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The effect of *Nigella sativa L.* (black cumin seed) on intractable pediatric seizures

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Despite the availability and use of numerous antiepileptic drugs (AEDs), nearly 15% of childhood epilepsy cases are resistant to treatment. However, in traditional medicine, *Nigella Sativa L.* ("black cumin seed") has been known for its anticonvulsant effects. This plant is naturally distributed in Iran and has been widely used as a natural remedy for a long time. In this study the efficacy of this agent in reducing the frequency of seizures in childhood refractory epilepsy was assessed.

Material/Methods: In this double-blinded crossover clinical trial conducted on children with refractory epilepsy, the aqueous extract of black seed was administered as an adjunct therapy and the effects were compared with those of a placebo. Twenty-three children were entered in the study and 20 remained in the study (13 months to 13 years old, 10 boys and 10 girls). All patients were receiving constant treatment for at least one month before the study. They received extract (40 mg/kg/8 h) or placebo for a period of four weeks and between these periods for two weeks they received only their pre-existing anti-epileptic drugs (AEDs).

Results: The mean frequency of seizures decreased significantly during treatment with extract ($p<0.05$).

Conclusions: It can be concluded that the water extract of *Nigella sativa L.* has antiepileptic effects in children with refractory seizures.

key words: **nigella sativa • intractable seizures • children • aqueous extract**

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BACKGROUND

There are numerous antiepileptic drugs (AEDs) to treat intractable seizures, but nearly 15% of childhood epilepsy cases are resistant to treatment; these drugs fail to provide adequate control of epileptic seizures and do not prevent progressive epileptogenic changes [1,2]. Many of them also produce unwanted side effects or are capable of producing serious adverse events, so recurrent seizures are still a common clinical problem of hospitalized pediatric patients and in organizing a considerable number of outpatients referred to pediatric neurology clinics [3].

"Black cumin seed" (the botanical name is *Nigella sativa L.* of the family *Ranunculaceae*), or "black seed" for short, although believed to be indigenous to the Mediterranean region, has been cultivated in other parts of the world. It seeds, c*yah dane* in Persian, have played an important role through the years in ancient Islamic practice. Many studies are available on its various therapeutic effects, such as anticancer [4], diuretic and hypotensive [5], antihistaminic [6,7], antihypertensive [8], hypoglycemic [9], anti-inflammatory and analgesic [10], and antifungal and antibacterial [11,12] effects. The oil is useful in diseases in which free radicals are involved, e.g. anoxia and ischemia of the brain and heart as well as arteriosclerosis, rheumatism, and cancer [8,11,13–15].

In ancient Islamic medicine, *Nigella sativa* (black seed) was known for its anticonvulsant effects [16]. Water extract of *Nigella sativa* suppressed penicillin-induced epileptiform activity in rat; in this animal study, elevation of serotonin (5HT) and decreased dopamine level in the cerebral cortex, caudate nucleus, and midbrain as well as decreased norepinephrine levels in the cerebral cortex were reported. The authors concluded that water extract of black seed has anticonvulsant effects by selectively altering the monoamine level in different brain regions [17]. Black seed, in particular its major constituent, thymoquinone, had shown antiepileptic effects in mice [18]. In another study, intracerebro-ventricular administration of thymoquinone suppressed epileptic seizures in rat [19]. The anticonvulsant and antioxidant effects of *Nigella sativa* oil against PTZ-induced kindling in mice were investigated; this study clearly demonstrated a potent anticonvulsant property for *Nigella sativa* oil against the development of kindling consequences in PTZ-kindled mice, and it was more potent as an anticonvulsant agent than Valporate when they were compared. The mechanism for the anticonvulsant effect seems to be correlated with the antioxidative effect [20].

Furthermore, several studies based on the toxicity of black seed have been reported. It has been shown that there were no toxic effects when *Nigella sativa* seed oil was given to mice via the stomach; it has also been reported that *Nigella* seed powder does not produce any toxic effect when given to rabbits by gastric intubation [21]. Acute and chronic toxicity of *Nigella sativa*-fixed oil were also investigated in rats and mice and there was no evidence of toxicity [22]. Recently the possible hepatotoxicity of black seed was studied and no consistent significant histopathological evidence of this toxicity was shown.

The oil extracted from the seeds contains saturated and unsaturated fatty acids and 1.1–1.4% volatile oil, the major components of which are thymoquinone and nigellone (polythymoquinone) [23]. In a new study, Tunisian and Iranian varieties of *Nigella sativa* seeds had, respectively, 26.7% and 22.6% protein, 28.48% and 40.35% oil, 4.86% and 4.41% ash, and 40.0% and 32.7% total carbohydrate. The major unsaturated fatty acids were linoleic acid (50.3–49.2%), saponification numbers 211 and 217 [24].

In this study we investigated the effect of *Nigella sativa* on intractable seizures of children, with the goal of reducing seizure frequency as well as AED dosage. We assessed the efficacy of oral administration of a black seed aqueous (Soxhlet) extract as an adjunct to AEDs in a double-blinded clinical trial and compared the results with those of a placebo.

MATERIAL AND METHODS

This study was performed between Sept. 2003 and Nov. 2004 in a tertiary referral center (Ghaem Medical Center, Mashhad, Iran). Black seeds were collected from the southern part of Khorasan province in Iran. These seeds were authenticated by a pharmacologist experienced in medicinal plants. The seeds were washed to remove sand and other debris and air-dried. In the first step the seeds (100 g each time) were extracted in a Soxhlet extractor with distilled water (for 4 hours) and then the solvent was evaporated in vacuum with a rotatory evaporator, which yielded a blackish-brown concentrate (28.1 g from 100 g of seeds). On average, this extract contained 11.5% water. It was kept at 4°C before administration, for less than three days. In this study we chose syrup form because of its easier preparation and use in children. We added purified extract to a 60% sucrose solution to produce a syrup with 100 mg of purified extract per ml. The placebo was also prepared with the same specification (especially the color of the solutions).

Patients and their relatives were advised that black seed extract was registered for sale in the USA as an immune modulator [25] but without proven efficacy in epilepsy and asked to give informed consent. The parents underwent a further interview with the clinician to ensure that informed consent was unambiguous.

To be included in this pilot study the patients had to have intractable epilepsy according to the definition [26] with occurrence of at least one seizure during the four-week baseline period, relative absence of confounding illnesses, and constant antiepileptic treatment at least one month before the study. Seizure types of all patients were diagnosed according to the standard of the International classification of Epilepsy (ILAE) [27,28]. Patients with more than two types of seizure were designated as having "polymorph" seizures. Current AED treatment included at least two but not more than five drugs. No other AEDs had been added to or withdrawn from their regimens within one month before the study.

Exclusion criteria were a history of status epilepticus within the three months prior to the first visit, a history of pseudoseizures, seizures that due to their rapid and repetitive nature could not be reliably counted, current renal and cardiac or hepatic dysfunction, lack of cooperation (incorrect dose or irregular use of the prescribed syrup and unreliable registration of events by parents), severe exacerbation of

their seizures, and withdrawal of the patients by their parents from the study.

The patients were selected in sequential order of presentation from the routine clinical caseload. Based on their type of seizures and poor control with established AEDs, the patients were selected over a consecutive period of 11 months. In this period, 23 patients were enrolled, but only 20 patients completed the study.

Initially, before enrollment, each child underwent clinical examinations, both general and systemic. The patients were visited once a week in the baseline period (4 weeks) and throughout the study. All information related to the number of seizures, history of duration, and possible changes in seizures was obtained from the parents. The parents were previously trained and had to fill out a questionnaire to better characterize what was being measured. The clinicians were familiar with the nature and treatment of epilepsy.

We designed an add-on, double-blinded, placebo-controlled, randomized, crossover study with a two-week washout period between treatments. Crossover-designed studies do not give very valid results when using curable therapy or drugs with long-term effects, but in our study, refractory seizures are essentially almost incurable and only can only be controlled. Likewise, a crossover study helps to remove some confounding factors in two groups of the study. During the study the patients entered the study gradually and were given a number from one on, in a sequential process; then it was randomly ("toss-up") determined that patients with even numbers take syrup A for first four weeks and, after the treatment was discontinued for two weeks, receive syrup B for the second four weeks, while the other patients (with uneven numbers) take the syrups in the opposite order. The patients were provided with the syrup free of charge, and neither the pharmacologist, physicians, nor patients knew the contents of the syrups (A and B) until they were identified by the pharmacist at the end of the study. This method of randomization and blinding helped us to avoid bias.

Both types of syrups were prescribed at a dosage of 0.4 ml/kg/8-hours (for the extract, this was equivalent to 40 mg/kg/8-hours) throughout these periods. The parents reported the frequency, duration, and quality of seizures at each visit; in addition, any adverse effects that occurred were reported to the clinicians. This protocol provided a uniform measure of seizure frequency for comparison. At the end of each period (of placebo or extract) the degree of parental satisfaction was assessed.

The study was reviewed and approved by the Research and Ethics Committee of the Mashhad University of Medical Sciences of Iran.

Statistical analysis was done using the SPSS statistical software package and a probability value of less than 0.05 was considered statistically significant.

Results

Twenty-three children (12 males, 11 females) were enrolled in the study. Three patients were withdrawn (2 boys, 1 girl), only one of whom was on the extract, because of inappropriate collaboration and parental refusal. A total of 20 children (10 boys and 10 girls), ranging in age from 13 months to 13 years (mean: 66.95±45.39 months) completed the double-blinded, placebo-controlled parallel study (Table 1).

Table 1. Type of seizures and history of patients.

Patient (name)*	Gender	types of seizure
MS	M	MC
MR	M	MC+GTC
ZZ	F	GTC
SG**	M	GTC
AE	M	MC
FN	F	MC
SE	M	AB
AB	M	MC
SN	F	MC
FZ	F	GTC
KS	F	PM
AA**	M	GTC
SH	M	MC
FH	M	GTC
ZK	F	MC
AA	M	SA+GTC
ZK	F	MC
MJ	F	GTC
AP	M	CPS
MS	M	AB
AM**	F	GTC
HN	F	AB
MA	F	CPS

* Abbreviations of patients' names; ** Withdrawn. MC – Myoclonic; GTC – Generalized tonic-clonic; AB – Absence; SA – Salaam attack; CPS – Complex Partial seizure; M – Male; F – Female.

Seizure types were: 4 patients with generalized tonic-clonic, 8 myoclonic, 2 complex partial, 1 polymorphic, 3 absence, 1 myoclonic with generalized tonic-clonic, and 1 tonic-clonic with infantile spasm attack (salaam attack). Twenty-five percent of the children were mentally retarded or had abnormal findings in their neurological examinations.

Electroencephalograms (EEGs) and computed tomograms (CTs) were abnormal in 90% and 20% of the patients, respectively. Mean age of seizure onset was 19.15±23.06 months. Patients used between 2 and 5 AEDs at the time of entry in the study, the most common concomitantly used AEDs were carbamazepine and phenobarbital and the most frequent psychotropic AEDs were benzodiazepines. Compliance with the extract was found to be very good, as verified by

Table 2. Weekly comparison results of the Wilcoxon test for frequency of seizures (seizures/day).

Seizures: number/week	1st week	2nd week	3rd week	4th week
Extract period	6.00±7.44	5.03±7.31	4.74±6.89	4.21±5.77
Placebo period	5.55±7.00	5.34±6.79	5.7±7.14	6.14±6.75
p value	0.381	0.132	0.011	0.001

Table 3. Weekly comparison of seizure frequency throughout the study.

Time	E>p[a]	E<p[b]	E=p[c]
1st week extract – 1st week placebo	7 (35%)	6 (30%)	7 (35%)
2nd week extract – 2nd week placebo	3 (15%)	13 (65%)	4 (20%)
3rd week extract – 3rd week placebo	4 (20%)	14 (70%)	2 (10%)
4th week extract – 4th week placebo	3 (15%)	16 (80%)	1 (5%)

[a] Number of patients whose seizers in the extract period were more than in the placebo period;
[b] Number of patients whose seizers in the placebo period were more than in the extract period;
[c] Number of patients whose number of seizers were equal in the two periods.

Table 4. Parental satisfaction at the end of each period.

Time/ satisfaction	Satisfied	Ineffective	Dissatisfied
Extract period	75%	25%	0%
Placebo period	30%	50%	20%

Table 5. Comparison of seizure frequency of patients between extract/ placebo and baseline periods (each period 4 weeks).

	Number (percent)		P-value
Total seizure frequency (E[a]–B[b])	E<B	16 (80%)	0/007
	E>B	3 (15%)	
	E=B	1 (5%)	
Total seizure frequency (P[c]–B)	P<B	9 (45%)	0/896
	P>B	9 (45%)	
	P=B	2 (10%)	
Total seizure frequency (E–P)	E<P	17 (85%)	0/003
	E>P	2 (10%)	
	E=P	1 (5%)	

[a] Extract period; [b] Baseline period; [c] Placebo period.

the remaining syrup at the end of each week. Improvement (marked or mild) in seizure frequency was observed in 65% and 20% of patients at the end of the extract period and the placebo period, respectively. Thirty percent and 5% of patients in the extract period and 60% and 20% in the placebo period showed no change and worsening, respectively.

The mean frequency of seizures in children at the end of the extract period decreased from 5.78±7.2 seizures/day before initiation of the study to 4.21±5.77 seizures/day. At the end of the placebo period, the mean frequency of seizures reached 6.14+6.75 seizures/day. The results of the Friedman statistical test on these data showed a significant difference in seizure frequency between the extract period and other periods ($p<0.001$). The number of seizures in children varied widely, related to their types of seizures, for example one patient with one generalized tonic-colonic seizure/month and another with more than 20 salaam attack seizures/day. This difference in the number of seizures can explain the high standard deviations in our statistical results, and it was required to use a non-parametric statistical test independent of the mean. Therefore, the Wilcoxon test was used. The results demonstrating a significant difference between the extract period and the period before initiation of the study, with *p* value of 0.007. Data from these two periods were compared weekly with the Wilcoxon test; which showed statistically significant difference (Tables 2, 3).

The degrees of parental satisfaction at the end of the extract period and the placebo period also showed a significant difference (Table 4), which indicates a better quality of life after administration of the *Nigella sativa* water extract.

There were no treatment-related serious adverse events, with only three patients reporting adverse effects. One patient reported constipation in the 2nd and 3rd weeks of the extract period, another had an increase in laughing at the time of seizure during the placebo period, and the third developed a maculopapular rash on the trunk at the end of the study.

Discussion

An intensive search of literature failed to reveal any clinical trial on the anticonvulsant effects of *Nigella sativa L* in humans to compare our findings with other results, but in view of the above considerations, aqueous extract of *Nigella sativa* in oral administration suppressed penicillin-induced seizures in rats [17] and the antiepileptic effects of thymoquinone, the major constituent of *Nigella sativa L*, have been described [18,19].

In our study, during the extract period the mean number of seizures decreased gradually, whereas this was not the case

in the placebo period. Weekly comparison of seizure frequency between the extract and placebo periods became statistically significant in the third week, indicating a rapid onset of black seed extract action (Table 2). Moreover, in the last week of the extract period, sixteen patients (80% of all) had fewer seizures than in the last week of the placebo period (Table 3). Three of the participants became seizure free at the fourth week of the extract period; two of whom had myoclonic seizures, but we do not conclude that the water extract has a specific effect on myoclonic seizures because the number of our patients was low. Only in one patient with polymorph seizures (a case of Lennox-Gastault) was the frequency of seizures during treated with extract more than during the placebo period.

The results of our study showed that the aqueous extract of *Nigella sativa* has an anticonvulsant effect. This effect may be due to thymoquinone, the major constituent of *Nigella sativa* oil, but we used a water extract, which has lesser amount of thymoquinone and is a multi-component agent, so the antiepileptic effect of the water extract may be due to other neurobiological components. However, the water extract may alter the monoamine level in the central nervous system (CNS) [17], and these changes inhibited the epileptic activity of patients. This warrants systematic studies with the aim of determining which components of the aqueous extract mediate this antiepileptogenic effect and which mechanism is exactly responsible.

The number of adverse events reported with this trial (described in the "Results" section) was low and their severity was mild and did not demand discontinuation of treatment.

Conclusions

It can be concluded that the aqueous extract of *Nigella sativa L.* has anticonvulsant effects and can improve seizure control in children suffering from refractory epilepsy. However, more extensive trials should be conducted in such patients to confirm these preliminary findings. In this study we had patients with a broad range of seizure frequency and type; future studies should have restricted types of seizures to have more type-specific results. Furthermore, in future studies the effect of extract on the serum levels of AEDs should be assessed, because an alteration in AED metabolism with *Nigella sativa* extract cannot be ruled out, and as yet there is no confirmation of this.

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