JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH
Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 13, No. 1, 2022 (pp. 22-26)
RESEARCH ARTICLE
WWW.JOCMR.COM

Evaluating the Efficacy and Sa fety of *Dorema Ammoniacum* and *Ferula Persica* oleo-gum Resins Combination Product on Seizure Control in Epileptic Patients: A Randomized, Double-blind, Placebo-controlled Study

Omid Hesami[1], Mohammad Sistanizad[2,3], Behnam S. Lima[1], Tahereh Hosseinabadi[4], Niloufar Taherpour[3], Ladan Ayazkhoo[2*]

[1]*Department of neurology, Imam Hussein educational hospital, Tehran, Iran*
[2]*Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
[3]*Prevention of Cardiovascular Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[4]*Department of pharmacognosy, school of pharmacy, shahid beheshti university of medical sciences, Tehran, Iran*

ABSTRACT

Aim: This study aimed to evaluate the efficacy and safety of a herbal compound consisting of 350mg Vosha and 150mg Sakbinaj which has been used traditionally in uncontrolled seizures.

Methods: This was a double-blind, randomized, placebo-controlled, phase-III-trial, conducted at a teaching hospital in Tehran, Iran. In this study, patients were randomly assigned in 1:1 ratio into placebo/drug groups to receive a capsule of drug/identical placebo three times a day for three months. At the end of each month, seizure frequency was recorded. The primary outcome of the study was a decrease in the seizure frequency of patients after taking the full course of the drug/placebo. The safety endpoint was the reported adverse effects.

Results: A total number of 162 individuals were screened for eligibility, 58 were eligible, and were randomized into two groups (27: intervention and 31: control groups). The two groups were not significantly different at baseline characteristics. The median of seizures respectively were 4, 1, 1, 1 at baseline, after one, two, and three months in the intervention group, and 3, 2, 1, 2 in the placebo group. So, Seizure frequency did not reduce significantly in the intervention vs placebo group after one, two, and three months periods. No significant adverse effect was observed during the study.

Conclusion: The present study showed that the administration of Vosha and Sakbinaj, statistically did not reduce seizure frequency significantly. Larger studies with higher doses are recommended for better conclusions. safety was similar to placebo.

Corresponding Author e-mail: Ladan.ayazkhoo@gmail.com, *Phone: 00989122941938*

How to cite this article: Hesami O, Sistanizad M, Lima BS, Hosseinabadi T, Taherpour N, Ayazkhoo L (2022). Evaluating the Efficacy and Safety of Dorema Ammoniacum and Ferula Persica oleo-gum Resins Combination Product on Seizure Control in Epileptic Patients: A Randomized, Double-blind, Placebo-controlled Study. Journal of Complementary Medicine Research, Vol. 13, No. 1, 2022 (pp. 22-26).

INTRODUCTION

Epilepsy is one of the most common debilitating neurological disorders in which abnormal electrical discharges of the brain neurons lead to recurrent seizures.[1, 2] Epilepsy has different types, with an estimated incidence of 33 to 57 people per hundred thousand a year.[3-5] With effective pharmacotherapy, epilepsy can be controlled in approximately 70% of the patients.[6-8] In the remaining patients, seizures occur frequently, requiring combination therapy with two or more drugs or non-pharmacological approaches such as surgery.[2, 9]

In most cases, the adverse drug profile of antiepileptics limits the concurrent use of multiple drugs in the management of seizures, thus the need for newer drugs with better efficacy and lower risk of side effects is strongly felt.[10] Because of the high burden of the disease and the high complications of seizures, finding medications that can reduce the incidence of recurrent seizures has always been a concern.

KEYWORDS:
Dorema ammoniacum,
Epilepsy,
Ferula persica,
Sakbinaj,
Seizure,
Vosha

ARTICLE HISTORY:
Received Nov 30, 2021
Accepted Jan 13, 2022
Published Feb 18, 2022

DOI:
10.5455/jcmr.2022.13.01.05

Medicinal plants and herbal compounds are always considered important sources for treatment of the diseases. *D.ammoniacum*'s oleo-gum resin, which is known as Vosha, is an oily resin that is extracted from the damaged roots and leaves of the *D. ammoniacum* from the Umbelliferae family. In ancient literature, it is known as anticonvulsant, anti-inflamatory, expectorant, Analgesic, antibacterial and vasodilatory agent.[11-14] The proposed mechanism for controlling seizures by D.ammonium gum is the stimulation of the gabaergic system and opioid system.[15]

Another herbal product of the Umbelliferae family that has been used as an anticonvulsant in ancient literature is *F.persica*'s oleo-gum resin that is called Sakbineh or Sakbinaj. Also, it is known as antibacterial, anti-fungal, anti-leishmanial, anti-inflammatory, cytotoxic, skin whitening.[16, 17] The anticonvulsant mechanism of this oleo-gum resin is unknown.

This study aimed to evaluate the efficacy and safety of a herbal compound consisting of 350mg Oshagh and150mg Sakbinaj which has been used traditionally in controlling seizures.[15, 18]

METHODS

Ethical consideration

This was a double-blind, randomized, placebo-controlled, phase-III trial, conducted between August 2018 and December 2019 at neurology clinical of Imam Hossein educational hospital, affiliated to Shahid Beheshti University of Medical Sciences in Tehran, Iran. This research has complied with all the national regulations and is following the tenets of the Helsinki Declaration, the protocol of the study was approved by the domestic ethics committee with the code of IR.SBMU.PHARMACY.REC.1397.122 and was registered in the Iranian Clinical Trial center platform, IRCT with Trial Id of 36659 and IRCT Id of IRCT20120703010178N17.

Chemicals

Placebo and drugs were prepared by Afkare-e-talaei institute, in the same packaging. Each package contained 90 capsules of either drug or placebo. Drug capsules contain 350 mg of *Dorema ammoniacum* oleo-gum resin and 150mg of *Ferula Persica* oleo-gum resin. Placebo Capsules were filled with 500 mg lactose powder.

Plant material

The plants used in this study were both prepared by the Afkar-e-Talaee Institute with the registration number of 43624, from Afghanistan and approved in the botanical laboratory of Shahid Beheshti School of Pharmacy. We choose α-pinen as an indicator component to standardized the gum. To extract the essence from the gum combination 54.86 g of plant powder (equivalent to 110 capsules) was poured into a 1000 ml balloon and 750 ml of water was added to it. The essential oil was removed from the device and the volume of extracted essential oil was measured equal to 0.5 cc. After injecting the essential oil into the device 3 times and placing the mean area below the curve in the line equation, the amount of Pinen in 54.86 g of gum was calculated to be 0.37 mg of α-pinen. Therefore, there is 3 mcg of α-pinen in each capsule. The microbial analysis had been conducted by Tekaj Co.

Calculating sample size

According to the proposed mechanism of action for the main components of the drug under study (Vosha), pregabalin with a similar mechanism has been chosen to estimate the effectiveness of this drug on the frequency of seizures. In a study of the effectiveness of anticonvulsant drugs, the number of patients who responded to pregabalin 150 mg/day (50% reduction in seizure frequency) was 41/185 versus 20/196 in the placebo group, which reveals around 50% reduction in seizure frequency. Based on the result of this study, we assumed an about 50% reduction in seizure frequency.[19] Power analysis assigned at least 22 cases in each group with an α(the probability of type I error) as 0.05, and ¤(the probability of type II Error) as 0.20. Considering a 20% dropout, the sample size was determined as 26 patients in each group.

Experimental groups

All participants aged more than 15 years old with at least three episodes of seizure during the past three months despite receiving one or two effective antiepileptic therapy with an appropriate dose, were evaluated for recruitment (If the patient agrees). Pregnancy and lactation, asymptomatic simple partial epilepsy, known and progressive neurological disorder, status or cluster epilepsy during the 3 months before enrollment, history of psychogenic epilepsy in the past 2 years, an uncontrolled underlying disease associated with impaired patient laboratory data (liver enzymes at least twice the highest normal level or creatinine clearance less than 50 ml/min) and patient non-cooperation were among the criteria for non-inclusion.

Patients recruitment

Patients were randomized in 1:1 ratio to placebo or intervention (herbal combination) groups using block randomization (4-blocks). Placebo and drug were prepared by Afkare-e-talaei institute, in the same packaging and received 4-characters unique codes by the principal investigator (who was blinded to the study subjects). Neurology and clinical pharmacy specialist, who were responsible for patient visits and completing Case Report Forms (CRFs), were kept blinded to the study arms until the end of the study.

Baseline data gathering

At baseline, physical examination, related imaging, necessary changes in drug regimen based on guidelines released by the American Academy of Neurologists in 2004 and National Institute for Health and Care excellence, blood tests including CBC, platelets, liver function tests (AST, ALT, ALP), BUN, Cr, PT, PTT, INR, and therapeutic drug monitoring for anti-epileptics(if applicable) were requested by the neurologist. Then, the patient was referred to a clinical pharmacy specialist who was responsible for patient follow-up and data gathering. In this phase, the data related to the study was explained in detail to the patient and the informed consent form was completed and signed by the patient with the supervision of the clinical pharmacist (and after at least 24 hours of thinking), and the patient was recruited in the study. Then a pre-designed CRF including demographic, clinical, and laboratory data, seizure type and duration, medications, and past medical and drug history was filled in by the clinical pharmacist. Then the subjects randomly (permuted block randomization) were assigned to control/intervention groups.

The intervention and follow-ups

Patients received one capsule of drug/placebo(lactose powder, 500mg) three times/day, for three months. Standard treatments were performed based on valid guidelines by a neurologist along with medication/placebo prescribed. During the first month of the study, patients were visited by a clinical pharmacist weekly and referred to the neurologist if necessary. During this visit, the number of seizures, adherence to the treatment, and possible side effects of drug/placebo were recorded. Then patients visited monthly, till 3months. Upon completion of three months, the patients were visited and examined by the neurologist and the clinical pharmacist.

Study outcomes

The primary outcome of the study was a decrease in the seizure frequency of patients after taking a three-month course of the drug/placebo. The secondary end-point was the percentage of patients who had at least a 50% reduction in their seizure frequency. The drug was defined as effective if it decreased seizure frequency by more than 50% compared with the baseline. The safety endpoint was the reported adverse effects. For the patient's safety, all participants were asked to report any side effects of the medication during their follow-up visits. A phone number was also given so, urgent adverse events could be informed.

Statistical Analysis

For a description of quantitative variables median and Interquartile Range (IQR) and qualitative variables frequency (percentage) were used. The normality assumption was assessed using the Shapiro-Wilk test and Q-Q plot. Due to the non-normality of quantitative variables for comparison of means between groups, we used from Mann-Whitney test. In addition, for comparing the frequency of qualitative variables between groups, was used chi-square or Fisher's exact test. The mean changes in the frequency of seizures during 12 weeks were assessed used from non-parametric Friedman's test. A two-sided P_value<0.05 was considered statistically significant. All of the statistical analysis was used from STATA version 14.

RESULTS

This prospective, randomized, double-blind, placebo-controlled study was conducted in a referral neurology clinic of a 540-bed university hospital. The study protocol was approved by the appropriate ethics committee and written informed consent was obtained from each patient or the patient's legal guardian. The study started in August 2018.

A total number of 162 individuals were screened for eligibility, 58 were eligible, and were randomized into two groups (27:intervention vs. 31:control groups). From all recruited patients, 3 from the intervention and 6 from the control groups did not complete the study. Explanations include poor compliance (2 vs 5) and refusal to follow-up (1 vs. 1). Overall, 49 patients (24 vs. 25) completed the study. See the CONSORT chart in figure 1.

The demographic data and baseline seizure characteristics of the participants were not significantly different at baseline (Table1). There was no significant difference between the two groups in the type of concomitant drugs used or comorbid diseases. (data not shown)

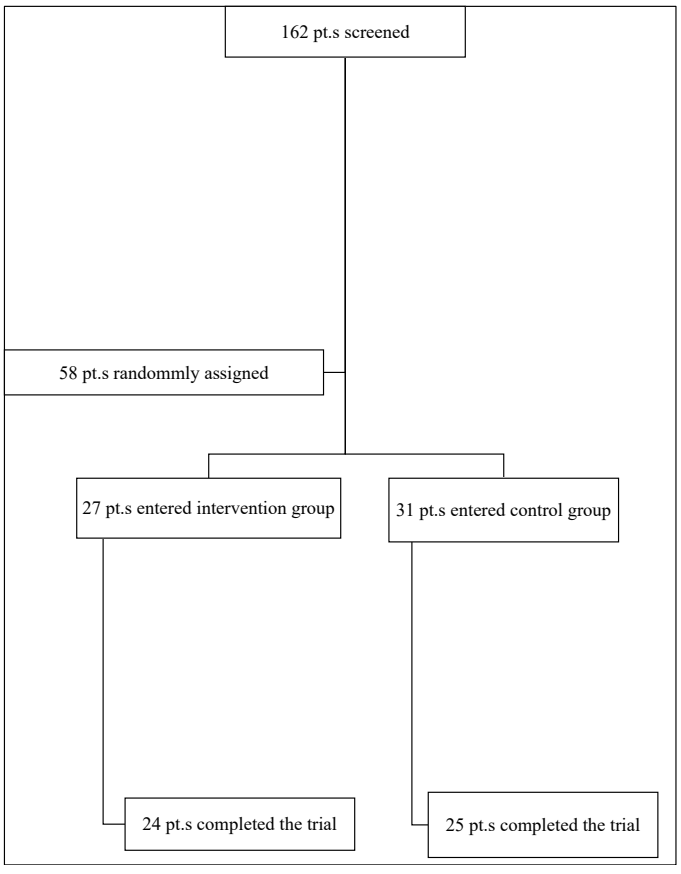

Fig. 1: CONSORT chart of the study

Table 1: Demographic data and baseline seizure characteristics of the participants

Parameter	*Group*				*P-value*
	Intervention		*Control*		
	Mean	*SD*	*Mean*	*SD*	
Age	38.41	11.63	39.16	17.02	0.84
BMI	25.28	4.40	26.11	3.32	0.42
Baseline seizure	8	16	16	33	0.806

Parameter		*Intervention group (number)*	*Control group (number)*	*P-value*
Status Epilepticus	Yes	7	1	NS
Family history of seizure	Yes	7	5	0.49
Induced seizure	Yes	13	9	0.16
Aura	Yes	7	9	0.94
Seizure type	GTC	12	9	0.54
	Focal seizure with retained	7	14	
	Myoclonic	2	1	
	Focal seizure l	6	5	
	Others	0	2	
Sex	Female	13	19	0.24

Due to non-parametric data, the median was reported as an indicator of seizure frequency. The median of seizures respectively were 4, 1, 1, 1 at baseline, after one, two, and three months in the intervention group, and 3, 2, 1, 2 in the placebo group. (Table 2, figure 2)

Secondary outcome and complete response after treatment were not significantly different between the two groups. (Table 3)

Repeated measure ANOVA test also revealed that there was not a significant main effect for treatment vs. placebo, F(1.49, 1.49) = 0.531, p = 0.54 (by Greenhouse-Geisser)

Safety Analysis

Adverse events including orthostatic hypotension, palpitation, anxiety, headache, somnolence, insomnia, hair fall, menstrual dysregulation, weight gain, nausea, dyspepsia, GERD, bloating, constipation, increased liver enzymes, and eye pain occurred in 20 patients taking herbal combination (all reported once except weight gain that reported by 4 cases and increased liver enzyme by 2 cases). Also19 subjects in the placebo arm of the study reported adverse effects including palpitation, dizziness, decentralization, agitation, diplopia, paresthesia, weight gain, acne, nausea, constipation, increased salivation, diarrhea, tremor, weakness, nasal congestion, and increased hemoglobin from13mg/dl to 15mg/dl (all reported once except dizziness and decentralization that was reported by 2 cases). None of the reported adverse effects was serious, and just two, one in each group, led to discontinuation of therapy at the patient's request due to elevated liver enzymes which were less than 2times upper normal limits of AST and ALT.

DISCUSSION

The combination of 350mg oleo-gum resin of *D.ammoniacum* and 150mg oleo-gum resin of *F.persica* didn't decrease seizure frequency significantly after 12- weeks of consumption three times a day. Over 50% of participants in the intervention group reported a reduction of more than 50% from baseline seizures with herbal combination after 12 weeks, but it was not significantly greater than the placebo. After three months, the average number of seizures was 1 and 11 in the intervention and control groups. There was no statistically significant difference between the two groups in the mean number of seizures after three months. At the end of the study complete remission was reported in 8 (33.33%) and 6 (20.69%) of the patients in the intervention and placebo arms of the study.

More participants reported adverse events on herbal combination drugs, but safety was similar to placebo. About 33% of participants became seizure-free after 12 weeks of treatment that it was not significantly different from placebo.

To our knowledge, this is the first randomized trial comparing the effect of *D.ammoniacum* and *F.persica* resins in humans. *D.ammoniacum* has been used in traditional medicine for many years to treat seizures.[15] Several books including Zakhireh Kharazmshahi, Tohfat al Momenin, Maaref-e Giahi, Makhzan al Advieh, and Alhavi have been mentioned the effects of oshagh in the treatment of epilepsy. Motevalian *et al*.[15] showed that *D. ammoniacum* gum has significant anticonvulsant activity in pentylenetetrazole-induced seizures, and suggests that GABAergic and opioid systems may be involved. Also, Abizadeh *et al*.[20] in 2014 evaluated the effect of *D.ammoniacum* gum on PTZ- induced seizure in the rat. Their result suggests that this gum has an antiepileptic effect in the chemical kindling model of seizure. Numerous *Ferula* species have been used in the traditional medicine of Iran as an anticonvulsant agent.[21, 22] Maaref-e Giahi, Makhzan al Advieh, and Alhavi books have pointed to the effects of Sakbinaj in the treatment of epilepsy.

Kiasalari et al.[23] have studied the anti-epileptic effect of the *F.assafoetida* gum extract by pentylenetetrazole(PTZ) kindling

Table 2: Comparison of the median of seizure frequency between two groups after three months of treatment

	Median (Q1-Q3)		
Time	*Intervention*	*Control*	**P_value*
baseline	4(2-5)	3(2-6)	0.806
First month	1(0-5)	2(0-4)	0.874
Second month	1(0-1.5)	1(0-2)	0.439
Third month	1(0-3)	2(0-3)	0.129

*based on Mann-Whitney test

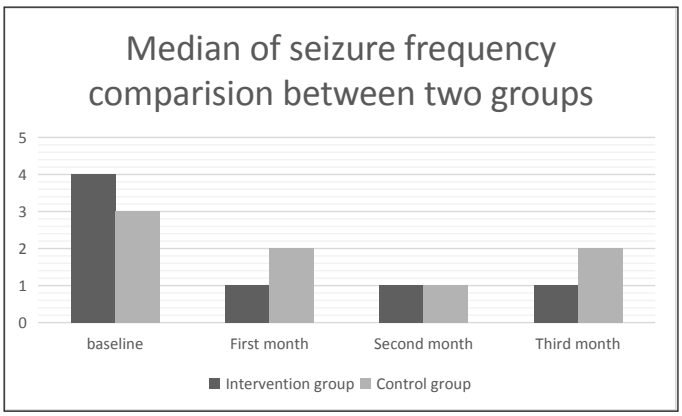

Figure 2: The comparison of seizure frequency between two groups after first, second and third month of drug/placbo use

Table 3: Primary endpoint (50% reduction in seizure) and Complete response (100% response) analysis

% of reduction	*Time from baseline*	*Total N (%)*	*Intervention N(%)*	*Control N(%)*	*P-value*
50%	One month N=48	27(58.70)	13(59.09)	14(58.33)	0.958
100%		16(33.33)	7(30.43)	9(36.0)	0.683
50%	Two months N=43	32(74.42)	16(80.0)	16(69.57)	0.501
100%		15(34.88)	6(30.0)	9(39.13)	0.531
50%	Three months N=37	25(67.57)	13(76.47)	12(60.0)	0.319
100%		14(37.84)	8(47.06)	6(30.0)	0.286

method using sixty male Albino mice. They randomly assigned mice into 6 groups. The control group, PTZ-kindled mice, and positive control group (valproate (100mg/kg)), other three remaining groups were kindled mice pretreated with 25, 50, and 100 mg/kg doses of *F.assafoetida* gum extract. Kindling with 11 PTZ injections has been done in groups (except the control group) every other day for a total of 22 days. PTZ challenge dose was injected at the dose of 75mg/kg two days after completing kindling injections. The seizure intensity was perceived and recorded until 30 minutes after PTZ injection. Results demonstrated that *F.assafoetida* gum extract can reduce seizure duration and intensity and may be able to show an anti-epileptic effect.

CONCLUSION

The present study showed that the administration of Vosha and Sakbinaj (350 mg and 150 mg, respectively) despite a decrease in the number of seizures and an increase in the percent of the patients with complete remission, statistically did not reach a significance level. Major limitations that could describe these results are the small sample size and the single-center design of the study. Larger studies with higher doses are recommended for better conclusions.

ACKNOWLEDGEMENT

Special thanks to miss Tavakoli the pharmacognosy Lab technician of the faculty of pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

FUNDING

This project has been funded by the Afkar-e-Talaee Institute, Tehran, Iran.

ABBREVIATIONS

CRF: Case Report Forms
CBC: Complete blood count
AST: Aspartate transaminase
ALT: alanine transaminase
ALP: Alkaline Phosphatase
BUN: Blood Urea Nitrogen
Cr: Creatinin
PT: Prothrombin Time
PTT: Partial thromboplastin time
INR: International Normalized Ratio
RCT: Randomized Clinical Trial
IQR: Interquartile Range

REFERENCES

1. Stafstrom, C.E. and L. Carmant, *Seizures and epilepsy: an overview for neuroscientists.* Cold Spring Harb Perspect Med, 2015. 5(6).
2. Lattanzi, S., et al., *Brivaracetam add-on for refractory focal epilepsy: A systematic review and meta-analysis.* Neurology, 2016. 86(14): p. 1344-1352.
3. Annegers, J.F., et al., *The incidence of epilepsy and unprovoked seizures in multiethnic, urban health maintenance organizations.* Epilepsia, 1999. 40(4): p. 502-6.
4. Hirtz, D., et al., *How common are the "common" neurologic disorders?* Neurology, 2007. 68(5): p. 326-37.
5. Olafsson, E., et al., *Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study.* Lancet Neurol, 2005. 4(10): p. 627-34.
6. Davis, J., et al., *Implementation strategies for a Scottish national epilepsy guideline in primary care: results of the Tayside Implementation of Guidelines in Epilepsy Randomized (TIGER) trial.* Epilepsia, 2004. 45(1): p. 28-34.
7. Hauser, W.A., J.F. Annegers, and L.T. Kurland, *Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984.* Epilepsia, 1993. 34(3): p. 453-68.
8. Cockerell, O.C., et al., *Remission of epilepsy: results from the National General Practice Study of Epilepsy.* Lancet, 1995. 346(8968): p. 140-4.
9. Kwan, P. and M.J. Brodie, *Early identification of refractory epilepsy.* N Engl J Med, 2000. 342(5): p. 314-9.
10. Brigo, F., et al., *Efficacy and tolerability of brivaracetam compared to lacosamide, eslicarbazepine acetate, and perampanel as adjunctive treatments in uncontrolled focal epilepsy: Results of an indirect comparison meta-analysis of RCTs.* Seizure, 2016. 42: p. 29-37.
11. Pandpazir, M., et al., *Anti-Inflammatory Effect and Skin Toxicity of Aqueous Extract of Dorema ammoniacum Gum in Experimental Animals %J Research Journal of Pharmacognosy.* 2018. 5(4): p. 1-8.
12. Shojaii A, B.A.a.H.S., *Evaluation of analgesic and anti-inflammatory activity of Dorema ammoniacum gum in animal model.* Int J Pharm Sci Res 2017. 8(7): p. 5.
13. Rajani, M., et al., *Evaluation of the Antimicrobial Activity of Ammoniacum Gum from Dorema ammoniacum.* Pharm Biol, 2008. 40: p. 534-541.
14. Ghasemi, F., et al., *Effects of Dorema ammoniacum Gum on Neuronal Epileptiform Activity-Induced by Pentylenetetrazole.* Iran J Pharm Res, 2018. 17(2): p. 735-742.
15. Motevalian, M., et al., *Anticonvulsant activity of Dorema ammoniacum gum: evidence for the involvement of benzodiazepines and opioid receptors.* Res Pharm Sci, 2017. 12(1): p. 53-59.
16. Sattar, Z. and M. Iranshahi, *Phytochemistry and pharmacology of Ferula persica Boiss.: A review.* Iranian Journal of Basic Medical Science, 2017. 20: p. 1-8.
17. Hajimehdipoor, H., et al., *The cytotoxic effects of Ferula persica var. Persica and Ferula hezarlalehzarica against HepG2, A549, HT29, MCF7 and MDBK cell lines.* Iranian Journal of Pharmaceutical Sciences, 2012. 8.
18. Abdollahi Fard, M. and A. Shojaii, *Efficacy of Iranian traditional medicine in the treatment of epilepsy.* Biomed Res Int, 2013. 2013: p. 692751.
19. Slater, J., et al., *Efficacy of antiepileptic drugs in the adjunctive treatment of refractory partial-onset seizures: Meta-analysis of pivotal trials.* Epilepsy Res, 2018. 143: p. 120-129.
20. Abizadeh M, H.N., Ebrahimi S, Janahmadi M, Shojaii A, Motamedi F., *The effect of Dorema ammoniacum pretreatment on the progression of seizures induced by chemical kindling in rats.* Pejouhandeh, 2014. 19(5): p. 228-234.
21. Bagheri, S.M., et al., *Anticonvulsant effect of ferula assa-foetida oleo gum resin on chemical and amygdala-kindled rats.* N Am J Med Sci, 2014. 6(8): p. 408-12.
22. Mahboubi, M., *Ferula gummosa, a Traditional Medicine with Novel Applications.* J Diet Suppl, 2016. 13(6): p. 700-18.
23. Kiasalari, Z., et al., *Antiepileptic and Antioxidant Effect of Hydroalcoholic Extract of Ferula Assa Foetida Gum on Pentylentetrazole- induced Kindling in Male Mice.* Basic Clin Neurosci, 2013. 4(4): p. 299-306.