**Anti-epileptogenic Potential effect of ethanol leaf extract of *Pygeum africanum* in mice**

**Abstract**

Several current pharmaceuticals are derived from medicinal plants, either in pure or semisynthetic forms. Drug discovery via natural product research has long been fruitful. Traditionally, *Pygeum africanum* (PA) is used to treat various ailments in Africa. This study explores the anticonvulsant effect of ethanol leaf extract of *Pygeum africanum* in rodents, assessing activity with picrotoxin-, strychnine-, isoniazid-, and pilocarpine-induced seizures in both sexes. Its sedative and hypnotic effects were also evaluated using open field and righting reflex tests, respectively. PA (50–150 mg/kg) significantly reduced both duration and frequency of strychnine-induced seizures, and delayed seizure onset dose-dependently in the picrotoxin model (p < 0.05). For both ~~clonic and tonic seizures~~ tonic and clonic seizers, PA also significantly reduced duration (p < 0.05). It reduced mortality in pilocarpine-induced seizures, though it was less potent than diazepam, and had similar efficacy. The extract also showed sedative-hypnotic effects in righting reflex and open field tests. The anticonvulsant and sedative activities of the extracts were antagonized by flumazenil, indicating that benzodiazepine receptors are probably involved in the effects. In isoniazid-induced seizures, PA (150 mg/kg) significantly (*p* < 0.05) delayed onset and prolonged latency to death. Overall, PA demonstrates notable anticonvulsant properties.

1. **INTRODUCTION**

Epilepsy is a neurological condition affecting people of all ages. It is marked by excessive or abnormal electrical activity in part or all of the brain (WHO, 2019). Seizures occur spontaneously and repeatedly and are outward signs of epilepsy. These seizures may be triggered by stroke, brain tumour, head injury, or central nervous system infection (WHO, 2019). About fifty million people worldwide currently live with epilepsy. The disorder causes one percent of the global disease burden (Beghi et al., 2019) and is typically more prevalent in low- and middle-income countries (Naimo et al., 2019).

Despite a wide range of approved drugs for epilepsy, many people remain nonresponsive or refractory to antiepileptic therapy. This makes pharmacoresistant a major clinical issue in managing the disease (Naimo et al., 2019). Additionally, current treatments only address symptoms. They do not effectively prevent or permanently stop seizures (Clossen & Reddy, 2017). There is a need for new antiepileptic drugs (AEDs) with better safety and efficacy profiles. Traditional medicine has led to the discovery of important drugs, such as morphine, digoxin, quinine, and atropine (Choudhury et al., 2020).

Plant extracts are appealing sources for new drugs, and promising results have been seen in epilepsy therapy. Examples include *Antiaris toxicaria*, *Pseudospondias microcarpa*, and *Mallotus oppositifolius* (Kukuia et al., 2016). About 80% of people in developing countries use herbal remedies for primary health care (Nsagha et al., 2020). Thus, conditions like epilepsy and pain are often managed with herbs. Plant products traditionally used for epilepsy may help identify alternative antiepileptics. These may contain bioactive compounds that help control seizures (Amtul , 2018).

*Pygeum africanum* is a medicinal plant used traditionally for Benign Prostatic Hyperplasia, also known as the African cherry; belong to the family of Rosaceae. Its bark has been traditionally used for its medicinal properties, particularly in treating. The bark contains bioactive compounds, including phytosterols, fatty acids, and pentacyclic triterpenes (Anonymous, 2002). The extract of *Pygeum africanum* has been extensively researched for its potential therapeutic benefits. It’s pharmacological properties include Anti-inflammatory effects through the inhibition of pro-inflammatory mediators such as prostaglandins and 5-lipoxygenase metabolite production. It has Antiproliferative and secretory properties (Yablonsky et al., 1997).

**2. MATERIALS AND METHODS
2.1 Plant material
2.1.1 Identification, collection, and authentication of plant materials.**Fresh stem bark of *Pygeum africanum* was used for this study and was collected from bush in Iwo, Osun State, Nigeria.The plant was extracted followed the methods of Wadood et al.,2013). *Pygeum africanum*, weighing 2.0 kg, was air-dried for eight weeks. It was then reduced to coarse powder using an electric blender (Christy and Norris – 47362, England). Extraction was performed by adding the powdered stem bark to 5 liters of absolute methanol in a sterile flask with a stopper to prevent loss of volatile liquid. The mixture was agitated, and after 24 hours, it was decanted and filtered using filter paper No. 1 (Whatmann, London, UK).
The filtrate was evaporated to dryness using a rotary evaporator (Buchi Rota Vapour R110). It was then freeze-dried until a solid mass was obtained. The dried residue (85.6 g) was sealed tightly in glass vials and stored in a refrigerator at 4°C until use.

**2.2 Animal materials**Healthy male Swiss mice (20-30 g) were obtained from the Animal House of Ladoke Akintola University of Technology, Ogbomosho, Oyo State, Nigeria. Animals were housed in standard cages, six per cage. General housing was temperature-controlled (22.5°C ±2.5°C), with lights on/off at 7 o'clock. Mice had free access to food and water except during behavioural tests.
All animals were fed commercial standard rodent chow (calories: 29% protein, 13% fat, 58% carbohydrate) throughout the experimental period. All rules applying to animal safety and care were observed.

**3.0 ASSESSMENT OF SEDATIVE ACTIVITY**

**3.1 Measurement of locomotor activity**

The animals of either sex were divided into five groups (n = 6), with six animals in each group. Group I received normal saline, Group II received standard drug Diazepam (DZP) 1 mg/kg, i.p., Groups III-V were administered *Pygeum africanum* extract (50, 100, and 150 mg/kg, i.p.). The activity of animals was again observed after 30 min of intraperitoneal administration. dose respectively by placing them in the actophotometer. The animals were observed for a period of 5min in a square (30 cm) closed arena fitted with infrared light-sensitive photocells. The values were expressed as counts per 5 min (Sundriyal et al., 2013).

 3.2 **Pentobarbitone sleeping time**

The animals were divided into five groups, each consisting of six animals. Group I received normal saline, Group II received standard drug Diazepam (DZP) 1 mg/kg, i.p., Groups III-V groups were administered *Pygeum africanum* extract (50, 100, and 150 mg/kg, i.p.). After 30 min pentobarbitone sodium (20 mg/kg, i.p.) was administered to all the mice. Each animal was observed for the loss of righting reflex. The parameter for hypnotic effect was the duration between loss and recovery of righting reflex (Gupta et al., 2012).

**3.3 Effect of PA on strychnine-Induced Seizure Test**

The experimental model used was as described previously (Aashish et al., 2023). Briefly, strychnine seizures were induced in mice by a strychnine nitrate injection (0.5 mg/kg i.p.). This injection occurred 1 h after extract administration (50-150 mg/kg,) or 30 min after diazepam (1.0 mg/kg, i.p.). The duration, frequency, and latency to myoclonic jerks were recorded for extract- and diazepam-treated groups. These were compared to saline-treated (control) animals. Observations were made via video recording for 30 min (Cela et al., 2019).

**3.4 Effect of PA on pilocarpine-Induced *Status Epilepticus***

This experiment followed a previously described procedure (Eduardo et al., 2023). Pilocarpine (400 mg/kg, i.p.) was used to induce seizures in mice (Alharbi, 2021). PA (50-150 mg/kg, i.*p.*), diazepam (1.0 mg/kg, i.p.), or normal saline (10 mL kg-1 p.o.) was given 1 h after oral or 30 min after i.p. administration before induction. After pilocarpine injection, each animal was placed in a transparent observational chamber. Latency and duration of clonic tonic seizures were observed

**3.5Effect of PA Isoniazid-Induced Seizure Model**

The method followed was as previously described (Thijs et al., 2019). Animals were acclimatized for one week before treatment. They were administered with PA at doses of 50, 100, and 150 mg/kg, diazepam at a dose of 1 mg/kg, or 10 mL/kg of saline, all administration was through intraperitoneally. 150mg/kg body weight of isoniazid was used to induce seizures. Administration occurred 30 min after intraperitoneal treatment.

**3.6 Effect of PA on picrotoxin-Induced Seizure Model**

Mice were pretreated with PA at doses of 50, 100, and 150 mg/kg body weight. Thirty minutes after picrotocin at a dose of 3 mg/kg body weight was administered intraperitoneally to induce convulsion (File, 1983). Control animals and reference drug (diazepam) received normal saline 10 mL/kg and 1 mg/kg respectively. Video recordings for each mouse were used to record latency to tonic convulsions, latency to myoclonic jerks, frequency, and duration of tonic convulsions.

 **3.7 Involvement of the GABAergic System**

Flumazenil (a selective benzodiazepine receptor antagonist), was used in this study to investigate the involvement of GABAA receptor in the anticonvulsant mechanism of PA. Animals were administered with PA at doses 50, 100, and 150 mg/kg, similarly, diazepam (1 mg/kg, i.p.), flumazenil (2 mg/kg), and normal saline (10 mL/kg, i.p*.*) were also administered 30 min before administration of picrotoxin (3 mg/kg i.p.). Latency, frequency, and duration of clonic convulsions were recorded.

 **4.0 Statistical analysis**

All results are expressed as mean±standard error of the mean. The data were analyzed statistically using one way analysis of variance ANOVA, followed by the Dunnett’s post hoc test for multiple comparisons. P<0.05 was taken to be statistically significant.

**5.0 Results**

**5.1 Assessment of sedative activity**

**5.1.1 Measurement of locomotor activity**

 *Pygeum africanum*  in doses of (50–150 mg/kg) has shown significant reduction in locomotor activity in rats when compared with vehicle-treated control animals. The standard diazepam treated group at the dose (1 mg/kg, i.p.) also showed a significantly reduction in locomotor activity in animals (Table 1).

**Table 1: Effect of PA on locomotor activity**

|  |
| --- |
| Pretreatments Doses (mg/kg) Locomotor activity at the count of 10 minutes\*\* |
| Control 0 197.3±0.21Diazepam 1 51.7±0.32\*PA 50 175.4±0.51PA 100 113.5±0.05\*PA 150 93.6±0.65\* |

\*\*Values are mean ± SEM (n=5).

\*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett’s

**5.1.2 Pentobarbitone sleeping time**

Table 2 revealed the effect of *Pygeum africanum* at dose (50–150 mg/kg, p. o.) on pentobarbitone induced sleep latency produced a dose dependently reduction of sleeping time with significant effects shown at a dose level (150 mg/kg). Diazepam (1 mg/kg, i.p.) served as positive control significantly decreased the latency to sleep and also increased the duration of sleep.

**Table 2: Effect of PA on Pentobarbitone sleeping time in mice**

|  |
| --- |
| Pretreatments Doses (mg/kg) Onset of sleep(min)\*\* Duration of sleep(min)\*\* |
| Control 0 17±0.25 54±1.03Diazepam 1 3±0.31\* 117±3.01\*PA 50 15±1.72\* 57±2.21PA 100 14±1.07\* 97±3.62\*PA 150 4±0.45\* 119±4.35\* |

\*\*Values are mean ± SEM (n=5).

\*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett’s

**5.2 Strychnine-Induced Seizures**

Table 3 Shows that PA at all doses and diazepam did not alter strychnine-induced clonic convulsions in mice. However, the extract inadequately delayed seizure onset. All the animals died in the process

**Table 3: Effect of PA on Strychnine-Induced Seizures**

|  |
| --- |
| Pretreatments Doses (mg/kg) Latency of seizure(sec) % Mortality |
| Control 0 253±7.31 100Diazepam 1 463±7.03 100PA 50 321±6.45 100PA 100 325±5.05 100PA 150 337±7.41 100  |

\*\*Values are mean ± SEM (n=5).

\*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett’s

**5.3 Pilocarpine-Induced Status Epilepticus**

One-way ANOVA showed that PA delayed the onset of clonic and tonic convulsions in a dose-dependent manner. Diazepam (DZP, 1.0 mg/kg), used as a reference anticonvulsant, produced similar increases in latency. Oral PA at doses of 100 and 150 mg/kg administered to mice offered 60 % protection against pilocarpine-induced death.

**Table 4: Effect of *Pygeum africanum* on Pilocarpine-Induced Status Epilepticus**

|  |  |  |
| --- | --- | --- |
| Pretreatments Doses (mg/kg) | Latency of convulsions (s) | % mortality  |
| Clonic convulsion (s)\*\* Tonic convulsion(s)\*\* |
| Control 0 247±2.31 7±0.62 100Diazepam 1 431±9.03 13±2.49 20PA 50 271±9.12 13±0.37 100PA 100 329±7.35 16±0.52 40PA 150 365±7.39 19±2.33 40 |

\*\*Values are mean ± SEM (n=5).

\*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett’s

**5.4 Isoniazid-Induced Seizure Model**

*Pygeum africanum* and diazepam prolonged seizure onset in isoniazid-induced seizures significantly (p < 0.05). However PA at all doses and the reference drug failed to protect animals against death.

**Table 5: Effect of PA and diazepam on the latency to convulsion and percentage mortality**

|  |
| --- |
| Pretreatments Doses (mg/kg) Latency of convulsions (min)\*\* % mortality |
| Control 0 41.7 ±2.35 100Diazepam 1 87.1±7.25 100PA 50 42.5±3.61 100PA 100 43.3±4.83 100PA 150 85.9±4.22 100 |

\*\*Values are mean ± SEM (n=5).

\*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett’s

**5.5 Effect of PA on picrotoxin-Induced Seizures**

The extract-treated groups showed a significant anticonvulsant effect. PA at all doses delayed the onset of clonic and tonic convulsions in a dose-dependent manner. The extract also significantly reduced the duration of both clonic and tonic convulsions. Diazepam (1.0 mg/kg), the reference anticonvulsant, produced similar increases in latency and duration. Both treatments significantly reduced the frequencies of clonic and tonic seizures.

**Table 6: Effect of PA on picrotoxin-Induced Seizures**

|  |  |
| --- | --- |
| Pretreatments Doses (mg/kg) | Latency of **Seizures** Duration of **Seizures** Frequency of **Seizures** |
| CC (s)\*\* TC (s)\*\* CC(s)\*\* TC(s)\*\* CC\*\* TC\*\* |
| Control 0 253.1±9.06 523.0±9.63 257.3±7.21 30.2±3.51 63.1±5.30 17.3±2.05Diazepam 1 475.5±9.13 948.5±9.35 10.1±0.52 5.5±0.35 3.6±0.42 2.1±0.01PA 50 257.3±7.31 521.7±9.41 113.7±7.13 15.3±1.11 39.3±3.53 13.7±2.14PA 100 298.1±6.53 734.3±7.35 30.4±1.75 12.1±1.17 21.1±1.07 9.4±1.83PA 150 373.8±7.31 891.1±8.05 10.3±0.41 6.4±0.67 6.2±0.91 3.3±0.15 |

\*\*Values are mean ± SEM (n=5).

\*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett’s

**5.6 Effect of flumazenil on anticonvulsant activity of ethanol extract of *Pygeum africanum*  against picrotoxin-induced seizures in mice**

Administration of picrotoxin induced myoclonic seizures in all mice in the negative control group. PA at 150 mg/kg significantly (*P* < 0.05) increased seizure onset latency compared to the negative control. Diazepam (1 mg/kg) provided 80% protection against picrotoxin-induced seizures. When flumazenil, a benzodiazepine receptor antagonist administered, it significantly (*P* < 0.05) reduced the anticonvulsant activity of PA, suggesting PA’s action may involve benzodiazepine receptors. Similarly, flumazenil reduced the anticonvulsant effect of diazepam, changing its effect from complete seizure abolition to a significant (*P* < 0.05) but incomplete reduction in seizure activity. 100% mortality was recorded in both the extract and standard drug (Table 7).

**Table 7: Effect of flumazenil on anticonvulsant effect of *Pygeum africanum***

|  |
| --- |
| Pretreatments Doses (mg/kg) Onset of seizures(s)\*\* Duration of seizures(s)\*\*% Mortality  |
| Control 0 261.2±7.35 257±9.05 100Diazepam 1 578.3±7.21 10.7±0.31 100PA 50 20.7±2.03 43.3±5.63 100PA 100 19.5±2.19 76.3±4.48 100PA 150 9.15±0.51 17.5±2.41 100 |

\*\*Values are mean ± SEM (n=5).

\*Values are statistically significant (P<0.05) compared with control using one-way ANOVA followed by Dunnett’s

**6.0 Discussion**

The ethanol leaf extract of *Pygeum africanum* was evaluated for its anticonvulsant properties using various seizure models, including Picrotoxin-, Strychnine-, Isoniazid-, and Pilocarpine-induced seizures. Interestingly, the extract did not exhibit anticonvulsant activity against Strychnine-induced seizures. However, it demonstrated protective effects against Picrotoxin-induced seizures, suggesting its potential as an anticonvulsant agent. Meanwhile, it has a partial effect against pilocarpine-and isoniazid-induced seizure. The glycine receptor plays a crucial role in regulating inhibitory neurotransmission in the central nervous system. As a result, this receptor has emerged as a potential target for the development of antiepileptic drugs. Strychnine-induced seizures are attributed to the blockade of strychnine-sensitive glycine receptors, leading to increased postsynaptic excitability and sustained neural activity in the brainstem and spinal cord. In this study the extract did not nullify strychnine-induced convulsion in mice, it is therefore indicates that extract did not interacts with glycine receptors or related pathways. This implied that extract did not contain bioactive compounds that modulate glycinergic inhibitory neurotransmission, to exert its anticonvulsant effects.

Systemic administration of pilocarpine induces in animal model of intractable epilepsy, characterized by temporal lobe seizures. As a non-selective muscarinic agonist, pilocarpine's effects can be used to evaluate potential treatments for temporal lobe epilepsy. Notably, our extract demonstrated protective effects against pilocarpine-induced status epilepticus, suggesting its potential utility in treating temporal lobe epilepsy or other partial seizures. This is supported by our survival curve analysis and hazard ratio calculations, which indicate a lower risk of death compared to untreated populations. The anticonvulsant properties of the extract may be attributed to its constituent secondary metabolites, including alkaloids, saponins, and sterols.

Furthermore, isoniazid-induced status epilepticus is linked to the inhibition of glutamate decarboxylase (GAD) (Joshi et al., 2013), an enzyme essential for GABA synthesis. Decreased GABA levels in the brain have been correlated with seizures in animals administered high doses of isoniazid. Additionally, isoniazid's depletion of pyridoxine can lead to reduced GABA production, thereby increasing the risk of seizures, particularly in cases of acute toxicity. Unfortunately (De Sarro et al., 2003), the extract did not offer any protection against isoniazid-induced convulsion. Diazepam only demonstrated efficacy by prolonging the latency to death, highlighting the limitations of its clinical effectiveness in treating isoniazid toxicity due to variability and rapid onset of ingested isoniazid (Gottesmann, 2002). Research indicates that anticonvulsant agents primarily delay the onset of seizures rather than preventing them altogether (Page, 2002). Compounds that solely prolong latency to convulsions likely inhibit the spread of seizures within the epileptic brain.

Picrotoxin, a GABAA receptor antagonist, induces convulsive activity by blocking the chloride ion channel associated with the GABAA receptor (Möhler, 2006). This receptor typically facilitates chloride ion flow upon activation by gamma-aminobutyric acid (Cheng et al., 2006). GABAergic ionotropic receptors mediate pre- and postsynaptic inhibition, with presynaptic GABA inhibition often reducing neurotransmitter release from excitatory neurons (Attack, 2003). The extract's efficacy in the picrotoxin-induced seizure test suggests that it may act on GABA-mediated neurotransmission.

Barbiturates and benzodiazepines enhance the inhibitory action of GABAA receptors, reducing neuronal excitability and increasing the convulsion threshold (McKernan et al., 2000). The extract demonstrated effectiveness in both pentylenetetrazole- and picrotoxin-induced seizures, prompting an investigation into potential GABAergic mechanisms using flumazenil, a benzodiazepine receptor antagonist, in the picrotoxin-induced seizure test. Flumazenil failed to reverse the extract's antiseizure effect, indicating a distinct or complex mechanism underlying its anticonvulsant action. These findings align with previous studies on aqueous *Pygeum africanum* leaf extract in pentylenetetrazole-induced seizures (Fradley et al., 2007), which showed that the extract increased the onset and duration of convulsions without altering GABA levels, suggesting an alternative pathway for its anticonvulsant effects. The attenuation of the extracts' effects, as well as those of diazepam, by flumazenil in the picrotoxin test suggests that their mechanisms of action involve, at least in part, benzodiazepine receptors. Benzodiazepines potentiate the effects of the neurotransmitter GABA at the GABAA receptor, leading to sedative, hypnotic, and anticonvulsant properties, depending on the specific GABAA receptor subtype involved (Newland & Cull-Candy, 1992; Goutman et al., 2003). Previous studies have demonstrated that drugs targeting alpha-1 and alpha-5 subunits are associated with sedative effects (Leila et al., 2014), whereas anticonvulsant effects can be mediated through all subunits (Shafaroodi et al., 2013). The extracts exhibited significant sedative effects, as evidenced by the reduced total distance moved in mice 30 minutes after administration. Furthermore, the extracts prolonged pentobarbital-induced sleep duration in mice, suggesting sedative-hypnotic effects likely mediated via alpha-1 subunits of GABAA receptors (Bahremand et al., 2009). These findings collectively support the conclusion that the extracts exert sedative-hypnotic effects through modulation of the benzodiazepine site on GABAA receptors, particularly by influencing alpha-1 subunits.

The models employed in this study establish a solid basis for continued investigation into the antiepileptic potential of *Pygeum africanum*. However, since the present study utilized crude extract without isolating specific compounds, the exact mechanism of action remains unclear. Future research should focus on isolating bioactive compounds from the crude extract and elucidating their precise receptor interactions to better understand their anticonvulsant properties.

**Conclusion**

This study provides robust scientific evidence that ethanol leaf extract of *Pygeum africanum* possess pharmacological activity, potentially attributable to the presence of flavonoids. These findings suggest that the extract may have therapeutic potential in the treatment of convulsive and sleep disorders. Notably, the reversal of the extracts' protective effects against seizures by flumazenil implies that they may interact with benzodiazepine receptors. Further research is currently underway to isolate and characterize the biologically active compounds responsible for the observed effects, with the ultimate goal of elucidating and exploring their potential therapeutic applications.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing up of this manuscript

CONSENT

It is not applicable.

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