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Evaluation of the Antioxidant, Anti-Proliferative and Anti-Seizure Effects of Ethanol Leaf Extract of *Strychnos innocua* Del.

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Abstract

Strychnos innocua is a small tree belonging to the Loganiaceae family. In ethnomedicine, it has been used to treat bacterial infections, central nervous system disorders, and other ailments, with anecdotal claims of anticancer efficacy. This study aimed to evaluate the antioxidant, antiproliferative, and anti-seizure activities of an ethanolic leaf extract of *S. innocua*. The antioxidant effect was evaluated using 2,2'-azino-bis (3ethylbenzthiazoline-6sulphonic acid) (ABTS) radical scavenging activity, total flavonoid, total phenolic, ferric reducing antioxidant power, and total antioxidant capacity assays. The effects of the rapidly proliferating seed radicles were evaluated to determine their antiproliferative potential. The LD_{50} was evaluated in mice using Lorke's method, while the isoniazid-induced seizure mouse model was used to assess the anti-seizure effect. The results revealed that the extract demonstrated good antioxidant activity, with 55.69% inhibition at 400 µg/mL in the ABTS assay. The extract also showed significant ($P < 0.05$) antiproliferative activity at 10 – 50 mg/mL. The extract LD_{50} was greater than 5000 mg/kg p. o. and demonstrated a significant ($P < 0.05$) antiseizure effect at all doses (250 – 1000 mg/kg).

Keywords: Antioxidant, antiproliferative, antiseizure, *Strychnos innocua*, ABTS

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Introduction

Antioxidants are agents that prevent oxidation, a process often caused by free radicals. Adequate intake of antioxidants elicits prophylactic effects against oxidative stress-related diseases (Tan *et al.,* 2018). These agents exert their effects through several mechanisms, including scavenging reactive oxygen species (ROS), inhibition of ROS formation, prevention of hydroxyl radical generation, and lipid hydroperoxide decomposition (Afzal *et al*., 2023). Oxidative damage has been linked to the pathogenesis of various diseases including cancer (Chaudhary *et al*., 2023). Cancer is a complex genetic disorder characterized by sustained and uncontrolled proliferation of abnormal body cells. Scientific evidence indicates that brain tumors can trigger seizures as secondary complications (Sanchez-Villalobos *et al*., 2022). Therefore, the development of novel anticancer drugs should adopt a multifaceted approach, targeting not only cancer therapy, but also the management of secondary conditions such that they may develop in this disease state or coexist with it, such as seizures. Medicinal plants remain a major source for drug discovery and development (Zahra *et al*., 2021). *S. innocua*, a small tree belonging to the family Loganiaceae, is one of many plants used in traditional medicine. In ethnomedicine, *Strychnos innocua* has been employed in the treatment of bacterial infections, central nervous system disorders and other ailments, with anecdotal claims of anticancer efficacy (Ayo *et al*., 2022; Sallau *et al*., 2022). Hence, this study aimed to evaluate the antioxidant, antiproliferative, and antiseizure activities of ethanolic leaf extract of *S. innocua*.

Materials and methods

Plant materials

Fresh leaves of *Strychnos innocua* were collected from its habitat in the Jos-North Local Government Area in the Plateau state, Nigeria. The collected leaves were identified and authenticated as *Strychnos innocua* by Jeffery Azila, a taxonomist at the Federal College of Forestry, Jos Plateau State, Nigeria.

Extraction

The leaves of *S. innocua* were air-dried for two weeks at room temperature until an even weight of the dried leaves was obtained. The dried leaves were pulverized using an electrical milling machine. Using the standard procedure described by Handa *et al*. (2008), pulverized (2 kg) leaves were macerated in 6 liters of 70% ethanol at room temperature for 72 h with periodic shaking. After 72 h, the micelle solution was filtered through a mesh sieve, cotton wool, and filter paper (Whatman No. 1).

Experimental animals

Swiss albino mice of both sexes (20 – 30 g) housed at the Animal Facility, Department of Pharmacology, Novena University, Ogume, Delta State were used for the study. The mice were housed under standard laboratory conditions in accordance with international principles guiding the use and handling of experimental animals (NIH, 1985) and the Novena University ethical codes and regulations for the use of laboratory animals. The animals were maintained on pelleted mouse feed and water, *ad libitum*.

Phytochemical analysis

Qualitative phytochemical analysis was performed to identify the bioactive compounds present in the extract using the methods described by Harbone (1998) and Trease and Evans (2005).

Acute toxicity test (LD_{50})

The oral acute toxicity of the extract was evaluated in mice using Lorke's method (1983) The study involved two phases. In the first phase, nine mice were randomly divided into three groups of three mice each (groups 1 – 3) and administered extract at doses of 10, 100, and 1000 mg/kg p. o. They were observed critically for the first four hours after dosing and subsequently for 24 h for signs of toxicity and mortality. In the second phase, three fresh mice were divided into three groups (one per group). The extract doses of 1600, 2900, and 5000 mg/kg were administered orally to the animals. The animals were observed for signs of toxicity and mortality. The LD_{50} (acute toxicity dose) was calculated using the following equation.

$LD_{50} = \sqrt{}$ (highest non-lethal dose × least lethal dose)
All animals used in the study were continually observed daily for two weeks (14 days) for delayed signs of toxicity and mortality.

Antioxidant study

2,2'-azino-bis (3ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical scavenging activity

The ABTS radical scavenging activity was determined according to the method described by Re *et al*. (1999). The ABTS radical cation was formed following the reaction of ABTS stock solution (5 mL)

and 2.45 mM potassium persulphate ($K_2S_2O_8$) solution (5 mL), then stored in a dark room at ambient temperature for 16 hours. The extract (0.5 ml) was added to 4.5 ml ABTS radical cation solution in test tubes and incubated at ambient temperature for 6 min. The absorbance was measured at 734 nm. Blanks were used for each assay. The inhibition percentage was calculated using the following formula:

ABTS scavenging activity = [(A0 - A1)/A0] x 100

A0 = absorbance of the control; A1 = absorbance of the extract.

Total flavonoid assay

The total flavonoid content of the extract was determined using the colorimetric aluminum chloride method described by Ebrahimzadeh *et al.* (2008). Five milliliters (5 ml) of 2% aluminum (III) chloride ($AlCl_3$) in methanol was mixed with 5 ml of the extract. Absorbance was read at 415 nm after 10 min against a blank sample consisting of 5 ml extract solution and 5 ml methanol without $AlCl_3$. The total flavonoid content of the extract was calculated using a standard curve with rutin (0-100 mg/l) as the standard.

Total phenolic content

The total phenolic content of the extract was determined according to the method described by Dewanto *et al.* (2002). The extract (0.5 mg) was dissolved in Folin–Ciocalteu reagent (100 µl) and distilled water (6 ml). The mixture was vortexed for 1 min, and then 2 ml of 15% Na_2CO_3 was added and vortexed again for 30 s. The solution was made up to a volume of 10 ml. After 1 h 30 min, the absorbance was measured at 750 nm using a UV spectrophotometer. Gallic acid solution was used to prepare the calibration curves. The total phenolic content of the extract was expressed as milligrams of gallic acid equivalent (mg GAE)/100 g dry weight.

Ferric reducing antioxidant power (FRAP) assay

The ferric reducing antioxidant power was measured using the method described by Benzie and Strain (1996). The FRAP reagent was prepared by mixing 300 mM sodium acetate buffer (pH 3.6), 10.0 mM TPTZ tripyridyltriazine TPTZ (solution and 20.0 mM $FeCl_3.6H_2O$ solution in a 10:1:1 volume ratio. Different concentrations of the extract (100 – 400 µg/ml) (0.5 ml) were added to the FRAP reagent (3 ml). The reaction mixture was then incubated at 37°C for 30 min. The increase in the absorbance was measured at 593 nm using a spectrophotometer. Ferric reducing antioxidant power was calculated using the following formula:

FRAP = [(A1 – A2)/A1] × 100
A1 = absorbance of the control and A2 = absorbance of the extract.

Total antioxidant capacity (TAC)

Total antioxidant capacity of the extracts was evaluated using the method described by Prieto *et al.* (1999). The extract (0.1 mL) was added to 1 mL of the reagent (28 mmol/L Na_3PO_4, 4 mmol/L ammonium molybdate and 0.6 mol/L H_2SO_4) in test tubes. The tubes were incubated in a thermal block at 95 °C for 90 min. The mixture was allowed to cool to room temperature. The absorbance was measured at 695 nm against a blank. Antioxidant capacity was expressed as milligram gallic acid equivalent per gram of dry weight (mg GAE/g DW). The calibration curve range was 0–500 mg/ml

Antiproliferative study

Viability of the experimental seeds

The experimental plant *Sorghum bicolor* was purchased from a local market in Abraka, Delta State, Brazil. The cells were subjected to viability tests by placing in a quarterly vessel filled with water. Floating seeds were considered non-viable and disposed of, whereas submerged seeds were considered viable. The samples were cleaned with alcohol and dried at room temperature.

Anti-proliferative activity

This study was conducted following the procedures described by Ayinde *et al.* (2011) and Enegide *et al.* (2014), with slight modifications. Twenty viable seeds were submerged in 20 ml of distilled water, methotrexate (0.1 mg/mL), or *S. innocua* ethanol extract (0.1 – 50 mg/mL) in small sample bottles for 24 h. Thereafter, they were transferred to individual petri dishes layered with cotton wool and filter paper (Whatman No. 1). The seeds were incubated in a dark room and observed for growth after 24 h. The length (mm) of the radicles emerging from the seeds was measured after 48 h and 72 h. The procedure was performed in duplicate.

Isoniazide induced seizure test

Twenty-five male and female Swiss albino mice of both sexes were used in this study. The animals were randomly assigned to five groups of five animals each. They were treated with vehicle, extract, or a

standard drug. Group 1 received distilled water 10 ml/kg p.o., groups 2 – 4 were administered graded doses of the extract (250, 500, and 1000 mg/kg p.o., respectively), and group 5 was administered diazepam 0.5 mg/kg i.p. One hour after oral administration or 30 min after i. p. administration, isoniazid 300 mg/kg was administered to each mouse. The onset of seizures and survival times were recorded.

Statistical analysis

Data are expressed as the mean ± standard error of the mean (mean ± SEM). One-way analysis of variance (ANOVA), followed by Dunnett's post-hoc test, was used to test for significance. Statistical significance was set at $P < 0.05$. GraphPad Prism (version 8.0) was used for all the analyses.

Result

Phytochemical constituents of the extract

The phytochemical screening of the extract revealed the presence of tannins, alkaloids, cardiac glycosides, phenols, and flavonoids in high quantities. Steroids and saponins were also detected in the extract (Table 1). *Acute oral toxicity (LD_{50})*

No treatment-related signs of toxicity were observed at any of the extract doses during or after the treatment. Mortality was not recorded at any dose for up to 14 d after oral administration. The LD_{50} of the extract in mice was considered greater than 5000 mg/kg p.o.

Antioxidant activity

Results of the ABTS test revealed that the inhibitory activity of the extract at 100 – 400 µg/mL was 22.66 – 51.69 % (Table 2). For the total phenolic content, the highest concentration (400 µg/mL) of the extract was shown to contain 125.10±7.93 mg GAE/g dw (Table 2). The total antioxidant capacity was highest at 400 µg/mL, with 862.9 ± 6.00 mg GAE/g dw (Table 2). The ferric reducing antioxidant power assay revealed that 100 µg/mL of the extract had the highest FRAP (38.32 ± 2.72 µM Fe^{2+}/g), while in the total flavonoid content assay, 400 µg/mL had 87.49 ± 2.22 mg rutin/g dw (Table 2).

Antiproliferative activity

The antiproliferative assay revealed that graded concentrations of the extract demonstrated significant ($P < 0.05$) activity after 48 and 72 h. The threshold concentration of the extract was set at 10 mg/mL. The highest extract concentration (50 mg/mL) showed the greatest inhibitory effect on radicle proliferation after 72 h (Figure 1 – 2). Methotrexate also showed significant inhibitory activity throughout the study.

Anti-seizure activity

The extract prolonged both seizure onset and survival times compared to those in untreated animals. The extract demonstrated significant ($P < 0.05$) activity at all test doses (250 – 100 mg/kg) in a non-dose-dependent manner, with the 250 mg/kg extract having the highest effect (Figure 3). Diazepam also demonstrated anti-seizure activity during the study period.

Table 1: Qualitative phytochemical screening of the extract

Phytochemical	Inference
Tannins	++
Saponins	+
Alkaloids	++
Cardiac glycosides	++
Steroids	+
Phenols	++
Flavonoids	++

+=Present; ++=Highly present

Table 2: Antioxidant property of the extract

Concentration (µg/mL)	Total flavonoids content (mg rutin/g dw)	FRAP content (µM Fe (II)/g)	TAC (mg GAE/g dw)	ABTS (% inhibition)	Total phenol content (mg GAE/g dw)
100	63.83 ± 5.11	38.32 ± 2.72	262.7 ± 7.37	22.66±1.05	108.00±4.50
200	71.07 ± 5.90	25.69 ± 10.21	469.4 ± 7.38	31.31±2.91	114.40±5.87
300	80.20 ± 3.50	20.29 ± 2.72	438.0 ± 12.10	41.61±0.33	119.00±6.16
400	87.49 ± 2.22	32.00 ± 1.37	862.9 ± 6.00	51.69±2.22	125.10±7.93

n = 3, Values are expressed as the mean ± SEM. FRAP = Ferric reducing antioxidant power, TAC = Total antioxidant capacity, ABTS = 2,2'-azino-bis (3ethylbenzthiazoline-6-sulphonic acid

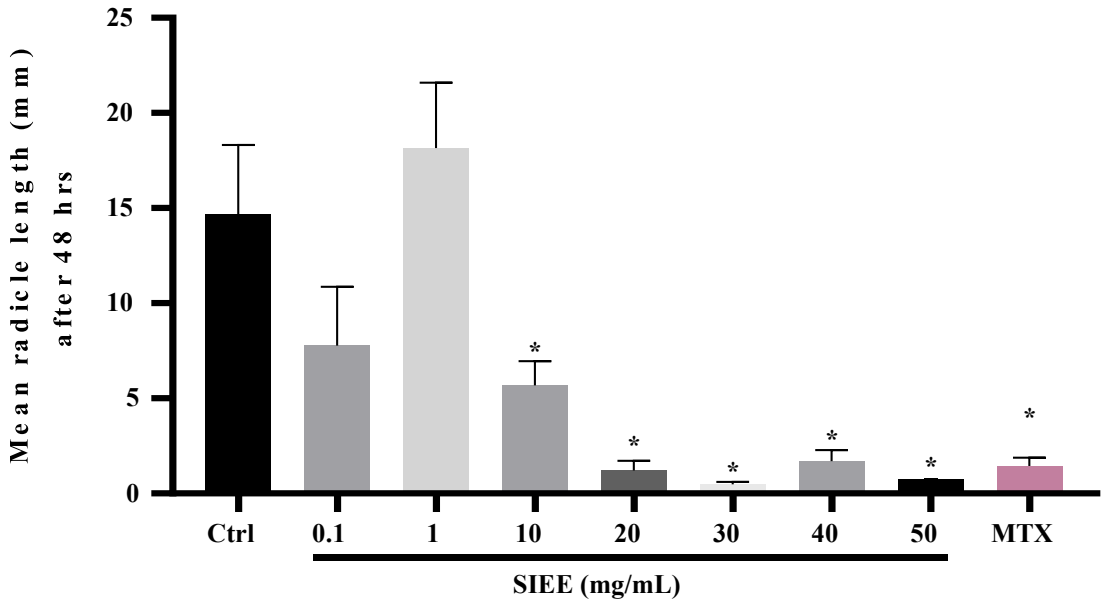

Figure 1: Antiproliferative effects of the extract after 48 h Values expressed as mean ± SEM, n= 5, *P < 0.05 using ANOVA and Dunnet's post-hoe test. SIEE = *Strychnos innocua* ethanolic leaf extract, Ctrl = control, MTX= methotrexate

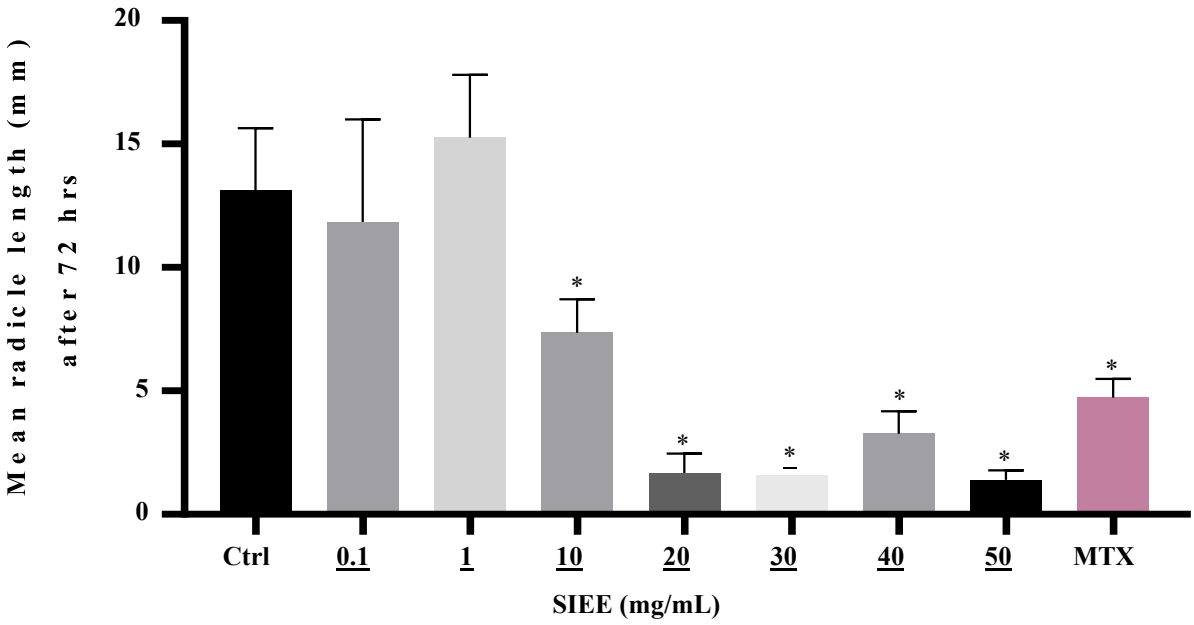

Figure 2: Antiproliferative effects of the extract after 72 h Values expressed as mean ± SEM, n= 5, *P < 0.05 using ANOVA and Dunnet's post-hoe test. SIEE = *Strychnos innocua* ethanolic leaf extract, Ctrl = control, MTX= methotrexate

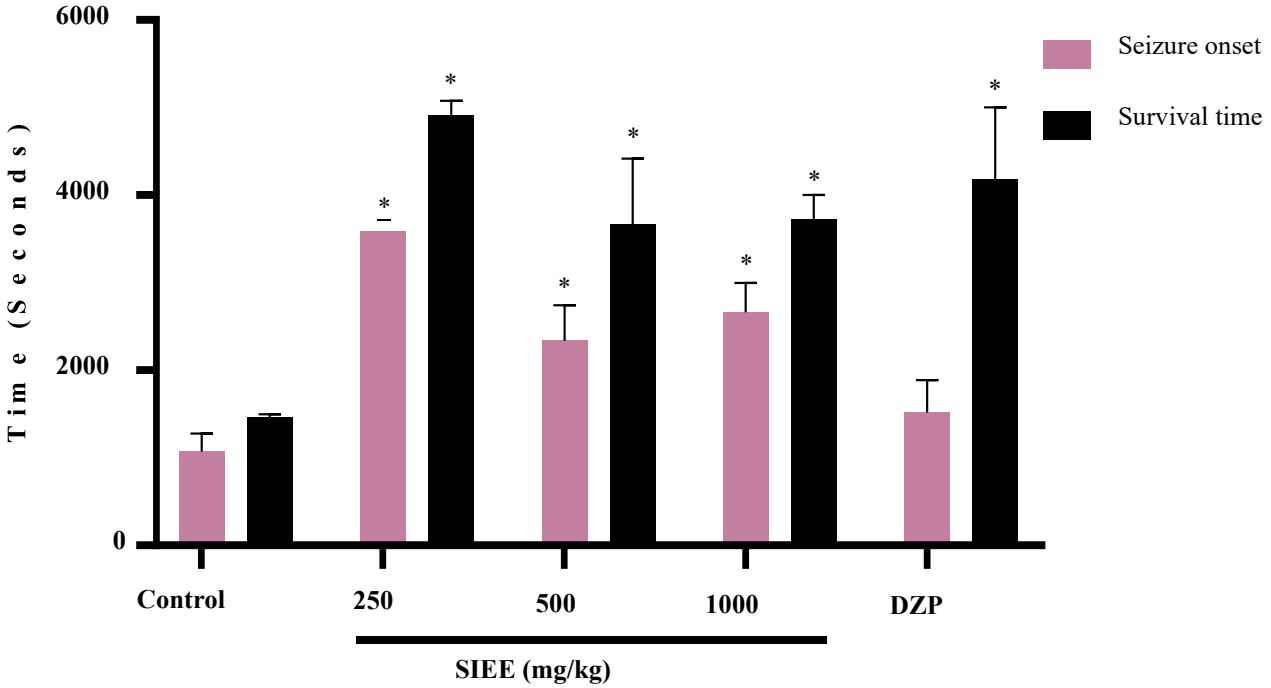

Figure 3: Anti-seizure effect of the extract on isoniazide-induced seizures. Values expressed as mean ± SEM, n= 5, *P < 0.05 using ANOVA and Dunnet's post-hoe test. SIEE = *Strychnos innocua* ethanolic leaf extract, Ctrl = control, DZP = diazepam

Discussion

Strychnos innocua is a herbal plant with several medicinal applications. This study evaluated the antioxidant, anti-proliferative, and anti-seizure potential of ethanolic leaf extracts using preclinical models. The study outcomes indicated that the extract has potent antioxidant, anti-proliferative, and anti-seizure potential, as demonstrated by the different models employed in this study. Qualitative screening of the extracts revealed the presence of important bioactive phytochemicals. Some phytochemicals have been reported to exert several therapeutic effects. Phenols have been widely reported to elicit potent antioxidant activities in several experimental models (Alakrishnan *et al*., 2021). In addition, the anticancer and anti-seizure activities of alkaloids, flavonoids, phenols, and saponins from different plants have been reported (Waris *et al.,* 2024). Thus, the bioactivity demonstrated by the extract could be attributed to the array of phytochemicals present therein. In the antioxidant study, the extract demonstrated good activity in different models used to evaluate antioxidant properties. The extract had a high total antioxidant capacity with its best effect observed at 400 µg/mL Its ABTS inhibitory activity was 51.69% at the highest dose

Cancer cells are known to proliferate rapidly, and this is also observed in the meristematic cells of *S. bicolor* seeds under suitable conditions (Manzano *et al*., 2013), which is the basis for their use. The use of rapidly proliferating seed radicles as a preliminary test for evaluating suspected anti-cancer agents is a well-established experimental model that has been used previously (McLaughlin *et al*. 1991, Sogbaike *et al*. 2002, Ayinde *et al*. 2010, Mannino *et. al*., 2022, Kaur *et. al*., 2022). The antiproliferative study revealed that the radicles from untreated seeds grew rapidly throughout the study period, demonstrating their ability to mimic the rapid proliferation of cancerous cells. The extract demonstrated significant ($P < 0.05$) inhibition of radicle proliferation at concentrations of ≥ 10 mg/mL. This is in line with the findings of Milella *et al*. (2023) that there is a correlation between antioxidant and anticancer activities and the phenolic profile.

An acute toxicity test showed that the lethal dose of the extract was greater than 5000 mg/kg in mice.

According to previous studies (Corbett *et al.,* 1984; Kennedy *et al*., 1986; Syahmi *et al.*, 2010), substances with LD_{50} values exceeding 5000 mg/kg are considered safe or practically non-toxic. The absence of mortality and other observable signs of adverse effects at doses of up to 5000 mg/kg indicates that the extract is practically non-toxic in mice orally, thus justifying the extract doses used for the anti-seizure study.

Isoniazid-induced seizures are among the most widely accepted preclinical models for screening pharmacological agents for potential antiseizure activity (Kupferberg, 2001). Isoniazid induces seizures through a cascade of events that culminate in the reduction of GABA and increase in glutamate in the CNS, leading to excessive firing of brain neurons (Sumadewi, 2023). Agents that inhibit or delay seizure onset and prolong the survival of animals are considered potent anti-seizure agents (Eltokhi *et al*., 2021). The extract demonstrated a significant ($P < 0.05$) non-dose-dependent antiseizure effect. This activity may be due to inhibition of excessive brain firing by inhibiting GABA depletion or excessive glutamate activity in the brain. It may also prevent oxidative damage in neurons by neutralizing reactive oxygen species.

Conclusion

This study revealed that the extract of *Strychnos innocua* demonstrated potent antioxidant, antiproliferative and anti-seizure activities and shows good potentials as a novel anti-cancer agent

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Conflict of interest

The authors declare that they have no conflicts of interest.

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