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The effect of curcumin on epilepsy: an experimental review

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ABSTRACT

Nearly 70 million people worldwide suffer from epilepsy. Despite administration of routine antiepileptic drugs (AEDs), nearly 30% of seizures are resistant to treatment called drug resistant epilepsy (DRE). Since the epilepsy treatment may result in consequences of multi-drugs administration or sometimes invasive surgical methods in DRE, herbal treatment can be a good alternative choice due to its easy accessibility, lower cost and fewer side effects. Although turmeric has been one of a very commonly used dietary spices and traditional herbal remedies, its derivation as a newly introduced medicine-curcumin has not been used to a large extent. In this literature, we have reviewed the available trial researches, which studied specifically antiepileptic effect of curcumin. We searched databases of Science direct, PubMed and Google Scholar (2008 to 2016) with key words of turmeric, curcumin, Diferuloylmethane, Epilepsy, and Seizure to find the related references. The major extract of turmeric curcumin has found to have antiepileptic effect according to recent surveys. It not only has no critical adverse effect, but also can protect patients from other AEDs severe side effects. It also makes it possible to gradually decrease the dose of AEDs in long-term combination therapy.

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Introduction

Almost 70 million people worldwide are affected by epilepsy and its consequences (1). Epilepsy is commonly observed in two ranges of younger ages and above 60 years (2). Despite administration of the routine antiepileptic drugs (AEDs), nearly 30% of the seizures are resistant to antiepileptic drugs called drug resistant epilepsy (DRE) (3). Since the treatment may result in consequences of multi-drugs administration, interactions and side effects or sometimes invasive surgical methods in DRE, herbal treatment can be a good alternative choice due to its easy accessibility, lower cost and fewer side effects. Different medicinal plants have been recommended due to their antiepileptic effects including *Rosa Damascena, Citrus aurantium L, Chaihu-longu-mulitang, Thymoquinone, Zhenxianling, Nigella Sativa* (4-7). Turmeric derived from the rhizome of Curcuma Longa is an Indian dietary spice, which has been used as a herbal remedy in Ayurveda (Indian

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traditional medicine). Recently, there has been an upward trend in active compounds of turmeric called curcuminoids, which the major compounds is curcumin (Diferuloyl Methane) making 90% of the curcuminoid content of the original spice (8,9). Its beneficial properties have been known as anti-inflammatory, and anti-oxidant, as well as supportive effects in chemotherapy (10). Its positive effects have been reported on various diseases and conditions including topically administration in wounds, blistering diseases like pemphigus and herpes zoster, acne and skin infections, oral administration in common cold, liver diseases, urinary tract diseases, diabetes, Alzheimer's disease, epilepsy, cognitive disorders and various cancers, and also via inhalation in chronic rhinitis and coryza (11-14). One of the suggested mechanisms of curcumin effects is decreasing inflammatory cytokines (15), which are known to play a dominant role in epilepsy pathophysiology (16). Epigenetic mechanism through regulating miRNA expressions is another pathway, which explains the long-term antiepileptic effect of this beneficial medicine (17). Recent emphasis on the use of natural and complementary medicine in western societies has drawn the interest of scientific community to this remedy.

In this literature, we have reviewed the available trial researches, which studied specifically antiepileptic effect of curcumin.

Literature Review

In recent years, there has been an upward trend in researching the administration of herbal medicine as adjuvant therapy in chronic diseases including epilepsy. Due to the cultural aspects in Iran, this trend has been well accepted by the patients. Although turmeric has been one of a very commonly used dietary spice and traditional herbal remedies, its derivation as a newly introduced medicine-curcumin has not been used to a large extent. Therefore, it was an area for investigation the beneficial properties, molecular mechanisms, safety of use, effective dose, administration route and possible adverse effects to make the medicine fully known and introduced to be used in every condition it might have a positive outcome. However, as in trials the antiepileptic effect has been studied only in animal models, this is one step toward the clinical human study.

The mentioned animal studies' different details are summarized in Tables 1. As the first executive

Table1. The Effect of Curcumin on epilepsy. Summarized Experimental Studies

Author Year Reference	Study Population	Sample size (n)	Seizure Type	Curcumin Dose & administration route	Outcome of Curcumin administration
Bharal 2008 (18)	Swiss albino mice	Acute study: 6 case and 6 control Chronic study: 8 case and 8 control	Electoshock induced seizure (2 mA for 0.2 s)	50, 100 and 200 mg/kg PO[1]	Curcumin in dose of 100 mg/kg increased seizure threshold in ICES test on both acute and chronic administration
Gupta 2009 (19)	Albino Wistar rat	6 groups of 7 rats each	Kainic-acid induced status epilepticus (10 mg/kg IP)	50, 100 and 200 mg/kg IP	Pretreatment with 100 and 200 mg/kg of Curcumin increased the latency of seizures
Mehla 2010 (20)	Albino Wistar rat	5 groups of 4 rats each	PTZ[2] induced seizure (30 mg/kg IP)	100, 200 and 300 mg/kg PO	Pretreatment with Curcumin ameliorates seizures, oxidative stress and cognitive impairment
Said 2010 (21)	Swiss albino mice	7 groups of 8 rats each	PTZ induced seizure (70 mg/kg IP)	300 mg/kg PO	Curcumin can confer protection from sodium valproate induced hepatotoxicity. It does not affect the anticonvulsant activity of SVP[3]
Bharal Agarwal 2011 (22)	Swiss albino mice	5 groups of 6 mice each	PTZ induced seizure (25 mg/kg IP)	50, 100 and 200 mg/kg PO	Curcumin offers protection against Seizure and reduces the kindling progression
Reeta 2011 (23)	Albino Wistar rat	5 groups of 6 rats each	PTZ induced seizure (60 mg/kg IP) MES[4] induced seizure (70 mA for 0.2 s)	300 mg/kg PO	Curcumin potentials the anticonvulsant activity of valproate, phenytoin, phenobarbitone and carbamazepine and provides decrease in necessary dose of AED[5] by the same effect
Aboul Ezz 2011 (24)	Albino Wistar rat	60	Pilocarpine induced seizure (380 mg/kg IP)	80 mg/kg PO	Curcumin has anticonvulsant effect and also has long-term mechanism as well as short-term

Author Year Reference	Study Population	Sample size (n)	Seizure Type	Curcumin Dose & administration route	Outcome of Curcumin administration
Orellana-Paucar 2012 (25)	Zebrafish and C57B1/6 mice	1. 96 well plate; one larva of zebrafish per well 2. 5 groups of 6 mice each	PTZ induced seizure (Zebrafishes were allowed to swim in a well of 400 µl with 40 mM PTZ; PTZ dose for mice was calculated by formula)	Zebrafishes were allowed to swim in a well of 400 µl with 10 µg/ml turmeric oil, 50 and 100 mg/kg PO of turmeric oil for mice	Curcumin has anticonvulsant effect in both models
Noor 2012 (26)	Albino Wistar rat	5 groups of 38 rats	Pilocarpine induced seizure (380 mg/kg IP)	80 mg/kg PO	Curcumin ameliorates the abnormalities obtained in the major neurotransmitters and improves histological changes induced by Pilocarpine and also improves some of adverse effects of AEDs
Anovadiya 2013 (27)	Swiss albino mice	6 groups of 6 mice each	MES induced seizure (36 mA for 0.2 s) PTZ induced seizure (95 mg/kg IP)	50 and 100 mg/kg IP	Curcumin is safe and has antiepileptic activity in dose of 100 mg/kg. It also has synergistic activity in combination with sodium valproate
Choudhary 2013 (28)	Swiss albino mice	6 groups of 6 mice each	PTZ induced seizure (35 mg/kg IP)	50, 100 and 200 mg/kg IP	Curcumin has antiepileptic effect and ameliorates depression like behavior, learning and memory impairment
Ahmad 2013 (29)	Swiss albino mice	4 groups of 6 mice each	Lithium-Pilocarpin induced seizure (Li: 3 mEq/ml/kg IP Pc: 20 mg/ml/kg SC)	50, 100 and 200 mg/kg PO	Curcumin significantly ameliorates SE-induced cognitive dysfunction and oxidative damage
Kiasalari 2013 (30)	Albino Wistar rat	56	Kainate induced temporal lobe seizure (4 µg intrahippocampal inj)	100 mg/kg PO	Pretreatment with Curcumin can attenuate seizures, lower oxidative stress markers and prevent hippocampal neuronal loss
Kumar 2014 (31)	Swiss albino mice	4 groups of 6 mice each, for every type of seizure (Myoclonic, Generalized clonus, Tonic extension) n=72	PTZ induced seizure (20 to 120 mg/kg IV)	40 and 80 mg/kg PO	Curcumin has antiepileptic effect and the effect involves an interaction with adenosine A1 receptor on neuronal cell membrane
Jiang 2015 (32)	Albino Wistar rat	3 groups of 6 rats each	Kainic-acid induced temporal lobe seizure (2 µg intrahippocampal inj)	100 mg/kg IP	Curcumin has protective effect against cognitive impairment and has beneficial effects on modifying epileptogenesis
Kaur 2015 (33)	Albino Wistar rat	4 groups of 8 rats each	PTZ induced seizure (40 mg/kg IP)	100 mg/kg PO	Curcumin inhibits activation of astrocytes and microglia along with the decrease in expression of proinflammatory cytokines. It also prevents from cognitive deficits in chronic epilepsy
Drion 2016 (34)	Swiss albino mice		Electrically induced seizure (Intrahippocampal electrodes with 50 Hz pulse trains)	150 mg/kg PO	Curcumin had no effect on chronic seizures, possibly because it didn't reach the brain at adequate effect levels

[1]PO: Per-Oral; [2]PTZ: pentylenetetrazole; [3]SVP: Sodium Valproate; [4]MES: Maximal Electroshock Seizure; [5]AED: Anti Epileptic Drug

step, 8 out of 17 studies induced seizures by pentylenetetrazole (PTZ) kindling, 3 by kainic-acid, 3 by pilocarpine and 4 trials worked with side effect related to curcumin was reported between the ranges of administration doses 40 to 300 mg/kg orally or 50 to 200 mg/kg intraperitoneal. All the studies' outcomes supported the anticonvulsant effect of curcumin in different dose and different administration rout except one which showed oral administration has no effect on chronic seizure, possibly because it did not reach the brain at adequate effect levels (34). As curcumin makes a fine adjuvant therapy for epilepsy, some researchers investigated its interactions with the currently used AEDs. Said and Noor confirmed that curcumin definitely reduced the adverse effects caused by some AEDs by reducing the dose of AEDs(21,26). Reeta and Anovadiya reported that the adjuvant therapy make it possible to gradually decrease the dose of AEDs while obtaining the same positive clinical outcome (23,27). Although the synergistic effect of curcumin was found and presented by Anovadiya, Said research showed no such effect (21,27).

Conclusion

Epilepsy is one of the worldwide important diseases, which both the seizure frequency and the treatment with AEDs affect the quality of life of patients and many suffer from the consequences. Herbal medicine has been presented to be a safe adjuvant therapy with lower cost and better outcome. Curcumin- the major extract of turmeric- has found to have antiepileptic effect according to recent investigations. It has been demonstrated to be safe in animal studies in a number of species. But, it has to be mentioned that the metabolism of curcumin between human and rats is different and humans can tolerate higher doses of this medicine without significant side effects. It not only has no critical adverse effect, but also can protect patients from other AEDs severe side effects and hopefully it makes it possible to gradually decrease the dose of AEDs in long-term combination therapy. This article reviewed animal studies from 2008 up to now studying the antiepileptic effect of curcumin in order to take a step toward the clinical human study in future.

Conflict of Interest

The authors declare no conflict of interest.

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