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Anticonvulsant Effects of Matricaria chamomilla Extract and Rosa damascena Oil in a Pentylenetetrazol-Induced Seizure Model: A Comparative Study

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Abstract

Background: Seizures are paroxysmal events that cause abnormal brain activity. They manifest as convulsions and loss of consciousness. Pharmaceutical treatments have many severe side effects, thus people are investigating alternative therapies involving essential oils. This research project has investigated the anticonvulsant effects of *Matricaria chamomilla* extract (MCE) and *Rosa damascena* oil (RDO) on mice with induced seizures.

Methods: In this study, 64 male mice in 8 groups were examined independently for the behavioral responses to Pentylenetetrazole (PTZ) after receiving saline, diazepam (4 *mg/kg*), MCE, and RDO (100, 200, or 400 *mg/kg*). The efficacy of the treatments was assessed by evaluating the occurrence of the first facial or forelimb movements, Minimal Clonic Seizure (MCS), first Generalized Tonic-Clonic Seizure (GTCS), the number of leg stretches, and the mortality rate. The data was separately evaluated using one-way ANOVA, and significance was determined at $p<0.05$.

Results: Seizure symptoms were absent in mice treated with diazepam, MCE, and RDO until one hour after PTZ administration, while all mice in the PTZ and normal saline group died. MCE and RDO at 200 and 400 *mg/kg* increased the latency of MCS and first facial or forelimb movements and reduced leg stretching in PTZ-treated mice. Both compounds delayed the onset of GTCS.

Conclusion: Consequently, MCE and RDO demonstrate promising anticonvulsant effects in a preclinical model, warranting further investigation into their therapeutic potential and mechanisms of action in seizure disorders. They also offer potential alternatives to traditional antiseizure agents.

Keywords: Anticonvulsants, Matricaria, Mice, Seizures, Pentylenetetrazole

Introduction

Seizures are a very complex and disabling condition that millions of people around the world are suffering from, with most of the cases occurring in children and adults with no previous medically known conditions (1). Treatment options for seizures have, over the decades, remained largely the same despite big strides made in understanding the underlying mechanisms and diagnosis (2). Thus, most patients continue to experience frequent and severe seizures, which cause a reduction in the quality of life, mental decline, and an increase in the risk of sudden death (3). There is a desperate need for new and innovative treatments that will bring adequate seizure control without long-term damage to the brain (4).

Inadequate seizure control with current treatments of seizure disorders, including antiepileptic drugs phenytoin, carbamazepine, *etc*. often is burdened by significant cognitive, psychiatric, and suicidal side effects (5). Many of these conventional medicines also have narrow therapeutic windows, which may require adjustment of the doses to fine-tune them for optimal benefits (6). Conventional treatments' failures place herbal sources at the forefront of needing alternative and complementary approaches (7). Already, herbal medicines have shown some promising results in pilot studies, which further opens up one potential avenue for developing new and more effective treatments with fewer side effects (8). In addition, herbal remedies can probably offer seizure disorder management a more sustainable and cost-effective solution, thus becoming very attractive to healthcare providers and patients (9).

Matricaria chamomilla extract (MCE) and *Rosa damascena* oil (RDO) are herbal ingredients used in herbal medicine to induce rest, relaxation, calmness, and relief from stress (10,11). Recent studies show that the two ingredients may be helpful in the prevention and treatment of some neurologic disorders affecting the central nervous system (12,13). The extract of *Matricaria chamomilla* is reported to reduce oxidative stress and inflammation linked with neurodegenerative diseases like Alzheimer's disease and Parkinson's through its antioxidant and anti-inflammatory activities (14). While RDO has neuroprotective and neurogenerative features, which help protect against neuronal damage and foster neuroplasticity, it may be helpful in combination with these natural compounds (15). In this respect, these natural compounds could be safely used and efficiently applied as part of complementary medicine to alleviate the symptoms, thus improving the quality of life of patients suffering from central nervous system disorders such as anxiety, depression, and insomnia (16,17). While much more research is needed, it will help uncover the complete healing capabilities of botanicals, paving the way for their inclusion in holistic treatment strategies (18).

The hypothesis of the study was that MCE and RDO could exhibit significant anticonvulsant effects in a Pentylenetetrazole (PTZ)-induced seizure model in mice. The current study compares the anticonvulsant effects of RDO and MCE in a seizure model of PTZ-induced chemical kindling in mice. For this purpose, the researchers employed the standardized seizure model to understand the anticonvulsant properties of RDO and MCE that might lead to new and effective treatments against seizure disorders.

Materials and Methods

Reagents and animals

Pentylenetetrazole was acquired as an active ingredient agent from Sigma Aldrich Co., Germany. Diazepam, a 5 *mg/ml* ampoule final product, was acquired from Caspian Pharmaceutical Co. *Matricaria chamomilla* extract (MCE) standardized based on the presence of 0.01 *mg* of apigenin per gram of extract and *Rosa damascena* oil (RDO) standardized based on the presence of 0.2 *mg* of nerol per milliliter of essential oil, sourced from Barij Essential Oil Co., Tehran, Iran. To make the oral emulsion of RDO, different concentrations of essential oils were combined with a solution that included 1% v/v Tween 80 in sterile water and then stirred together (19). To prepare the desired concentrations, the extract was diluted with normal saline.

This research involved 64 male NMRI mice, ranging in weight from 20-30 *g*. The animals were obtained from Baqiyatullah University's animal facility and kept in the pharmacology laboratory at Baqiyatullah University of Medical Sciences. According to similar research, the study comprised eight groups, each group containing eight mice (20,21). The studied agents were given to mice (by gavage) one hour

before intraperitoneal injection of PTZ, as presented in table 1 (22). The selection of the administered dose of diazepam was based on previous studies in this experimental model, and the significant difference in seizure symptoms between the diazepam group and the saline group indicates the validity of this study (23). The doses of MCE and ERD were based on prior studies that investigated the effects of *Matricaria chamomilla* extract and *Rosa damascena* oil on neural disorders or related conditions, ensuring that the chosen amounts were effective yet safe (24,25).

Inducing convulsions and checking for symptoms

The pentylenetetrazole test is a standard method for inducing seizures in animal models, particularly in laboratory mice. In this test, PTZ is given intraperitoneally to animals, which, by inhibiting inhibitory neurotransmitters such as Gamma-aminobutyric Acid (GABA) and stimulating glutamate receptors, leads to increased electrical activity in the brain and the onset of seizures. The seizure behaviors of the mice after receiving PTZ are monitored, and parameters such as the time of seizure onset and the type of movements are recorded. This test allows researchers to evaluate the effectiveness of different drugs in reducing or delaying the onset of seizures and serves as a valid model for studying seizure mechanisms and evaluating anticonvulsant treatments. This animal model is used to induce generalized seizures, particularly tonic-clonic seizures. Therefore, findings related to this model suggest potential anticonvulsant effects specifically against this type of seizure (20).

To investigate the behavior of convulsive activity, the animals were placed inside a Plexiglas chamber with dimensions of 30x30x30 *cm* on the day of the experiment. Then, animals (groups of eight) were injected intraperitoneally with PTZ and the animals were examined for one hour to evaluate the occurrence of convulsive activity by a camera. To check the behavioral response of animals to the administration of PTZ, the following factors were used:

- The latency time between the injection of PTZ and the occurrence of the first facial or forelimb movements
- The latency time between the injection of PTZ and the occurrence of Minimal Clonic Seizure (MCS)
- The number of leg stretches after PTZ injection
- The latency time between the injection of PTZ and the first Generalized Tonic-Clonic Seizure (GTCS)
- The mortality rate

Statistical analysis

All the data were presented as the mean±Standard Deviation (SD) of mice tested in each group. The authors chose to use SD instead of Standard Error of the Mean (SEM), since SD accurately reflects data variability within a sample and provides a clearer understanding of individual differences, especially

Table 1. Agents and administrated doses for the studied groups (n=8)

Groups	Agents used
Controls	PTZ (100 *mg/kg*)+Saline
Groups receiving *Matricaria chamomilla* extract (MCE)	PTZ (100 *mg/kg*)+Diazepam (4 *mg/kg*)
	PTZ (100 *mg/kg*)+MCE (100 *mg/kg*)
	PTZ (100 *mg/kg*)+MCE (200 *mg/kg*)
	PTZ (100 *mg/kg*)+MCE (400 *mg/kg*)
Groups receiving *Rosa damascena* oil (RDO)	PTZ (100 *mg/kg*)+Diazepam (4 *mg/kg*)
	PTZ (100 *mg/kg*)+RDO (100 *mg/kg*)
	PTZ (100 *mg/kg*)+RDO (200 *mg/kg*)
	PTZ (100 *mg/kg*)+RDO (400 *mg/kg*)

in small sample sizes where SEM may misrepresent precision. This choice enhances the clarity of statistical analysis and helps readers better assess the consistency of the results. A one-way analysis of variance was conducted, with Tukey's post hoc test for statistical analyses. In this research, the SPSS version 24.0 and Microsoft Excel 2016 software were used for the analysis of data and plotting graphs, with $p<0.05$ as the level of significance.

Results

The results of the present study indicated that the separate treatment with MCE or RDO, especially with their high dose, significantly affected the clonic convulsion indicators that were evaluated by observing the behavior of the mice. In the group receiving diazepam (4 *mg/kg*), none of the investigated symptoms of seizures were observed until one hour after PTZ administration. All the animals in the group that gave PTZ and normal saline died within one hour after the PTZ, whereas no deaths occurred in the other groups.

Az presented in figure 1 (A and B) receiving amounts of 200 and 400 *mg/kg* MCE or RDO one hour before the induction of convulsions by PTZ significantly increased the first facial or forelimb movements latency [alpha level=0.05, F(1,10)=14.66, p=0.004]. All the agents tested in the experiment were found to greatly improve the minimum clonic seizure latency when compared to the group that was given just saline.

In figure 1C, it is evident that only large quantities of MCE or RDO (400 *mg/kg*) could decrease the occurrence of leg stretching in PTZ-treated mice. Finally, both studied compounds were able to delay the onset of GTCS seizure [alpha level=0.05, F(1,9)=9.52, p=0.01]. Various groups showed no significant differences in increasing this index compared to one another (Figure 1D).

Discussion

This investigation endeavored to elucidate the anticonvulsant potential of *Rosa damascena* oil and *Matricaria chamomilla* extract, employing a

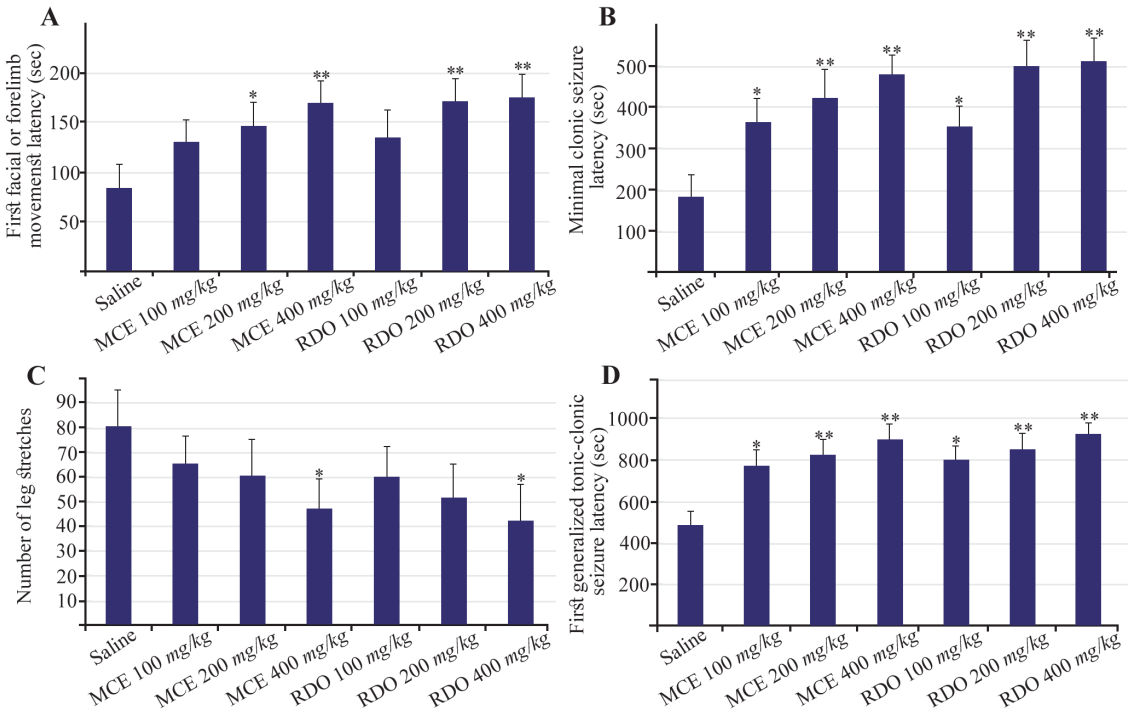

Figure 1. Comparison of the effect of different doses of Matricaria chamomilla extract (MCE) and Rosa damascena oil (RDO) on the latency time of the first facial or forelimb movements (A), the latency of minimal clonic seizure (B), the number of leg stretches (for one *hr*) (C) and the latency of the first generalized tonic-clonic (D) seizure after injection of pentylenetetrazole. The results are reported as Mean±SD, n=8. *, ** Significant difference compared to the control group (saline) ($p<0.05$, $p<0.001$ respectively).

PTZ-induced seizure model in animal studies. In the present research, it was shown that both MCE and RDO have potent anticonvulsant activity, especially at higher dosages.

Pentylenetetrazol is a tetrazole derivative that functions as an agonist for ion channels responsible for the transportation of sodium and calcium (26). Additionally, it impacts the functioning of GABA receptors. Therefore, high levels of PTZ can cause sudden bursts of activity in brain cells leading to kindling and tonic-clonic seizures (27). In the present study, the administration of PTZ as expected could induce all the symptoms of the onset of a generalized seizure, which would lead to the death of the animal if not intervened with a secondary factor. As expected, the administration of diazepam was able to eliminate all the symptoms of seizures.

The primary active components of MCE are Apigenin, Luteolin, and Geraniin (flavonoids) as well as Chamazulene and Alpha-bisabolol (sesquiterpene lactones), recognized for their anti-inflammatory and antioxidant properties (11,28). Ingredients such as Nerol, Beta-Citronellol, Geraniol, and fatty acids are the key ingredients in RDO and are known for their antioxidant and protective effects against cell damage (29,30). It seems that these components together are responsible for the pharmacological effects of these agents.

One of the most striking findings of this study was that RDO and MCE significantly affected the latency of clonic convulsions. Latency for the first facial or forelimb movements in mice administered RDO or MCE in all applied doses of 200 and 400 *mg/kg* showed a statistically significant prolongation, indicating a delay in the appearance of clonic convulsions. It significantly improved the minimum clonic seizure latency in all the groups treated with RDO or MCE, compared with the saline control group. These results align with previous research that highlighted the anticonvulsant properties of both MCE and RDE, suggesting that these natural products may offer a safer alternative to conventional antiepileptic drugs, which often come with significant side effects (31-33).

In line with the results of our research, the animal studies of Suleiman *et al* and Rostampour *et al* demonstrated that the MCE significantly reduced the severity of seizures in all the tested models (34,35). In patients with epilepsy, it was revealed that people who received chamomile extract during anesthesia had fewer seizures compared to people who did not receive the extract (36).

Research in the RDO oil confirmed anticonvulsant activity by delaying seizure onset, reducing tonic-clonic seizure duration in acute PTZ models, and increasing latency before seizure onset in chronic models (37). Another animal study revealed that RDO demonstrates the potential for managing epilepsy in rats with penicillin-induced seizures (38). Homayoun *et al*'s research revealed that the hydro-alcoholic extract of R. damascena shows promise in protecting the brain in a rat seizure model by decreasing apoptotic neurons in various parts of the hippocampus (39).

The results also support that a high dosage of RDO and MCE (400 *mg/kg*) may be the most potent in reducing the frequency of leg stretching, as an indicator commonly used for seizure severity. In terms of the onset time course for GTCS, however, no significant differences among these groups were noted. In Marques *et al*'s study, the administration of 90 *mg/kg* nerol indicated anti-anxiety effects by reducing twisting, and tremors in albino mice (40). Recently, it was demonstrated that administration of 400 *mg/kg* of MCE in mice can prevent seizures caused by PTZ by reducing the levels of nitric oxide metabolites (41). While previous studies have revealed that doses above 500 *mg/kg* are necessary to produce anticonvulsant effects of MCE, the present study showed that these effects can be observed to a lesser extent in the dose range of 100 *mg/kg* (35).

The main mechanisms through which these agents possibly lower the seizure threshold include inhibition of excitatory neurotransmitters, enhancement of inhibitory neurotransmitters, and hyperpolarization of the membrane potential by acting on ion channels. It has been shown that apigenin exerts its neuroprotective effects by modulating the activity of the Gabaergic and glutamatergic neurons of the cortex (42). It also helps calm down neural activity in the temporal lobe and reduces the likelihood of seizures (43). Studies have demonstrated that overactivity of the mammalian Target of Rapamycin (mTOR) within the central nervous system can result in seizures,

however, apigenin has displayed anti-epileptogenic properties by suppressing the activity of this target (44).

Calcium ions play a crucial role in neural excitation (45). Geraniol and Luteolin have been shown to inhibit certain calcium channels thereby reducing the influx of calcium ions into neurons and decreasing the likelihood of seizure activity (46,47). Apigenin can activate certain potassium channels, which help regulate the resting membrane potential of neurons. By increasing potassium channel activity, apigenin may stabilize the neural membrane and reduce the likelihood of excessive neural activity that can lead to seizures (48). Both MCE and RDO likely exert their anticonvulsant effects through the modulation of sodium and potassium channels (49-51). The investigation of Suleiman and Hassan has shown that higher doses of the extract lead to increased serum sodium ion concentrations, which may contribute to its anticonvulsant effects (52).

Numerous epidemiological studies have implicated oxidative stress as a potential underlying factor in the pathophysiology of seizures, with evidence suggesting that chronic antioxidant deficits may contribute to the development and exacerbation of epilepsy (53,54). Bioactive components in MCE and RDO have antioxidant properties, which may help reduce oxidative stress and inflammation in the brain. These processes can contribute to the development of seizures, therefore MCE and RDO's antioxidant effects may help mitigate these mechanisms (55,56).

Previous studies have investigated the anticonvulsant properties of individual components of these herbs, however, this study is one of the first to comprehensively evaluate the comparative anticonvulsant effects of *Matricaria chamomilla* extract and *Rosa damascena* oil in a chemical kindling model. The present study aimed to provide valuable insights into the potential therapeutic applications of MCE and RDO in treatments of epilepsy and other seizure disorders.

Conclusion

These results strongly suggest that MCE and RDO may be beneficial in convulsive disorder treatment. More studies should be conducted to fully elucidate the mechanism through which these compounds would be exerting their anti-convulsant effects and also to confirm the effectiveness that clinical trials have shown. These findings not only enhance our understanding of the therapeutic potential of these herbal extracts but also pave the way for further investigations into their application in epilepsy treatment. As the search for effective and safe alternatives to conventional anticonvulsants continues, the role of medicinal plants like RDO and MCE becomes increasingly significant in neuropharmacology.

Limitations

This study has several limitations that could affect its results and generalizability. First, current research was conducted only on male NMRI rats and the results may not be extensible to other species or genders. Second, the doses of MCE and RDO used in this study were limited to specific values, and investigating higher or lower doses may yield different results. Also, this study only investigated the short-term effects of these compounds and long-term studies are required to assess the side effects and chronic impacts of these agents. On the other hand, investigating the exact mechanisms of action of these compounds in reducing seizures requires further research that may lead to a better understanding of their effects. Finally, the interaction of MCE and RDO on seizure threshold also needs to be evaluated separately.

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Conflict of Interest

There is no conflict of interest related to this manuscript.

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