MA (2022) Anti-anxiety properties of selected medicinal plants. *Current Pharmaceutical Biotechnology* 23(8):1041-1060. doi: 10.2174/1389201022666210122125131
14. Sanabria E, Cuenca RE, Esteso MÁ, Maldonado M (2012) Benzodiazepines: Their use either as essential medicines or as toxics Substances. T*oxics* 9(2):25. doi: 10.3390/toxics9020025
15. Edinoff AN, Nix CA, Odisho AS, Babin CP, Derouen AG, Lutfallah SC, Cornett EM, Murnane KS, Kaye AM, Kaye AD (2022) Novel designer benzodiazepines: comprehensive review of evolving clinical and adverse effects. *Neurology International* 14(3):648-663. 10.3390/neurolint14030053
16. Edinoff AN, Nix CA, Hollier J, Sagrera CE, Delacroix BM, Abubakar T, Cornett EM, Kaye AM, Kaye AD (2021). Benzodiazepines: Uses, Dangers, and Clinical Considerations. *Neurology International* 13(4):594-607. doi: 10.3390/neurolint13040059.
17. Singh MF, Singh VV, Shalini R, Himani B, Anupam B (2013) Memory enhancing effect of mirtazapine with ascorbic acid on scopolamine induced amnesia in rats. *Guru Drone Journal of Pharmaceutical Research International* 1(1): 29-38.https://api.semanticscholar.org/CorpusID:152048041
18. Briggs R, Kennelly SP, O'Neill D (2016). Drug treatments in Alzheimer's disease. Clinical Medicine (Lond) 16(3): 247- 253. http://doi.org/:10.7861/clinmedicine.16-3-247.
19. Panegyres PK. (2004) The contribution of the study of neurodegenerative disorders to the understanding of human memory. *QJM: International Journal of Medicine* 97(9):555–567. doi: 10.1093/qjmed/hch096
20. Tanwar A, Bafna PA, Bafna AR (2014) Anti-amnesic effect of aqueous extract of Crataeva nurvala stem bark in scopolamine induced amnesia. *Journal of Applied Pharmaceutical Science* 4(9):66-72. doi: 10.7324/JAPS.2014.40912
21. Ogunwande IA, Ascrizzi R and Guido F (2019) Essential oil composition of Terminalia ivorensis A. Chev. flowers from Northern Nigeria. *Trends in Phytochemical Research* 3(1): 77-82.
22. Burkill HM (1985) Entry for *Lasiurus hirsutus* (Forssk.) Boiss. [family POACEAE]. In: The useful plants of West tropical Africa, 2nd edition. Royal Botanic Gardens, Kew, 1:960-97. https://plants.jstor.org/collection/UPWTA
23. Akinyemi KO, Oluwa OK, Omomigbehin EO (2006) Antimicrobial activity of crude extracts of three medicinal plants used in south-west Nigerian folk medicine on some food borne bacterial pathogens. *African Journal of Traditional Complementary and Alternative Medicine* 3(4):13-22. doi: 10.4314/ajtcam.v3i4.31173
24. Sitapha O, Elisee KK, Joseph DA (2013) Antifungal activities of *Terminalia ivorensis* A. Chev. bark extracts against Candida albicans and Aspergillus fumigatus. *Journal of Intercultural Ethnopharmacology* 2(1):49-52. doi: 10.5455/jice.20121205083931
25. Lawal IO, Uzokwe NE, Igboanugo AB, Adio AF, Awosan EA, Nwogwugwu JO (2010) Ethno-medicinal information on collation and identification of some medicinal plants in Research Institutes of South-west Nigeria. *African*

Journal of Pharmacy and Pharmacology 4:001-007. https://api.semanticscholar.org/CorpusID:73072898

26. Moomin A, Mensah KB, Forkuo AD, Adu-Gyamfi PKT, Ansah C (2020). Ethanolic stem bark extract of *Terminalia ivorensis* A. Chev. protects against potassium dichromate–induced nephrotoxicity in rats. *Scientific African* 08:e00410. doi.org/10.1016/j.sciaf.2020.e00410
27. Ponou BK, Teponno RB, Ricciutelli M, Nguelefack TB, Quassinti L, Bramucci M, Lupidi G, Barboni L, Tapondjou LA (2011) Novel 3-oxo- and 3,24- dinor-2,4-secooleanane-type triterpenes from *Terminalia ivorensis* A. Chev. *Chemistry and Biodiversity* 8(7):1301-1309. doi:10.1002/cbdv.201000145.
28. Adeoluwa OA, Aderibigbe AO, Agu GO, Adewole FA, Eduviere AT (2015) Neurobehavioural and analgesic properties of ethanol bark extract of Terminalia ivorensis A Chev. (Combrataceae) in mice. *Drug Research* (Stuttg). 65(10):545-551. doi: 10.1055/s-0034-1394417.
29. Avoseh NO, Adebayo MA, Lawal OA, Ogunwande IA (2018). Anti-inflammatory and antinociceptive activities of *Terminalia ivorensis*. South *Asian Research Journal of Natural Product* 1(3):1-8. doi:10.9734/SARJNP/2018/43614
30. Ben-Azu B, Aderibigbe AO, Adeoluwa OA, Iwalewa EO (2016) Ethanol extracts of Terminalia ivorensis (Chev A.) stem bark attenuates the positive, negative and cognitive symptoms of psychosis in experimental animal models. *British Journal of Pharmaceutical Research* 12(6):1-14. doi: 10.9734/BJPR/2016/28629.
31. Mani V, Sajid S, Rabbani SI, Alqasir AS, Alharbi HA, Alshumaym A (2021). Anxiolytic-like and antidepressant-like effects of ethanol extract of *Terminalia chebula* in mice. *Journal of Traditional and Complementary Medicine* 11(6):493-502. doi: 10.1016/j.jtcme.2021.04.003.
32. Chandrashekar R, Manohar V.R, Poovizhi BR (2017) Attenuation of anxiety on acute administration of aqueous extract of *Terminalia belerica* fruit pulp in swiss albino mice. *International Journal of Basic and Clinical Pharmacology* 6(2):303–307. https://doi.org/10.18203/2319-2003.ijbcp20170319
33. Kim, MS., Lee, D.Y., Lee, J. Kim HW, Sung SH, Han JS, Jeon WK, WK (2018) *Terminalia chebula* extract prevents scopolamine-induced amnesia via cholinergic modulation and anti-oxidative effects in mice. *BMC Complementary and Alternative Medicine* 18:136.doi: 10.1186/s12906-018-2212-y.
34. Reddy NVLSV, Raju GM, Goud RM, Shabnamkumari T (2020) Neuroprotective activity of methanolic extract of *Terminala bellerica* fruit against aluminium chloride and haloperidol induced amnesia in mice. *Journal of Young Pharmacist* 12(2):87-90. doi: 10.5530/jyp.2020.12s.53
35. NIH. (1985). Guide for the use of laboratory animals. DHHS, PHS, NIH Publication No. 1985:85-23 (Revised).
36. Adebayo MA, Akinpelu LA, Okwuofu EO, Ibia DE, Lawson-Jack AF, Igbe I (2020) Anticonvulsant, antiamnesic and anxiolytic activities of methanol leaf extract of Bambusa vulgaris (Poaceae) in mice. *Journal of African Association of Physiological Science* 8(2): 149-157. https://www.ajol.info/index.php/jaaps/article/view/205716
37. Bourin M (2015) Animal models for screening anxiolytic-like drugs: a perspective. *Dialogues in Clinical Neuroscience* 17(3):295-303. 10.31887/DCNS.2015.17.3/mbourin
38. Murade V, Waghmare A, Pakhare D, Dichayal S, Patil R, Wanjari M, Hase D (2021). A plausible involvement of GABAA/benzodiazepine receptor in the anxiolytic-like effect of ethyl acetate fraction and quercetin isolated from *Ricinus communis* Linn. leaves in mice. *Phytomedicine plus* 1(3):100041. http://doi.org/10.1016/j.phyplu.2021.100041
39. Akinpelu LA, Adebayo MA, Fajana A, Adeniyi-Akee MA, Ubogu SE, Aminu NS (2019) Phytochemical analyses, anxiolytic and anti-amnesic effect of methanol stem bark extract of *Vitex doniana* (Sweet) in mice. *Nigerian Journal of Natural Product and Medicine* 23: 104-111. doi:10.4314/njnpm.v23i1.14