*Original Article*

# Anticonvulsant and Anxiolytic Properties of the Roots of *Grewia bicolor* in Rats

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## ABSTRACT

**Background:** *Grewia bicolor* (*G. bicolor*) root is used in traditional medicine in Sudan to treat diseases of the nervous system such as anxiety and epilepsy and also to tranquilize agitated patients.
**Objectives:** To explore the anticonvulsant and anxiolytic activities of this medicinal plant in rats.
**Materials and Methods:** The ethanolic extract of the root of *G. bicolour*at (200, 400 and 800 mg/kg, i.p was studied for its anticonvulsant effect on four in vivo rat models (Maximal Electroshock Seizure (MES), Pentylenetetrazole (PTZ)-, picrotoxin (PIC)- and Strychnine (STR) - induced seizures). Simple activity meter was used for the evaluation of the anxiolytic properties. Sodium valproate (400 mg kg) was used as a reference anticonvulsant drug for all models. The protection from tonic convulsions and the number of protected animals from seizures were noted. The numbers of movements between the squares in the activity meter were counted in the consecutive 5 minutes and the motor activity was observed.
**Results:** *G. bicolour*root extract showed marked anxiolytic effect and significant decrease in the motor activity ($p< 0.05$) since the first dose (200mg/kg) in a dose-dependent manner. The doses (400-800 mg/kg) of the extract significantly ($p < 0.01$ - $p < 0.001$) reduced the duration of seizures induced by maximal electroshock (MES) and delayed the onset of tonic-clonic seizures produced by strychnine, whereas, all the tested doses significantly protected the animals (up to 100%) from pentylenetetrazole- and picrotoxin- induced seizures.
**Conclusion:** *G. bicolour*root seemed to possess anticonvulsant and anxiolytic effect in rats.

**Keywords:** Anxiety, Epilepsy, Extract, *G. bicolour*, Seizures, Traditional medicine.

Traditional medicine in many areas of the world relies on the use of a wide variety of plant species. Only 10% of plants have been studied for their pharmacological properties[1]. In folk medicine, a number of species of genus *Grewia* have been used as medicinal agents to treat several diseases in different parts of the globe. The extract and preparation from various species exhibited various biological effects, e.g. antioxidant, anti- bacterial and analgesic effect[2]. *G. bicolor* is one of the medicinal plants used in Africa and Sudan. The Petroleum ether extract of *G.bicolor* is used for treating postulant skin lesions and sometimes also as a tranquilizer[3]. The three alkaloids: Harman, 6-methoxyharman and 6-hydroxyharman isolated from the methanol extract of this plant, have antibacterial properties[3]. Mohammed *et al*[4] reported pharmacological activities of *G. bicolour* roots and proved that the active compound, apparently a peptide, exerted a serotonin-like effect on rat uterus, rat fundus and rabbit jejunum.

This research work aimed to assess and evaluate the anticonvulsant and anxiolytic activity of *G. bicolour* root extract through using different animal models.

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## MATERIALS AND METHODS:

### Plant material:

*G. bicolour*roots were purchased from its natural homeland at Kurdufan Province, southwest Sudan. The plant was authenticated by Taxonomy Department of Medicinal and

Aromatic Herb Research Institute, National Council for Research, Khartoum, Sudan.

The roots were then washed and allowed to dry in open air for 7 days. The dried plant material was crushed manually using manual grinder into a fine powder.

Ethanolic extraction process was followed according to Pavia *et al*[5]. 100g of the grounded roots were transferred into a round bottom flask and submerged in 80% ethanol. The flask was stoppered and left for 24 hours. The extract was then filtered using sterile cotton pieces. The filtrate was re-submerged in the re-collected ethanol (from the previous step) and left again for 24 hours. This process was repeated 7 times till the remaining solvent became clear. Then, the filtrate was concentrated to a powdered form through complete evaporation of the extraction solvent at 80$^{o}$C, using gentle heat. The resultant residue was dried by dry air to a constant weight.

**Chemicals:**

Pentylenetetrazole, sodium valproate, picrotoxin and strychnine were used to induce seizers and all were from Sigma Chemical, USA.

**The experimental animals:**

Adult male rats, Wister Albino Rats (WAR), weighting 110-125g were housed in standard cages under controlled conditions at temperature (25°C) and relative humidity (40%) with a 12h light cycle beginning at 7 am. The rats were provided with standard diet (laboratory rodent's chow) and tap water. All experiments were carried out between 8 a.m. and 12 noon[6]. Rats were divided into five groups; each group received 3 different doses (200, 400 and 800 mg/kg. i.p) of the plant extract as one dose for one rat in each group. One group was given 400 mg/ kg. i.p sodium valproate as a reference drug (positive control). The last group was given 10ml/kg. i.p distill water (negative control).

**Phytochemical screening:**

Preliminary phytochemical characterization of the extract was done using methods already described for the determination of alkaloids, anthraquinones, flavonoids, glycosides, phenols, saponins and tannins by Harbone[7] with many few modifications.

**Measurement of anxiolytic activity in rats:**

An anxiety model, simple activity meter test, was used to explore the anti- anxiolytic effect of the tested extracts[8]. The simple activity meter is a box composes of two glassy and two wooden sides stand on 625 cm$^2$ wooden plane board divided into 25 squares, each square was 25 cm$^2$. A rat was placed on the center of the board and left to move freely for a period of 5 minutes. The number of movements between the squares were counted in the consecutive 5 minutes. Decrease in number of movements/5 minutes was taken as an indication of anti-anxiety activity and reflected the decrease in motor activity.

**Pharmacological tests and assessment of anticonvulsant activity:**

**Pentylenetetrazole (PTZ) -induced seizure test:** Myoclonic jerks seizures were induced in male rats by subcutaneous injection of 70 mg/kg pentylenetetrazol (PTZ) [9, 10, 11 and 12].

The protective effect of the different doses of the extract was recorded. The tested extract was given 45 minutes before PTZ injection. The positive control group received 400mg/kg. ip sodium valproate.

**Picrotoxin (PIC) - induced seizure test:** This model acts to disrupt the inhibition/excitation balance and creates an epileptogenic focus[13].

Clonic seizures were induced in male rats by subcutaneous injection of 10 mg/kg/i/p picrotoxin. The various doses of the decoction were given 45 minutes before picrotoxin administration while sodium valproate was given 15 minutes before picrotoxin injection. The protective percentage was then recorded.

**Maximal electroshock test (MES):** Tonic convulsions of the hind extremities of mice were induced by passing an alternating electrical current (50 mA, of 100 Hz frequency pulse/sec.) for 0.5 sec. duration through ear electrodes [11, 12, 13, and 14]. One group of five rats received distilled water and served as a negative control group. Another group of five rats received sodium valproate 400 mg/kg ip and served as a positive control

group. The other three groups received the three different doses of the extract. The number of animals protected from tonic hind limb extension was determined in each dose group.

**Strychnine (STR) test:** Convulsions followed by death were induced in male mice by the subcutaneous injection of 2.5 mg/kg strychnine (STR) nitrate. The protective effect of different intraperitoneal treatments given 45 minutes prior to STR was recorded. Animals that survived more than10 minutes were classified as protected. The positive control group received 400 mg/kg. ip sodium valproate [9, 11,15].

**Statistical analysis:**

The values are expressed as mean ± standard error mean (M ± SEM) and the data were analyzed using one way ANOVA followed by Tukey-Krammer test. The level of significance was set at $P < 0.05$. Median anticonvulsant dose ($ED_{50}$) was calculated according to the method of Litchfield and Wilcoxon[16]. A computer program was used to calculate 95% confidence limit of $ED_{50}$.

**RESULTS:**

**Phytochemical characterization:** Chemical characterization showed that the extract of *G. bicolor* contained alkaloids, anthraquinones, flavonoids, glycosides, phenols, saponins and tannins.

Table (1): The effects of *Grewia bicolor* extract on the motor performance in the simple activity meter test in the studied rats.

| Dose (mg/kg) i.p | | 200 (mg/kg) | 400 (mg/kg) | 800 (mg/kg) |
|---|---|---|---|---|
| Movements count/5 minutes | Mean ±SEM Control group | 39.4 ± 3.67 | 39.4 ± 3.67 | 39.4 ± 3.67 |
| | Mean ±SEM treated group | 28.6 ± 3.97 * | 12.4±1.54 *** | 10.4±1.63 *** |

Treatment was compared with control group. * $p< 0.05$, *** $p< 0.001$

Table (2): The effect of *G. bicolor* on Pentylenetetrazole (PTZ) – induced convulsions among the studied rats.

| Treatment | Sodium valproate | *Grewia bicolor* |
|---|---|---|
| $ED_{50}$ | 162 | 167.20 |
| (95% C.L.), mg/kg | (140-185) | (107.91 – 201.37) |

Three to 5 doses were used to calculate $ED_{50}$ (in mg/kg).

Table (3): The effect of *G. bicolor* against Picrotoxin (PIC)- induced convulsion in the studied rats

| Treatment | Sodium valproate | *Grewia bicolor* |
|---|---|---|
| $ED_{50}$ | 192.6 | 208.78 |
| (95% C.L.),mg/kg | (159-207) | (123.43 – 385.79) |

3 to5 doses were used to calculate $ED_{50}$ (in mg/kg).

**The effects of *G. bicolour*extract on the motor performance in the simple activity meter test:** The plant showed marked anxiolytic effect and significant decrease in the motor activity ($p< 0.05$) since induction of the first dose (200mg/kg) in a dose-dependent manner (Table (1)).

**Effect of *G. bicolor* on pentylenetetrazol-induced seizures:** *G. bicolor*extract exhibited appreciable anticonvulsant protection to the rats against PTZ-induced seizures. All the tested doses (200,400 and 800 mg/kg. ip) as well as sodium valproate 400 mg/kg. ip provided 100% protection to rats against PTZ-induced seizures as shown in table (2).

**The Effect of *G. bicolor* against Picrotoxin (PIC)- induced convulsion:** The plant extract proved a potent anticonvulsant activity against PIC-induced seizures. A dose of 200 mg/kg, ip appeared 40% protection against PIC-induced seizures while the protection ratio increased up to 80% after the administration of 400mg/kg ,ip. 100% protection was observed in the group that

Table (4): The effect of *G.bicolor* extract on maximal electroshock (MES)- induced seizures among the studied rats.

| Type of treatment | Dose rate (mg/kg) | Protection rate against MES % | Time (sec) for duration of recovery (Mean ± SEM) | Recovery/ death |
|---|---|---|---|---|
| Saline (Control) | ( 1 ml/rat) | 0 % | 174.20±23.01 | Recovery |
| Standard valproate | 400 | 100% | 0.00 ± 0.00*** | Recovery |
| *G.bicolor* | 200 | 0 % | 95.80±4.48* | Recovery |
| | 400 | 60 % | 12.20±9.89*** | Recovery |
| | 800 | 80 % | 4.00±4.00*** | Recovery |

*p < 0.05 significant, ***p < 0.001 highly significant (compared with the respective control).

Table (5): The effect of *G. bicolor* extracts on strychnine (STR) - induced seizuresin the studied rats.

| Type of treatment | Dose rate (mg/kg) | Protection rate against STR % | Time (Min) of the latency of convulsions (Mean ± SEM) | Survive/ death |
|---|---|---|---|---|
| Saline (Control) | ( 1 ml/rat) | 0 % | 3.20±0.86 | Death |
| Standard valproate | 400 | 100% | 0.00 ± 0.00*** | Survive |
| *G. bicolor* | 200 | 0% | 9.00±1.22 | Death |
| | 400 | 40% | 22.60±1.77* | Death |
| | 800 | 60% | 45.60±3.14*** | Death |

*p < 0.05 significant, ***p < 0.001 highly significant (compared with the respective control).

administered 800 mg/kg, ip. (Table (3)). Al the affected animals were recovered and no incidence of deaths was recorded.

**Effect of *G. bicolor* on maximal electroshock (MES) -induced seizures**: The anticonvulsant compound sodium valproate completely protected rats against MES-induced seizures (P < 0.001). The dose of 800 mg/kg showed 80% protection in the tested group and significantly (p< 0.001) decreased the recovery period by (4.00 ± 4.00) compared to the control group (174.20 ± 23.01 sec ). 400 mg/kg induced 60% protection against the MES with significant (p <0.001) decrease in the recovery period by (12.20± 9.89 sec) compared to the control. 200 mg/kg,ip showed significant (p <0.05) reduction in the recovery period which was (95.80±4.48 sec) (Table (4)).All the animals recovered and no deaths were recorded.

**Effect of *G.bicolor* on strychnine (STR)-induced seizures:** Sodium valproate completely protected the rats against STR-induced seizures (p< 0.001). In the same way, *G. bicolor* significantly increased the number of protected rats by increasing the delay of convulsions occurrence induced by strychnine. 800 mg/kg, ip of the plant extract appeared significant (p< 0.001) increase in the latency of seizures by (45.60 ± 3.14 min) compared to the negative control (3.20 ± 0.86 min), whereas, 400mg/kg significantly (p<0.05) increased the latency of seizures by (22.60±1.77 min) (Table (5)).

## DISCUSSION:

The results of the current study indicate that *G. bicolour*have potential anxiolytic properties. This potentiation of anti-anxiety suggests the presence of anxiolytic-sedative properties in the extract of *G. bicolor*[15, 17].

The result corresponds to the finding of Tijani *et al*[18] who reported that the methanolic extract of *G. lasiodiscus* root at 25, 50 and 100 mg/kg prolonged duration of sleep in

pentobarbitone-induced hypnosis in mice when compared with the control groups. This prolongation of pentobarbitone induced hypnosis observed in this study, strongly suggests that the genus *Grewia* possess central depressant activity[19]and supports our study suggestion that *G. bicolor* root extract may depresses the motor activity performance and induce anxiolytic- sedative effect.

The anxiolytic- sedative properties found here could explain the use of this plant in traditional medicine in Africa, particularly in Sudan, in the treatment of the nervous system diseases such as insomnia, anxiety and epilepsy and also to tranquilize agitated patients.

*G. bicolour* also showed significant anticonvulsant properties by inhibiting convulsions induced chemically or electrically.

The extract protected rats against PTZ-, PIC- and STR-induced seizures in a dose- depend manner. As PTZ has been shown to interact with the gamma amino butyric acid (GABA) neurotransmitter[6], the antagonism of PTZ-induced seizures suggests that *G. bicolor* interacts with GABA ergic neurotransmission since PTZ is a selective blocker of the chloride ionophore complex to the GABA-A receptor. Picrotoxin (PIC)- induced seizures is known to be a non-competitive GABA antagonist, exerting its effect by blocking the chloride channel in the $GABA_A$ receptor complex[20, 21 and 22]. It is used to induce acute simple partial seizures and generalized tonic-clonic seizures[23]. The antagonism of PIC-induced seizures suggests the interaction of the plant extract with the GABA-ergic neurotransmission.

The inhibition of STR-induced seizures by *G. bicolor* extract suggests that it possesses anticonvulsant properties[24,25] and that glycine neurotransmission is involved[26].*G. bicolor* completely antagonized MES-induced seizures probably by prolonging the inactivation of sodium channels[12].

Correspondingly, many previous studies on *Grewia* species proved that the genus *Grewia* has a potential depressant effect on the CNS. The ethanolic extract of *G. elastic*, *G. microcos*, *G. tiliaefolia*, *G. emarginata*, *G. rothii* and *G. rotundifolia* showed CNS depressant activity when tested against MES-induced seizures assay and exhibited significant decrease in the tonic-clonic phase [2, 27-31].

Besides, the genus *Grewia* contains harman alkaloids which belong to the class of β-carbolines which stimulate the GABAergic axons and act strongly as a benzodiazepine agonist in the brain and thus enhance the effect of the neurotransmitter (GABA) at the $GABA_A$ receptor, resulting in sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties[2,32]. These alkaloids implicated in a number of human diseases including Parkinson's disease, tremors and addiction due to its depressant effect on the CNS[33].

Mohammed *et al* [4] reported that the active compound of *G. bicolour* possesses a serotonin-like effect. Many studies in experimental models have suggested apotential role for serotonergic transmission in epilepsy. Serotonin plays an important role and enhances the action mechanism of some antiepileptic drugs like carbamazepine and valproate which release 5-HT as a part of their mechanism of action[34]. Agents that elevate extracellular serotonin (5-HT) levels, such as 5-hydroxytryptophan and serotonin reuptake blockers, inhibit both focal and generalized seizures[35]. Another relation between the GABA receptors and the serotonin receptors was reported by Chintawar et al[36] who reported that the extract of *Albizzialebbeck* was found to be anticonvulsant in mice as well as it decreased the brain concentrations of GABA whereas the 5-HT level was increased.

Also, reduced $5HT_{1A}$ binding, without significant neuronal loss, induced seizures in animal models[37]. Finally, the phytochemical screening of tested extract revealed the presence of alkaloids, tannins, triterpenes, flavonoids, phenols, saponins and glycosides. The phytochemicals such as tannins, triterpenes and glycosides were reported as active substances for anticonvulsant activity[38,39]. Also, many animals' models

showed that flavonoids exerted their effects through the central benzodiazepine receptors as well as GABAA receptor ligands[40, 41 and 42]. Hence, these phytochemicals might be contributing to the anticonvulsant activity of the tested extract.

These findings and facts about the genus *Grewia* and particularly *G. bicolor* strongly support the suggestion in this study that *G. bicolor* root extract may possesses anticonvulsant activity and it may induce this action through the GABAergic neurotransmission and by prolonging neurons sodium channels inactivation with probably serotonin modulating.

## CONCLUSION:

In conclusion, it could be suggested that *G. bicolour* seems to possess anticonvulsant and anxiolytic properties in rats. These properties could explain the use of this plant in traditional medicine in Africa, especially in Sudan, in the treatment of anxiety and epilepsy.

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