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EXPERIMENTAL STUDY

Effects of *Cichorium Intybus* on $GABA_A$ Receptors and Apoptosis in Pentylenetetrazole-Induced Kindling in Rats

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Abstract

Objectives: This study was designed to determine the effects of *Cichorium intybus* (CI) on apoptosis and $GABA_A$ receptor density in the brains of rats in pentyleneterazole induced kindling.

Methods: The rats were divided into three groups: Control group, pentylenetetrazol administered (PTZ) group, and PTZ+CI extract administered (PTZ+CI) group. Control group received only physiological saline (0.5 ml). PTZ (35 mg/kg) injected to the animals in the PTZ and PTZ+CI groups. The CI extract (200 mg/kg) was also administered to the PTZ+CI group. A 75 mg/kg challenge dose of PTZ was administrated to the PTZ treated groups, on the 12th injection.

Results: A significant increase was found in the number of neurons expressing the $GABA_A$ receptor in the brain tissue (hippocampus and cerebral cortex) of the PTZ group when compared to the control. The density of $GABA_A$ receptor of the neurons in the cerebral cortex significantly increased in PTZ administered groups compared to the control. The number of apoptotic neurons was found non-significant between groups in the brain.

Conclusion: CI treatment prolonged the onset of the first seizure activity and seizure latency at a convulsive dose, and kept the number of $GABA_A$ receptors close to that of the control in the hippocampus.

Keywords: Brain; *cichorium intybus*; epilepsy; hippocampus; kindling; pentyleneterazole; seizure.

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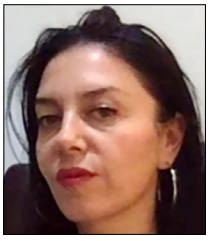
Introduction

The World Health Organization reports epilepsy as among the most common and serious brain disorders.[1] About 50% of patients who have been under current antiepileptic drugs treatment continue to have seizures, and the seizure frequency and cognitive weakness have been increasing in some of these patients.[2] Current treatments are symptomatic and have anticonvulsive effects rather than antiepileptic.[3] Therefore, current investigations are focused on the search for new antiepileptic drugs with neuroprotective effects.[4] Repeated usage of sub-convulsive stimulus, such as pentylenetetrazol-(PTZ), results in the progressive development of seizures.[5] Although the mechanism of action from PTZ is not understood completely,[6] it is thought that PTZ influences the glutamatergic and GABAergic systems in the hippocampus and several brain regions.[7] PTZ kindling is thought to be related with a decrease in the inhibitory activity of the GABAergic system in the brain.[8]

Cichorium intybus (CI) (Family: Asteraceae), also known as chicory, is a medicinally important herb.[9] Historically, chicory was cultivated as a medicinal herb by ancient Egyptians.[10] The root of CI was traditionally used for jaundice, liver enlargement, gout, rheumatism, and diabetes.[11] CI was also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Sıçanlarda Pentilentetrazol Kindlingde *Cichorium Intybus*'un $GABA_A$ Reseptörleri ve Apoptoz Üzerine Etkileri

Öz

Amaç: Bu çalışma, pentileterazole indüklü kindlingte, *Cichorium intybus*'un sıçanların beyinlerinde apoptoz ve $GABA_A$ reseptör yoğunluğu üzerindeki etkilerini belirlemek için tasarlanmıştır.

Gereç ve Yöntem: Sıçanlar üç gruba ayrıldı: Kontrol grubu, pentilentetrazol uygulanan (PTZ) grup ve PTZ + *Cichorium intybus* ekstresi (PTZ + CI) uygulanan grup. Kontrol grubu sadece serum fizyolojik (0.5 ml) aldı. PTZ ve PTZ + CI gruplarındaki hayvanlara PTZ (35 mg/kg) enjekte edildi. PTZ + CI grubuna ayrıca CI ekstraktı da (200 mg/kg) uygulandı. PTZ uygulanan gruplara 12. enjeksiyonda 75 mg/kg'lık bir PTZ dozu uygulandı.

Bulgular: PTZ grubunun beyin dokusunda (hipokampus ve tüm beyin) $GABA_A$ reseptörünü ifade eden nöronların sayısında kontrole göre önemli bir artış bulundu. Tüm beyindeki nöronların $GABA_A$ reseptör yoğunluğu, kontrol grubuna kıyasla PTZ uygulanan gruplarda önemli ölçüde artmıştır. Beyindeki apoptotik nöronların sayısı gruplar arasında anlamsız bulundu.

Sonuç: Sonuç olarak, *Cichorium intybus* uygulması, konvülsif dozda ilk nöbet aktivitesi oluşumu ve nöbet latansını geciktirdi ve hipokampusta $GABA_A$ reseptörlerinin sayısını kontrole yakın tuttu.

Anahtar sözcükler: Beyin; *cichorium intybus*; epilepsi; hipokampus; kindling; nöbet; pentileneterazol.

used traditionally in central Europe before modern antiepileptic drugs.[12] CI roots are used for the management of epilepsy in folk medicine in eastern Anatolia.[13] The plant is also used as food; the aerial parts are consumed as salads and the processed roots are used as food ingredients and coffee substitutes.[14] CI roots contain lactucin and lactucopicrin.[15] Lactucin and lactucopicrin have antimalarial,[15] sedative, and analgesic effects.[16]

The neuroprotective effect of *Cichorium intybus* has been reported[17] previously. However, there are no available reports on the effects of its aqueous root extract on any chronic models of epilepsy. Therefore, the present study was planned to investigate the effects of aqueous root extract of CI on apoptosis and $GABA_A$ receptors in PTZ-induced kindling model.

Materials and Methods

Plant extract– CI was collected in the campus of Bezmialem Vakif University, and identified by the Department of Botany. The voucher specimen (VANF163742) is available in the herbarium of the department. Dried slices of the root were ground into fine powder using a Micro mill. Distilled water was added to the powder, which was mixed by continuous stirring for 50 min at 70°C and then allowed to cool for 10 min. The aqueous extract was obtained by filtering the mixture through filter paper.

Animals– 27 Wistar albino rats (400–430 g) were purchased from Bezmialem Vakif University, Experimental Animal Centre. The animals were kept under standard laboratory conditions: A light/dark photoperiod of 12:12 and humidity (50–60%) and a constant temperature (25±1°C). The rats were allowed free to access standard diet ad libitum. Experimental procedure was approved by the Bezmialem Vakif University, Laboratory Animals Ethical Committee (Date: 31.10.2013, Number: 2013/216).

Experimental protocol– The rats were divided into three groups: (1) Control: Saline (0.5 ml; ip), (2) PTZ: Pentyleneterazole (35 mg/kg; ip) treated group, and (3) PTZ+CI: CI extract (200 mg/kg, po)[18]+pentyleneterazole (35 mg/kg; ip) treated group. The aqueous extract was prepared freshly each experimental day and administrated 2 h before each PTZ injection.

Induction of kindling– PTZ (35 mg/kg; Sigma) was dissolved in 0.9% physiological saline and intraperitoneally (ip) injected to the animals (Monday, Wednesday, and Friday) for a total of 11 applications. After the induction of kindling, a challenge dose of PTZ (75 mg/kg)[19,20] was administered to induce clonic-tonic seizures on the 12^{th} injection (26^{th} day of the study). After each PTZ injection, the animals were observed for 30 min. The seizures were scored according a modified scale;[19] Stage 0: No answer; stage 1: Ear and face twitching; Stage 2: Convulsive wave that spreads throughout the body; Stage 3: Myoclonic jerks; Stage 4: Clonic seizures; Stage 5: Generalized seizures with extensions; and Stage 6: death.[19]

Sample preparation and histological evaluations– On day 26 of the study, cerebral cortex and hippocampus samples were harvested under xylazine (15 mg/kg, ip) and ketalar (50 mg/kg, ip) anesthesia. Samples were fixed in 10% neutral buffered formaldehyde, dehydrated, cleared, and embedded in paraffin. Paraffin sections of cerebral cortex and hippocampus (5 µm) were stained with $GABA_A$ receptor-alpha immunohistochemistry and the terminal deoxynucleotidyl transferase-mediated dUTP nick-end label-

ing-(TUNEL) method was used for apoptosis. The samples were examined under a photomicroscope (Nikon Eclipse i5).

Immunohistochemistry– Sections were kept overnight at 37°C, then deparaffinized with xylene and rehydrated through graded concentrations of ethanol. The sections were incubated in 3% H_2O_2 for 5 min to inhibit endogenous peroxidase activity, and then microwaved with citrate buffer, pH 6.1, for 20 min for antigen retrieval. After incubation with rabbit anti-$GABA_A$ receptor primary antibody (33299; Abcam, Cambridge, MA) diluted 1:100 in antibody diluent (003118; ThermoFisher Scientific, Waltham, MA) overnight at 4°C, secondary antibody (Histostain®-Plus 3rd Gen IHC Detection Kit, 85–9073, Invitrogen) was applied to the sections for 10 min. The sections were washed with phosphate-buffered saline (PBS), incubated with diaminobenzidine for 15 min to visualize immunostaining, and then counterstained with Mayer's hematoxylin (Zymed Laboratories, San Francisco, CA). Control sections were processed identically except that the primary antibody was omitted. An observer blinded to the experimental groups evaluated five different areas on each section at ×200 magnification to calculate the number of stained cells and staining intensity using Photoshop CS6 (Adobe Systems Software, Dublin, Ireland) according to the software manufacturer's instructions. Positive staining cell counting was done with images that were taken from five randomly selected similar fields (at ×200 magnification). Photoshop CS6 was used to evaluate the color intensity of the staining cells.

TUNEL assay– Deoxyribonucleic acid (DNA) fragmentation was detected using a TUNEL kit (Apoptag Fluorescein *in situ* Apoptosis Kit; Millipore, S7110) following the manufacturer's instructions. Briefly, sections slides were deparaffinized in xylene and rehydrated through a graded series of ethanol and distilled water. Sections were rinsed in PBS, pH 7.4, and then permeabilized with 2% Triton X-100. The TdT labeled nucleotide mixture was added to each slide and incubated in a humidified chamber at 37°C for 60 min in the dark. Sections were rinsed twice in PBS, counterstained with Hoechst 33342 (Life Technologies, Warrington, UK) and coverslipped. At least ten different areas were analyzed at ×200 magnification for each section (Nikon Eclipse i5, Tokyo, Japan). The final percentage of cells with fragmented DNA among total stained and unstained cells was considered the percent TUNEL-positive cells for each sample.

Statistical analysis– The Kruskal–Wallis test was used to compare groups for the studied continuous variables. Following Kruskal–Wallis, the Dunn test was carried out for determination of the different groups. The Friedman test was also used for comparison periods. Statistical significance was considered as 5%. The SPSS for Windows software (ver.: 18; SPSS Inc. Chicago, USA) statistical program was used for all statistical computations.

Results

CI extract treatment significantly decreased the seizure scores on the 2nd and 4th injection days ($p<0.05$) when compared to the PTZ group (Fig. 1a), while on the 8th injection day, the seizure scores of the PTZ+CI group were found significantly higher than those in the PTZ group ($p<0.05$). The PTZ+CI group had longer ($p<0.05$) seizure latency on the 6th, 11th, and 12th injection days, but shorter ($p<0.05$) seizure latency on the 4th, 8th, and 9th injection days when compared to the PTZ group (Fig. 1b). CI extract treatment prolonged the seizure latency at a convulsive dose (on the 12th injection day) (Fig. 1b).

A significant increase ($p<0.05$) was found in the number of hippocampal neurons expressing $GABA_A$ receptor of the PTZ group when compared to the control (Fig. 2, 3a). However, an insignificant increase was observed in the number of hippocampal neurons expressing $GABA_A$ receptor in the PTZ+CI group when compared to the control (Fig. 2, 3a). PTZ treatment significantly ($p<0.05$) increased the number of neurons expressing $GABA_A$ receptor in the cerebral cortex when compared to the control (Fig. 3b).

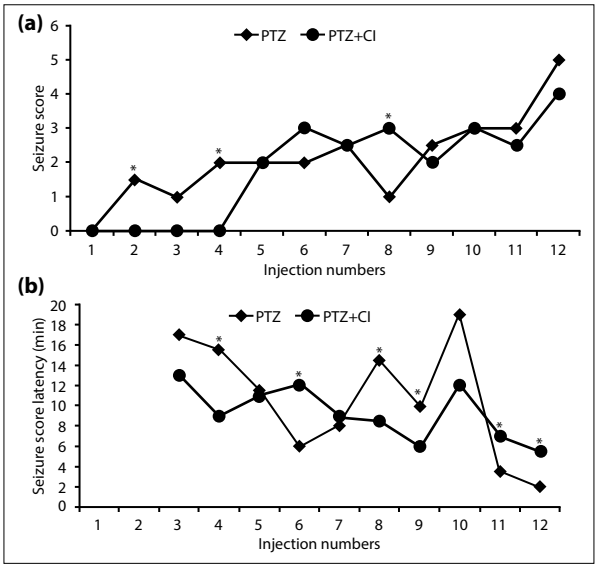

Fig. 1. The effect of CI extract on seizure scores **(a)**, and the latencies of score 3 and above seizures **(b)** of PTZ and PTZ+CI groups. (PTZ = Pentyleneterazole administrated group, PTZ+CI = PTZ and *Cichorium intybus* extract-administrated group. The values are expressed as the median [*p< 0.05]).

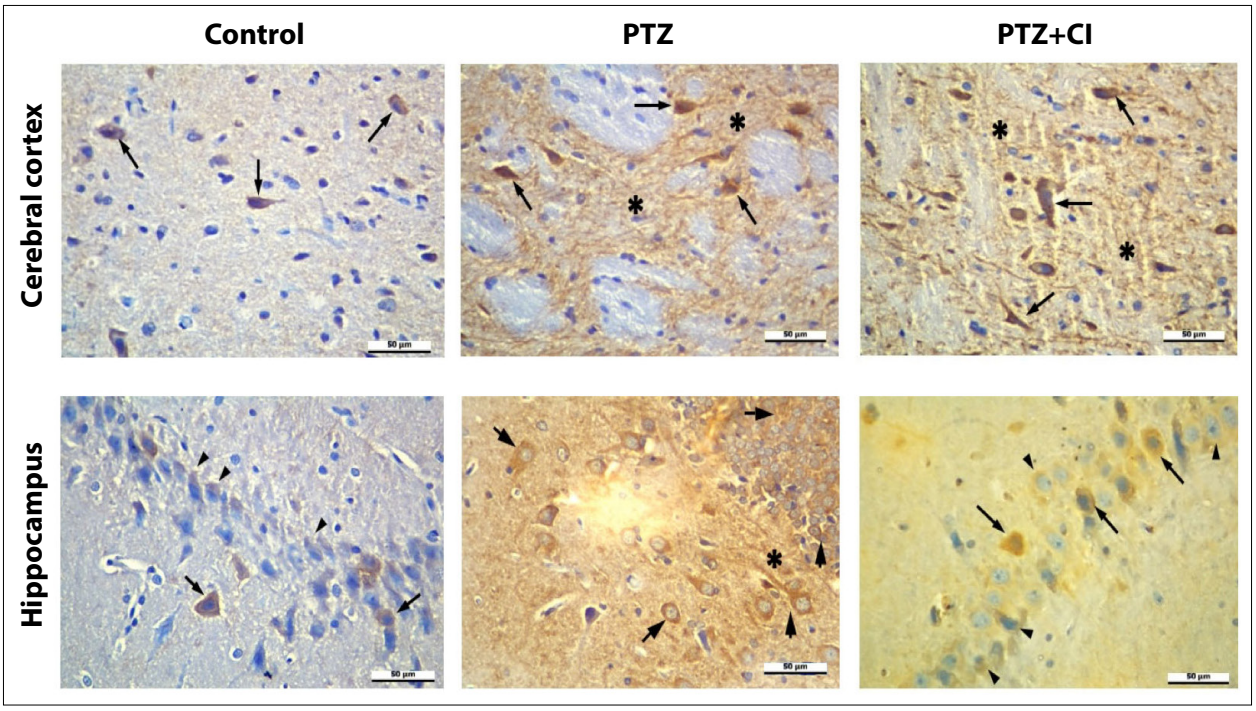

Fig. 2. Immunohistochemically staining of $GABA_A$ receptors in the hippocampal and cerebral cortex tissues of rats. *=The cell bodies and processes of neurons, arrow=Strong staining intensity, arrowhead=Weak staining intensity. (Scale-bar= 50 μm. Original magnifications=×200).

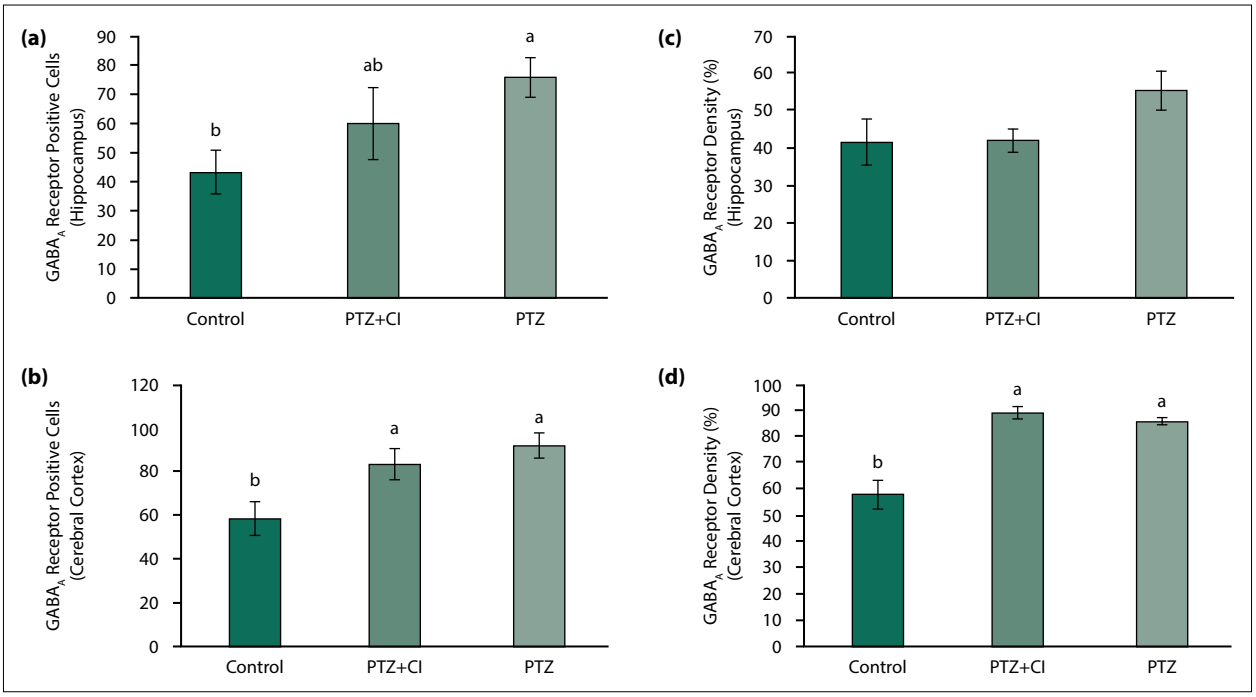

Fig. 3. $GABA_A$ receptor positive cell numbers of the **(a)** hippocampus, and **(b)** cerebral cortex and the staining intensity of the $GABA_A$ receptor positive cells in **(c)** hippocampus and **(d)** cerebral cortex. The values are expressed as the median. Different letters indicate significant differences between the groups ($p<0.05$). (PTZ: Pentyleneterazole administrated group, PTZ+CI: PTZ and *Cichorium intybus* extract administrated group [$p<0.05$]).

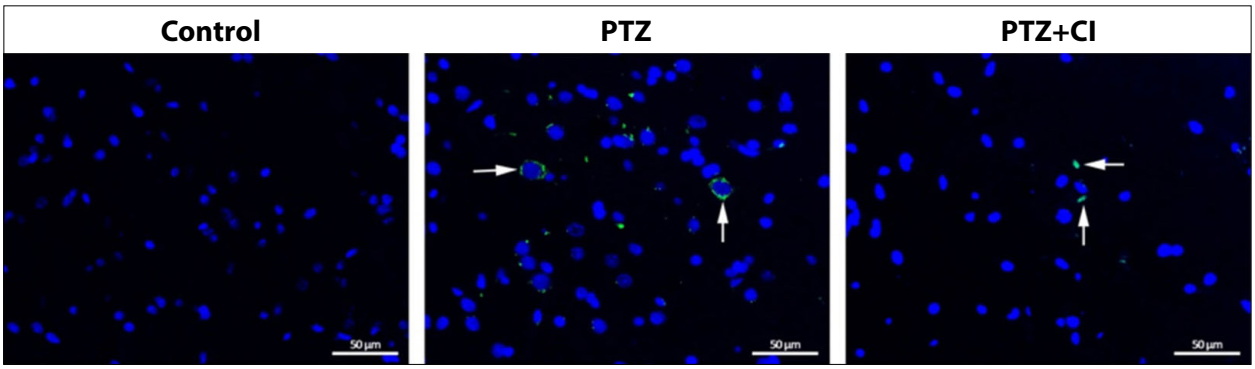

Fig. 4. Transferase-mediated dUTP nick-end labeling immunofluorescence staining of the cerebral cortex. Apoptotic neurons were stained green while others were counterstained blue (Scale-bar=50 µm. Original-magnifications=×200).

$GABA_A$ receptor density of hippocampus was insignificant among groups (Fig. 2, 3c). However, it was found significantly ($p<0.01$) higher in cerebral cortex cells of the PTZ and PTZ+CI groups when compared to the controls (Fig. 2, 3d).

Number of apoptotic neurons in the brain between the groups was insignificant ($p>0.05$, data not shown, Fig. 4).

Discussion

OThe present study was planned to investigate the effects of CI on seizure scores, apoptosis and $GABA_A$ receptors in the brain in PTZ-induced kindling in rats. The first seizure activity seen with the 5th injection day in the PTZ plus CI group and CI prolonged the seizure latency at convulsive dose on the 26th test day. Kindling is defined as the repeated application of sub-convulsive stimuli.[21] Sub-convulsive applications result in progressive increase of seizure activity and the emergence of generalized seizures.[21] Therefore, it may be suggested that CI application might delayed the seizure activity until the 5th injection, despite the sub-convulsive applications of PTZ. Similarly, CI treatment is reported to delay the onset of the PTZ-induced seizures.[9] CI contains lactucin and lactucopicrin which have sedative effects.[16] In the present study, this sedative effect probably prolonged the onset of the first seizure activity and prolonged the seizure latency at a convulsive dose.

In this study, the number of apoptotic neurons in the cerebral cortex was found insignificant. In a previous study a significant increase was reported in the number of apoptotic neurons in the cerebral cortex of the PTZ group while it was insignificant in the hippocampus.[20] In consistent with our study, in a previous study no significant difference was found between PTZ and control groups in terms of the number of apoptotic neurons.[22] A changed GABAergic inhibition has been reported in hippocampus in numerous epilepsy models. It is thought to be caused in part by a reduction in the function of the receptor of postsynaptic $GABA_A$.[23] Considerable evidence suggests that alterations in the function and expression of $GABA_A$ receptors are related with epilepsy pathogenesis.[24] In this study, the number of neurons expressing $GABA_A$ receptors was significantly increased in the hippocampus and cerebral cortex of the PTZ group compared to the control. Similar with our results, the number of neurons which expressed $GABA_A$ receptor was found significantly increased in the rat brain in PTZ-kindling.[20] In the present study, $GABA_A$ receptor density in the cerebral cortex was significantly higher in the PTZ group when compared to the control. While, the $GABA_A$ receptor density in the hippocampus was non-significant between the PTZ and control group. Consistent with our results, it was reported that the $GABA_A$ receptor density of the hippocampus is insignificant between the PTZ-kindled and control groups, but it was significant in the cortex.[20] It was reported that the post-synaptic insertion of novel $GABA_A$ receptors and corresponding rise in post-synaptic responses, increase the effectiveness of mammalian inhibitory synapses.[25] Receptor upregulation of surviving cells suggesting the existence of the compensatory mechanisms in response to the seizure activity.[26] The surviving neurons increase their sensitivity to inhibitory neurotransmitter by increasing the number of $GABA_A$ receptors, and thus handle with the repetitive stimulus.[26]

The limitation of our study is that we used a plant extract. An extract can potentially contain many diverse constituents which can hinder the action of the primarily anticonvulsant chemical. However, our purpose in this study was to evaluate the antiepileptic potential of the plant which is traditionally used by the epilepsy patients. In further studies, the content of the CI herb should be investigated and the anticonvulsant potential of the main content of the plant should be tested in the same way.

Conclusion– It has been concluded that PTZ administration increased the $GABA_A$ receptor positive cell number and $GABA_A$ receptor density in the brain. CI prolonged seizure latency at a convulsive dose, and kept the number of $GABA_A$ receptors close to that of the control group, despite PTZ application in the hippocampus. However, we used only a 200 mg/kg dose of CI extract. Further studies are needed to determine whether different doses of CI extract alter seizure scores in experimental models of epilepsy.

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Ethics Committee Approval– Experimental procedure was approved by the Bezmialem Vakif University, Laboratory Animals Ethical Committee (Date: 31.10.2013, Number: 2013/216).

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Conflict of interest– The authors declare that they have no conflict of interest.

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