Original Research Article

Protective effect of Picrorhiza kurroa on Alzheimer’s disease induced by aluminium chloride in rats

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INTRODUCTION

Alzheimer’s disease (AD) is a neurodegenerative disorder that leads to memory loss and nerve cell death throughout the brain. This disorder is characterized by worsening in cognition and memory, progressive impairment in the ability to carry out activities of daily living, as well as a number of neuropsychiatric and behavioural symptoms. Most often, Alzheimer’s disease is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer’s can occur much earlier. Alzheimer’s is predicted to affect 1 in 85 people globally by 2050. At present, the etiology of Alzheimer’s disease is still not clearly known. Multiple pathogenic factors, including aggregated beta-amyloid (Aβ), neurofibrillary tangles (NFTS), cholinergic dysfunction and oxidative stress are involved in AD. The formation of hyper phosphorylated Tau (microtubule associated protein) in the neurons is also linked with AD. The selective deficiency of acetylcholine in AD, has given rise to the cholinergic hypothesis which propose that a deficiency of acetylcholine is critical in the genesis of the symptoms of AD. Early disease shows a loss of short-term memory, inability to learn new information, mood swings, difficulty in finding words, forgetting names, frustration, hostility and irritability are common emotional features exhibited by patients with AD. When the condition progresses, additional cognitive abilities are impaired, as

ABSTRACT

Background: Alzheimer’s disease is a progressive neurodegenerative disorder characterized by cognitive deterioration together with declining activities of daily living and behavioural changes. The present work is aimed to investigate the effect of methanolic extract of rhizomes of Picrorhiza kurroa against aluminium chloride induced Alzheimer’s disease.

Methods: Wistar rats were selected in this study and were divided into 5 groups (6 each). Group I served as normal control. Group II received aluminium chloride (300mg/kg, P.O.). Group III and IV received ethanolic extract of Picrorhiza kurroa (200mg/kg, 400mg/kg, P.O. respectively) and inducing agent (AlCl₃ 300mg/kg, P.O.). Group V received rivastigmine (0.3mg/kg, I.P.) and inducing agent (AlCl₃ 300mg/kg, P.O.). The rats were given respective treatment for 20 days and behavioural parameters were determined on 20th day. After 20th day rats were sacrificed and anti-oxidant parameters, brain acetylcholinesterase content were determined.

Results: Oral administration of ethanolic extract of Picrorhiza kurroa at doses 200, 400mg/kg body weight showed improve in behavioural parameters when compared to AlCl₃ induced rats, showed increase in superoxide dismutase, catalase, reduced glutathione and decreased levels of malondialdehyde and showed decrease in brain acetylcholinesterase content when compared to AlCl₃ induced rats.

Conclusions: The study clearly demonstrated the beneficial effects of Picrorhiza kurroa by improving biochemical and behavioural parameters.

Keywords: Alzheimer’s disease, AlCl₃, Antioxidant parameters, Behavioural parameters, Picrorhiza kurroa
the ability to calculate, and use common objects and tools.9 The current symptomatic treatment of patients with mild to moderate AD is based on drugs such as donepezil, rivastigmine, galantamine and memantine which are associated with side effects.10 These drugs may help keep symptoms from getting worse for a limited time. To cure the disease development and progression medicinal plants and their ingredients are widely used since ancient time.11 So drugs for fundamental cure of Alzheimer’s disease are not clinically available and greatly needed.12 Picrorhiza kurroa is also known as kutki. It belongs to the family Scrophulariaceae.13 Picrosides I and II are the active agents responsible for the medicinal effects of Kutki.14 It is widely used as a hepatoprotective. Picrorhiza kurroa has many medicinal benefits such as immunomodulatory, anti-allergic, antianaphylactic and anti-neoplastic activities.15,16 The flavonoid apocynin is one of the active metabolites of P. kurroa and has been reported to attenuate Parkinson’s, hypoxia and ischemia-reperfusion by its inhibitory action on NADH oxidase; expressed during oxidative stress.17,18 The primary aim of this investigation was to evaluate the anti-Alzheimer’s activity of ethanolic extract of rhizomes of Picrorhiza kurroa.

METHODS

Plant material

Powder of rhizomes of Picrorhiza kurroa was obtained from Nepal region as a gift sample. It was identified and authenticated by Dr. J. Raveendra Reddy, Pharmacognosist, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), Anantapuramu, Andhra Pradesh, India.

Extraction procedure

The powder (500g) was soaked in 1 litre of 95% ethanol for 7 days with intermittent shaking. On 8th day, the whole material was filtered through muslin cloth. The obtain filtrate was evaporated under water bath to obtain solid blackish-brown mass. The residue was stored at 4°C until use.

Animals

Male albino wistar rats weighing 200-250g were used for the present study. The animals were obtained from Raghavendra enterprises, Bangalore, India. The animals were maintained under controlled conditions of temperature (22±2°C), humidity (50±5%) and 12 h light-dark cycles. All the animals were acclimatized for seven days before the study. They had free access to standard pellets as basal diet and water ad libitum. The study was approved by the institutional animal ethical committee (Approval no. 878/ac/05/CPCSEA/005/2016).

Experimental design

Animals were randomly divided into 5 groups of 6 animals each and they received the following treatment as follows. Group I served as normal control. Group II received aluminum chloride (300mg/kg, P.O.). Group III and IV received ethanolic extract of Picrorhiza kurroa (200mg/kg, 400mg/kg, P.O. respectively) and inducing agent (AlCl3 300mg/kg, P.O.). Group V received Rivastigmine (0.3mg/kg, I.P.) and inducing agent (AlCl3 300mg/kg, P.O.). The rats were given respective treatment for 20 days and behavioural parameters were determined on 20th day. After 20th day rats were sacrificed and anti-oxidant parameters were determined.

Behavioural study

One week training was performed in rats in order to prepare them for behavioural study. During the training period only food and water were administered to rats. The fully trained rats were choice for the study.

Locomotor activity

Locomotor activity was performed in animals using a digital photoactometer. The ambulatory movements were recorded for a period of 10min and expressed in terms of total photo beam counts for 10min per animal.19

Motor coordination

Motor coordination of rats was performed by using rota rod according to the described procedure by.20

Conditioned avoidance response test

Conditioned avoidance response test in rats was performed by using the Pole climbing apparatus.21

Spatial long-term memory assessment

The spatial long-term memory of rats was assessed by using the Elevated plus-maze test.22

Spatial memory assessment

The Morris water maze (MWM) was performed under red light as described previously.23

Cognitive abilities assessment

Spontaneous alternation behaviour in the Y-maze test is used to determine the assessment of short-term memory of animals.24

Biochemical Parameters

- Assessment of oxidative stress markers: The animals were anesthetized and sacrificed by cervical
dislocation method; the brain was transferred to ice cold phosphate buffered saline quickly. It was blotted to free of blood, tissue fluids, weighed and chopped with surgical scalpel into fine slices. Then suspend in chilled 0.25M sucrose solution and quickly blotted on a filter paper and homogenized in chilled phosphate buffer to a concentration of 10% w/v. Homogenization is continued under hypotonic condition to release soluble proteins. The homogenate was centrifuged at 7000 rpm for 25 minutes using Remi (RM-12C) high speed centrifuge. The clear supernatant was used for the determination of lipid peroxidation [LPO (nmol MDA/mg wet tissue)], superoxide dismutase [SOD (Unit/mg wet tissue)], catalase [CAT (µ mol H₂O₂ decomposed/mg wet tissue)], reduced glutathione [GSH (nmol GSH/mg wet tissue)].

- Assessment of Acetylcholine esterase content: In the brain tissue homogenate, Acetylcholine esterase content was assessed according to the manufacturer’s instructions.

RESULTS

Statistical analysis

The outcomes are expressed as the mean±SEM. Statistical evaluation was carried out by using one way analysis of variance (ANOVA) followed by Bonferroni multiple comparison test. P<0.05 was considered to be significant.

Effect of the ethanolic extract of Picrorhiza kurroa (EPK) on locomotor activity

Table 1: Effect of ethanolic extract of Picrorhiza kurroa and rivastigmine on locomotor activity.

| Group          | Locomotor activity (No. of counts/5 min) |
|---------------|----------------------------------------|
| Normal control| 436.5±13.29                             |
| Negative control| 319.2±1.72                          |
| EPK (200mg/kg)| 333.9±4.84***                         |
| EPK (400mg/kg)| 407.0±21.40***                        |
| Rivastigmine (0.3mg/kg)| 451.9±17.35**                        |

All values are expressed mean ± SEM. ***P<0.001 compared with normal control, ##P<0.01, ns-non significant compared with negative control respectively.

The results in Table 1 showed significant decrease in locomotor activity in rats treated with AlCl₃ when compared to normal control rats. Treatment of rats with ethanolic extract of *Picrorhiza kurroa* at dose 400mg/kg significantly increased the locomotor activity when compared to negative control rats.

Effect of the ethanolic extract of Picrorhiza kurroa (EPK) on motor coordination

The results in Table 2 showed significant decrease in the fall of time in rats treated with AlCl₃ when compared to normal control animals. Treatment of rats with ethanolic extract of *Picrorhiza kurroa* at dose 200, 400mg/kg significantly increased the fall of time when compared to negative control rats in dose dependent manner.

Table 2: Effect of ethanolic extract of Picrorhiza kurroa and rivastigmine on motor coordination.

| Group          | Rota rod test (Fall of time in sec) |
|---------------|-------------------------------------|
| Normal control| 14.37 ± 0.250                        |
| Negative control| 5.320 ± 0.310                      |
| EPK (200mg/kg)| 13.78 ± 0.396***                  |
| EPK (400mg/kg)| 15.08 ± 0.605***                  |
| Rivastigmine  | 16.54 ± 1.078***                   |

All values are expressed mean ± SEM. **P<0.01 compared with normal control, ***P<0.001 compared with negative control respectively.

Effect of the ethanolic extract of Picrorhiza kurroa (EPK) on conditioned avoidance response

Table 3: Effect of ethanolic extract of Picrorhiza kurroa and rivastigmine on conditioned avoidance response.

| Group          | Time taken to climb pole (sec) |
|---------------|-------------------------------|
| Normal control| 0                            |
| Negative control| 155±2***                    |
| EPK (200mg/kg)| 135±3***                     |
| EPK (400mg/kg)| 131±2***                     |
| Rivastigmine  | 128±1***                     |

All values are expressed mean ± SEM. **P<0.01 compared with normal control, ***P<0.001 compared with negative control respectively.

The results in Table 3 showed significant increase in time taken to climb the pole in rats treated with AlCl₃ when compared to normal control animals. Treatment of rats with ethanolic extract of *Picrorhiza kurroa* at dose 200, 400mg/kg significantly decreased in time taken to climb the pole when compared to negative control rats in dose dependent manner.

Effect of the ethanolic extract of Picrorhiza kurroa (EPK) on spatial memory using elevated plus maze

Table 4: Effect of ethanolic extract of Picrorhiza kurroa and rivastigmine on spatial memory.

| Group          | Elevated plus maze test (Transfer of latency in secs) |
|---------------|-----------------------------------------------------|
| Normal control| 23.16±1.365                                        |
| Negative control| 42.01±0.650***                                   |
| EPK (200mg/kg)| 17.78±1.525***                                   |
| EPK (400mg/kg)| 33.62±3.233***                                   |
| Rivastigmine  | 47.12±1.034***                                   |

All values are expressed mean ± SEM. **P<0.01 compared with normal control, ***P<0.001 compared with negative control respectively.
The results in Table 4 showed significant increase in transfer of latency of rats treated with AlC3 when compared to normal control animals. Treatment of rats with Ethanolic extract of Picrorhiza kurroa at dose 200, 400mg/kg significantly decreased in transfer of latency when compared to negative control rats in dose dependent manner.

**Effect of the Ethanolic extract of Picrorhiza kurroa (EPK) on spatial memory using morris water maze**

**Table 5: Effect of Ethanolic extract of Picrorhiza kurroa and rivastigmine on spatial memory using water maze.**

| Group          | Water maze test (Swim latency in sec) |
|----------------|---------------------------------------|
| Normal control | 20.00±1.22                            |
| Negative control | 38.73±1.39                           |
| EPK (200mg/kg) | 22.10±0.73                            |
| EPK (400mg/kg) | 19.20±0.62                            |
| Rivastigmine   | 17.15±0.54                            |

All values are expressed mean ± SEM. ***P<0.001 compared with normal control, ###P<0.001 compared with negative control.

The results in Table 5 showed significant increase in swim latency of rats treated with AlC3 when compared to normal control animals. Treatment of rats with Ethanolic extract of Picrorhiza kurroa at dose 200, 400mg/kg significantly decreased in swim latency when compared to negative control rats in dose dependent manner.

**Effect of the Ethanolic extract of Picrorhiza kurroa (EPK) on cognitive abilities using Y-Maze**

**Table 6: Effect of Ethanolic extract of Picrorhiza kurroa and rivastigmine on cognitive abilities using Y-maze.**

| Group          | Y-maze test (Time to reach previsited arm in sec) |
|----------------|-----------------------------------------------|
| Normal control | 25±2.12                                       |
| Negative control | 47±5.25   ***                             |
| EPK (200mg/kg) | 35±±3.32   **                          |
| EPK (400mg/kg) | 30±±2.91   **                         |
| Rivastigmine   | 28±1.98   ***                        |

All values are expressed mean ± SEM. ***P<0.001 compared with normal control, ###P<0.001, ##P<0.01, #P<0.05, ns- non significant compared with negative control.

The results in Table 6 showed significant increase in time to reach previsited arm of rats treated with AlC3 when compared to normal control animals. Treatment of rats with Ethanolic extract of Picrorhiza kurroa at dose 200, 400mg/kg significantly decreased in time to reach previsited arm when compared to negative control rats in dose dependent manner.

**Effect of the Ethanolic extract of Picrorhiza kurroa (EPK) on brain anti-oxidant status**

The results in Table 7 showed significant decrease in superoxide dismutase, catalase, reduced glutathione and increase in lipid peroxidation of brain homogenate of rats treated with AlC3 when compared to normal control animals.

**Table 7: Effect of Ethanolic extract of Picrorhiza kurroa and rivastigmine on oxidative parameters in brain homogenate.**

| Group          | SOD      | CAT     | GSH      | MDA      |
|----------------|----------|---------|----------|----------|
| Normal control | 30.39±0.743 | 339.2±5.093 | 168.9±2.620 | 72.72±2.41 |
| Negative control | 20.29±0.779 | 145.7±7.140 | 109.0±1.22 | 165.6±60.8*** |
| EPK (200mg/kg) | 22.90±1.016 | 300.4±12.76 | 139.4±1.600 | 85.94±4.81 *** |
| EPK (400mg/kg) | 25.08±0.984 | 327.4±17.0** | 159.4±3.429 | 111.1±3.95** |
| Rivastigmine   | 29.26±0.607 | 327.4±17.0** | 172.7±5.964 | 65.58±7.33 |

All values are expressed mean ± SEM. ***P<0.001 compared with normal control, ###P<0.001, ##P<0.01, #P<0.05, ns- non significant compared with negative control.

Treatment of rats with Ethanolic extract of Picrorhiza kurroa at dose 200, 400mg/kg significantly increased the superoxide dismutase, catalase, reduced glutathione and decreased the lipid peroxidation when compared to negative control rats in dose dependent manner.

**Effect of the Ethanolic extract of Picrorhiza kurroa (EPK) on brain acetyl cholinesterase content.**

**Table 8: Effect of Ethanolic extract of Picrorhiza kurroa and rivastigmine on brain acetyl cholinesterase content.**

| Group          | Acetyl cholinesterase content (µmol/min/mg wet tissue) |
|----------------|--------------------------------------------------------|
| Normal control | 15.00±1.03                                              |
| Negative control | 29.00±2.10   **                                         |
| EPK (200mg/kg) | 19.00±0.08**                                           |
| EPK (400mg/kg) | 18.15±0.10**                                           |
| Rivastigmine   | 16.34±1.07**                                           |

All values are expressed mean ± SEM. ***P<0.001 compared with normal control, ###P<0.001 compared with negative control.
Treatment of rats with ethanolic extract of Picrorhiza kurroa at dose 200, 400mg/kg significantly decreased the brain acetyl cholinesterase content when compared to negative control rats in dose dependent manner.

**DISCUSSION**

One of the major challenges facing the modern health care system is the neurodegenerative disease such as Alzheimer’s disease that represents the most prevalent dementia. The incidence of Alzheimer’s disease increases with age. Anders and Martin mentioned that there were 35.6 million people living with dementia worldwide, which will increase to 65.7 million by 2030 and 115.4 million by 2050. Aluminium causes oxidative deterioration of cellular lipids, proteins and DNA. Therefore, aluminium can be considered as a contributing factor in AD. At present, there is no definitive evidence to support that any particular measure is effective in preventing Alzheimer’s disease. Herbal medicine offers several options to modify the progress and symptoms of Alzheimer’s disease. There has been a new trend in the preparation and marketing of drugs based on medicinal plants, and their scientific and commercial significance appears to be gathering momentum in health relevant areas.

**CONCLUSION**

In the present study we have been tried to investigate the protective and therapeutic effect of Picrorhiza kurroa on Alzheimer’s disease. Phenolic substances and flavonoids have been shown to be responsible for antioxidant activity.

The ethanolic extract of Picrorhiza kurroa was found to be having maximum antioxidant activity which may be due to the presence of high amount of flavonoids and moderate amount of phenols. In the present study AlCl₃ induced rats showed decrease in locomotor activity, Motor coordination and increase in time taken to climb the pole, increase in transfer of latency in sec, increase in swim latency, increase in time to reach previsited arm when compared to normal rats. Oral administration of ethanolic extract of Picrorhiza kurroa at doses 200, 400 mg/kg body weight showed increase in locomotor activity, Motor coordination and decrease in time taken to climb the pole, decrease in Transfer of latency in sec, decrease in swim latency, increase in time to reach previsited arm in a dose dependent manner significantly when compared to AlCl₃ induced rats.

Reduction in anti-oxidants like superoxide dismutase, catalase, reduced glutathione and increased levels of malondialdehyde were observed in AlCl₃ induced rats significantly when compared to normal control rats. Oral administration of ethanolic extract of Picrorhiza kurroa at doses 200, 400 mg/kg body weight showed increase in superoxide dismutase, catalase, reduced glutathione and decreased levels of malondialdehyde significantly in a dose dependent manner when compared to AlCl₃ induced rats. In the present study, results suggest that treatment with ethanolic extract of Picrorhiza kurroa exerted neuroprotective action against AlCl₃ induced behavioural parameters and oxidative parameters. Yet, advance studies are needed to characterize the active compound(s) and expose the possible mechanism of action.

**ACKNOWLEDGEMENTS**

The authors express sincere thanks to the management of Raghavendra Institute of Pharmaceutical Education and Research (RIPER) for providing necessary chemicals and apparatus.

**Funding:** No funding sources  
**Conflict of interest:** None declared  
**Ethical approval:** The study was approved by the Institutional Ethics Committee

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Cite this article as: Reddy SK, Sudheer A, Arunamma M, Sree PL, Jyothishmayi E. Protective effect of Picrorhiza kurroa on alzheimer’s disease induced by aluminium chloride in rats. Int J Basic Clin Pharmacol 2017;6:602-7.