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RESEARCH ARTICLE

The effect of hydroalcoholic extract of *Mentha piperita* on pentylenetetrazol-induced convulsion in mice

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ABSTRACT

Background: Convulsion is one of the most important disorders of the central nervous system. On account of their lower side effects, the use of medical herbs for treating diseases, including convulsion, is on the rise. **Aims and Objectives:** The present study aimed at investigating the effect of peppermint extract on pentylenetetrazol (PTZ)-induced convulsion in small white (laboratory) rats. **Materials and Methods:** This study was conducted on 64 mice. The treatment groups received various (400, 600, and 800 mg/kg) doses of hydroalcoholic peppermint extract. The positive and negative control groups received Diazepam (1 mg/kg) and normal saline (10 ml/kg)30 min before intraperitoneal PTZ injection (85 mg/kg), respectively. Such factors as the onset, length, and severity of convulsion were then studied. To determine the best extract dose, the response times for min 15, 30, 45, and 60 before PTZ injection were studied. **Results:** Results from the administration doses of the extract revealed that it had a dose-dependent effect in that no convulsion was seen at 800 mg/kg. To investigate the effect of interval between appropriate extract dose injection (800 mg/kg) on PTZ levels, 15-, 30-, 45-, and 60-min intervals were chosen. Results showed that the best result of the 800 mg/kg extract dose was achieved 30 min before PTZ injection where no convulsion was observed. **Conclusion:** The overall result revealed that peppermint extract had preventive effects on PTZ-induced epileptic attacks in mice where the 800 mg/kg dose brought about the best result, i.e., no convulsion.

KEY WORDS: Peppermint; Pentylenetetrazol; Convulsion; Mice

INTRODUCTION

Convulsion is a symptom of epilepsy which is a complex neurobehavioral disorder resulting from the abnormal irritability of nerve cells in different regions of the brain.[1,2] An approximate 1% of the world population suffers from seizure disorders and epilepsy which is the second leading cause of neurological diseases after strokes.[1,3]

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Epileptic seizures can cause extensive constraints in patients and affect various individual abilities.[4-6] Therefore, persistent measures need to be taken to treat convulsion in epileptic patients.

Various pharmaceutical drugs are currently being used to treat epilepsy and subsequent seizures including carbamazepine, phenytoin, phenobarbital, diazepam, and valproic acid.[1,7] However, despite extensive research on new anticonvulsants, no full treatment has yet been found for epilepsy.[8-10] In addition, despite the multiplicity of drugs for controlling epileptic attacks, 30% of patients still show resistance to all pharmacotherapeutic methods in that such attacks cannot be controlled.[1,11] Furthermore, more than 50% of epileptic patients exhibit undesirable life-threatening side effects during treatment by antiepileptic drugs,[8,10] diminishing

(body) coordination, and disrupting treatment.[1] In the same vein, research to obtain more effective antiepileptic drugs with lesser side effects is in progress.[10] To attain low-risk medications with minimum side effects, traditional medicine and herbal remedies should take priority.[1,3]

Peppermint (scientific name: *Mentha piperita*) is an annual scented plant grown in most regions of Iran, in particular, the foothills of the Alborz mountains, northern-, and northeastern Iran among other regions.[12] Peppermint is a firm perennial plant whose height occasionally reaches 1 meter. All parts of the plant have a strong penetrating scent and a spicy refreshing taste.[13] The most important peppermint components are menthol, menthone, neomenthol, methyl acetate, and 1,8 cineole. In addition, peppermint is a rich source of essential oils with major food values and which has spasmolytic, antibacterial, and digestive boosting properties in terms of pharmaceutical use.[14] In traditional medicine, peppermint is used as a stomach booster, pain reliever, anticonvulsant, and tranquilizer.[12] Since free radicals are conducive to convulsion and owing to the antioxidant properties of peppermint, the use of this herb's extract can prove beneficial in treating convulsion.[15] Therefore, the present study aimed at investigating the effect of peppermint extract on pentylenetetrazol (PTZ)-induced convulsion in mice.

MATERIALS AND METHODS

This study was conducted in the following steps:
Hydroalcoholic peppermint extract preparation: Peppermint leaves were obtained from Ramhormoz city, Khuzestan, shadow-dried, and then ground by a mechanical mill to prepare the extract. 300 of ground leaves were then weighed and poured into a beaker. Ethanol, 70%, was then added and the contained was covered with a lid and kept for 72 h. The content was stirred every few hours during this time. After 72 h, the content was filtered through a filter paper and kept in a container. The residuum was washed again by ethanol, 70%, filtered, and added to the existing extract. The available extract was condensed by a distiller in vacuum and was put in an oven at 38°C until dried, producing 42.5 g dry extract.

Animal preparation: 64 mice) 25-30 gr) were purches from Ahvaz Jundishapur University of Medical Sciences' Laboratory Animal Reproduction Center. The animals were kept in the faculty animal room at 23 ± 2°C and 50% humidity under 12 h of light and 12 h of darkness. They were given compressed animal feed and tap water and were then weighed and numbered. (Approval no. IR.AJUMS.REC.1395.407).

To perform the test, the animals were divided into five groups, weighed, numbered, and administered as follows. The experimental groups were intraperitoneally injected 400, 600, and 800 mg/kg of hydroalcoholic peppermint extract. The negative and positive controls, respectively, received saline (10 ml/kg) and diazepam (1 mg/kg) through intraperitoneal injections.

Studying Response Dose

PTZ (85 mg/kg) was administered to all groups after 30 min through IP injection. The onset, length, and severity of convulsion as well as mortality rate were then evaluated in all groups.

The intervals between PTZ injection and the onset of jerky movements were measured to determine the onset of convulsion. To measure the severity of convulsion, the rats were placed on a table and were given a score of 0–4 on the following basis:

- In case of normal movements, they were given 0;
- In case of slight jerky movements in head, they were given score 1;
- In case of severe jerky movement in head and jaw, they were given score 2;
- In case of slight jerky movements in the body, they were given score 3; and
- In case of severe jerky movements in the body, they were given score 4.
- The length of convulsion was measured as the interval between the onset of convulsion and its complete conclusion.

Studying Response Time

The response time of the selected dose (800 mg/kg) was measured at 15, 30, 45, and 60 min before PTZ injection. The onset, length, and severity of convulsion were also evaluated.

RESULTS

The comparison of the mean latency of convulsion for the groups receiving various doses of hydroalcoholic peppermint extract with the positive (diazepam) and negative (physiological saline) control groups is displayed in Figure 1. Results showed that the mean latency of convulsion for 600 and 800 mg/kg doses of hydroalcoholic peppermint extract increased significantly compared with the negative (physiological saline) control group ($P < 0.05$). However, the mean latency of convulsion for 400 mg/kg dose of hydroalcoholic peppermint extract decreased significantly compared with the positive (diazepam) control group ($P < 0.05$). The mean latency of convulsion for 600 and 800 mg/kg doses of hydroalcoholic peppermint extract exhibited a significant increase compared with the 400 mg/kg dose ($P < 0.05$) (Figure 1).

In addition, comparison of the mean intensity of convulsion in the groups receiving various doses of hydroalcoholic

peppermint extract with the positive (diazepam) and negative (physiological saline) control groups is displayed in Figure 2. Results revealed that the mean intensity of convulsion for the groups receiving 800 mg/kg dose of hydroalcoholic peppermint extract decreased significantly compared with the negative (physiological saline) and positive (diazepam) control groups as well as with the groups receiving 400 and 600 mg/kg doses of the same substance ($P < 0.05$). However, no significant difference was seen in the mean intensity of convulsion for the groups receiving 400 and 600 mg/kg doses of hydroalcoholic peppermint extract compared with the diazepam-receiving group ($P > 0.05$) (Figure 2).

The mean duration of convulsion for the groups receiving various doses of hydroalcoholic peppermint extract was compared with those of the positive (diazepam) and negative (physiological saline) control groups. Results showed that the mean duration of convulsion for 400, 600, and 800 mg/kg doses of hydroalcoholic peppermint extract decreased significantly compared with the negative (physiological saline) control group ($P < 0.05$). In addition, the mean duration of convulsion for 800 mg/kg dose of hydroalcoholic peppermint extract demonstrated a significant decrease compared with the positive (diazepam) control group ($P < 0.05$). The mean duration of convulsion for 800 mg/kg dose of hydroalcoholic peppermint extract decreased significantly compared with 400 and 600 mg/kg doses of the same substance ($P < 0.05$). However, no significant difference was seen in the mean duration of convulsion for the groups receiving 400 and 600 mg/kg doses of hydroalcoholic peppermint extract compared with the diazepam-receiving group ($P > 0.05$) (Figure 3).

The response time for the selected dose (800 mg/kg) was another area of investigation in this study. Comparison of the mean latency of convulsion for 800 mg/kg dose of hydroalcoholic peppermint extract at 15, 30, 45, and 60 min before PTZ injection demonstrated that no seizure was seen in the group receiving the extract 30 min before PTZ injection compared with the other three groups ($P < 0.05$). The onset of seizure was significantly delayed in the group receiving the extract 45 min before PTZ injection compared with those receiving it 15 and 60 min before PTZ injection ($P < 0.05$). The same thing was also observed in the group receiving the extract 60 min before PTZ injection compared with those receiving it 15 and 45 min before PTZ injection ($P < 0.05$) (Figure 4).

Comparison of the mean intensity of seizures in the group receiving 800 mg/kg dose of hydroalcoholic peppermint extract at 15, 30, 45, and 60 min before PTZ injection suggests that no seizure was seen in the group receiving the extract

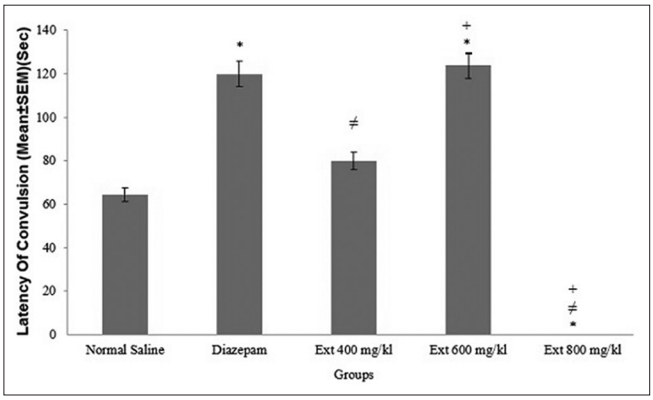

Figure 1: Comparison of the mean latency of convulsion in groups receiving various doses of hydroalcoholic peppermint extract with the positive (diazepam) and negative (physiological saline) control groups. *Significant difference with the group receiving normal saline ($P < 0.05$); ≠significant difference with the group receiving diazepam ($P < 0.05$);+significant difference with the group receiving 400 mg/kg ($P < 0.05$)

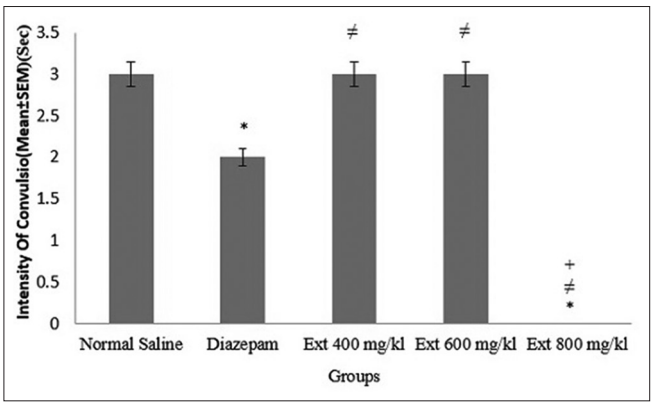

Figure 2: Comparison of the mean intensity of convulsion in the groups receiving various doses of hydroalcoholic peppermint extract with the positive (diazepam) and negative (physiological saline) control groups. *Significant difference with the group receiving normal saline ($P < 0.05$); ≠significant difference with the group receiving diazepam ($P < 0.05$);+significant difference with the group receiving 400 and 600 mg/kg ($P < 0.05$)

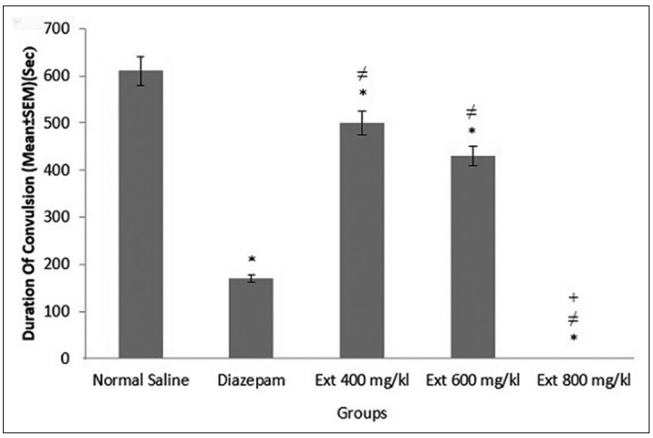

Figure 3: Comparison of the mean duration of convulsion for the groups receiving 400 and 600 mg/kg doses of hydroalcoholic peppermint extract compared with the diazepam receiving group. *Significant difference with the group receiving normal saline ($P < 0.05$); ≠significant difference with the group receiving diazepam ($P < 0.05$);+significant difference with the group receiving 400 and 600 mg/kg ($P < 0.05$)

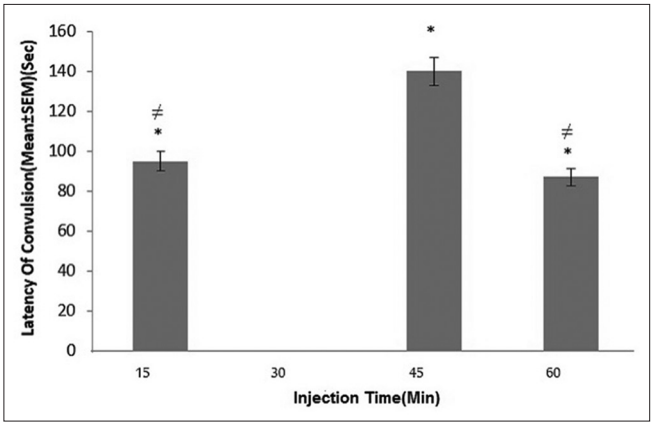

Figure 4: Comparison of the mean latency of convulsion for 800 mg/kg dose of hydroalcoholic peppermint extract at 15, 30, 45, and 60 min before PTZ injection. *Significant difference with the group receiving 800 mg/kg 30 min before PTZ injection compared with min 15, 45, and 60 ($P < 0.05$); ≠Significant difference with the group receiving 800 mg/kg 60 min before PTZ injection compared with min 45 ($P < 0.05$)

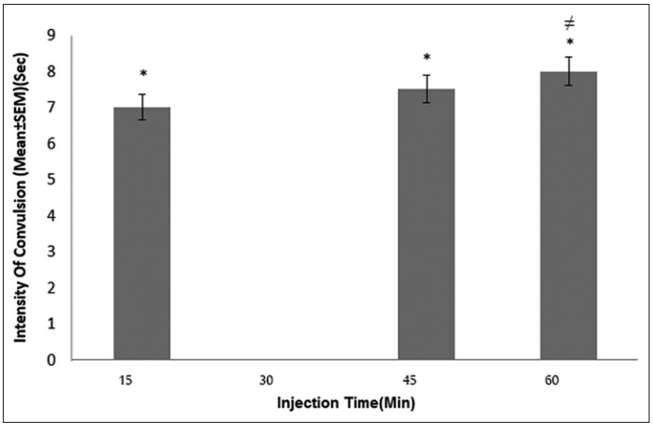

Figure 5: Comparison of the mean intensity of convulsion in the groups receiving 800 mg/kg at different intervals before PTZ injection. *Significant difference with the group receiving 800 mg/kg 30 min before PTZ injection compared with min 15, 45, and 60 ($P < 0.05$); ≠Significant difference with the group receiving 800 mg/kg 45 min before PTZ injection compared with min 60 ($P < 0.05$)

30 min before the PTZ injection compared with the other three groups ($P < 0.05$). The mean intensity of seizures in the group receiving the extract 45 min before PTZ injection was significantly decreased compared with those receiving it 15 and 60 min before PTZ injection ($P < 0.05$) (Figure 5).

The mean duration of convulsion in the groups receiving 800 mg/kg dose of hydroalcoholic peppermint extract at 15, 30, 45, and 60 min before PTZ injection suggests that those receiving it 30 and 45 min before PTZ injection demonstrated a significantly less duration of convulsion compared with those receiving it 15 and 60 min before PTZ injection ($P < 0.05$). Additionally, duration of convulsion was significantly increased in the group receiving the extract 45 min before PTZ injection compared with the one receiving it 30 min before PTZ injection ($P < 0.05$) (Figure 6).

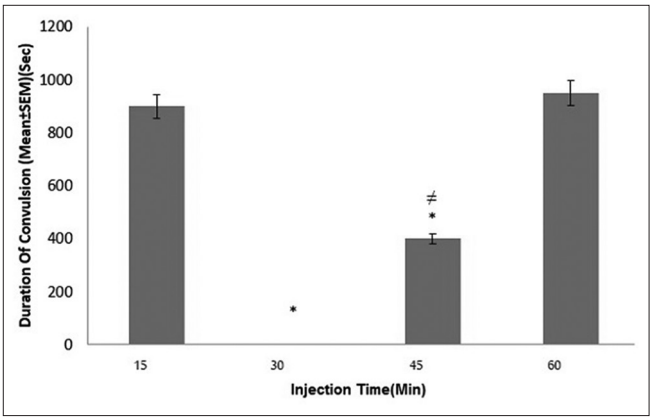

Figure 6: Comparison of the mean duration of convulsion in groups receiving 800 mg/kg at different intervals before PTZ injection. *Significant difference with the group receiving 800 mg/kg 30 and 45 min before PTZ injection compared with min 15 and 60 ($P < 0.05$); ≠Significant difference with the group receiving 800 mg/kg 45 min before PTZ injection compared with min 30 ($P < 0.05$)

DISCUSSION

The result of the study showed that peppermint extract had anticonvulsant properties in various doses which was most remarkably seen at 800 mg/kg 30 min before PTZ injection, producing more favorable results than diazepam.

What is certain, is that such therapeutic effects can be attributed to the existing components in the derived extract. Studies on peppermint and its species shows that its leaf and essential oil include such components as acetaldehyde, amyl alcohol, esters of mannitol, limonene, pinene, phellandrene, cadinene, pulegone, dimethyl sulfide, alpha-pinene, sabinene, terpinolene, ocimene, gamma-terpinene, alpha- and beta-thujone, and citronellol.[16] Peppermint also has various compounds such as monoterpenes, terpenes, tannins, flavonoids, and phenolic acids. Other scholars have reported such compounds as 1,8 cineole, limonene, linalool, and menthol in peppermint.[17-19] Studies show that many herbal extracts with similar components as those of peppermint have exhibited antiepileptic effects.[20-22] For instance, a major component of peppermint is limonene. Studies have shown that limonene reduced simultaneous collective activity of neurons in the central nervous system (CNS). It enters the brain through peripheral circulation and binds with $GABA_A$ receptors, whose activation result in anxiolytic effects.[23,24] Other studies have pointed to strong antistress effects of limonene brought about by affecting $GABA_A$ receptors and increasing GABA concentration.[25] Other studies suggest an anticonvulsant sedative effect for limonene in animal models.[26] Linalool is among the other components of peppermint which has a diminishing effect on CNS activity. Studies have shown that the suppressive effect of linalool is rooted in the inhibition of acetylcholine release.[24,27]

Moreover, according to a number of experts, linalool is a competitive N-methyl-D-aspartate (NMDA) receptor antagonist and the blockage of glutamate NMDA receptor contributes to its antiepileptic properties.[26-28] Studies on Syrian mice have shown that linalool plays an effective role in protecting the animal from induced epileptic seizures.[29,30] In the study by Brum et al., the operative mechanism of linalool has been reported as GABAergic system adjustment.[25] In addition, according to scholars, flavonoids, as an the other components of peppermint have a very strong tendency toward benzodiazepine (BDZ) receptors of the CNS, causing repression and relaxation therein.[24] As well, many flavonoids serve as ligands in the CNS for $GABA_A$ receptors leading to this view that they can function as BDZ-like molecules. Such theory has been corroborated by their behavioral effects in animal models of anxiety, depression, and seizure.[24,31,32] Furthermore, the anticonvulsant properties of menthone, as another component of peppermint extract, have been demonstrated in previous studies such as that by Jain et al., 2011, in which the effect of menthone compounds on seizures caused by electroconvulsive therapy and subcutaneous PTZ-induced seizures were investigated in three groups of laboratory rats. They reported that (±) 3-menthone prevented seizures by increasing GABA levels in the midbrain.[33] Based on these, it can be argued that there are many similarities in the results of the study and similar studies which surveyed the peppermint components. In addition to studies on various peppermint extract components, several studies have investigated the general benefits of this herb, pointing to it pain-relieving, anxiolytic, and anticonvulsant properties. For instance, in a study by Koutroumanidou et al., the effect of prescribed herbal essences on the onset of seizure and reducing the severity of PTZ-induced seizures in mice was investigated. Results showed that mice receiving peppermint oil experienced no seizure and had a 100% survival rate[22] that these findings are in agreement with our study. Atta and Alkofahi studied the analgesic effects of the peppermint ethanolic extract on Swiss mice. IP Acetic acid 0.7% injection was used to inflict pain. The severity of pain was investigated based on the jerky movement by animals. Results showed that pain-induced squirms in treated animals with peppermint were significantly lower than the control group ($P < 0.05$).[34]

The strength of the study is using different doses of the peppermint extract at different times before induction of seizure. The limitations of this study included the small sample size, thereby limiting the generalized applicability of the results. Furthermore, it should be noted that effective components, the main part and the percentage ratio of the constituents of medical plants are naturally subject to their growth conditions, i.e., it cannot be argued that the extract components used in this study are exactly similar to those used in other studies. Therefore, the findings of this study should be reassessed after similar studies have been replicated in other laboratories and context.

CONCLUSION

The overall results showed that peppermint extract had preventive effects on PTZ-induced seizure attacks in mice, with the best result observed at 800 mg/kg. Such dose-dependent effect of peppermint extract in controlling seizure can be attributed to existing compounds in this herb's extract such as flavonoids, limonene, menthone, and linalool. Therefore, it is suggested that more extensive studies be conducted to determine the exact operative mechanism of such components.

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