Biomedical & Translational Science

Original Article

Ameliorating effects of cinnamon and curcumin on oxidative stress in lithium-pilocarpine induced status epilepticus model

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- Received Date: 23 May 2022
- Accepted Date: 28 May 2022
- Publication Date: 03 June 2022

Abstract

The lithium-pilocarpine (Li-Pc) model of status epilepticus (SE) is most convenient and is frequently used for pathophysiological and management strategies in search of new, safe and effective therapeutic agents including the natural remedies for SE. Oral administration of cinnamon (CIN) and curcumin (CUR) can reduce neuroinflammation which is a common feature of neurodegenerative pathophysiological disorders. Although many studies on CUR effects on SE has been undertaken, to our best knowledge no study has been conducted on studying the effect of CIN on SE.

The present study explores the neuroprotective effects of natural food products CUR and CIN on Li-Pc induced SE in rats.

SE was induced in experimental rats using lithium – pilocarpine model. Besides control groups, the animals were also grouped as treatment groups which received CIN and CUR pre-treatment before induction of SE. Besides severity of the seizures, cognitive dysfunctions, oxidative stress parameters were also estimated in the forebrain tissue of all group of animals.

Treatment with CIN and CUR significantly ameliorated the frequency and severity of epileptic seizures in a dose-dependent manner. The cognitive dysfunctions as well as the oxidative stress indices (enzymatic as well as non-enzymatic) were ameliorated significantly and dose-dependently by CIN and CUR pre-treatment in the order CUR<CIN in all parameters.

Possible therapeutic application of CIN and CUR as antiepileptic and as antioxidant for the treatment of SE has a great potential and warrants further studies.

Introduction

Status epilepticus (SE) is a neurodegenerative pathophysiological condition causing neuronal injuries in brain [1] due to neurochemical imbalance in affected brain regions [2]. Ample evidence exists for the association of such chemical imbalances with excessive generation of free radicals suggesting vulnerability of the brain tissue to the oxidative stress [3,4]. Lithium (Li) Pilocarpine (PC) induced SE in rodent models have provided information regarding oxidative stress-related epileptic activity [5-7]. Furthermore, oxidative stress has also been related with cognitive impairment [7-9]. SE affects brain cell survival and function by targeting multiple adversities in the neuronal microenvironment such as inflammation, oxidative stress, mitochondrial alterations, calcium excitotoxicity, and bioenergetic challenges. The Li–Pc model of SE reproduces most clinical, temporal and neuropathological features of SE [2,10]. Although the anticonvulsant effect of several agents having antioxidant properties has been demonstrated in various studies [2,11,12], the unsatisfactory outcomes of available SE pharmacotherapy necessitate the search for alternative natural resources that can target the various underlying mechanisms of SE pathology and reduce disease occurrence and/or progression. Among the natural resources, many studies on curcumin (CUR) effects on SE has been undertaken [7,13,14] but no study as such has been conducted on studying the effect of cinnamon (CIN) on SE for having antiepileptic potential in experimentally induced SE.

Many recent studies have reported protective effects of Cur against oxidative damage and antioxidant and anticonvulsant properties exerting powerful oxygen free radical scavenging effects [5,6,8,9,15-17].

Although CIN is widely used as a spice and as a traditional medicine, it is shown to be effective in improving health due to its functional properties. These functional properties could act beneficially for the treatment of different

Citation: Ahmad M, Alshehri AS, Alharbi H. Ameliorating effects of cinnamon and curcumin on oxidative stress in lithium-pilocarpine induced status epilepticus model. Biomed Transl Sci. 2022; 2(2):1-6

Doi: 10.33425/2768-4911.1027

disease including diabetes mellitus, cardiovascular diseases, cancer, and neurological disorders. The medicinal beneficial uses of cinnamon and its isolated compounds, cinnamaldehyde including polyphenols, are attributed to their antioxidant activities and properties. Scientists believe that this compound is responsible for most of cinnamon's powerful effects on health and metabolism [18] anti-oxidant [19], an inhibitory effect on Tau aggregation related to AD [20], neuroprotective/ neurodegenerative purposes [20-22,], to the authors best knowledge, no studies have been undertaken to see effects of CIN on epilepsy or SE as anticonvulsant.

In the light of the above, the present study explores the neuroprotective effects of natural food products CUR and CIN on Li-Pc induced SE and understand indirectly the importance of screening natural food products that are beneficial in ameliorating convulsions, brain oxidative stress and cognitive dysfunctions in SE through SE experimental models.

Materials and methods

Experimental animals

Adult male Sprague Dawley rats (weighing 200–250 g, 2 months old) were used in the present study. The animals were taken care under controlled conditions at 22 ± 1°C, humidity at 50–60% with 12 hours light-dark diurnal cycle with free access to food and water except during experimental handlings. All animal handling procedures and study protocols were followed as according to the approved directions from the Research and Ethics Committee of King Saud University, Riyadh, Saudi Arabia for executing the experiments.

Induction of status epilepticus (SE) and treatment groups

Animals were randomly assigned into ten groups (n = 20 per group). Groups 1, 2, 3, 4 and 5 served as controls receiving saline, Li (3 mEq/ml/kg, i.p.), Pc (20 mg/ml/kg, s.c.), 50 % dimethyl sulfoxide (DMSO) and 0.5% methylcellulose (MC) respectively. SE was induced in groups 6–10 by administering an aqueous (saline) solution of Li (BDH Laboratory Supplies, Poole, England in a dose as in control), followed by (20 h later) Pc (Sigma Chemical Co., St. Louis, MO, USA, in the dose as used for control). Group 6 served as the experimental control of SE group and groups 7–10 served as the CUR (group 7 and 8) and CIN (group 9 and 10) test groups. CUR (Sigma, USA), was dissolved in 50% DMSO, and was administered at doses of 50 and 100 mg/kg body weight/ml orally; whereas CIN (Sigma-Aldrich, FG, approximately 95% pure) was dissolved in 0.5% MC, and was administered at doses of 25 and 50 mg/kg body weight/ml orally, for seven days prior to the administration of Li and Pc for the induction of SE as described above. All the animals treated with Li–Pc or Pc alone exhibited cholinergic symptoms including miosis, piloerection, diarrhea, and mild tremors followed by seizures; There was not any significant difference in seizure episodes and behavior between these two groups. Although Li has been shown to potentiate Pc-induced cholinergic activity, except that mortality in the Pc-alone group is higher as compared with that in the Li–Pc group [23].

After the Pc injections, the animals (n =20 per group) were observed for a sequence of convulsive behavioral alterations, including peripheral cholinergic signs (PCS), stereotyped movements (STM), clonic movements of forelimbs, head bobbing, tremors and seizures, which developed progressively within 1–2 h into SE [24]. All seizure activities were presented as latencies to develop seizure and SE. Mortality (if any) within 24 h, was also recorded.

Cognitive performance in Morris water maze

After three days of induction of SE, the animals (n= 10 to 12 per group) were subjected to cognitive behavioral studies over a period of 6 days according to the method of Morris water-maze test [25] which has been extensively used to assess cognitive functions in a variety of epilepsy models [26, 27] for visual-spatial memory performance. Animals were allowed to acclimatize to the testing room for 2 h before testing all tests were performed between 10:00 and 15:00 h of the lighted phase. The details of test are described elsewhere [2,7]. The testing procedure used during the four days of locating the hidden platform provides a measure of hippocampal-dependent spatial reference memory [28], whereas the probe trials of water maze test (measured on 5th day of the test for 120 s in which the platform was removed from the pool) measures the strength of spatial learning or memory recall, the closest parallel to episodic memory in humans [29].

Biochemical studies in the fore-brain tissue

Based on our pilot studies and literature survey [30-32], biochemical studies were undertaken 1 h after Li–Pc treatment. Immediately after killing the animals (n = 8 from each group) by decapitation, brains were dissected on ice. The forebrain (which includes hippocampus and striatum in the cerebral areas) were removed and frozen in liquid nitrogen and stored at -70°C for determination of some nonenzymatic and enzymatic oxidative stress indices.

Determination of Nonenzymatic OS (Oxidative Stress) Indices

Lipid Peroxides: Lipid peroxides (LP) were determined spectrophotometrically as thiobarbituric acid-reactive substances (TBARS) according to the method of Ohkawa et al. [33]. Tissue lipid peroxide levels were quantified using extinction coefficient of 1.56 × 105 m−1 cm−1 and expressed as nanomoles of TBARS formed per g tissue weight. The results are expressed as nmol/g wet weight.

Glutathione: Reduced glutathione (GSH) level was measured enzymatically in the brain tissues by a slightly modified method of Mangino et al. [34]. The slope of the change in absorbance was used to quantitate total GSH by comparing the slope of the samples with a standard curve prepared with pure glutathione (Sigma). The specific activity is expressed into umol/g tissue weight.

Determination of Enzymatic OS Indices

Glutathione-S-Transferase: Glutathione S-transferase (GST) was estimated by the method of Habig et al. [35] by using 1-chloro-2,4-dinitrochlorobenzene (CDNB) as substrate at 340 nm. The GST activity is expressed as U/g tissue weight.

Catalase: Catalase (CAT) activity was measured by the method of Aebi [36], by tracking the decomposition of hydrogen peroxide by measuring decrease in extinction of H2O2 at 240 nm. The activity of CAT is expressed as rate constant of first order reaction K per gram tissue weight.

Superoxide Dismutase: Superoxide dismutase (SOD) activity was estimated by the method of Misra and Fridovich [37]. Activity is expressed as the amount of enzyme that inhibits the oxidation of epinephrine by 50% which is equal to U per gram tissue weight.

 Doi: 10.33425/2768-4911.1027

Table 1. *Dose-dependent antiepileptic activity of cinnamon (CIN) and curcumin (CUR) against Li-Pc induced status epilepticus (SE) in adult rats.*

Behavioral parameters observed	Control	Cinnamon (mg/kg)		Curcumin (mg/kg)	
		25	50	50	100
Latency to seizures (min)	9.82 ± 1.40	13.62ns ± 1.58	36.53a ± 1.52	12.46ns ± 1.17	38.46a ± 1.33
Seizures (%)	100	85	10.5a	83.2	22.8a
Latency to SE (min)	23.86 ± 1.54	34.61a ± 0.86	57.5a ± 1.82	32.52a ± 1.07	58.9a ± 1.63
SE (%)	100	50.5a	21.3a	51.4a	18.5a
Mortality (%) within 24 hours	10	0	0	0	0

Animals were observed for more than 1 h after Li-Pc (lithium-pilocarpine) injections for inducing SE in all groups, and all animals were observed for more than 24 hours for mortality.
ns Statistically nonsignificant.
a $P < 0.001$ as compared to control (0mg/kg) by ANOVA followed by Student-Newman-Keuls Multiple Comparisons Test.

Results

Behavioral features of Li-Pc induced SE

After injection of Pc, all animals started developing a gradual and significant change in behavior within 5 min. Changes in behavioral features included PCS (miosis, piloerection, diarrhea, mild tremors, scratching, and salivation) and STM (sniffing, paw licking, and rearing). Seizures in 100% animals (mean latency to develop seizures was 9.62 ± 1.2 min) were developed following the behavioral changes (Table 1). The convulsions in the animals consisted of head bobbing with intermittent clonus of forelimbs and hind limbs, hyperextension of tails, loss of posture, falling back, and myoclonic jerks building up to SE in 100% of tested animals. The mean latency to onset of SE was 23.86 ± 1.54 min (Table 1), and on average, the SE lasted for more than one hour. SE is a condition where these recurrent generalized seizures last for more than 30 minutes in the animals. Mortality of 10% were observed within 24 h following Pc injections (Table 1).

Effect of CUR and CIN pretreatment on Li-Pc induced SE

Pretreatment of animals with CUR and CIN increased the latencies to seizure and SE and decreased the percentages of seizures and SE significantly in a dose-dependent manner (Table 1). Furthermore, it also reduced the intensity and frequency of seizure, PCS, and STM episodes (not shown in Table 1). For comparative observations on the antiseizure effect of CIN and CUR, all seizure activities were presented as latency to develop seizure and SE. The intensity and frequency of seizures of treated animals were compared with the respective controls for statistical evaluations. The two natural food compounds were effective in the order CUR > CIN (Table 1). No mortality was observed in the rats pretreated with both natural food products, as compared to 10% mortality in the Li-Pc treated (SE) group (Table 1). The control groups that received saline, Li, DMSO and MC alone did not show any signs of seizure or SE.

Morris Water-Maze Test

Animals treated with Li-Pc only (SE group) exhibited longer escape latencies to reach the platform as compared to the control group ($P < 0.01$; Figure 1). However, all groups developed a gradual improvement in such performance over the 4 days of testing (training) period. The number of successful

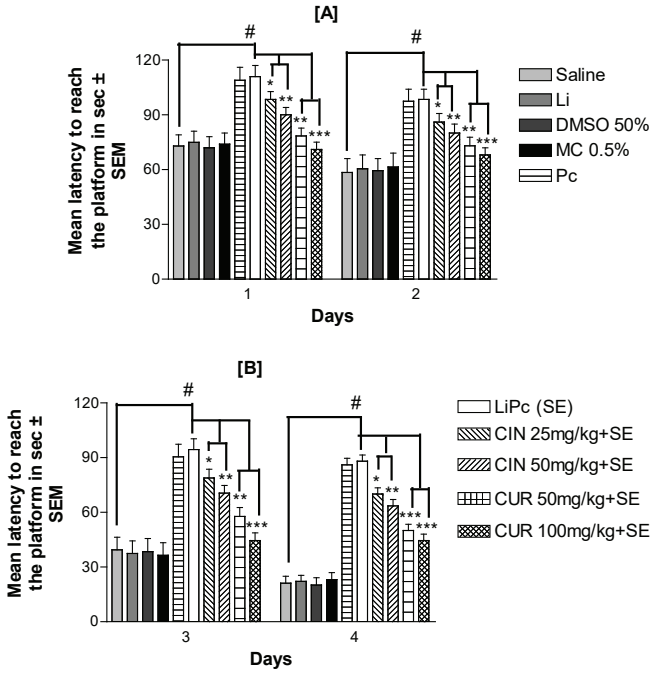

Table 1. *Performance in water-maze of animals that experienced SE along with their controls as well as the SE groups that were pretreated with CIN and CUR. Mean latency to reach the hidden platform in seconds ± SEM (Y-axis) on each testing day (X-axis) shows that animals subjected to SE were slower in finding the platform (cognitive effect) than the controls on all four testing days. Treatment with CIN and CUR in varying doses was effective in improving the cognitive function in the order CUR < CIN and dose-dependently.*

Li = Lithium chloride; DMSO = Dimethyl sulphoxide; MC = Methylcellulose; Pilo = pilocarpine; SE = status epilepticus; CIN = Cinnamon; CUR = Curcumin; doses of CIN and CUR in mg/kg body weight.
*# represents significance as compared to control ($P < 0.001$), whereas *, ** and * * * show $P < 0.01$, $P < 0.05$, and $P < 0.001$, respectively, as compared to SE group by one-way ANOVA*

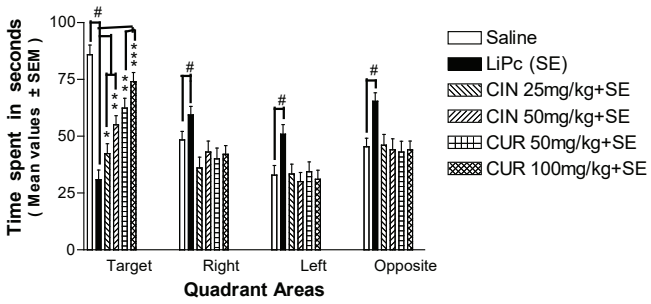

Figure 2. *Performance in water-maze of animals that experienced SE along with their controls (controls of DMSO, and MC not shown here) as well as the SE groups that were pretreated with CIN and CUR. The probe test shows that the SE-induced animals spent less time in the target quadrant than the control group. Pre-treatment of SE-induced animals with CIN and CUR had an attenuating effect in the order CUR < CIN and the animals spent more time in the target quadrant. Abbreviations and statistical significance are the same as in Figure 1.*

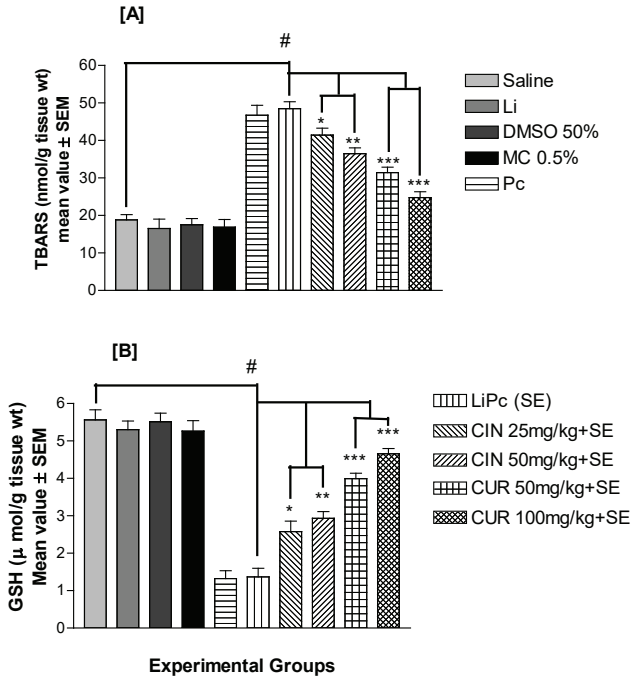

Figure 3: *Comparative effect of CIN and CUR on the nonenzymatic oxidative stress indices like (A) lipid peroxidation content (TBARS) and (B) total glutathione level (GSH), in the forebrain tissue of rats after Li-Pc induced SE. The comparative effects are in the order CUR < CIN and dose-dependent. TBARS = Thiobarbituric acid; other abbreviations and statistical significance are the same as in Figure 1.*

animals to reach the platform was significantly higher in the CUR and CIN pretreated groups as compared to Li-Pc (SE) group on all the four testing days and the effectiveness was in the order CUR > CIN ($P < 0.001$; Figure 1). Attempts were made to selectively include rats for behavioral and biochemical studies in proportion to the observed symptoms in each group. Hence, we included animals that had SE and the animals that had not developed SE were not included for the tests. In this way, the animals in each study were derived from SE group proportionally on a symptom basis.

The probe trial studies showed that CUR and CIN pretreated animals spent more time in the target (platform) quadrant as compared to the Li–Pc only (SE) group and the effectiveness was in the order CUR > CIN ($p < 0.001$; Figure 2).

Biochemical studies

Nonenzymatic OS Indices in the fore-brain:

TBARS: The lipid peroxidation level (TBARS) in the forebrain was markedly ($P < 0.001$) increased after 1h of Li-PC (SE) treatment as compared to the control group (Figure 3A). Pretreatment with natural compounds significantly ($P < 0.001$) and dose-dependently attenuated Li-Pc induced increase in TBARS in the order CUR > CIN (Figure 3a) as compared to Li-Pc (SE) group.

GSH: A highly significant ($P < 0.001$) depletion of GSH was observed in the fore-brain tissue of Li-Pc (SE) group (Figure 3B). Pretreatment with natural compounds significantly and dose-dependently attenuated this depletion of GSH in the order CUR > CIN (Figure 3b) as compared to Li-Pc (SE) group.

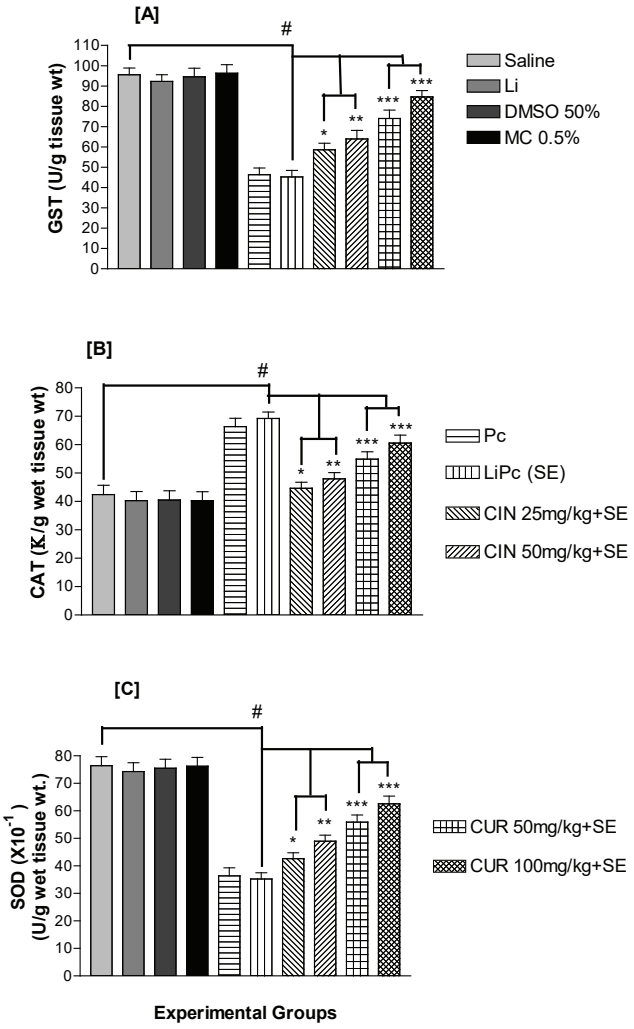

Figure 4: *Comparative effect of CIN and CUR on the enzymatic oxidative stress indices like (A) glutathione S-transferase (GST), (B) catalase (CAT), and (C) superoxide dismutase (SOD), in the forebrain tissue of rats after Li-Pc induced SE. The comparative effects are in the order CUR < CIN and dose-dependent. Abbreviations and statistical significance are the same as in Figure 1.*

Doi: 10.33425/2768-4911.1027

Enzymatic OS Indices in the for-brain:

GST: A highly significant ($P < 0.001$) reduction of GST was also observed in Li-Pc (SE) group (Figure 4A). Pretreatment with the natural products significantly and dose-dependently attenuated this depletion of GST in the order CUR > CIN (Figure 4A) as compared to Li-Pc (SE) group.

CAT in Hippocampus and Striatum: The CAT level in the forebrain was markedly ($P < 0.001$) increased after 1h of Li-PC (SE) treatment as compared to the control group (Figure 4B). Pretreatment with natural compounds significantly ($P < 0.001$) and dose-dependently attenuated Li-Pc induced increase in CAT in the order CUR > CIN (Figure 4B) as compared to Li-Pc (SE) group.

SOD: The SOD level was significantly ($P < 0.001$) decreased after 1 h of Li-PC (SE) treatment as compared to the control group (Figure 4C). Pretreatment with natural food compounds significantly ($P < 0.001$) and dose-dependently attenuated Li-Pc induced decrease in SOD in the order CUR > CIN (Figure 4C) as compared to Li-Pc (SE) group.

Discussion

The present experimental findings demonstrate that Pc administration in the pretreated rats with Li, causes cholinergic symptoms followed by seizures. Within 20 to 30 minutes after Pc administration, SE developed in the rats exhibiting continuous head bobbing, intermittent forelimb and hind limb clonus, hyperextension of tail and hind limb along with loss of posture resulting into falls (fall back from the rearing postures). Impaired visual-spatial memory and cognitive deficit were observed in the SE-induced animals when tested in Morris water-maze test [38]. SE-induced rats took longer time to reach escape platform or completely failed to reach the platform and spent less time in target quadrant as reported earlier [2,39]. The specific cause of cognitive dysfunction following SE is far from clear. However, reports suggest that neurochemical imbalance and alterations in neuronal structure in the forebrain region following SE are possibly responsible for neurobehavioral changes [2,25,27,31,40]. The biochemical results in the present study further indicates a significant disruption in the levels of oxidative indices (enzymatic as well as non-enzymatic) in the forebrain of the rats treated with Li-Pc suggesting for a preliminary and significant level of oxidative stress. It has been reported that over activation of excitatory amino acid receptors is an important pathogenic factor that has been implicated in the mechanisms of excitotoxicity-induced neurodegeneration leading to seizures and increased oxidative stress [41] and furthermore, neuronal loss and mossy fiber sprouting in the forebrain following SE has been attributed to the excessive production of reactive oxygen species [2,42].

Use of antioxidants could be a potential approach in arresting the seizure genesis caused by excitotoxic agents [43]. Potent antioxidant activities have been reported for CUR [5,6,8,9,17] as well as CIN [19]. Although CUR has been reported for having neuroprotective in the SE-induced models, to the best of author's knowledge, no precedent has been reported for CIN. Only during the past decade, scientists devoted to explore the neuroprotective/neurodegenerative aspects of cinnamon and it was shown that multidisciplinary mechanisms are involved in this regard [20-22]. In the SE group of the present study, a significant disruption in levels of oxidative stress indices in the forebrain was observed. Pretreatment with CUR and CIN significantly and dose-dependently attenuated Li-Pc induced OS related indices (enzymatic as well as non-enzymatic) in the forebrain region as compared to SE group. Earlier studies have also reported that Li-Pc disrupts the OS related indices in brain regions [2,3,44]. Thus, it is likely that similar pathomechanism might be contributing at least in part to the pathophysiology of the seizure activity herein. The present study clearly suggests at a preliminary level that both natural food products CUR and CIN have a promising anticonvulsant and antioxidant activity against SE in rats in the order CUR>CIN. However, further studies on these lines may be encouraging.

Conclusion

Possible therapeutic application of CIN and CUR as an antiepileptic and as an antioxidant for the treatment of SE has a great potential and warrants further studies.

Acknowledgments

The authors are thankful to the Deanship of Scientific Research, College of Nursing, Research Centre at King Saud University for supporting this research.

Conflicts of interest

The authors declare that they have no known conflict of interest and no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors contribution

Study conception and design: MA; ASL; HA

Data collection: MA

Data analysis and interpretation: MA; ASL; HA

Drafting of the article: MA

Critical revision of the article: ASL; HA

References

1. Chen S, Fujita S, Koshikawa N, Kobayashi M. Pilocarpine-induced status epilepticus causes acute interneuron loss and hyper-excitatory propagation in rat insular cortex. Neuroscience. 2010;166(1):341-353.
2. Tariq M, Ahmad M, Moutaery KA, Deeb SA. Pentoxifylline ameliorates lithium-pilocarpine induced status epilepticus in young rats. Epilepsy Behav. 2008;12(3):354-365.
3. Freitas RM, Vasconcelos SM, Souza FC, Viana GS, Fonteles MM. Oxidative stress in the hippocampus after pilocarpine-induced status epilepticus in Wistar rats. FEBS J. 2005;272(6):1307-1312.
4. Freitas RM. Investigation of oxidative stress involvement in hippocampus in epilepsy model induced by pilocarpine. Neurosci Lett. 2009;462(3):225-229.
5. Ezz HS, Khadrawy YA, Noor NA. The neuroprotective effect of curcumin and Nigella sativa oil against oxidative stress in the pilocarpine model of epilepsy: a comparison with valproate. Neurochem Res. 2011;36(11):2195-2204.
6. DU P, Tang HY, Li X, et al. Anticonvulsive and antioxidant effects of curcumin on pilocarpine-induced seizures in rats. Chin Med J (Engl). 2012;125(11):1975-1979.
7. Ahmad M. Protective effects of curcumin against lithium-pilocarpine induced status epilepticus, cognitive dysfunction and oxidative stress in young rats. Saudi J Biol Sci. 2013;20(2):155-162.
8. Reeta KH, Mehla J, Pahuja M, Gupta YK. Pharmacokinetic and pharmacodynamic interactions of valproate, phenytoin, phenobarbitone and carbamazepine with curcumin in experimental models of epilepsy in rats. Pharmacol Biochem Behav. 2011;99(3):399-407.

9. Ataie A, Sabetkasaei M, Haghparast A, Moghaddam AH, Kazeminejad B. Neuroprotective effects of the polyphenolic antioxidant agent, Curcumin, against homocysteine-induced cognitive impairment and oxidative stress in the rat. Pharmacol Biochem Behav. 2010;96(4):378-385.
10. Dubé C, Boyet S, Marescaux C, Nehlig A. Relationship between neuronal loss and interictal glucose metabolism during the chronic phase of the lithium-pilocarpine model of epilepsy in the immature and adult rat. Exp Neurol. 2001;167(2):227-241.
11. Gupta YK, Briyal S. Protective effect of vineatrol against kainic acid induced seizures, oxidative stress and on the expression of heat shock proteins in rats. Eur Neuropsychopharmacol. 2006;16(2):85-91.
12. de Freitas RL, Santos IM, de Souza GF, Tomé Ada R, Saldanha GB, de Freitas RM. Oxidative stress in rat hippocampus caused by pilocarpine-induced seizures is reversed by buspirone. Brain Res Bull. 2010;81(4-5):505-509.
13. Choudhary KM, Mishra A, Poroikov VV, Goel RK. Ameliorative effect of Curcumin on seizure severity, depression like behavior, learning and memory deficit in post-pentylenetetrazole-kindled mice. Eur J Pharmacol. 2013;704(1-3):33-40.
14. Adami R, Bottai D. Curcumin and neurological diseases. Nutr Neurosci. 2022;25(3):441-461.
15. Kuhad A, Pilkhwal S, Sharma S, Tirkey N, Chopra K. Effect of curcumin on inflammation and oxidative stress in cisplatin-induced experimental nephrotoxicity. J Agric Food Chem. 2007;55(25):10150-10155.
16. Kalpana C, Sudheer AR, Rajasekharan KN, Menon VP. Comparative effects of curcumin and its synthetic analogue on tissue lipid peroxidation and antioxidant status during nicotine-induced toxicity. Singapore Med J. 2007;48(2):124-130.
17. Noor NA, Aboul Ezz HS, Faraag AR, Khadrawy YA. Evaluation of the antiepileptic effect of curcumin and Nigella sativa oil in the pilocarpine model of epilepsy in comparison with valproate. Epilepsy Behav. 2012;24(2):199-206.
18. Tavares daSilva ML, Bernardo MAS, Singh J, deMesquita MF. Beneficial Uses of Cinnamon in Health and Diseases: An Interdisciplinary Approach. In : The Role of Functional Food Security in Global Health. 2019; Academic Press, pp. 565-576.
19. Dugoua JJ, Seely D, Perri D, et al. From type 2 diabetes to antioxidant activity: a systematic review of the safety and efficacy of common and cassia cinnamon bark. Can J Physiol Pharmacol. 2007;85(9):837-847.
20. Peterson DW, George RC, Scaramozzino F, et al. Cinnamon extract inhibits tau aggregation associated with Alzheimer's disease in vitro. J Alzheimers Dis. 2009;17(3):585-597.
21. Anderson RA, Qin B, Canini F, Poulet L, Roussel AM. Cinnamon counteracts the negative effects of a high fat/high fructose diet on behavior, brain insulin signaling and Alzheimer-associated changes. PLoS One. 2013;8(12):e83243.
22. Frydman-Marom A, Levin A, Farfara D, et al. Orally administrated cinnamon extract reduces β-amyloid oligomerization and corrects cognitive impairment in Alzheimer's disease animal models. PLoS One. 2011;6(1):e16564.
23. Jope RS, Morrisett RA, Snead OC. Characterization of lithium potentiation of pilocarpine-induced status epilepticus in rats. Exp Neurol. 1986;91(3):471-480.
24. Persinger MA, Bureau YR, Kostakos M, Peredery O, Falter H. Behaviors of rats with insidious, multifocal brain damage induced by seizures following single peripheral injections of lithium and pilocarpine. Physiol Behav. 1993;53(5):849-866.
25. Morris RG, Moser EI, Riedel G, et al. Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. Philos Trans R Soc Lond B Biol Sci. 2003;358(1432):773-786.
26. Faverjon S, Silveira DC, Fu DD, et al. Beneficial effects of enriched environment following status epilepticus in immature rats. Neurology. 2002;59(9):1356-1364.
27. Rutten A, van Albada M, Silveira DC, et al. Memory impairment following status epilepticus in immature rats: time-course and environmental effects. Eur J Neurosci. 2002;16(3):501-513.
28. Spiers HJ, Burgess N, Hartley T, Vargha-Khadem F, O'Keefe J. Bilateral hippocampal pathology impairs topographical and episodic memory but not visual pattern matching. Hippocampus. 2001;11(6):715-725.
29. Jeltsch H, Bertrand F, Lazarus C, Cassel JC. Cognitive performances and locomotor activity following dentate granule cell damage in rats: role of lesion extent and type of memory tested. Neurobiol Learn Mem. 2001;76(1):81-105.
30. Freitas RM, Vasconcelos SM, Souza FC, Viana GS, Fonteles MM. Monoamine levels after pilocarpine-induced status epilepticus in hippocampus and frontal cortex of Wistar rats. Neurosci Lett. 2004;370(2-3):196-200.
31. Nascimento VS, Oliveira AA, Freitas RM, et al. Pilocarpine-induced status epilepticus: monoamine level, muscarinic and dopaminergic receptors alterations in striatum of young rats. Neurosci Lett. 2005;383(1-2):165-170.
32. Freitas RM, Oliveira Ade A, Vasconcelos SM, Sousa FC, Viana GS, Fonteles MM. Expression of muscarinic and dopaminergic receptors and monoamine levels frontal cortex of epileptic rats. Pharmacol Biochem Behav. 2006;83(2):302-306.
33. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351-358.
34. Mangino MJ, Murphy MK, Grabau GG, Anderson CB. Protective effects of glycine during hypothermic renal ischemia-reperfusion injury. Am J Physiol. 1991;261(5 Pt 2):F841-F848.
35. Habig WH, Pabst MJ, Jakoby WB. Glutathione S-transferases. The first enzymatic step in mercapturic acid formation. J Biol Chem. 1974;249(22):7130-7139.
36. Aebi H. Catalase, in Methods of Enzymatic Analysis, H. U. Bergmeyer, Ed., vol. 2, 1972; Academic Press, New York, NY, USA.
37. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem. 1972;247(10):3170-3175..
38. Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods. 1984;11(1):47-60.
39. Wu CL, Huang LT, Liou CW, et al. Lithium-pilocarpine-induced status epilepticus in immature rats result in long-term deficits in spatial learning and hippocampal cell loss. Neurosci Lett. 2001;312(2):113-117.
40. Kubová H, Mares P, Suchomelová L, Brozek G, Druga R, Pitkänen A. Status epilepticus in immature rats leads to behavioural and cognitive impairment and epileptogenesis. Eur J Neurosci. 2004;19(12):3255-3265.
41. Wang Q, Yu S, Simonyi A, Rottinghaus G, Sun GY, Sun AY. Resveratrol protects against neurotoxicity induced by kainic acid. Neurochem Res. 2004;29(11):2105-2112.
42. Ueda Y, Yokoyama H, Niwa R, Konaka R, Ohya-Nishiguchi H, Kamada H. Generation of lipid radicals in the hippocampal extracellular space during kainic acid-induced seizures in rats. Epilepsy Res. 1997;26(2):329-333.
43. Schulz JB, Henshaw DR, Siwek D, et al. Involvement of free radicals in excitotoxicity in vivo. J Neurochem. 1995;64(5):2239-2247.
44. Xavier SM, Barbosa CO, Barros DO, Silva RF, Oliveira AA, Freitas RM. Vitamin C antioxidant effects in hippocampus of adult Wistar rats after seizures and status epilepticus induced by pilocarpine. Neurosci Lett. 2007;420(1):76-79.