İstanbul Journal of Pharmacy
Istanbul J Pharm2024, 54 (3): 378–385
DOI: 10.26650/IstanbulJPharm.2024.1467008

Original Article

Effects of Anatolian propolis on absence seizures and anxiety in rats with genetic absence epilepsy

Batuhan Yağmur[1], Şura Akat Pişkin[2], Erkan Civelek[3], Deniz Kaleli Durman[3] Nihan Çarçak[3]

[1]İstanbul University, Faculty of Pharmacy, İstanbul, Türkiye
[2]İstanbul University, Institute of Health Sciences, Faculty of Pharmacy, İstanbul, Türkiye
[3]İstanbul University, Faculty of Pharmacy, Department of Pharmacology, İstanbul, Türkiye

ABSTRACT

Background and Aims: Anatolian propolis, which is rich in phenolic compounds, may offer neuroprotective benefits due to its anti-inflammatory and antioxidant properties. This study explored how Anatolian propolis affects the frequency of absence seizures and anxiety levels in rats with genetic absence epilepsy from Strasbourg (GAERS).

Methods: Adult male GAERS were orally administered Anatolian propolis samples at concentrations of 15% (120 mg/kg/day) and 30% (180 mg/kg/day), whereas the control group received an equivalent volume of tap water by oral gavage for 35 days. A 3-h EEG was recorded 9.00 and 12.00 a.m after 35 days of sub-chronic administration. The effects of Anatolian propolis on spike-and-wave discharge (SWD) duration, number, and mean duration of each SWDs were evaluated and compared with the control group. The elevated plus maze test was then performed to measure the anxiety level of GAERS rats. Finally, brains were isolated, and interleukin-1 beta (IL-1β) levels were measured in freshly frozen isolated brains using an ELISA method.

Results: Oral administration of Anatolian propolis (180 mg/kg/day) significantly reduced the number of SWDs and decreased IL-1β levels in the brain tissue of adult GAERS after 35 days of sub-chronic administration ($p<0.05$). Propolis treatment did not alter anxiety levels in terms of time spent in the closed and open arms.

Conclusion: This study represents an initial exploration of the effects of Anatolian propolis on absence seizures in GAERS. Our findings indicate that Anatolian propolis could offer therapeutic advantages by reducing the levels of the brain's pro-inflammatory cytokine IL-1β in GAERS, potentially mitigating absence seizures. However, additional research is necessary to understand the potential mechanisms driving this benefit.

Keywords: Absence epilepsy, Anatolian Propolis, Anxiety, GAERS, IL-1β, Neuroinflammation

INTRODUCTION

Childhood absence epilepsy is a form of genetic generalised epilepsy characterised by bilateral synchronous spike-and-wave discharges (SWDs) at a frequency of 3–4 Hz on EEG, along with behavioural arrest and rhythmic eyelid movements (Crunelli & Leresche, 2002; Hirsch et al., 2022). Approximately 40% of children with absence epilepsy may also have behavioral and cognitive problems (Masur et al., 2013). Currently, the treatment of choice for absence epilepsy alone is ethosuximide (Shorvon, 2011), which is one of the oldest anti-absence drugs that was introduced into clinical practise in 1958 (Zimmerman & Burgemeister, 1958). Gastrointestinal side effects (nausea, vomiting, anorexia, and diarrhea) occur in 4%–29% of patients receiving ethosuximide (Shorvon, 2011). More than 50 years after its induction, ethosuximide still represents the optimal initial empirical monotherapy for absence epilepsy, and no new antiseizure drug has proven significant efficacy against typical absences (Vrielynck, 2013; Brigo, Igwe, & Lattanzi, 2019). Valproic acid and lamotrigine are effective in numerous patients, but they tend to elicit more adverse effects in comparison to ethosuximide (Kessler & McGinnis, 2019). Therefore, there is a need for more effective and better-tolerated treatments for absence epilepsy and related comorbidities (Löscher & Schmidt, 2011).

Propolis is a bee product with antibacterial, antioxidant, anti-inflammatory, and neuroprotective activities(Zulhendri, Perera, & Tandean, 2021). Bees produce it using a combination of beeswax and saliva to protect their hives. In general, propolis contains flavonoids, phenolic compounds, and terpenoids, although its exact chemical composition varies depending on the

Corresponding Author: Nihan Çarçak **E-mail:** nihan.carcak@istanbul.edu.tr
Submitted: 09.04.2024 • **Revision Requested:** 31.05.2024 • **Last Revision Received:** 13.06.2024 • **Accepted:** 29.06.2024

plant species native to the region where it is produced. Propolis exerts anti-inflammatory effects via mechanisms such as the inhibition of cyclooxygenase and prostaglandin synthesis, scavenging of free radicals, immunosuppressive activity, and reduction of inflammatory cytokine levels (Braakhuis, 2019; Zullkiflee, Taha, & Usman, 2022). Anatolian propolis composition differs from that of other propolis samples and has a high concentration of phenolic compounds, such as caffeic acid phenethyl ester (CAPE). CAPE, known for its anti-inflammatory and antioxidant properties, contributes to the neuroprotective potential of Anatolian propolis (Altuntaş, Güzel, & Özçelik, 2023). Preclinical studies testing the effect of bee products on experimental epilepsy models showed that propolis significantly decreased the frequency of seizures and reduced excitability (Kwon et al., 2004; Swamy, Suhaili, Sirajudeen, Mustapha, & Govindasamy, 2014). The effect of propolis on absence seizures has not been evaluated. In this study, for the first time, we aimed to investigate the possible effect of Anatolian propolis on absence seizures, anxiety levels, and brain pro-inflammatory cytokine interleukin-1β (IL-1β) levels in genetic absence epilepsy rats from strasbourg (GAERS), a thoroughly validated and commonly used rat model of genetic generalised epilepsy (Danober, Deransart, Depaulis, Vergnes, & Marescaux, 1998). Adult GAERS rats display SWDs on EEG that closely resemble absence seizures observed in patients with childhood absence epilepsy. Furthermore, their pharmacological response aligns with medications commonly used in clinical practice. Additionally, they exhibit pronounced anxiety- and depression like behaviours (Jones et al., 2008), which are commonly observed comorbidities in patients with epilepsy (Ott et al., 2003). Considering these characteristics, this model is an appropriate epilepsy model to investigate the effects of Anatolian propolis on spontaneous SWDs and anxiety levels.

MATERIALS AND METHODS

Drugs and chemicals

Anatolian propolis 15% and 30% were obtained as a gift from SBS Scientific Bio Solutions Co., Türkiye. BEE'O UP commercially available propolis preparations in standardized doses containing 15% or 30% pure Anatolian propolis extract were used. Extract analyses were already performed at the SBS Scientific Bio Solutions R&D centre, as shown in Table 1.

Animals and Experimental design

Male GAERS rats (n=22) weighing 250–300 g and aged 4-5 months were obtained from Mehmet Ali Aydınlar University, Animal Research and Application Centre (ACU-DEHAM).

All animals were maintained under standard laboratory conditions, with a 12/12 h light/dark cycle, 21±2°C, 45%–65% relative humidity, and free access to food and water. All procedures were carried out in the Experimental Animal Care and Research Unit of Istanbul University Faculty of Pharmacy (EDEHAB), according to approval by the Animal Ethics Committee of Istanbul University (2022/06) conforming with the EU Directive 2010/63/EU for animal experiments of the Istanbul University Local Ethics Committee of Animal Experiments (HADYEK).

Anatolian propolis at concentrations of 15% and 30% (BEE'O UP 15% Soluble Propolis Drops and BEE'O UP 30% Propolis Drops, SBS Scientific Bio Solutions Inc.) were administered orally for 35 days (Table 1). Adult GAERS rats were orally administered Anatolian propolis at a concentration of 15%, at a dose of 120 mg/kg (n=8), and at a concentration of 30% and at a dose of 180 mg/kg (n=6), based on previous studies that demonstrated the efficacy and safety of these concentrations in various experimental models (Oršolić & Bašić, 2003; Zingue et al., 2017; Gocmez et al., 2019; El Adaouia Taleb, Djebli, Chenini, Sahin, & Kolayli, 2020; Guler, Bilir, Kocak, Atas, & Samanci, 2022). The control group (n=8) received the same volume of tap water (Figure 1). EEG recordings were performed to evaluate the effect of Anatolian propolis on absence seizures. Subsequently, the rats underwent the elevated plus maze test to determine their anxiety levels. At the end of the protocol, the brains were isolated for pro-inflammatory cytokine; IL-1β measurements.

Stereotaxic surgery

EEG recording electrodes were implanted into the animals using stereotaxic surgery under ketamine/xylazine anaesthesia (100 mg/kg; 10 mg/kg; i.p.). Before surgery, carprofen (5 mg/kg) was administered subcutaneously for analgesia. The animals' levels of consciousness and anaesthesia depth were evaluated by pinching their hind paws. Cortical screw electrodes were implanted bilaterally into the frontal-parietal cortices for EEG recording. A reference cortical screw electrode was placed on the cerebellum. The EEG screw electrodes were soldered to the microconnectors, which were then fixed to the skull bone with cold acrylic cement. After the surgical procedure, the animals were placed in individual cages and allowed to recover for 1 week.

EEG recordings and analysis

After the recovery period, the animals were placed in plexiglass cages, and 3 h EEG recordings were recorded between 09:00 and 12:00 a.m. (ADI Instruments, Power Lab). EEG signals were amplified using a BioAmp ML 136 amplifier and filtered at bandpass settings of 1–40 Hz. These signals were then recorded and analyzed utilizing the Chart v.7 program (PowerLab8S ADI Instruments, Oxfordshire, UK). The cumulative SWD duration, number of SWDs, and mean duration of SWDs were evaluated after 35 days of oral Anatolian propolis administration.

Table 1. LC-MS/MS analysis of the phenolic substances in 15% and 30% Propolis drop soluble in water.

Phenolic compounds	15 % Propolis	30 % Propolis	Unit
p-Hydroxybenzoic acid	161,4	196,2	mg/L
Epicatechin	225,7	431,5	mg/L
Caffeic acid	858,7	1613,2	mg/L
p-Coumaric acid	392,6	669,4	mg/L
Ferulic acid	743,1	1938,7	mg/L
Resveratrol	32,5	63,9	mg/L
Luteolin	20,1	58,9	mg/L
Quercetin	123,6	249,4	mg/L
t-Cinnamic acid	58,2	186,3	mg/L
Apigenin	343	686,3	mg/L
Hesperetin	284,6	563,8	mg/L
Rhamnetin	374,2	592,8	mg/L
Chrysin	4416	8404,7	mg/L
Pinocembrin	790,3	1714	mg/L
Caffeic acid phenethyl ester (CAPE)	8152,5	11365	mg/L

LC-MS/MS: Liquid chromatography with tandem mass spectrometry.
Adapted from https://www.beeo.com.tr/analizlerimiz#fancybox-grup-84)

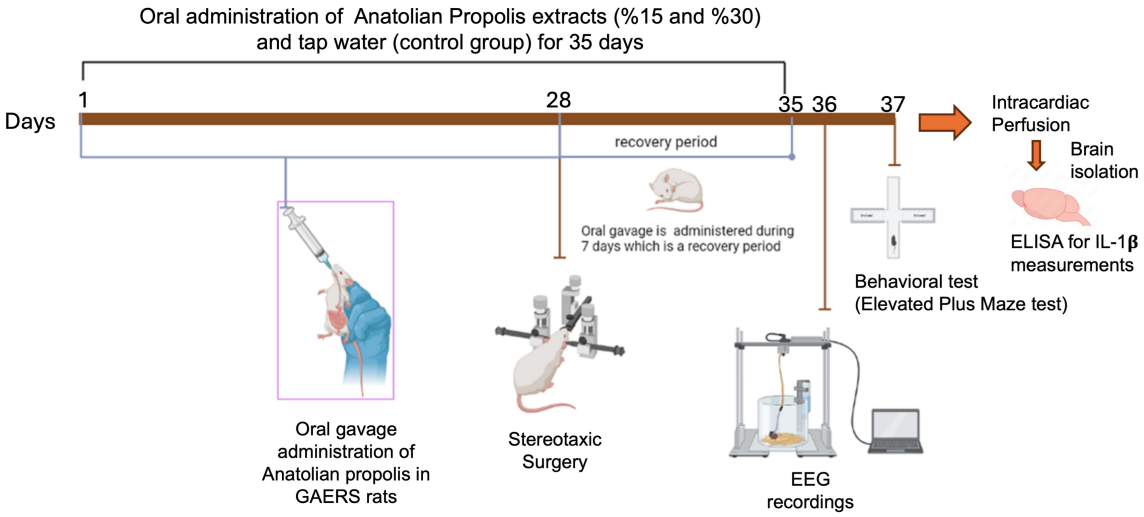

Figure 1. Experimental timeline. Adult GAERS rats were orally administered Anatolian propolis at a concentration of 15%, at a dose of 120 mg/kg (n=8), and at a concentration of 30% at a dose of 180 mg/kg (n=6). The control group (n=8) received the same volume of tap water. On the 28th day after the administration started, rats were implanted with EEG electrodes stereotaxically. After 7 days of recovery on the 36th day, EEG recordings were performed to evaluate the effect of Anatolian propolis on absence seizures. Subsequently, on day 37, rats underwent the elevated plus maze behavioral test to determine their anxiety levels. At the end of the protocol, rats were perfused and then brains were isolated for pro-inflammatory cytokine IL-1β measurements with ELISA metod.

Elevated plus maze test

The anxiety levels of the GAERS rats were measured using the elevated plus maze test. Adult male GAERS rats were placed on a platform that was 50 cm above the ground and consisted of two open arms (50 cm×10 cm), two closed arms (50 cm×10 cm×50 cm), and a central area (10cm×10cm) that connected the four arms. The rats were placed in the central area facing an open arm. Measurements of arm exploration (including duration and frequency of entries on open and closed arms and time spent in open and closed arms) were recorded and scored manually by a blind observer over 5 min (300 sec) (Hu et al., 2017; Mehta, Parashar, & Udayabanu, 2017; Słupski, Trocha, & Rutkowska, 2017). Using these measures, animal anxiety was estimated as an experimental outcome.

Measurement of proinflammatory cytokine (IL-1β) levels in brain tissue

At the end of the behavioural experiments, rats were deeply anaesthetised with ketamine/xylazine anaesthesia (100 mg/kg; 10 mg/kg; i.p.) and transcardially perfused with 0.1 M phosphate buffered saline (PBS). The brains of the rats were isolated and stored at -80 °C until the IL-1β measurements. For IL-1β measurements, brains were weighed and then homogenised in PBS (tissue weight (g): PBS (mL) volume = 1:9) with Omni Bead Ruptor®. The homogenates were then centrifuged for 10 mins 5000 x g at 4 °C to obtain the supernatant. IL-1β measurement in brain supernatant samples was performed using the ELISA method. To determine the dilution ratio that corresponds to the range of optical density (OD) values of the standards provided in the kit, a test was performed with different dilutions of one sample from each group. Based on the appropriate dilution ratio determined from the test, all samples were diluted with the sample diluent provided in the kit and processed according to kit instructions. All samples, standards, and blanks were studied in duplicate, and the average of two values was used for calculations. Diagnostic Automation, Inc.'s DA'R800 spectrometer and KC Junior software were used to determine the optical density values.

Statistical analysis

All data are given as the mean ± standard error of the mean (SEM). In all experiments, "n" represents the number of GAERS rats. One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test was used for the statistical analysis of the effect of propolis on SWDs (cumulative duration, number, and mean duration), IL-1β levels by ELISA, and anxiety scores. Statistical analysis was performed using Graphpad Prism version 9.0.1 program. *p<0.05 was considered statistically significant.

RESULTS

The effect of Anatolian propolis on SWDs

Cumulative SWD duration in the 15% (n=8) and 30% propolis (n=6) groups did not differ from that in the control (n=8) group (p>0.05; Figure 2A). Anatolian propolis administration had a significant treatment effect on the number of SWDs (F (2, 21) = 3.922; P=0.039; Figure 2B). The number of SWDs in the 30% Anatolian propolis group (147.8 ± 15.80) was significantly lower than that in the control (206.4 ± 14.08) group, as revealed by Tukey's multiple comparison test (P=0.039, Figure 2B). No significant change was observed in the mean duration of individual SWDs when comparing the propolis groups with the control group (p>0.05, Figure 2C).

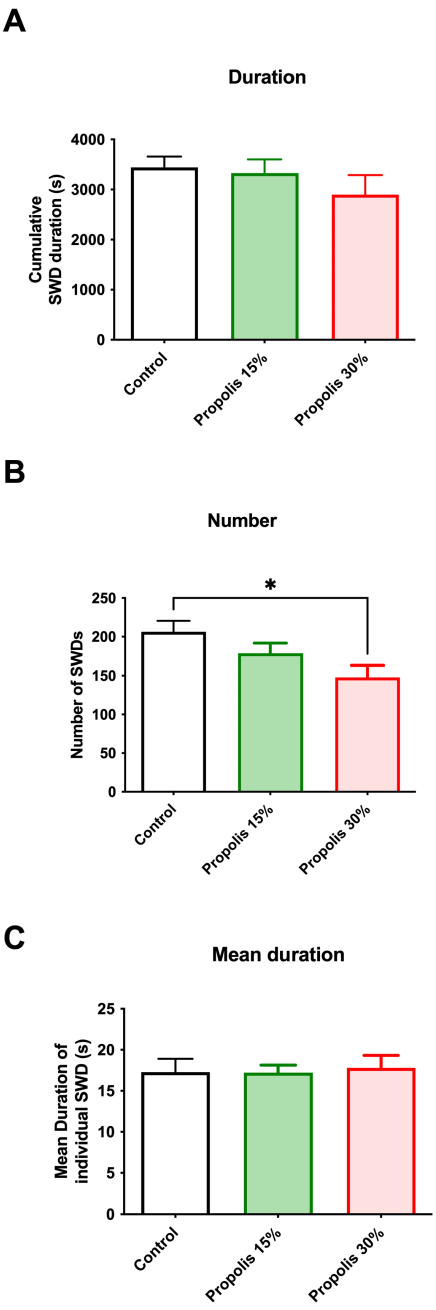

Figure 2. The effect of Anatolian propolis on absence seizures (SWDs). Effect of treatment with Anatolian propolis (15% and 30%) on cumulative SWD duration (A), number of SWDs (B), mean duration of individual SWD (C). *p<0.05, One-way analysis of variance, Tukey post-test. Data were expressed as mean±SEM.

Effect of Anatolian propolis on IL-1β levels

To evaluate whether Anatolian propolis administration affected neuroinflammation in GAERS, we measured IL-1β levels in brain tissue using ELISA. Anatolian propolis administration had a significant treatment effect on IL-1β levels (F (2, 21) = 3.341; P=0.048; Figure 3). Anatolian propolis at 30% concentration significantly reduced IL-1β levels (184.3 ± 15.15)

compared with the control (265.1 ± 33.04) group (P=0.034; Figure 3), as revealed by Tukey's multiple comparison test. Anatolian propolis at a 15% concentration also reduced IL-1β levels, but this change did not achieve statistical significance (p>0.05; Figure 3).

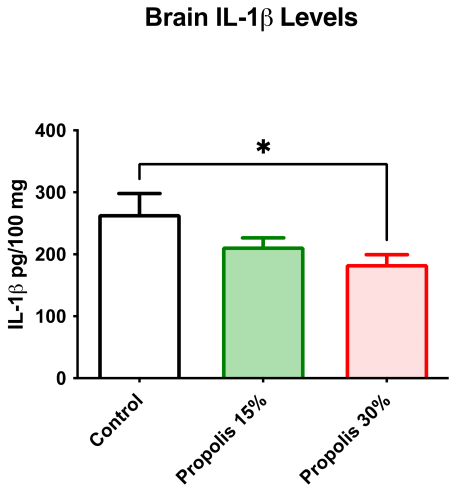

Figure 3. The effect of Anatolian propolis on IL-1β levels. Effect of treatment with Anatolian propolis (%15 and %30) on brain IL-1β Levels in GAERS, * p<0.05, One-way analysis of variance, Tukey post-test. Data were expressed as mean±SEM.

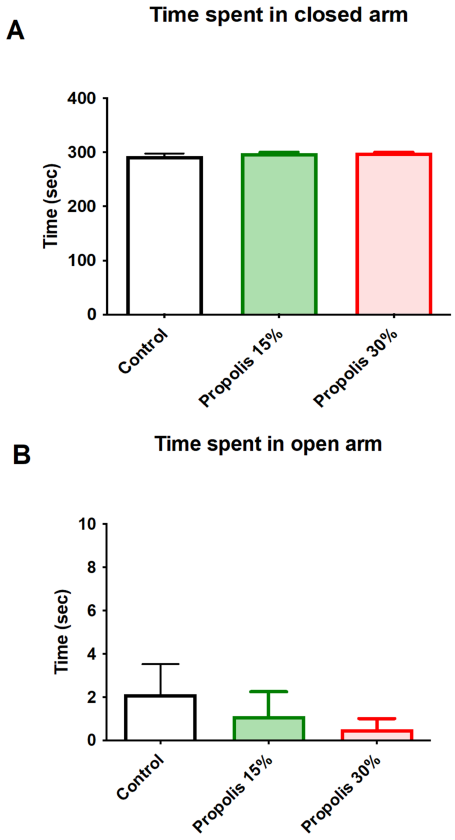

Figure 4. The effect of Anatolian propolis on anxiety levels. Effect of treatment with Anatolian propolis (%15 and %30) on time spent in closed (A) and open (B) arms. One-way analysis of variance, Tukey post-test. Data were expressed as mean±SEM.

Effect of Anatolian propolis on anxiety levels

After propolis administration, we compared the effect of propolis on the time spent in the open and closed arms to estimate the anxiety level of GAERS rats. No significant change was observed in the time spent in the closed and open arms in the propolis groups compared with the control (Figure 4A-B, p>0.05).

DISCUSSION

In the present study, oral administration of 30% Anatolian propolis (180 mg/kg/day) reduced the number of SWDs by decreasing brain pro-inflammatory cytokine; IL-1β levels in GAERS after 35 days of sub-chronic administration. However, propolis treatment did not change the anxiety levels in terms of the time spent in the closed and open arms. This is the first study to demonstrate the effect of Anatolian propolis on SWDs and brain IL-1β levels in GAERS.

Limited data have demonstrated that propolis significantly attenuates seizures in temporal lobe epilepsy rat models (Kwon et al., 2004). This effect has been attributed to the neuroprotective and anti-inflammatory effects of propolis (Kwon et al., 2004; Mannaa, El-Shamy, El-Shaikh, & El-Kassaby, 2011; Kulkarni, Vaidya, Narula, & Sharma, 2021; Zulhendri et al., 2021). Our results also confirmed these findings, suggesting that the effect of propolis on absence seizures in the GAERS model may be associated with its anti-inflammatory properties, potentially mediated by a decrease in the pro-inflammatory cytokine IL-1β.

Considering that the exact substance in propolis that is responsible for this effect has not yet been identified, CAPE is a possible candidate (Kulkarni et al., 2021). Anatolian propolis composition differs from other propolis samples and boasts an exceptionally rich content of phenolic constituents, notably CAPE, which is renowned for its neuroprotective potential due to its anti-inflammatory and antioxidant properties (Altuntaş et al., 2023). The anti-inflammatory and antioxidant properties of Anatolian propolis containing high levels of CAPE might play a significant role in attenuating absence seizures in GAERS. Further studies investigating the specific role of CAPE in absence seizures might provide better insight into the involvement of neuroinflammation in absence epilepsy.

The increase in the expression of the pro-inflammatory cytokine IL-1β was shown to be linked to the onset of absence seizures in GAERS. In rat models of genetic absence epilepsy, there was an observed tendency for the expression of IL-1β to increase before the onset of seizures. (Akin et al., 2011). Our data showing the reduced IL-1β levels in Anatolian propolis-

treated GAERS demonstrate that blocking IL-1β biosynthesis as a specific anti-inflammatory approach that may be helpful for managing absence epilepsy. Research further supports this by showing that in the GAERS model, a specific anti-inflammatory approach suppressed the progression of absence seizures and comorbid depressive-like symptoms. This approach involved blocking the IL-6 signaling pathway using tocilizumab, a monoclonal antibody targeting the IL-6 receptor (Leo et al., 2020). In line with previous studies, levels of IL-6 and IL-8 in the CSF fluid were found to be linked with childhood absence epilepsy in humans (Billiau et al., 2007), and valproic acid treatment lowers plasma levels of IL-6 in children with tonic-clonic generalised seizures (Steinborn et al., 2014). Addressing pro-inflammatory cytokines and chemokine could offer a promising avenue for developing targeted anti-epileptogenic therapies aimed at managing non-convulsive epilepsy and related neuropsychiatric comorbidities.

There are studies showing the anxiolytic effects of propolis (Reis et al., 2014; Da Silveira et al., 2016) in experimental animals. In the present study, however, anxiety levels did not differ between the propolis administration and tap water-treated control groups. This finding could be attributed to variations in the experimental setup for measuring anxiety levels or the duration of propolis treatment. Longer treatment protocols with propolis extract or CAPE may reveal promising effects on anxiety levels in GAERS.

As confirmed by our findings, previous studies have largely demonstrated the beneficial effects of bee products, such as propolis, on various health conditions, including their antioxidant, anti-inflammatory, and neuroprotective properties. However, emerging evidence shows that not all bee products exert beneficial effects. For instance, Kuru et al. (2014) explored the effect of toxic honey, specifically grayanotoxin-containing honey, in genetic absence epilepsy rat model (Kuru et al., 2014). Bees that feed on the nectar of certain Rhododendron species produce this type of honey, also known as "mad honey." The intracerebroventricular administration of toxic honey led to generalised seizures in both GAERS and non-epileptic Wistar rats. This finding is particularly intriguing because it highlights the dualistic nature of bee products, in which certain types can intensify rather than alleviate seizure activity. Our study underscores the importance of considering the specific type and source of bee products when evaluating their neurological effects. It also emphasises the need for rigorous chemical characterisation and standardisation of bee products used in experimental settings. Thus, although the therapeutic potential of bee products is promising, it is crucial to recognise and account for the variability in their chemical composition and biological effects.

CONCLUSION

Overall, Anatolian propolis (30%) treatment reduced pro-inflammatory cytokine (IL-1β) levels in GAERS but did not modify anxiety levels. The potential effects of Anatolian propolis in absence seizure and anxiety have not been evaluated in GAERS, and thus, this study constitutes original findings on this promising relationship with the anti-inflammatory effect of Anatolian propolis and absence seizure in epilepsy. On the other hand, addressing some limitations in the current study may provide a better understanding of the anti-inflammatory effects of Anatolian propolis. We suggest that measurement of plasma IL-1β levels along with brain sample measurements may be more supportive of the correlation between the systemic and local anti-inflammatory effects of Anatolian propolis treatment. Further investigation to understand the neuroprotective effect of Anatolian propolis in relation with absence seizure will be an intriguing research target in favour of epilepsy and its associated neuropsychiatric comorbidities.

Ethics Committee Approval: All procedures were carried out in the Experimental Animal Care and Research Unit of Istanbul University Faculty of Pharmacy (EDEHAB), according to approval by the Animal Ethics Committee of Istanbul University (2022/06) conforming with the EU Directive 2010/63/EU for animal experiments of the Istanbul University Local Ethics Committee of Animal Experiments (HADYEK).

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study: B.Y., N.Ç.; Data Acquisition: B.Y., Ş.A.P., E.C .; Data Analysis/Interpretation: B.Y., Ş.A.P., E.C., D.K.D., N.Ç.; Drafting Manuscript: B.Y., E.C.; Critical Revision of Manuscript: Ş.A.P., D.K.D., N.Ç.; Final Approval and Accountability: B.Y., Ş.A.P., E.C., D.K.D., N.Ç.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: TUBITAK-2209A University Students Research Projects Support Program. (Project number: 1919B012104927).

ORCID IDs of the authors

Batuhan Yağmur	0009-0006-2560-5008
Şura Akat Pişkin	0000-0002-0437-3379
Erkan Civelek	0000-0002-6503-5226
Deniz Kaleli Durman	0000-0002-8669-7480
Nihan Çarçak	0000-0001-6254-4319

REFERENCES

Akin, D., Ravizza, T., Maroso, M., Carcak, N., Eryigit, T., Vanzulli, I., ... Onat, F. Y. (2011). IL-1β is induced in reactive astrocytes in the somatosensory cortex of rats with genetic absence epilepsy at the onset of spike-and-wave discharges, and contributes to their occurrence. *Neurobiology of Disease, 44*(3), 259–269. https://doi.org/10.1016/J.NBD.2011.05.015

Altuntaş, Ü., Güzel, İ., & Özçelik, B. (2023). Phenolic constituents, antioxidant and antimicrobial activity and clustering analysis of Propolis samples based on PCA from different regions of Anatolia. *Molecules (Basel, Switzerland), 28*(3). https://doi.org/10.3390/MOLECULES28031121

Billiau, A. D., Witters, P., Ceulemans, B., Kasran, A., Wouters, C., & Lagae, L. (2007). Intravenous immunoglobulins in refractory childhood-onset epilepsy: effects on seizure frequency, EEG activity, and cerebrospinal fluid cytokine profile. *Epilepsia, 48*(9), 1739–1749. https://doi.org/10.1111/J.1528-1167.2007.01134.X

Braakhuis, A. (2019). Evidence on the health benefits of supplemental Propolis. *Nutrients, 11*(11). https://doi.org/10.3390/NU11112705

Brigo, F., Igwe, S. C., & Lattanzi, S. (2019). Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. *The Cochrane Database of Systematic Reviews, 2*(2). https://doi.org/10.1002/14651858.CD003032.PUB4

Crunelli, V., & Leresche, N. (2002). Childhood absence epilepsy: genes, channels, neurons and networks. *Nature Reviews. Neuroscience, 3*(5), 371–382. https://doi.org/10.1038/NRN811

Da Silveira, C. C. S. D. M., Fernandes, L. M. P., Silva, M. L., Luz, D. A., Gomes, A. R. Q., Monteiro, M. C., Maia, C. S. F. (2016). Neurobehavioral and Antioxidant Effects of Ethanolic Extract of Yellow Propolis. *Oxidative Medicine and Cellular Longevity, 2016*. https://doi.org/10.1155/2016/2906953

Danober, L., Deransart, C., Depaulis, A., Vergnes, M., & Marescaux, C. (1998). Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Progress in Neurobiology, 55*(1), 27–57. https://doi.org/10.1016/S0301-0082(97)00091-9

El Adaouia Taleb, R., Djebli, N., Chenini, H., Sahin, H., & Kolayli, S. (2020). In vivo and in vitro anti-diabetic activity of ethanolic propolis extract. *Journal of Food Biochemistry, 44*(7). https://doi.org/10.1111/JFBC.13267

Gocmez, S. S., Şahin, T. D., Yazir, Y., Duruksu, G., Eraldemir, F. C., Polat, S., & Utkan, T. (2019). Resveratrol prevents cognitive deficits by attenuating oxidative damage and inflammation in rat model of streptozotocin diabetes induced vascular dementia. *Physiology & Behavior, 201*, 198–207. https://doi.org/10.1016/J.PHYSBEH.2018.12.012

Guler, E., Bilir, O., Kocak, A. O., Atas, I., & Samanci, A. E. T. (2022). The prophylactic efficacy of Anatolian propolis in individuals at high risk of COVID-19. DOAJ (DOAJ: Directory of Open Access Journals), 26(2 Suppl), 53–60. https://doi.org/10.26355/eurrev_202212_30483

Hirsch, E., French, J., Scheffer, I. E., Bogacz, A., Alsaadi, T., Sperling, M. R., ... Zhou, D. (2022). ILAE definition of the Idiopathic Generalized Epilepsy Syndromes: Position statement by the ILAE Task Force on Nosology and Definitions. *Epilepsia, 63*(6), 1475–1499. https://doi.org/10.1111/EPI.17236

Hu, C., Luo, Y., Wang, H., Kuang, S., Liang, G., Yang, Y., ... Yang, J. (2017). Re-evaluation of the interrelationships among the behavioral tests in rats exposed to chronic unpredictable mild stress. *PloS One, 12*(9). https://doi.org/10.1371/JOURNAL.PONE.0185129

Jones, N. C., Salzberg, M. R., Kumar, G., Couper, A., Morris, M. J., & O'Brien, T. J. (2008). Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy suggesting common causation. *Experimental Neurology, 209*(1), 254–260. https://doi.org/10.1016/J.EXPNEUROL.2007.09.026

Kessler, S. K., & McGinnis, E. (2019). A Practical guide to treatment of childhood absence epilepsy. *Paediatric Drugs, 21*(1), 15–24. https://doi.org/10.1007/S40272-019-00325-X

Kulkarni, N. P., Vaidya, B., Narula, A. S., & Sharma, S. S. (2021). Neuroprotective Potential of Caffeic Acid Phenethyl Ester (CAPE) in CNS Disorders: Mechanistic and Therapeutic Insights. *Current Neuropharmacology, 19*(9), 1401–1415. https://doi.org/10.2174/1570159X19666210608165509

Kwon, Y. S., Park, D. H., Shin, E. J., Kwon, M. S., Ko, K. H., Kim, W. K., ... Kim, H. C. (2004). Antioxidant propolis attenuates kainate-induced neurotoxicity via adenosine A1 receptor modulation in the rat. *Neuroscience Letters, 355*(3), 231–235. https://doi.org/10.1016/j.neulet.2003.10.075

Kuru, P., Torun, M., Halac, H. M., Temiz, G., Iskender, E., Karamahmutoglu, T., ... Onat, F. Y. (2014). Electroencephalographic and behavioral effects of intracerebroventricular or intraperitoneal injections of toxic honey extract in adult Wistar rats and GAERS. Neurological Sciences, 35(12), 1903–1908. https://doi.org/10.1007/s10072-014-1858-6

Leo, A., Nesci, V., Tallarico, M., Amodio, N., Gallo Cantafio, E. M., De Sarro, G., ... Citraro, R. (2020). IL-6 receptor blockade by Tocilizumab has anti-absence and anti-epileptogenic effects in the WAG/Rij rat model of absence epilepsy. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics, 17*(4), 2004–2014. https://doi.org/10.1007/S13311-020-00893-8

Löscher, W., & Schmidt, D. (2011). Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. *Epilepsia, 52*(4), 657–678. https://doi.org/10.1111/J.1528-1167.2011.03024.X

Mannaa, F., El-Shamy, K. A., El-Shaikh, K. A., & El-Kassaby, M. (2011). Efficacy of fish liver oil and propolis as neuroprotective agents in pilocarpine epileptic rats treated with valproate. *Pathophysiology: The Official Journal of the International Society for Pathophysiology, 18*(4), 287–294. https://doi.org/10.1016/J.PATHOPHYS.2011.04.002

Masur, D., Shinnar, S., Cnaan, A., Shinnar, R. C., Clark, P., Wang, J., ... Glauser, T. A. (2013). Pretreatment cognitive deficits and treatment effects on attention in childhood absence epilepsy. *Neurology, 81*(18), 1572–1580. https://doi.org/10.1212/WNL.0B013E3182A9F3CA

Mehta, V., Parashar, A., & Udayabanu, M. (2017). Quercetin prevents chronic unpredictable stress induced behavioral dysfunction in mice by alleviating hippocampal oxidative and inflammatory stress. *Physiology & Behavior, 171*, 69–78. https://doi.org/10.1016/J.PHYSBEH.2017.01.006

Oršolić, N., & Bašić, I. (2003). Immunomodulation by water-soluble derivative of propolis: A factor of antitumor reactivity. *Journal of Ethnopharmacology, 84*(2–3), 265–273. https://doi.org/10.1016/S0378-8741(02)00329-X

Ott, D., Siddarth, P., Gurbani, S., Koh, S., Tournay, A., Shields, W. D., & Caplan, R. (2003). Behavioral disorders in pediatric epilepsy: unmet psychiatric need. *Epilepsia, 44*(4), 591–597. https://doi.org/10.1046/J.1528-1157.2003.25002.X

Reis, J. S. S., Oliveira, G. B., Monteiro, M. C., Machado, C. S., Torres, Y. R., Prediger, R. D., & Maia, C. S. F. (2014). Antidepressant- and anxiolytic-like activities of an oil extract of propolis in rats. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 21*(11), 1466–1472. https://doi.org/10.1016/J.PHYMED.2014.06.001

Shorvon, S. (2011). *Handbook of Epilepsy Treatment, Third Edition. Handbook of Epilepsy Treatment, Third Edition*. https://doi.org/10.1002/9781444325201

Słupski, W., Trocha, M., & Rutkowska, M. (2017). Pharmacodynamic and pharmacokinetic interactions between simvastatin and diazepam in rats. *Pharmacological Reports: PR, 69*(5), 943–952. https://doi.org/10.1016/J.PHAREP.2017.03.012

Steinborn, B., Zarowski, M., Winczewska-Wiktor, A., Wójcicka, M., Młodzikowska-Albrecht, J., & Losy, J. (2014). Concentration of Il-1β, Il-2, Il-6, TNFα in the blood serum in children with generalized epilepsy treated by valproate. *Pharmacological Reports: PR, 66*(6), 972–975. https://doi.org/10.1016/J.PHAREP.2014.06.005

Swamy, M., Suhaili, D., Sirajudeen, K. N. S., Mustapha, Z., & Govindasamy, C. (2014). Propolis ameliorates tumor nerosis factor-α, nitric oxide levels, caspase-3 and nitric oxide synthase activities in kainic acid mediated excitotoxicity in rat brain. *African Journal of Traditional, Complementary, and Alternative Medicines: AJTCAM, 11*(5), 48–53. https://doi.org/10.4314/AJTCAM.V11I5.8

Vrielynck, P. (2013). Current and emerging treatments for absence seizures in young patients. *Neuropsychiatric Disease and Treatment, 9*, 963–975. https://doi.org/10.2147/NDT.S30991

Zimmerman, F. T., & Burgemeister, B. B. (1958). A new drug for petit mal epilepsy. *Neurology, 8*(10), 769–775. https://doi.org/10.1212/WNL.8.10.769

Zingue, S., Nde, C. B. M., Michel, T., Ndinteh, D. T., Tchatchou, J., Adamou, M., . . . Njamen, D. (2017). Ethanol-extracted Cameroonian propolis exerts estrogenic effects and alleviates hot flushes in ovariectomized Wistar rats. *BMC Complementary and Alternative Medicine, 17*(1). https://doi.org/10.1186/S12906-017-1568-8

Zulhendri, F., Perera, C. O., & Tandean, S. (2021). Can propolis be a useful adjuvant in brain and neurological disorders and injuries? A systematic scoping review of the latest experimental evidence. *Biomedicines, 9*(9). https://doi.org/10.3390/BIOMEDICINES9091227

Zullkiflee, N., Taha, H., & Usman, A. (2022). Propolis: Its role and efficacy in human health and diseases. *Molecules (Basel, Switzerland), 27*(18). https://doi.org/10.3390/MOLECULES27186120

How cite this article

Yağmur, B., Akat, Pişkin, Ş., Civelek, E., Kaleli Durman, D., Çarçak, N. (2024). Effects of Anatolian propolis on absence seizures and anxiety in rats with genetic absence epilepsy. *İstanbul Journal of Pharmacy, 54*(3): 378–385. DOI: 10.26650/IstanbulJPharm.2024.1467008