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ARTICLE**

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The Effect of Rose Oil on Penicillin-Induced Epileptiform Activity in Rats: An Electrophysiological Study

ABSTRACT

Objective: Rose oil (from *Rosa damascena*) has several effects which are analgesic, antispasmodic, antioxidant and neuroprotective role. Its antiepileptic effect has not been yet studied enough. In the present study, it was aimed to investigate acute effects of rose oil on the epileptiform activity in penicillin-induced epilepsy model in rats.

Methods: Forty-two male Wistar rats weighing 230 to 260 g were divided into six groups with seven rats in each group. Control (+Penicillin), RO alone, Diazepam, and different doses of Rose oil including 100, 500 and 1000 mg/kg. Rats were pretreated with different doses of RO 30 min prior to penicillin treatment. Electrocardiogram recordings were taken from each animal for 2 hours after penicillin treatment.

Results: Only the dose of 100 mg/kg of rose oil reduced significantly epileptic spike-wave frequency of epileptiform activity. However, comparing in terms of latency and spike-wave amplitude of epileptiform activity, there were no significant difference between the groups.

Conclusions: In conclusion, acute administration of rose oil reduces spike-wave frequency of penicillin-induced epileptiform activity in rats. Therefore, these findings indicate that rose oil has antiepileptic effects.

Keywords: Rose Oil, Epileptiform Activity, Epilepsy, Electrocardiography.

Gül Yağının Sıçanlarda Penisilin İle Tetiklenen Epileptiform Aktivite Üzerine Etkileri: Elektrofizyolojik Bir Çalışma

ÖZET

Amaç: Gül yağı analjezik, antispazmodik, antioksidan ve nöroprotektif etkilere sahiptir. Anti-epileptik etki üzerine yapılan çalışmalar ise yetersizdir. Sunulan çalışmada, gül yağının sıçanlarda penisilin ile tetiklenen epilepsi modelinde epileptiform aktivite üzerine akut etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: 230-260 gr ağırlığında kırk iki erkek wistar sıçan her grupta yedi olmak üzere altı gruba ayrıldı. Gruplar kontrol (penisilin), yalnız gül yağı, diazepam ve gül yağının 100, 500 ve 1000 mg/kg olmak üzere farklı dozlarından oluşmaktadır. Sıçanlara penisilin uygulamasından 30 dakika önce gül yağının farklı dozları uygulandı. Penisilin uygulamasından sonra 2 saat boyunca her bir hayvandan elektrokortikogram kayıtları alındı.

Bulgular: Gül yağının sadece 100 mg/kg dozu epileptiform aktivitenin epileptik diken-dalga frekansını önemli derecede azalttı. Bununla birlikte epileptiform aktivite latens ve diken-dalga amplitüdü açısından karşılaştırıldığında gruplar arasında anlamlı bir fark yoktu.

Sonuç: Gül yağının akut olarak uygulanması sıçanlarda, penisilin ile tetiklenen epileptiform aktivitenin diken-dalga frekansını azaltmaktadır. Böylece bulgularımız gül yağının anti-epileptik etkilere sahip olduğunu göstermektedir.

Anahtar Kelimeler: Gül Yağı, Epileptiform Aktivite, Epilepsi, Elektrokortikogram.

INTRODUCTION

Epilepsy is one of common chronic brain disorders and it is characterized by recurrent spontaneous seizures. In fact, epilepsy is not only a disorder but also a symptomatic situation that results from structural brain lesions, genetic factors, traumatic brain injury, central nervous system infections, and stroke or brain tumors. The etiology of epilepsy is still unknown for 65% of patients with epilepsy. Currently there are approximately 65 million people who have active epilepsy with continuous seizures worldwide and they need the treatment (1). Almost 30% of them are resistant to all antiepileptic drugs prescribed by physicians (2). In addition, current drugs used for epilepsy treatment have significant side effects. Therefore, there is still a need for investigations that explore pathophysiology of epilepsy and its efficacious treatment, as well as antiepileptic drugs with low-priced and minor side effect.

About 70% of epileptic seizures are controlled by monotherapy with existing antiepileptic drugs. On the other hand, researches on the herbal products have an important place in development of novel antiepileptic drugs. Various phytochemical, pharmacological and electrophysiological studies have been conducted on potential anticonvulsant effects of plants. It was discovered that many substances obtained from plants have antiepileptic effects (3,4).

Models of experimental epilepsy have been being used by researchers for a long time to explain the pathogenesis of epileptic seizures and to develop new antiepileptic drugs. Administration of chemical convulsants, such as penicillin, is simple and fast way to induce epileptic activity (5). Penicillin model of experimental epilepsy is one of the most common acute models used by researchers. In this model, cortical areas become the source of epileptic seizures after injection of penicillin (6). Topical application of penicillin to cortical surface is also capable of inducing epileptiform activity and it is used as a model of acute partial epilepsy. Penicillin induced-epileptic activity starts as a focal and then it spreads to cause a generalized epilepsy. From this point, it is like grand-mal epilepsy (7,8). Like penicillin, application of bicuculline (GABAA receptor antagonist) or picrotoxin (GABAA channel inhibitor) can also cause epileptiform field potentials and paroxysmal depolarization shifts. These epileptic activities can be inhibited by various antagonists, such as diazepam. On this basis, an increase in the levels of excitation would be expected as a result of decrease in the inhibitory effectiveness or amount of GABA in the brain. Moreover, considerable excitation could also occur as a result of over release of glutamate, the most common excitatory neurotransmitter in the brain (9). Previously, it was suggested that rose oil can have neuromodulator effect with antidepressant like

effects in mice (10). Moreover RO has various effects on GABAA receptors in rat brain and it strengthens the anticonvulsant effect of benzodiazepines (11). Isparta Rose (*Rosa damascena* Mill.) is a member of the Rosaceae family. It is a plant with large, pale pink and pink or white flowers. This plant contains numerous ingredients such as glycosides, flavonoids, anthocyanin, carboxylic acids, vitamin C, kaempferol, quercetin, and geraniol (Fig. 1, Table 1). However, the essential oil ratio of rose is very low (0.03–0.04%) compared to other aromatic plants. Rose oil has been produced in Turkey as “Isparta Rose” since 1888 and in Bulgaria as “Kazanlık Rose” since 1664 (12).

Table 1. Chemical composition and retention indices of the constituents of the RO used in the study (See Fig. 1 for Chromatogram of the Rose Oil)

RT (min) ^a	Compounds ^b	(%)
33.692	Hexadecane	0.16
37.246	Linalool	0.63
41.231	Caryophyllene	0.33
44.447	Citronellyl acetate	0.75
45.975	Heptadecane	0.47
47.833	Germacrene	0.55
49.269	Z citral	0.37
50.161	Geranyl acetate	1.60
50.708	Citronellol	42.13
52.767	Nerol	10.70
54.094	Phenyl ethyl acetate	0.41
55.414	Geraniol	23.36
57.967	Eicosane	7.23
58.983	9-nonadecene	1.78
59.535	Phenylethyl alcohol	1.71
63.539	Pentadecane	0.54
64.939	Methyl eugenol	2.79
68.689	Heneicosane	2.78
73.035	Eugenol	1.08
78.519	Tricosane	0.53
79.765	Farnesol	0.10
Total identified		100

a RT: Retention time

b Compounds: Compounds listed in order of elution from rose oil

In traditional medicine and industry, it has been used as reliever scent, rose water, essential oil, laxative for centuries. *R. damascena* is known to be used as a traditional drug in digestive disorders, joint pains, dysmenorrhea, constipation, and urinary disorders (12). Recent investigations have showed that RO has hypnotic, antispasmodic, and relaxant effects (13,14). In addition, it was suggested that RO has therapeutic effects on abdominal and chest pain and strengthening of the heart (15). Several experimental studies have shown that *R. damascena* has anti-HIV, antioxidant, antibacterial activity, hepatoprotective and antitussive effects (16-18).

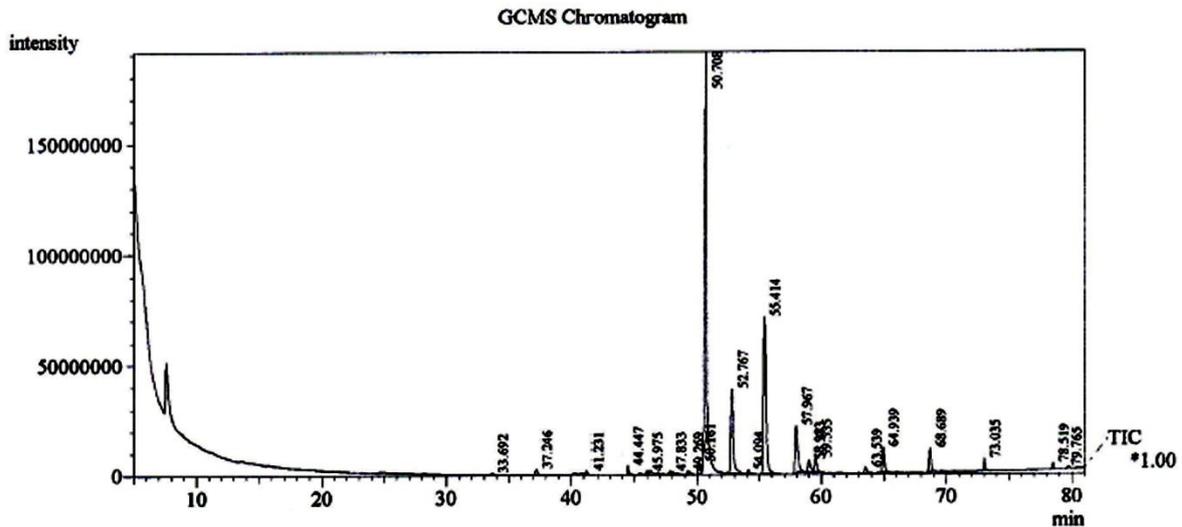


Fig. 1. Gas Chromatography Mass Spectrometry Chromatogram of the Rose Oil (See Table 1 for details).

In addition to this, long-term use of RO in high concentrations decreases stress (19). Furthermore, rose extract has analgesic effects in mice (18). In some clinical and experimental studies were demonstrated that RO has antiepileptic and anticonvulsant effects (10, 20-23). In a double-blind clinical trial was reported that essential oil of *R. damascena* showed antiepileptic effect in children with refractory seizures (20). Another study was reported that hydroalcoholic extract of *R. damascena* exhibited anticonvulsant effects on hippocampus in pentylenetetrazol (PTZ)-evoked seizure model in rats (23).

Penicillin-induced epilepsy model is widely used by researchers worldwide and it not only reveals increased or decreased motor activity but it also provides electrophysiological evidence for focal and generalized epilepsy (5, 6, 24). Therefore, in current study, we investigated the effect of RO on epileptiform activity in the penicillin-induced epilepsy model in rats.

MATERIAL AND METHODS

Animals: Forty-two male inbred Wistar rats weighing 230 to 260 g were used. Animals were provided from University of Bolu Abant İzzet Baysal, Experimental Animals Research Center, Bolu, Turkey. They were harbored at stable room temperature ($21\pm 2^{\circ}\text{C}$) under 12/12 h light/dark cycle. Rats were provided ad libitum reach to food and water. Experimental interventions were carried out between 08:00-12:00 a.m. to avoid the effects of circadian alteration. All experimental interventions were performed according to the ethical guidelines of the Ethics Committee of University of Bolu Abant İzzet Baysal, and the NIH Guiding Principles in the Care and Use of Animals. The experiments were carried out in Experimental Animals Research Center of University of Bolu Abant İzzet Baysal, Bolu, Turkey.

Drugs, doses and groups: The animals were randomly divided into 6 groups as Table 2.

Table 2. The drugs, doses, applying route of drugs and number of animals in the groups.

Group Name	Drugs	Dose	Route	n
Only RO	RO	100 mg/kg	i.p.	7
Control	Saline + Penicillin G*	0.2 ml	i.p.	7
100 mg/kg RO	RO + Penicillin G*	100 mg/kg	i.p.	7
500 mg/kg RO	RO + Penicillin G*	500 mg/kg	i.p.	7
1000 mg/kg RO	RO + Penicillin G*	1000 mg/kg	i.p.	7
Diazepam	Diazepam + Penicillin G*	5 mg/kg	i.p.	7

*500 IU/1 μ l, intracortically

RO: Rose oil, i.p.: intraperitoneal

Rats were anaesthetized with an intraperitoneal (i.p.) injection of 1.25 g/kg Urethane (Sigma-Aldrich Chemical Co., St. Louis, Missouri, USA). To induce epileptiform activity, penicillin (I.E. Ulugay, Istanbul, Turkey) were administered at 500 IU/2 μ l dose intracortically (i.c.). The GC/MS analysis of the prepared rose flower

extracts and diluted rose oil samples was carried out on GC/MS system equipped with non-polar column using helium 5.0 as a carrier gas at a septum purge flow of 3 ml/min, splitless injection of 1 μ l of the sample and the following acquisition parameters: injector temperature 250°C , oven program 40°C for 3 min then $5^{\circ}\text{C}/\text{min}$ to 300°C for 5 min, run time

60 min. Chemical composition of RO obtained from GC-MS analyses are shown in Table 1 and Figure 1. RO was dissolved in dimethylsulfoxide (DMSO, Loba Chemie, Mumbai, India) following dilution with saline (99% DMSO; 0.2 ml final solution DMSO/saline 1:4, v/v). Administered doses of RO in this study were chosen according to previous similar studies (10, 21-23). Rose oil was i.p. administered at 100 mg/kg, 500 mg/kg, and 1000 mg/kg doses. Certificated RO was purchased from the biggest RO producer in the world (Gulbirlık, Isparta, Turkey).

Surgical procedure: The surgical methods and electrophysiological recording were carried out in the same manner as described previously (6). Animals were anesthetized with urethane, and situated on a stereotactic apparatus (Harvard Instruments, South Natick, MA, USA). After shaving top of the head, the scalp was incised along the sagittal suture, from anterior to posterior. Left parietal bone was removed via a hand drill (Proxxon Minimot 40/E, Proxxon GmbH, Niersbach, Germany).

Electrophysiological recordings: Two Ag-AgCl ball electrodes were situated on the somatomotor cortex where was opened on the left hemisphere lateral to the Bregma line. After

electrode placements, electrocorticography (ECoG) recordings (PowerLab/8SP, ADInstruments Pty Ltd, Castle Hill, NSW, Australia) were collect along the experiment. Prior to injecting the substances to groups, basal activity was recorded for 5 minutes. After recording basal activity, the drugs were treated to rats in the control RO, and diazepam groups as shown table 2 and ECoGs were recorded for a further 30 minutes. At this point, epileptic activity was induced injecting i.c. penicillin into somatomotor cortex via a Hamilton micro-injector (701N, Hamilton Co., Reno, NV, USA). The injection coordinates are 2 mm lateral, 1 mm anterior of Bregma line, and 1.2 mm depth. The recordings were taken for a further 120 minutes. Thus, total 155 minutes of ECoG recording was taken for each animal. ECoG recordings from the experiments were analyzed using the PowerLab Chart v.7.2.1 software package (ADInstruments Pty Ltd, Castle Hill, NSW, Australia). Epileptiform activity observed as bipolar spike and spike wave complexes was evaluated. Spike wave frequency and amplitudes per minute in the 5 minute-periods of ECoG recordings from all rats were digitized and presented as the data. Figure 2 shows all experimental procedures as abstract.

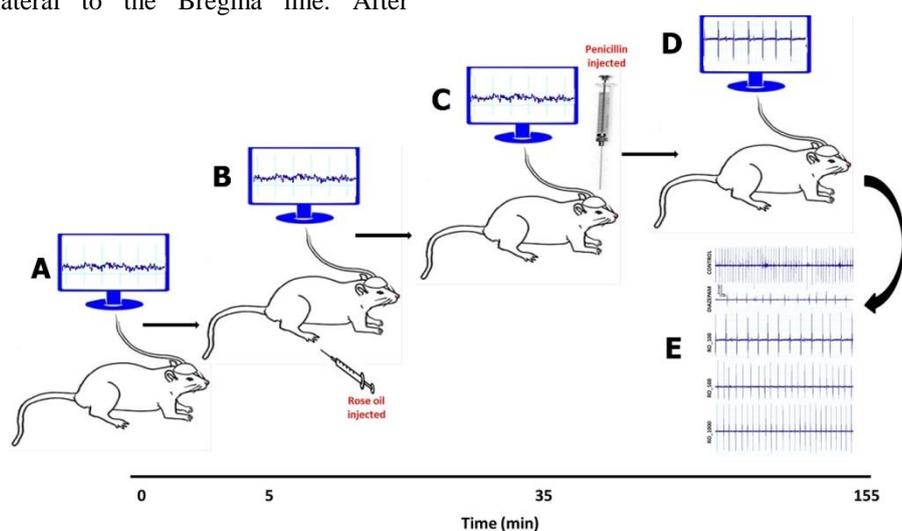


Fig. 2. The figure shows all procedures and ECoG records as abstract. A) Basal activity for 5 minutes B) ECoG after injection of the drugs for 30 minutes, C) Penicillin injection to induce epileptic activity, D) Recording of ongoing activity after penicillin, E) Representative examples of the records from ECoGs which belong to the groups.

Statistical analysis: While total spike-wave number and latency of the first epileptiform activity were given as mean \pm standard error of mean (SEM), spike-wave amplitude and frequency were given as median. Onset latency of the epileptiform activity, spike-wave frequency, and spike-wave amplitude from the recordings were calculated automatically by a macro in the software (ADInstruments Pty Ltd, Castle Hill, NSW, Australia). Differences between the groups in terms of latency, spike-wave frequency and amplitude for each period were analyzed by the Kruskal-Wallis

test. Groups with statistically significant differences were analyzed by Dunn's Multiple Comparison Test using SPSS v.22 software (Hong Kong, Republic of China). The level accepted for statistical significance was $p < 0.05$.

RESULTS

Penicillin causes epileptic discharges in 3–9 minutes after the administration of penicillin into the cortex. The epileptic discharges appear markedly in ECoG recordings as spike and spike-wave form. In the RO alone group, RO alone did not cause any epileptic discharge or change

ongoing activity throughout ECoG recordings. Likewise, in the 100, 500 or 1000 mg/kg dose groups, RO alone did not exhibit any effect until penicillin administration.

Effect of Rose Oil on Onset Latency of First Epileptiform Activity: In the control group, the latent period started immediately after penicillin injection and recordings appeared with lower amplitude compared to basal activity and it lasted 3–9 minutes on average. At the end of this period,

sudden and irregular onset of spike-waves was generally observed with no apparent transition period and then epileptic activity started. In the other groups, the latent periods were between 3rd and 15th minutes. When groups were compared in terms of onset latency of the first epileptiform activity, there was no statistically significant difference between groups ($p = 0.072$) (Fig. 3).

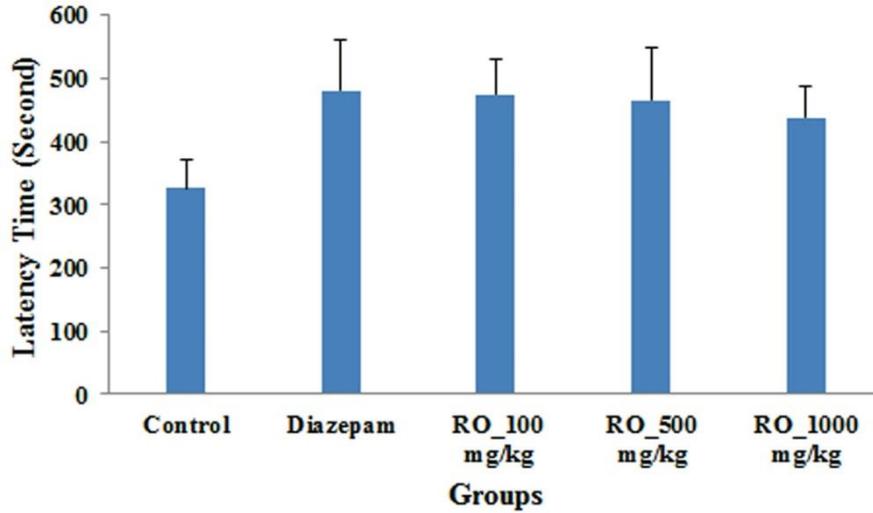


Fig. 3. Latency of the first epileptiform activity.

Effect of Rose Oil on Spike-Wave Frequency of Epileptiform Activity: There was not statistically significant differences between median values of the spike-wave frequency obtained from groups in the first five minutes after penicillin administration ($p = 0.407$) (Fig. 4). There were significant differences between median values of spike-wave frequencies of all groups during 6 - 120 minutes (Fig. 4). According to the results, median values of the spike-wave frequencies which

were obtained from 6–10, 11–15, 16–20, 21–25, 26–30, 31–35, 36–40, and 41–45 periods were found to be significantly lower in the 100 mg/kg RO group compared to control group ($p = 0.05$, $p = 0.013$, $p = 0.009$, $p = 0.010$, $p = 0.021$, $p = 0.023$, $p = 0.029$, and $p = 0.035$, respectively). On the other hand, there was no statistically significant difference between control and the 100 mg/kg RO groups during 46–120 minutes (Fig. 4).

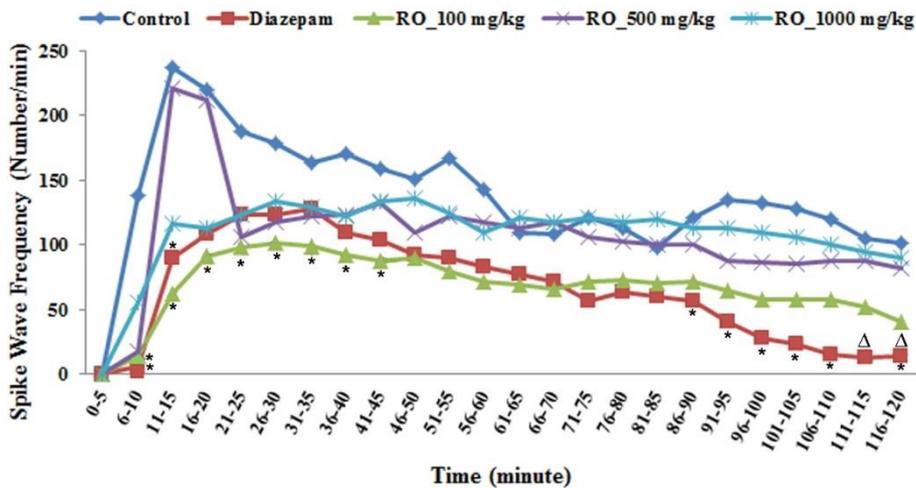


Fig. 4. Median values of spike-wave frequency (number/min) obtained from recording after penicillin (*Significance compared to control group [$p < 0,05$]; Δ Significance compared to 1000 mg/kg rose oil group [$p < 0,05$]). RO: rose oil.

In the diazepam group, median values of the spike-wave frequencies at 6–10, 11–15, 86–90, 91–95, 96–100, 101–105, 106–110, and 116–120 minutes were found to be significantly lower than the values of the control group ($p = 0.022$, $p = 0.028$, $p = 0.049$, $p = 0.028$, $p = 0.027$, $p = 0.020$, $p = 0.037$, and $p = 0.012$, respectively). In the diazepam group, median values of the spike-wave frequency during 111–115; and 116–120 minutes were found to be significantly lower compared to 1000 mg/kg RO group ($p = 0.044$ and $p = 0.011$,

respectively). There was no statistically significant difference between the groups in the remaining periods (Fig. 4). When mean value of total spike number were evaluated throughout all recording time, the 100 mg RO ($p=0.004$) and diazepam ($p=0.004$) groups were found significantly lower than the control group. However, there was no statistically significant difference between 500 mg/kg RO, 1000 mg/kg RO and control groups ($p>0.05$) (Fig. 5).

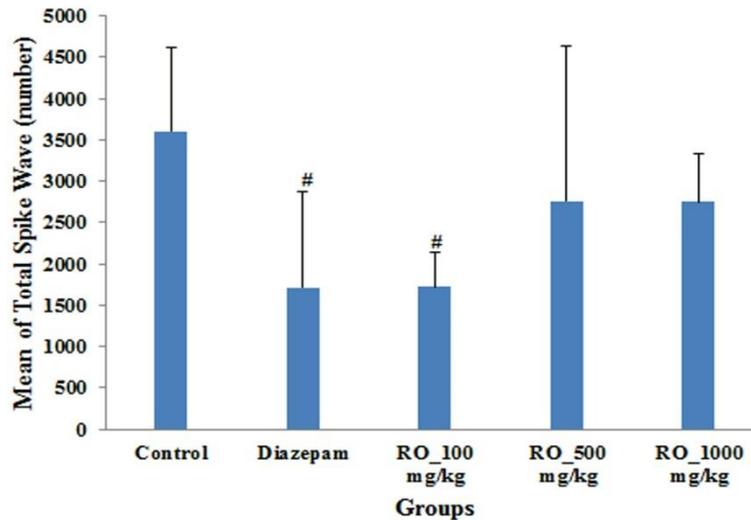


Fig. 5. Mean values of total spike-wave number obtained from recording after penicillin. (#Significance compared to control group [$p<0,01$]). RO: rose oil.

Effect of Rose Oil on Spike-Wave Amplitude of Epileptiform Activity: It was found that the median values of the spike-wave amplitude were not statistically different in periods of 0–100 minutes and 116–120 minutes in each group ($p>0.05$) (Fig. 6). According to the results, median values of the spike-wave amplitudes that were measured at 101–105, 106–110 and 111–115 minutes for the diazepam group were significantly lower than the values measured in the 500 mg/kg RO group ($p = 0.047$, $p=0.049$, and $p = 0.043$, respectively) (Fig. 6).

DISCUSSION

Rose oil has many therapeutic features such as anti-microbial activity, anti-inflammatory activity, antioxidant, anticancer, neuroprotection and memory enhancement, ionotropic and chronotropic effects, anti-convulsant effect, antihyperlipidemic effects, anti-depression, analgesic and antinociceptive effects (25). It has recently been demonstrated that polyphenolic fractions of rose oil distillation water has decreased gene-expression and cellular secretion of proinflammatory cytokines like IL-6 and IL-1 β in vitro (26). In a study was reported that rosa damascena extract enhanced antioxidant capacity and decreased oxidative markers in aluminum chloride-induced oxidative stress condition in rats

(27). Moreover it was demonstrated that Rosa damascena hydroalcoholic extract decreased the raising in liver fat accumulation and hepatic enzymes in rat model of nonalcoholic fatty liver disease (28).

In current study, the effect of RO administration at doses of 100, 500, and 1000 mg/kg on penicillin-evoked epileptiform activity was experimentally investigated in rats. Features of epileptiform activity observed on ECoG recordings were consistent with the literature (5, 6, 24). Intracortical application of 500 IU penicillin G to anesthetized rats resulted in spike-wave-form epileptiform activity between 3 to 15 minutes. RO treatment alone did not lead to epileptiform activity. These data suggested that RO treatment alone has not an epileptic effect. When groups were compared for onset latency of the first epileptic activity, there was no statistically significant difference between all groups. This result is consistent with several studies in the literature, but latencies for first epileptic activity were not electrophysiologically measured in those studies (10, 22). Latency results for RO are compatible with PTZ epilepsy model (7). Moreover, in the present study, used doses for RO are consistent with previous studies cited below. In one of those studies, RO were given to rats 30 minutes before PTZ at 250, 500, 750, and 1000 mg/kg doses (22).

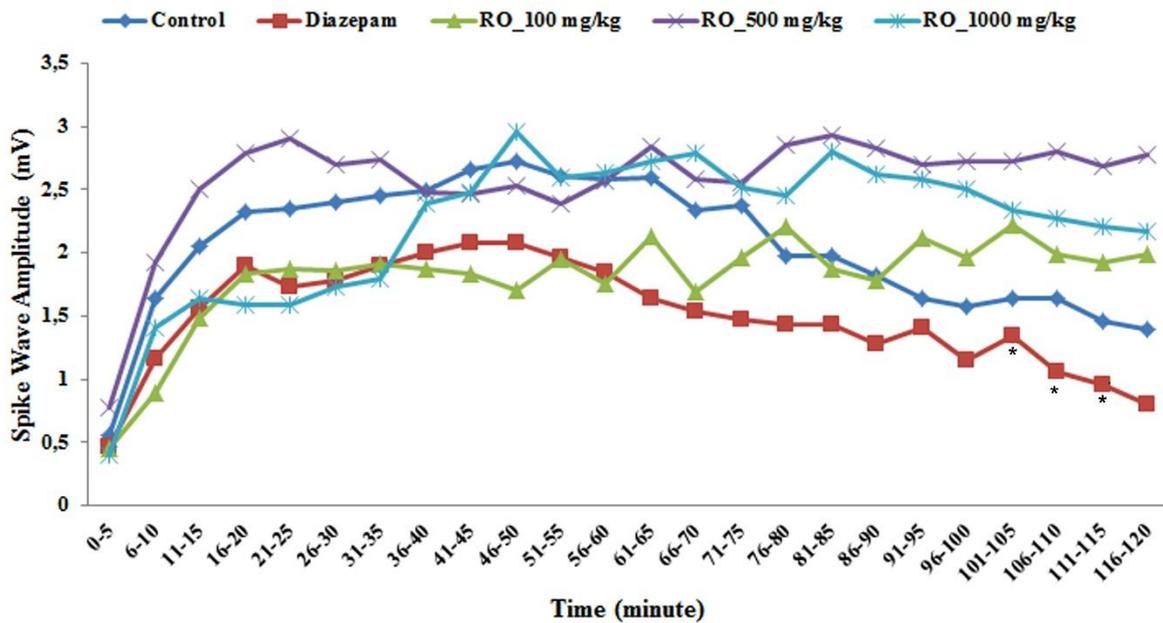


Fig. 6. Spike-wave amplitude (mV) median values obtained from recording after penicillin (* Significance compared to 500 mg/kg rose oil group [$p < 0,05$]). RO: rose oil.

At the end of experiment, it was observed that onset latency of the epileptic seizure was prolonged in the 750 mg/kg RO group whereas there was no effect in the other groups (22). In another study conducted by Hosseini et al.(10), intraperitoneal rose extract was used in 100, 500, and 1000 mg/kg doses; and it was reported that the rose extract prolonged the latency of onset of the first seizure (10).

Additionally, in another study, the administration of essential oil of *Rosa damascene* at doses of 750 and 1000 mg/kg decreased the increase of after discharge duration in the amygdala electrical kindling seizures in rat (21).

It is arguable that RO has antiepileptic effect because of the median values of spike-wave frequencies for the 100 mg/kg RO were significantly lower than control group values during 6-45 minutes (Fig. 4). Moreover, it seems that RO is more potent than diazepam in the first 45 minute but not after 1 hour of recording periods. In a similar study performed with kindling model was reported that i.p. injection of 750 and 1000 mg/kg RO to rats reduced the average discharge duration (21). Another study suggested that RO used as the treatment support against intractable seizures in children reduced the average seizure frequency (20). To prevent possible side effects, a substance should be tried in many different experimental models and proceed further clinical research before using as a drug for human. Our findings are consistent with above literature. In addition to previous limited number of studies, the results of present study also further provide important electrophysiological evidence to the literature. Although, Ramezani et al. (21) reported that 750

and 1000 mg/kg ip RO application reduced average discharge amplitude in their study, there was no significant difference between spike-wave amplitudes of the epileptiform activities of the RO groups in our study. In the other hand, it is not possible to say that antiepileptic effect of RO is dose-dependent manner according to our results. It is needed detailed pharmacological dose-response relationship studies, which are more frequent dosing starting at lower doses.

We did not measure concentration of brain neurotransmitters and this is one of the limitations of the study. It may not be impossible to suggest that in the present study, RO may exert its the antiepileptic activity via GABAergic and/or glutamergic mechanisms. Moreover, the antiepileptic effect of RO may be due to citronellol which is major (42.14%) constituent of used RO in the present study. Flavonoids of RO, such as geraniol and citronellol, may have a role as neuromodulator by facilitating release of inhibitor neurotransmitters such as GABA or by binding their receptors such GABA_A. Hypnotic and anti-seizure effects of geraniol compounds were shown in behavioral animal studies (29). In a study, researchers demonstrated that citronellol prevents not only the action of convulsants PTZ and picrotoxin, but also preserves the mice against maximal electroshock-evoked seizures (19).

Another limitation of the present study is that it did not investigate passing of RO or its compounds into the cerebrospinal fluid but previous studies reported that RO could pass to blood-brain-barrier and it can effect neuronal activity in the brain (30).

CONCLUSION

In conclusion, the fact that decreasing effect of 100 mg/kg RO on epileptiform activity during 6-45 minutes is a promising result in relation to the use of RO in epilepsy treatment in future. This study is the first attempt providing electrophysiological evidences with regard the effects of RO on epilepsy. These results can pioneer future electrophysiological studies. However, it would be useful to conduct studies investigating the mechanisms of action of RO at the molecular level.

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Conflict of interest statement: The authors declare that there is no any conflict of interest.

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