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Original Article

# Effects of *Curcuma longa* on Status Epilepticus Induced by Pilocarpine in Rats

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**ABSTRACT**

**Background and Aim:** The purpose of the present study is to provide a basis for the use of *Curcuma longa* extract as a therapeutic agent for status epilepticus. **Methods:** The effect of *Curcuma longa* extract on the status epilepticus in rat model was investigated. The rat's model of SE induced by pilocarpine and the effect of *Curcuma longa* extract was evaluated through the measurement of seizure duration, brain oedema and hippocampal oxidative stress in this model. **Results:** In rat pre-treated with *Curcuma longa* extract (400mg/kg) seizure duration, brain water content and the level of MDA significantly were decreased and activities of SOD and CAT significantly were increased in the hippocampal. **Conclusion:** Our data provide that *Curcuma longa* may be useful for management and treatment of SE.

**Key words:** *Curcuma longa*, Status epilepticus, Oxidative stress, Antioxidants, Rats.

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## INTRODUCTION

Status epilepticus (SE) is a neurologic emergency that requires prompt intervention to prevent long-term morbidity and mortality. Both human clinical studies and rodent models of SE indicate that prolonged seizure activity causes neuronal death via several pathways, and rapid treatment of SE reduces this injury and subsequent morbidity.[1] Status epilepticus is defined as epileptic activity that continues for longer than 5-30 min, either as a single seizure or as recurrent seizures without interictal return of consciousness. The seizure activity is usually classified as partial or generalized. Most episodes of status develop without a prior history of epilepsy. However, the mechanisms of epilepsy are still unknown. This fact is of major clinical relevance as the emergency management of all patients with status epilepticus must include a search for underlying causes. Convulsive seizure activity causes marked systemic disturbances and neuronal injury proportional to the duration of seizure activity. It is a severe clinical manifestation of epilepsy that causes severe brain injuries.[2] SE is also the most common pediatric neurologic emergency. SE is a condition that commonly presents to pediatric emergency care providers across the country, with an incidence of between 17 and 23 per 1,00,000.

The incidence is higher in younger children, reported to be as high as 51 per 1,00,000. There is a mounting body of scientific evidence suggesting that prolonged seizures are associated with an increased risk of neuronal damage and possible long-term sequelae. Increased recognition of this condition and subsequent aggressive treatment may impact long-term morbidity and improve outcomes.[3] *Curcuma longa* is a rhizomatous perennial herb that belongs to the family Zingiberaceae, native to South Asia and is commonly known as turmeric. Also, in our country, it is used as herbal remedy due to the prevalent belief that the plant has medical properties. In folk medicine, the rhizome juice from *Curcuma longa* is used in the treatment of many diseases such as anthelmintic, asthma, gonorrhea and urinary, and recently research has shown that *Curcuma longa* possesses antioxidant,[4] anti-tumor,[5] antimicrobial,[6] anti-inflammatory,[7] wound healing,[8] and gastroprotective activities,[9] but there has been no research to use this extract as traditional medicine for the treatment of SE. In this study, we assessed the neuroprotective effect of the extract of *Curcuma longa* rhizomes against pilocarpine-induced SE in immature rats.

## MATERIALS AND METHODS

### Animals

Immature Wistar rats (3 weeks old, 35-40g) were provided by Laboratory Animal Centre of the Pyongyang University of Medical Sciences and adapted in a lab environment before experiments for a week. 45 rats are randomly chosen and divided into three groups (Normal, Model and Experiment). During the experiment, food and water were available to rats at any time. The temperature was maintained at 20±2°C and the humidity was 55%. The study was approved by the Ethics Committee for Animal Experimentation, Faculty of Basic Medicine, Pyongyang University of Medical Sciences.



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### Preparation of *Curcuma longa* Rhizomes Extract

*Curcuma longa* rhizomes were obtained from Mannyon Pharmaceutical Company, DPR Korea and identified by comparison with the voucher specimen deposited at National drug certification institute of Pyongyang, DPR Korea. The rhizomes were cleaned, dried, ground, weighed and homogenized in 92% ethanol at a ratio of 1:10 of sample to ethanol and left to soak for 3 days at 25°C with occasional shaking and stirring. The mixture was then filtered and the resulting liquid was concentrated under reduced pressure at 45°C in rotary evaporator to yield a dark gummy-yellow extract (7%, w/w). The concentrated extract was then kept in the incubator at 45°C for 3 days to evaporate the ethanol residue yielding the crude rhizome extract. Extracts were then dissolved in 10% Tween-20 before being orally administrated to animals in concentrations of 400 mg/kg body weight (5ml/kg body weight).

### SE Model

Status epilepticus (SE) were induced by intraperitoneal injection of 50mg/kg pilocarpine in rats and terminated by diazepam after 40 min. The onset of SE was determined when an animal had a stage 4 or 5 seizure that was followed by continuous epileptic motor activity without showing any reaction to sensory stimuli such as gently touching against the whiskers.[10]

### Drug Administration

After 1 week of acclimatization to the cage, rats of experimental group were orally administrated with *Curcuma longa* rhizomes extract at daily doses 400mg/kg for 7 days. Next day, both rats of experimental and model group received pilocarpine hydrochloride intraperitoneally.

### Seizure Duration

The seizure duration was determined by the period time from the first seizure point to the end after pilocarpine injection.

### Preparation of Brain Tissue Sample for Biochemical Assay

Based on literature survey[11] the biochemical assay was undertaken 1h after pilocarpine injection and immediately after killing the rest of the animals by decapitation, brains of 7 rats were dissected on ice, and hippocampus was removed and frozen in liquid nitrogen and stored at −70°C for determination of some non-enzymatic and enzymatic oxidative stress indices.

### Brain Water Content

The traditional dry/wet weight method was applied to the brain of rats. As mentioned above, after decapitation the wet weight of the brain of 8 rats was measured, these were then placed in an oven (100°C) for 24 hr and then reweighed (dry weight). The percentage of brain water content was calculated as [(wet weight-dry weight)/wet weight of brain tissue×100%].[12]

### Malondialdehyde

Lipid Peroxides of hippocampus was expressed as malondialdehyde (MDA) level. MDA assay was determined spectrophotometrically as thiobarbituric acid-reactive substances (TBARS) according to the method of Ohkawa *et al.*[13] Tissue lipid peroxide levels were expressed as nanomoles of TBARS formed per g tissue weight. The results are expressed as nmol/g wet weight.

### Catalase

Catalase (CAT) activity was measured by the method of Aebi[14] by tracking the decomposition of hydrogen peroxide by measuring decrease in extinction of $H_2O_2$ 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.[15] 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.

### Statistical Analysis of Data

Results were expressed as the mean and SEM. Data were analyzed by one-way analysis of variance (ANOVA) using SPSS 16.0 and the differences between the mean assessed using Dunnet's multiple range test. P value of < 0.01 was taken as the level of statistical significance.

## RESULTS

### Seizure Duration and the Brain Water Content

As shown in Figure 1, in experimental group, the seizure duration was significantly decreased compared with model group (P<0.01). The results of Figure 2 showed that in experimental group, the brain water content was significantly decreased compared with model group (P<0.01).

### Level of MDA, activities of SOD and CAT

Table 1 showed that in experimental group, the level of MDA was significantly decreased and the activities of SOD and CAT were significantly increased compared with model group (P<0.01).

## DISCUSSION

Status epilepticus is a common neurologic emergency in children. Management requires simultaneous resuscitation and medical stabilization, diagnosis of the underlying cause, and definitive rapid treatment of both clinical and electrographic seizures. In some studies, necropsy materials on brain of decedent by SE were reported and common severe area was hippocampus and it has oedema and cellular damage.[12,16] In traditional medicine of our country, the aqueous extract of Curcuma longa rhizomes was used in the treatment of liver diseases such as chronic hepatitis, cholestasis, cirrhosis, etc. On the other hand, so far, the traditional medicines believe that the good control of liver function can lead to treat seizure. Therefor we were carried out to investigate the effect of Curcuma longa rhizomes extract on SE in rats' model.

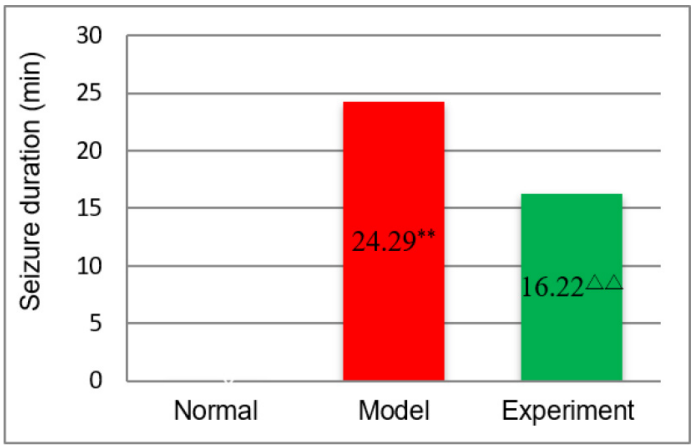


**Figure 1:** The effects of extract on the seizure duration.
Each value represents the mean ± SEM of 15 rats per group.
** P<0.01 as compared with normal group. △△P<0.01 as compared with model group.

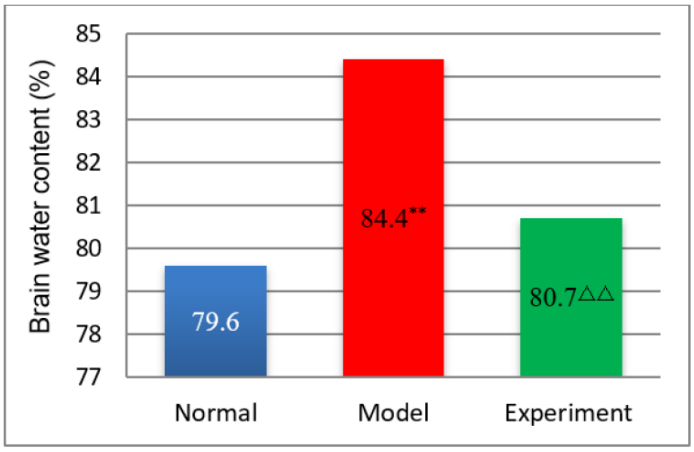


**Figure 2:** The effects of Extract on the brain water content. Each value represents the mean ± SEM of 7 rats per group. **P<0.01 as compared with normal group. △△P<0.01 as compared with model group.

**Table 1: The effects of extract on oxidative stress in hippocampus.**

| | MDA (nmol/g wet tissue) | SOD ($\times10^{-1}$) (U/g wet tissue wt) | CAT (k/g wet tissue wt) |
|---|---|---|---|
| Normal | 4.7 ± 0.3 | 59.8 ± 4.3 | 16.1 ± 0.5 |
| Model | 13.1 ± 0.9** | 22.2 ± 2.4** | 7.6 ± 0.7** |
| Experiment | 9.1 ± 0.2△△ | 44.9 ± 3.1△△ | 14.8 ± 0.7△△ |

Each value represents the mean ± SEM of 8 rats per group.

**P<0.01 as compared with normal group. △△ P<0.01 as compared with model group

According to our results, in the experimental group pre-treated with *Curcuma longa* rhizomes extract of 400mg/kg for 7 days before pilocarpine injection, the seizure duration and the brain water content were significantly decreased after pilocarpine injection.

Unless the treatment of SE is started in 20-30 min, the damage and necrosis of nerve cell is promoted. These damages of brain can be induced by several pathways and among them we focus on oxidative stress in brain tissue. So, we used *Curcuma longa* rhizomes as well-known anti-oxidant in our country in present study. As a result, in experimental group, the level of MDA was significantly decreased (P<0.01), and the activities of SOD and CAT were significantly increased (P<0.01) with compared model group in the hippocampus. The results showed that the extract of *Curcuma longa* rhizomes has also the anti-oxidant effects in SE rats. We suggest that the extract of *Curcuma longa* rhizomes has the positive preventive and therapeutic effects on status epilepticus induced by pilocarpine in rats.

## CONCLUSION

In conclusion, our results suggest that *Curcuma longa* rhizomes used in the present study have potential for being antiepileptic as well as antioxidant. However, further studies can confirm these effects and also investigate the potential components of *Curcuma longa* rhizomes that play a definite role in pathophysiology of SE. It is however assumed that *Curcuma longa* rhizomes might provide a beneficial effect in the treatment of SE.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**SE:** Status epilepticus; **MDA:** Malondialdehyde; **CAT:** Catalase; **SOD:** Superoxide Dismutase.

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