

## Antiepileptic effects of *Allium schoenoprasum* L. in the acute epilepsy model in rats

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Epilepsy is a chronic clinical disorder and does not have a rational treatment, which basically aims to prevent seizure activity. Therefore, developing new treatment strategies that can intervene in epileptogenesis will make important contribution to epilepsy treatment. In order to find new compounds and develop new treatment strategies, here, we explored the potential antiepileptic effects of *Allium schoenoprasum* L. commonly known as chives. Two different epilepsy models were used to study the potential antiepileptic effects of *A. schoenoprasum* L. The first epilepsy model was induced by intracortical injection of 500 IU penicillin. The second epilepsy model was induced by injecting pentylenetetrazol (PTZ) at the dose of 60 mg intraperitoneally (i.p.). In the penicillin model, the animals were given *A. schoenoprasum* L. extract (200 or 400 mg/kg i.p.) after penicillin was applied and electrocortical activity was recorded for 120 min. In the PTZ model, the animals were given *A. schoenoprasum* L. extract at doses of 200 or 400 mg/kg orally for 7 days, after which the PTZ was applied, and tonic-clonic seizures were video recorded. *A. schoenoprasum* L. did not significantly change either the spike frequency or amplitude in the penicillin epilepsy model. Although it did not change the seizure score in the PTZ epilepsy model it reduced the death rate and significantly decreased the tonic-clonic seizure duration. The result suggests that *A. schoenoprasum* L. may have antiepileptic effects when applied chronically.

**Keywords:** Antiepileptic drugs, Chives, Herbal, Seizure, Traditional medicine

Epilepsy is thought to affect 1% of the world's population<sup>1</sup>, making it a significant public health issue<sup>2</sup>. Since current epilepsy treatment is aimed at preventing seizure activity and does not cure epilepsy, it is suggested that developing new strategies that can intervene in epileptogenesis will make important contributions to epilepsy treatment<sup>3</sup>. Enlightening the basic mechanisms of epilepsy will make important contributions to the prevention and treatment of the disease<sup>4</sup>. To understand epilepsy better, appropriate experimental models with similar clinical features should be created in the investigation of epileptogenesis<sup>5</sup>. Despite the abundance of available medications, most seizures cannot be controlled<sup>6-9</sup>. In addition, side effects of antiepileptic drugs limits their use in epilepsy treatment<sup>10,11</sup>.

Pentylenetetrazol (PTZ), an antagonist of the GABAA receptor, is one of the most frequently used proconvulsant agents to create an experimental epilepsy model<sup>10,11</sup>. PTZ can be used to develop both

acute and chronic animal epilepsy models. Intraperitoneal injection of PTZ at a threshold dose (60-100 mg/kg) causes myoclonic jerks and tonic-clonic seizures in rodents<sup>12</sup>. Penicillin is one of the oldest antibiotic classes still commonly utilized in clinical practice. Amoxicillin, piperacillin, ticarcillin, ampicillin and oxacillin have all been linked to neurological and psychological side effects such as confusion, disorientation, myoclonus and seizures, as well as non-convulsive status epilepticus and encephalopathy. Whatever its concentration in cerebrospinal fluid, penicillin G has the highest epileptogenic potential<sup>13</sup>.

Research in recent years has turned to the medicinal properties of plants as the natural source with nil or low side effects and economical comparatively<sup>14</sup>. The use of complementary and alternative medicine is growing, notably among epileptic patients<sup>15,16</sup>.

The genus *Allium*, with a wide spectrum of medicinal properties as indicated by ancient records of herbal therapy, has popularity, dependability, and also vast demands from the pharmaceutical sectors<sup>17</sup>.

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The vegetable chive (*Allium scorodoprasum* L.), one of the oldest and commonly used medicinal plants, particularly for epilepsy therapies<sup>17</sup>, could be a promising source for new drug. *A. scorodoprasum* is an alternative plant used to improve shelf life, boost nutritive content, and for its health effects, in addition to its use as food by the general population<sup>18,19</sup>. More research is needed to determine its components and biological activity, as well as its application as a natural preservative and in alternative medicine to replace artificial antioxidants. Many epidemiological studies have suggested that some *Allium* species, such as *A. schoenoprasum* L., can help to prevent the development of many diseases. They have been proven to have a wide range of pharmacological effects, including tumor cell growth inhibition and chemoprevention<sup>20,21</sup>.

Literature review reveals no studies investigating the antiepileptic properties of the *Allium schoenoprasum* L. species. Its widespread use in folk medicine and its other biological effects like antioxidant effect reported in literature suggests that anticonvulsant activity could be present in the extract of this species, which has yet to be studied. In this context, here, we investigated the effects of *Allium schoenoprasum* L. on seizure activity in experimental epilepsy models induced by pentylenetetrazol and penicillin.

## Materials and Methods

### Plant extract

*Allium schoenoprasum* L. (chives) was procured from a local market in Van Province. The extraction process of the plant was carried out in the Department of Biology, Bolu Abant İzzet Baysal University. The leaves were powdered after drying in an incubator at 40°C without exposure to the Sun to prevent the loss of biological content and activity. Infusion technique was used for extraction. Boiling water was added to powdered leaf samples (15%, w/v), kept in a water bath at 40°C for 18 h and then centrifuged in refrigerated centrifuge (Nuve®) at 4°C and 4100 rpm for 10 min to precipitate the plant parts. Supernatant portion was then vacuum filtered and then freeze-dried at -65°C using lyophilizer (Christ®). Obtained powdered form extract was stored at -20°C. Extraction yield was 17.97% as calculated by the formula:

$$\text{Yield (\%)} = \frac{\text{Weight of extract (g)}}{\text{powdered plant material (g)}} \times 100$$

### Experimental animals

Animals were provided by the Bolu Abant İzzet Baysal University Experimental Animals Application and Research Center. The study used male rats of 2-4 months old Wistar albino strain, each 200-250 g. The animals were kept in Type IV cages in an environment with a constant temperature (24±2°C) and humidity (55±15%) until and during the study. Rats were allowed free access to standard rat food and water prior to testing. The study was approved (No. 2020/03) by the Animal Research Ethics Committee of Bolu Abant İzzet Baysal University.

### Epilepsy model induced by PTZ

In the epilepsy model induced by PTZ, the animals were divided into 4 groups (n = 7, in each group). The control group was given 1 mg/kg physiological saline solution orally (p.o.) for 7 days. The second and the third groups received oral *A. schoenoprasum* L. extract at doses of 200 and 400 mg/kg, respectively, for 7 days (100 mg of *A. schoenoprasum* L. extract in 1 mL DMSO)<sup>23</sup>. On the 8<sup>th</sup> day of the experiment the animals in the first three groups received saline or plant extracts respectively then after 60 min, they received 60 mg/kg PTZ intraperitoneally (i.p.). The animals in the fourth group received 5 mg/kg diazepam (i.p.) and 30 min later they were injected with, 60 mg/kg PTZ (i.p.). Thirty minutes video recordings were taken after PTZ injection in all groups to determine tonic-clonic seizures. Groups were compared in terms of seizure score, seizure latency, seizure duration, and protection from seizure-related death<sup>24</sup>. Seizure scoring is made according to the Racine scale<sup>25</sup>.

### Epilepsy model induced by penicillin

Penicillin's neurotoxic effects were first seen following an intraventricular infusion of penicillin G, which caused myoclonic twitching<sup>13</sup>. Penicillin G when applied locally to the cortex can block GABA receptors, and hence used in experiments to simulate acute focal epilepsy models. It prevents GABA-mediated inhibitory control of major groups of pyramidal neurons because the cerebral cortex is most sensitive to penicillin-mediated epilepsy formation<sup>13,26,27</sup>. This model was chosen for its prevalence and effectiveness.

Two-month-old Wistar rats were first anesthetized by injection with ketamine (90 mg/kg, intramuscular) and xylazine (5 mg/kg, i.p.) then placed in the stereotaxy apparatus in which the Bregma and Lambda points of the head were at the same level.

The scalp was applied in the rostro-caudal point, the cranium part over the left sensorimotor cortex was removed and the left cerebral cortex was exposed. 500 IU penicillin (in a volume of 2.5  $\mu$ L) was injected with a Hamilton micro-injector 1 mm deep into the left sensorimotor cortex. For intracortical injection (i.c.) Bregma was used as reference (AP = -1 mm, L = 1.5 mm)<sup>28,29</sup>.

In the epilepsy model induced by penicillin, the animals were divided into 4 groups (n = 7, in each group). The control group animals received i.p. injection of saline. The second and third groups received 200 and 400 mg/kg i.p. injection of *A. schoenoprasum* L. extract, respectively. The fourth group received i.p. injection of 5 mg/kg diazepam. All animals in the experimental groups were injected with 500 IU penicillin G potassium (i.c.) 30 min after the first injection.

**Electrocorticogram (ECoG) recordings**

For electrophysiological recording, the positive electrode was placed 2 mm anterior to Bregma and 3 mm posterior to the negative electrode and the grounding electrode was attached to the ear. In summary, as described in previous studies<sup>28-31</sup>, basal electrical activity was recorded for 15 min. Afterwards, the extract of *A. schoenoprasum* L. was injected in doses of 200 or 400 mg/kg then after 30 min the penicillin injection was given and recording continued for another 120 min, after which the experiment was ended. In the recordings, the frequency, amplitude, and latency of epileptic discharges were analysed.

**Statistical analysis**

Since the data were not normally distributed, the non-parametric Kruskal-Wallis H test was used, and different groups determined by post-hoc Dunn test. SPSS 22.0 was used as a statistics program.  $P < 0.05$  was considered statistically significant. Data of the control groups were compared to data of groups treated with the plants extracts and to data of the positive control groups.

**Results**

In the penicillin-induced epilepsy model, the groups were compared in terms of latency time, spike amplitude and spike frequency. There was no statistically significant difference between the groups in terms of the latency times of penicillin-induced seizures as shown in Fig. 1 ( $p=0,124$ ). In terms of

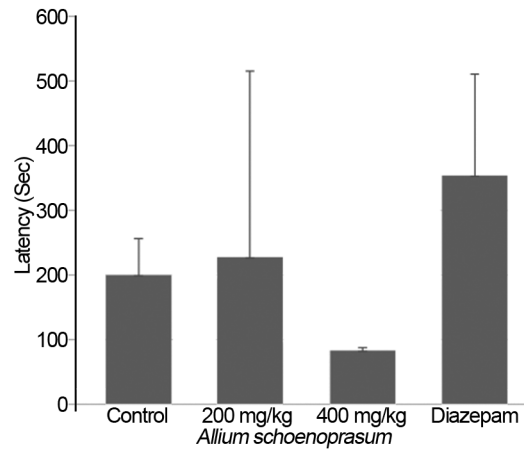


Fig. 1 — Comparison of latency times in penicillin-induced epilepsy model. [The error bars in the figure represents the standard deviation]

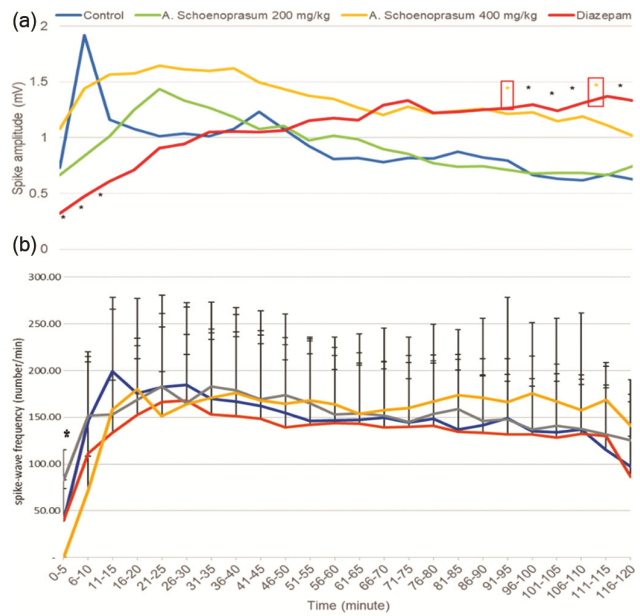


Fig. 2 — Comparison of (A) spike-amplitude (mV); and (B) spike-wave frequency (number/min) obtained from recording after penicillin injection. [\* $P < 0,05$ , when the Diazepam group is compared to the Control group]

spike amplitude, animals in Gr. III (400 mg/kg of the *Allium schoenoprasum* L.) showed statistically significant difference between 0-15 and later between 96-120 min after penicillin administration, compared to Gr. IV (diazepam group) ( $P < 0.05$ ). There was statistically significant difference between Gr. IV and II (diazepam group and *A. schoenoprasum* L. 200 mg/kg group) between 91-95 and 111-115 min as shown in Fig. 2A ( $P < 0.05$ ). As seen in Fig. 2B, there was a statistically significant difference in spike-wave frequency between the Gr. IV and III

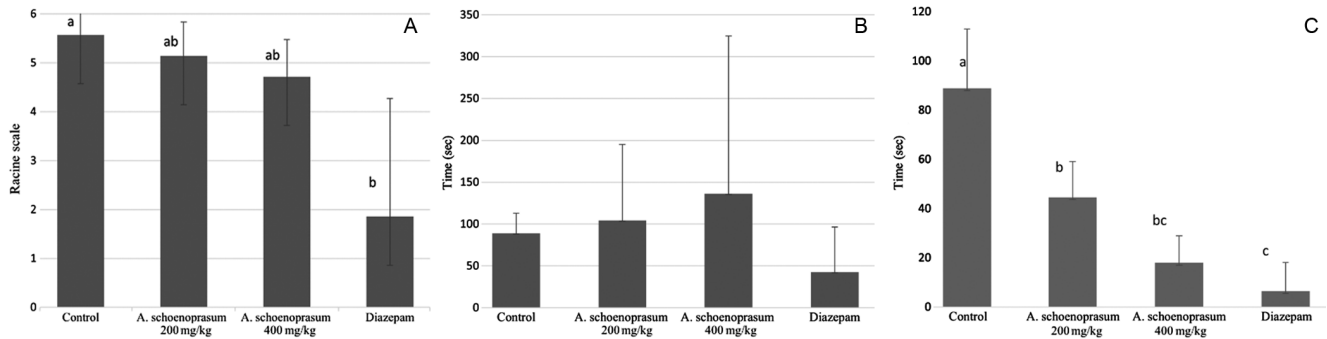


Fig. 3 — Comparison of groups according to (A) seizure score; (B) first myoclonic jerk time; and (C) tonic-clonic seizure duration. [a, b, c: The difference between groups with different letters is statistically significant. The error bars in the figure represent the standard deviation value]

(diazepam group and the control and *A. schoenoprasum* L. 400 mg/kg groups) between 0-5 min ( $P < 0.01$ ). When looking at the difference in patterns of activity between the groups there appears to be evidence of a slight negative effect from the *A. schoenoprasum* L. extract on the spike frequency at the beginning of epilepsy.

In the PTZ-induced epilepsy model, groups were compared in terms of seizure score, protection from seizure-related death, time to first myoclonic jerk and tonic-clonic seizure duration. As shown in Fig. 3A, there was statistically significant difference in seizure scores between the Gr. IV and the control group ( $P < 0.01$ ). There was no difference between the other two groups (Gr. II & III) compared to the control group in terms of the mean scores. While no post-seizure death was observed in the experimental animals in Gr. III and IV, there were 4 deaths in the control group and 2 deaths in Gr. II (Table 1). There was no statistically significant difference between the groups according to the time of first myoclonic appearance after PTZ application as shown in Fig. 3B ( $P > 0.05$ ). The tonic-clonic seizure duration was significantly longer in the control group compared to the other groups ( $P < 0.01$ ). While the seizure duration in Gr. II was significantly shorter than the control group ( $P < 0.01$ ), and it was longer than the Gr. IV, there was no significant difference between the Gr. III and IV as shown in Fig. 3C.

## Discussion

Epilepsy is a common chronic neurologic condition characterized by recurring spontaneous seizures in diverse parts of the brain. Many studies have attempted to find the pathogenetic process of epilepsy, however the problem remains unsolved. It is

an important public health problem increasing day by day, which affects individuals both physically and psychologically, decreasing their quality of life, often putting restrictions on their daily activities and in addition incurring medical costs<sup>32,33</sup>. The seizure is a temporary behavioral change due to the simultaneous and rhythmic output of neurons in the central nervous system which needs long-term, continuous, and multi-medicinal treatment, which can sometimes lead to the development of various side effects such as drug resistance and lack of access to more effective treatment procedures<sup>34</sup>. As a result, research has focused on plants as an important source of pharmaceuticals, focusing on the natural characteristics of herbal and traditional medicine to develop more effective, low-risk drugs with fewer side effects<sup>35</sup>.

Our study is one of the first of its kind on the antiepileptic effects of *Allium schoenoprasum* L. and there was no electrophysiological investigation into the antiepileptic activity of *A. schoenoprasum* L. by any induced epilepsy models that was found in the literature. The aim of this study was to reveal the potential anti-epileptic effects of the herb as suggested in previous studies to be effective in a variety of neurological and non-neurological diseases.

Our study revealed that, in the PTZ induced model, the plant extract was observed to decrease the mortality, especially the 400 mg/kg of *A. schoenoprasum* L. Most significant results are in the tonic-clonic seizure duration in Gr. III (*A. schoenoprasum* L. 400 mg/kg group), which was significantly shorter than the Control group and was not significantly different from the Diazepam group. Group III also showed significantly reduced the tonic-clonic seizure duration compared to the Control

group, but it was longer than the Diazepam group.

For the penicillin induced model, 200 and 400 mg/kg the *Allium schoenoprasum* L. extract did not show any effects on spike amplitude. However, there was a negative effect on the spike frequency only during the first 5 min after epilepsy induction. The extract did not show any effect between 6-120 min on the spike frequency but for a slight adverse effect of the *A. schoenoprasum* L. extract on the spike frequency at the beginning of the penicillin-induced epilepsy.

Phytochemical studies show that *Allium* species have various biological effects<sup>36</sup>. The ethanol extract of *Allium chinense* bulbs demonstrated anoxia-tolerant action in the cerebral anoxia mouse model by assessing the number of gasps and survival time<sup>37</sup>. *A. chinense*, which has a significant amount of secondary metabolites, steroidal saponins, nitrogenous chemicals, volatile oils (mostly sulfur-containing compounds) and amino acids, has been shown to have antioxidant and inhibitory effect on platelet aggregation. Essential oil from *Allium cepa* exhibits exceptional effectiveness against epileptogenesis in a kindling model produced in mice; nevertheless, the underlying mechanism of action remains unknown<sup>33</sup>.

*Allium* species including *A. schoenoprasum* L. contains many flavonoids like quercetin, luteolin, apigenin, and hyperon and they are reported to have antibacterial, antifungal, antioxidant, diuretic, hepatoprotective and antiviral properties<sup>38-41</sup>. Although its effect in epilepsy models has not been studied some effects of *A. schoenoprasum* L. are attributed to its antioxidant properties<sup>42,43</sup>. In an investigation on the effect of *Allium schoenoprasum* L. (known as Sirmo in Turkey) against acrylamide toxicity in rats, it was observed that *A. schoenoprasum* L. has benefits against oxidative stress caused by acrylamide toxicity<sup>38</sup>. *A. schoenoprasum* L. was also shown to increase blood nitric oxide levels, which is suggested to be responsible for its antihypertensive effects<sup>23</sup>. Both antioxidants and nitric oxide have been shown to be involved in the pathogenesis of epilepsy<sup>38,43</sup>.

The GABAergic system plays a critical role in the pathophysiology of cerebral ischemia, epilepsy, sleep disorders, and mood disorders. A reduction in GABAergic neurotransmission can result in increased neuronal excitability, which can contribute to

seizures<sup>11,22</sup>. GABA is the primary neurotransmitter with inhibitory characteristics in the central nervous system, and research has shown that boosting GABA neurotransmission can aid to relieve convulsions. Aged extract of *Allium sativum* L. was shown to change the level of glutamic acid decarboxylase, an enzyme converting glutamate to GABA<sup>44</sup>. Quercetin, a common ingredient of *Allium* species, was demonstrated to have moderate binding affinity to GABAA and GABA B receptors<sup>45</sup>. Allicin, an active compound rich in *A. schoenoprasum* L and garlic, also altered brain GABA levels in rats<sup>46</sup>. The current literature indicates that *A. schoenoprasum* L. extract may have an effect on GABA levels or GABA receptor activity in brain, which could be involved in the mechanism of its anticonvulsant effect.

## Conclusion

The extract of *Allium schoenoprasum* L. commonly called chives, has been demonstrated to have antiepileptic effects in the pentylenetetrazol (PTZ) induced epilepsy model in rats. It decreased the tonic-clonic seizure duration and decreased seizure-related mortality in the PTZ-induced epilepsy model. Antiepileptic effects of *A. schoenoprasum* L. in PTZ-induced epilepsy model in the current study could be related to its antioxidant properties due to its flavonoid contents or its effect on GABA transmission in the brain, which could be investigated in further studies.

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## Conflict of Interest

Authors declare no competing interests.

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