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"Evaluation of Antiepileptic and Histopathological Effects of Methanolic Leaf Extract of Amaranthus cruentus L. in Mice."

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KEYWORDS

Amaranth species, Antiepileptic activity, Histopathology , Caryophyllene.

GABA, CB2 receptors, PTZ Model.

ABSTRACT:

Introduction: Epilepsy is a major health issue with significant psychosocial consequences. Epileptic seizures are a relatively common issue in neurodegenerative illnesses. Antiepileptic medications treat seizures but do not prevent or reverse the underlying pathology.

Although medications are generally well tolerated, there is still a need to find new ones with fewer side effects and more efficacy. The goal of this research was to investigate albino mice for the antiepileptic properties of the leaf extract of Amaranthus cruentus L. in methanol.

Method: The Amaranthus cruentus L. leaves were extracted with methanol using the Soxhlet extraction method. The extract was examined for phytochemical testing. TLC and column chromatography were used to fractionate the chemical components. Fractions were analysed using FTIR and GCMS-MS. Methanolic extract was tested for acute oral toxicity and antiepileptic activity .Antiepileptic activity carried out by inducing seizures with an intraperitoneal dosage of 35 mg/kg PTZ in saline solution. The methanolic extract was tested for antiepileptic activity in Swiss albino mice using the PTZ technique at doses of 200 and 400 mg/kg body weight. The standared medicine used is diazepam at a dose of 2 mg/kg. Histopathological investigation of the brain tissue samples using microscopy to observe cellular changes, inflammation, or other pathological alterations that might be associated with antiepileptic effects.

Result: Amaranthus cruentus L plant leaf methanolic extracts contain phytochemicals such as alkaloids, steroids, glycosides, amino acid flavonoids, carbohydrates, and phenolic tannins. The methanol extract of Amaranthus cruentus yields 8%; FTIR and GCMS-MS analyses reveal distinct compounds. Amaranthus cruentus extract at 200 mg/kg and 400 mg/kg body weight resulted in p-values < 0.05 for epileptic score, $p < 0.001$ for convulsion latency, and $p < 0.001$ for convulsion duration. The percentage of protection value was $p < 0.001$. In addition, the extract has dosage-dependent activity; as the dose increases activity increases.Histopathology study of brain shows some neuroprotective activity.

Conclusion: Amaranthus cruentus L plant leaf methanolic extracts shows significant Antiepileptic activity

INTRODUCTION

One serious medical condition that has a significant emotional impact is epilepsy. Epileptic seizures are a prevalent issue in neurodegenerative diseases. [1,20,26]. Patients with epilepsy frequently exhibit psychological comorbidity, such as anxiety, which significantly affects their quality of life. Unquestionably, synthetic antiepileptic medications are effective; yet, the main problems are still their toxicity, side effects, and limited safety margin. [2-4]. However, natural compounds have been showing promise as substitutes for pharmaceutical

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anxiolytic and antiepileptic medications.[5,19,21,22;30,31,32]. Physicians in Europe and Asia are increasingly using traditional herbal medicines to treat various neurodegenerative diseases. [6]. Amaranth, also known as amaranthus, is one of the oldest plant crops and has a great tolerance for drought, salinity, alkalinity, and acidic soil conditions. It is a member of the Amaranthaceae family, which has 850 species and 65 genera. Amaranthus is a genus of 50–60 species that are grown for their leaves. Amaranthus cruentus, also known as A. caudatus, A. hybridusi, A. hypochondriacus, A. bilitum, A. tricolour, A. gangeticus, A. tristis, A. melonch, A. managostanus, and A. polygamous, is one of the main Amaranthus species.[7] Amaranthus is a crop with rapid growth that is primarily grown in Latin America, Africa, and Asia. Amaranthine, a component of the broad class of substances known as betacyanins, is found in amaranth.[8 Amaranth has medical benefits such as decreasing cholesterol, antioxidant, anticancer, an tiallergic, and antihypertensive activities due to its high protein level and amino acid com position.[9]Antiamnestic, antithrombotic, immunomodulating, opioid, regulating, antioxidant, ligand, activating ubiquitin-mediated proteolysis, immunostimulating, embryotoxic, protease inhibiting, and antihypertensive due to its active peptides were found in amaranth Proteins.[10] This suggests that amaranth lunasin is a more effective peptide for preventing cancer. A lipid-transfer protein contains the amaranth lunasin peptide, and not in conjunction with a Bowman-Birk protease inhibitor, as a soybean was reported. Plants that contain lunasin can bolster fresh study on amaranth as a substitute food, contains peptides with health-promoting properties.[11]

MATERIAL AND METHODS:

Material:

Methanol, Diazepam, PTZ , Normal saline

Collection, Identification, and Extraction of Plant Material

Fresh leaves of *Amaranthus cruentus L* were collected from the Miraj Local Area of Maharashtra State. Dr. S. M. Shendage Sir identified and authenticated the plant at the Department of Botony, Balwant College, Vita Dist Sangli outward No. 005/2022-2023

Preparation of Plant Material:

Fresh leaves of *Amaranthus cruentus* (Amaranthaceae) were separated from the plant, cleaned, air-dried in a shaded environment, and crushed into a coarse powder using a pestle and motor. 100 g of the crude powder was extracted 250ml methanol with soxhlet extraction. Solvent was evaporated to get dry extract. The resulting extract was stored in a tightly labelled container for subsequent experiments.

Phytochemical Analysis:

In phytochemical analysis we get phenolic, Flavonoid , Glycoside, carbohydrate, terpenoids alkaloid and amino acid test positive.

Isolation and Purification of Extract:

The separation and purification of plant components was achieved primarily by one or more fractionation procedures based on different chromatographic techniques. Thin layer Chromatography (TLCs), column Chromatography (CTs),

Column chromatography of methanol ether extract of plant *Amaranthus cruentus linn:*

A quantity (5 g) of extract was used for part isolation. The extract was dissolved in a minimal amount of ether which poured over the chromatographic bed and was coated in cotton wool.For isolation, a solvent mixture of increasing polarity, beginning with a petroleum ether, was eluted to the column, and then n-Hexne : Ethyl acetate: Formic acid (5:4.5:0.5) set volume fractions (e.g. 20ml), cumulative fractions from the column were collected. further study of its identification was carried out by means of analytical methods such as FTIR, GC-MS-MS

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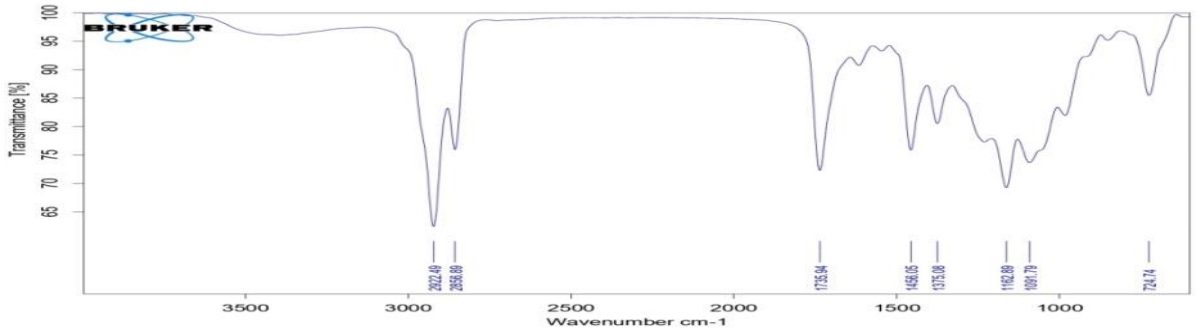
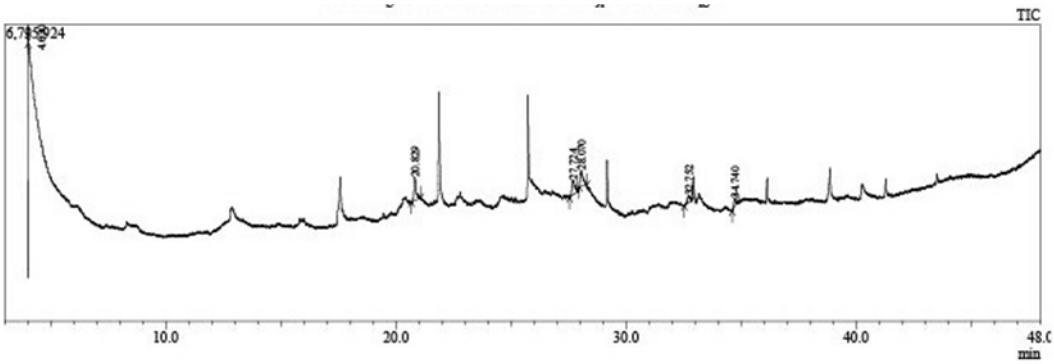
CHARACTERIZATION OF ISOLATED COMPOUNDS BY SPECTRAL DATA

Fig No. 1 FTIR spectra of *Amaranthus cruentus linn* Fraction A methanol.[40]



Sr,NO	Literature Value (cm-1)	Observed Value (cm-1)	Indication
1	2800-3000	2922.49	NH Stretch
2	2800-3000	2858.89	NH Stretch
3	1720-1740	1735.94	C=O Stretch
4	1450-1465	1456.05	C-H Sretch
6	1335-1370	1375.08	S=O Stretch
6	1163-1210	1162.89	C-O Stretch
7	1091	1091.79	C-O Stretch
8	680-724	724.74	C-H Stretch Benzene Derivative

Table No:1 IR intertpretation of *Amaranthus cruentus linn* Fraction A methanol. [40]



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Name
1	4.030	4.025	4.040	135748	1.14	Propanedioic acid, dihydroxy-
2	20.829	20.680	21.080	3615536	30.39	Caryophyllene
3	27.724	27.560	27.900	2977540	25.03	2-Pentadecanone
4	28.070	27.980	28.310	3119063	26.22	Pentadecanal-
5	32.752	32.540	32.880	1267320	10.65	2-Nonadecanone
6	34.740	34.620	34.815	781546	6.57	Docosanoic acid, ethyl ester
				11896753	100.00	

Fig No 2.GCMS Of Fraction A In Methanol [20,24,25,27,28]

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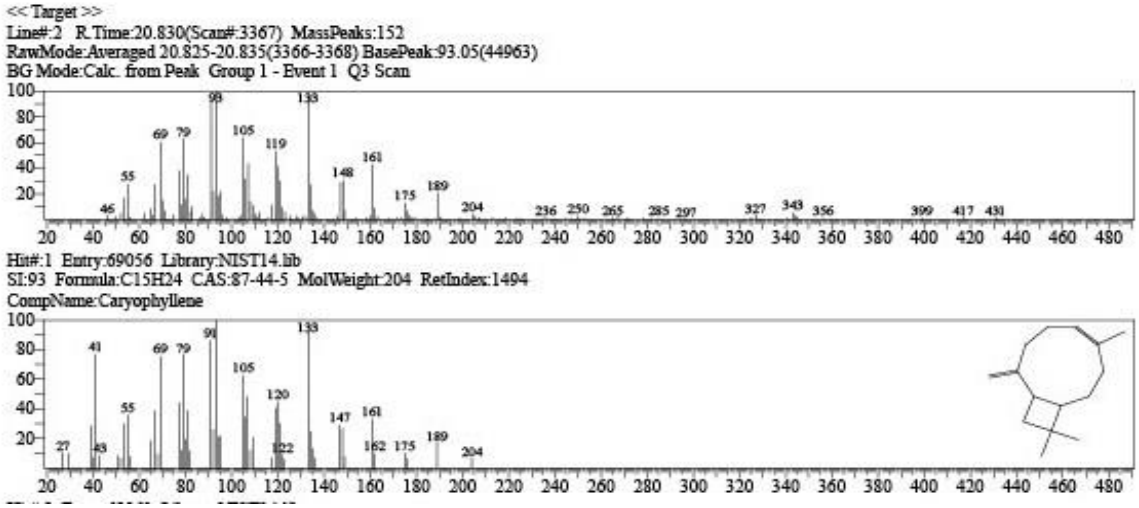
GCMS MS of fraction A in methanol of *Amaranthus cruentus linn* contain propanedionic acid, caryophyllene, 2-Pentadecanone ,pentadecanal,2- nonadecanone, docosanoic acid erthy ester as chemical components



ACUTE TOXICITY STUDIES

In accordance with updated OECD Guideline 423, the acute oral toxicity of an methanolic extract of *Amaranthus cruentus* was investigated. When extract administered orally to 3 mice in doses up to 2,000 mg/kg, the extract showed no toxicity. Therefore, during the study, extract dosages of 200 and 400 mg/kg were chosen.

ANTICONVULSANT ACTIVITY (PTZ INDUCED CONVULSION) [12,13 14,15]

1) We acquired adult male Swiss albino mice that were 7–10 weeks old and weighed 35–45 g.

2) The experimental animals were housed at the Laboratory Animal Research Centre, where they were given an abundance of food and water during the trial, as well as a 12-hour light/12-hour dark cycle at 20–24°C.

3) The Institutional Animal Care and Use Committee-approved guidelines were followed in all experimental operations. Ethics approval number is IAEC/AMCP/O4/387/2023-2024

4) The mice were split into Six groups at random:

Group-1 (n=6): Received normal saline (DW(10ml/kg)+0.1% Saline solution)

Group-2 (n=6): Disease Control (DW +PTZ)

Group-2(n=6): Received standard drug, diazepam (2mg/kg.oral*)*

Group-3(n=6): Received methanol extract of leaves of AV (200mg/kg;. oral Low dose)

Group-4(n=6): Received methanol extract of leaves of AV (400mg/kg;. oral High dose)

The mice were given two oral doses of Plant Extract A (200 and 400 mg/kg) 30 minutes before to PTZ injection.

5) An intraperitoneal injection of 35 mg/kg of PTZ in saline solution was administered to the male mice.

6) Following each injection, convulsive behaviour was monitored for 30 minutes, and the ensuing seizures were graded using the following system [16,17]

0 – No Response

1 - Immobilization and staring stage

2 – Head nodding

3 – Rearing accompanied by forelimb clonus and wet dog shakes

4 – Falling and wobbling stage

5 - Jumping circling or rolling

6 - Severe tonic clonic seizures

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The mice were killed nearly 30 minutes after the final treatment, and their brains were stored at -8°C in formalin solution until they were needed again. (Naseer et al., 2013).

Hematoxylin and Eosin Staining [18]

Tissue sections of each group (n = 4) were fixed in 4% formaldehyde with PBS (0.1 M) and washed with water. Brain sections were dehydrated with ethyl alcohol dilutions from 70 to 100%. After that, brain tissues were washed with xylene and fixed in paraffin. Paraffin blocks were cut into 4 µm sections, deparaffinized with xylene, and hydrated by graded ethyl alcohol dilutions (from 100 to 70%). Sections were stained with Harris' hematoxylin solution (Sigma-Aldrich, St. Louis, MO, United States) for 3 min and eosin Y (Sigma-Aldrich) for 1 min after that brain tissues were cleaned with water, dehydrated with graded ethyl alcohol series, mounted (Thermo Fisher Scientific, Waltham, MA, United States), and photographed using an Olympus microscope (Olympus, Tokyo, Japan).

Statistical Analysis

The collected data is reported as mean ± SEM, and results are presented in tables. Data were analysed using one-way ANOVA and the Dunnett post hoc test in SPSS version 22 software. A p-value of ≤0.05 was considered significant.

RESSULT:

Table No 2: Effects of *Amaranthus cruentus linn* methanolic extract on the Epileptic score, latency of convulsion, duration of convulsion, protection against seizures in mice.[39]

GROUPS	Number of Mice(n)	Epileptic Score (Racine scoring scale)	Latency of Convulsion (min)	Duration of Convulsions (min)	Protection Against Seizures (%)
DW +Saline	6	0	-	0	100
DW+ PTZ	6	5.833 ± 0.1667 #	4.115 ±0.9851 #	14.92 ± 1.003 #	8.833 ± 2.600 #
PTZ+Diazepam	6	2.333 ± 0.4944 ***	14.61 ± 2.409 ***	4.502 ± 2.256 ***	91.00 ± 1.125 ****
PTZ+200 mg/kg Extract	6	4.000 ± 0.5164 *	10.36 ± 1.115 *	9.333 ± 0.6807 *	48.50 ± 2.668 *
PTZ+400 mg/kg Extract	6	3.667 ± 0.6146 *	11.97 ± 1.570 **	7.607 ± 1.169 **	56.50 ± 4.153 **

Results are expressed as Mean ± SEM (n = 6 mice per group). Epileptic sore, Latencies, duration of convulsion and Protection agaist seizures were analysis by one-way ANOVA, * P < 0.05, * * P < 0.01; * ** P < 0.001 significantly different compared with treated PTZ group, Diazepam 2 mg/kg, 200mg/kg *Amaranthus cruentus* ,400mg/kg *Amaranthus cruentus ,* 35 mg/kg pentylenetetrazole

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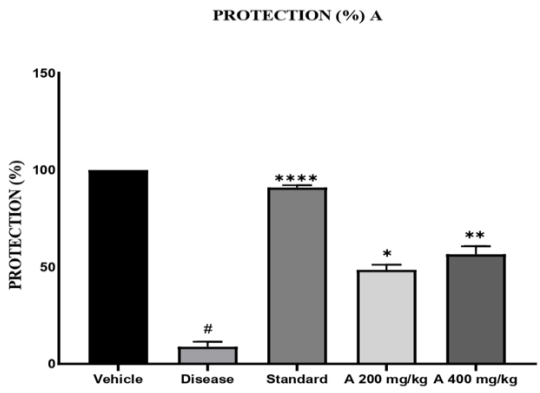
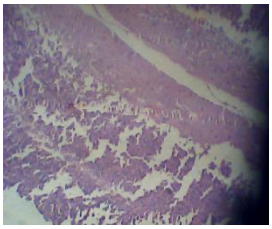
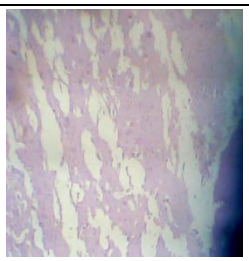
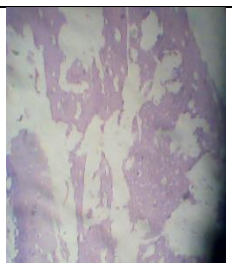
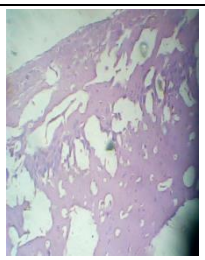
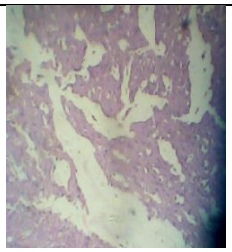
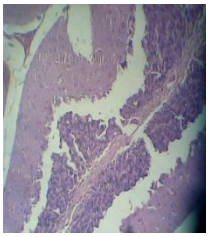
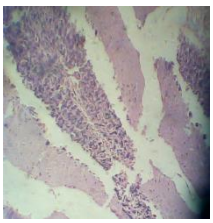
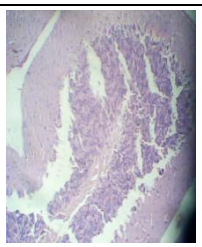
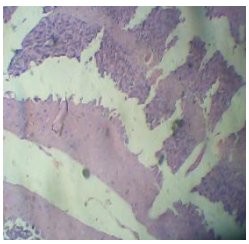
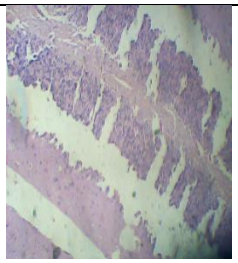
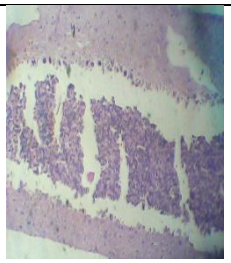
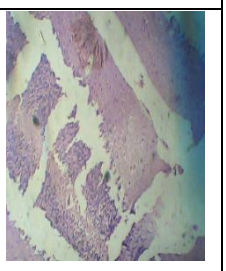


Fig No 3: % Protection against convulsion [18]

Percent Protection = [(Number of protected mice in control group - Number of protected mice in treated group) / Number of protected mice in control group] * 100

Histopathalogy[18]

The haematoxylin and eosin-stained sections clearly demonstrated that the neurones in the hippocampus CA1, CA3, dentate gyrus regions, and cortex of each mouse in the saline group were tightly packed together, with flawless contours and translucent cytoplasm (Fig. 4). The granule cell layers in the Disease group were drastically reduced, neurones were absent and arranged in an irregular manner. When compared to saline group, the plant extracts (200 mg/kg and 400 mg/kg) significantly reduced these structural changes in the hippocampus and prefrontal cortex, respectively. Amaranth-treated animals did not exhibit meningeal congestion, cerebral oedema, neuronal eosinophilia, meningeal inflammation, or cerebral congestion.These results indicate that the plant extract may have neuroprotective qualities, potentially decreasing the negative consequences of PTZ-induced neurotoxicity. Further research is necessary to establish the mechanisms behind these protective benefits.

GROUPS	IMAGES			
DISEASE DW+ PTZ				
VEHICLE DW +Saline				
STD 1 PTZ+Diazepam				

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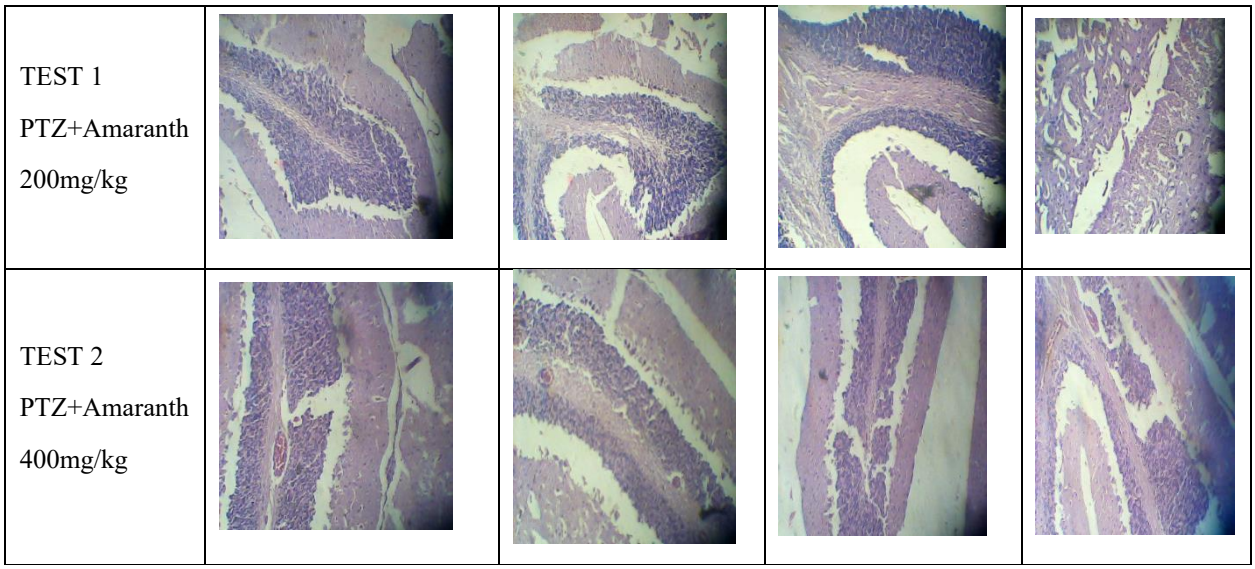

Fig No. 4 A photomicrograph, after haematoxylin and eosin staining of treated PTZ group,Saline, Diazepam 2 mg/kg, 200mg/kg Amaranthus cruentus ,400mg/kg Amaranthus cruentus. [18]

DISCUSSION: Preliminary phytochemical screening on the methanol leaves extract of Amaranthus cruentus revealed the presence of phenolic, Flavonoid, Glycoside, carbohydrate, terpenoids, alkaloid and amino acid. Previous studies on Amaranthus cruentus have reported the presence of various phytochemicals such as polyphenols, tannins, flavonoids, steroids, terpenoids, saponins and betalains. [33] In GCMS-MS analysis shows the peak of caryophyllene this constituent have been reported to be associated with different pharmacological activities and are explicitly related to some medicinal properties [34] Caryophyllene were reported to enhance GABA-mediated inhibitory neurotransmission and also it was found to elicit a full agonist action on cannabinoid type 2 (CB2) receptors . Seizures and epilepsy are associated with low levels of GABA. With decreased levels of inhibition in the cerebral cortex, cells become depolarized, leading to seizure activity. GABA agonists are used for the treatment of seizures. Activation of CB2 receptors notably appeared devoid of psychotropic adverse effect of cannabinoids contrary to the CB1 receptors. Activation of CB2 receptors has been shown to reduce neuroinflammation, a key factor in epilepsy development, and modulate seizure activity. [23,35,36] Thus, this active chemical constituent in the methanolic leaf extract of Amaranthus cruentus may be responsible for the anticonvulsant activities observed in this study. The anticonvulsant activity in this study might be attributed to different biologically active components in the leaf extract.

Pentylenetetrazole causes convulsive episodes by blocking gabaergic pathway Diazepam, a medication used to treat absence seizures, can also decrease PTZ-induced seizures by enhancing GABA-facilitated inhibition in the brain. [37] GABA has been identified as the primary inhibitory neurotransmitter in mammals' central nervous systems and has been linked to convulsions, as it mediates the inhibition of neuronal responsiveness and activity by increasing chloride-ion conductance via the opening of the chloride ion channel. [38] Although the plant extract greatly reduces the epileptic score, it is thought to have anticonvulsant properties since it delays the start of convulsions and shortens the length of disruptions. Additionally, some protection was demonstrated against seizures, indicating significant anticonvulsant efficacy against PTZ-induced seizures. According to the findings, the plant extract's anticonvulsant effects, which are similar to diazepam in the PTZ model, could be attributed to its influence on the GABA system.[29]

CONCLUSION: In the present study, we selected plant *Amaranth cruntus Linn*, which belongs to the family Amaranthaceae. In phytochemical screening of methanolic extract of plant we identified phenolic, flavonoid, glycoside, alkaloid, amino acid, steroid, protein and carbohydrate phytochemical constituents.

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These compounds demonstrate a wide range of biological activities, suggesting potential therapeutic applications. In spectroscopic analysis we reveal the presence of caryophyllene as an active component. While comparing *Amaranthus cruentus L.* methanol extracts of doses of 200 mg and 400 mg per kilogram of body weight with the standard, the 400 mg/kg body weight dose shows efficacy against PTZ-induced seizures. A histopathology study of the brain showed that plant extract reduces neuroinflammation in the hippocampus and prefrontal cortex. The activation of GABAergic neurotransmission by *Amaranthus cruentus L.* might also explain its anticonvulsant activity. These preliminary preclinical data indicate Amaranthus cruentus L. potential for the development of novel anticonvulsant activity. Future research should focus on elucidating the specific pathways involved in its neuroprotective effects and its long-term safety profile.

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