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## Differences of locomotor activities in the dementia rat model induced by oral d-galactose and intraperitoneal injection



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### ABSTRACT

**Background:** The aging process can increase the incidence of neurodegenerative diseases such as dementia. Dementia is characterized by a gradual loss of cognitive performance for locomotor activity in exploring new environments. Research on dementia in mice was carried out by administering d-galactose to induce mitochondrial dysfunction, oxidative stress, inflammation and apoptosis of neurons.

**Objective:** The purpose of this study was to determine differences in locomotor activity in rats induced by oral d-galactose and intraperitoneal injection.

**Methods:** An experimental study with a posttest control group design. The subjects were male Wistar rats aged 12-14 weeks with weighing 200-300gram obtained from the Animal Laboratory of the Pharmacology Unit of the Faculty of Medicine, Udayana University. The study was conducted for 8 weeks, from June to August 2019. A total of 20 rats induced d-galactose dose of 100 mg/kg/day orally

and intraperitoneal injection. The use of animals was carried out after obtaining ethical clearance from the ethical committee of the Faculty of Medicine, Udayana University. Y maze test is conducted for 5 minutes at the end of week 8.

**Results:** There was a decrease in locomotor activity in both groups. The average locomotor activity in the oral group was  $6.5 \pm 0.268$ , and the injection group was  $5.5 \pm 0.341$ . Bivariate analysis with unpaired t-test showed significant differences in locomotor activity between groups given oral d-galactose compared to the intraperitoneal injection group with  $p=0.034 (<0.05)$ .

**Conclusion:** Alzheimer's dementia induced d-galactose mice to have a different locomotor activity after administration by oral or intraperitoneal injection of d-galactose. This study supports the results of previous studies that the administration of d-galactose can cause impaired locomotor activity.

**Keywords:** dementia, d-galactose, locomotor activity

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### INTRODUCTION

Normal aging is characterized by a gradual loss of cognitive and motor performance. The pathology of aging in Alzheimer's disease is associated with mitochondrial dysfunction due to decreased oxidative phosphorylation, increased free radicals and reactive oxygen species (ROS).<sup>1</sup> Neurodegenerative disorders that occur can be a cognitive decline, decreased learning ability and memory and also locomotor disorders.<sup>2</sup> Cerebellum is a brain region that functions a lot for motor coordination, posture and maintenance of body position and cognitive function. Aging affects cerebellum neurons that appear earlier than in the hippocampus and cerebral cortex areas.<sup>3</sup> Changes in the cerebellum during aging include decreased motor function, morphological changes, and changes in Purkinje cells.<sup>4</sup> The Y-Maze test was developed to assess working memory based on spatial learning and locomotor activity by assessing the activity of mice in exploring new environments and looking for food quickly and efficiently.<sup>5</sup>

D-galactose is a physiological nutrient and reducing sugar that reacts with amines free of amino acids in proteins to form the final product through nonenzymatic glycation.<sup>1</sup> D-galactose induction is an effective alternative to accelerate the aging process in experimental animals.<sup>6</sup> Aging of the brain induced by d-galactose is very dose-dependent, starting from 100 mg/kg/day to 500 mg/kg/day with 6-8 weeks of administration.<sup>7</sup>

There are many studies of dementia model mice with a focus on d-galactose administration through intraperitoneal and subcutaneous injection, whereas oral d-galactose administration has not received enough attention.<sup>8</sup> However, several studies show that oral administration of d-galactose also causes age-related changes.<sup>7</sup> Chronic administration of d-galactose can cause memory impairment and locomotor activity in mice while the acute effect of d-galactose administration is not yet clear.<sup>9</sup> Administration of oral d-galactose can be an alternative induction of aging over a longer

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period of time. This study aims to evaluate the effect of d-galactose induction on locomotor activity in Wistar rats via the oral and intraperitoneal injection routes.

## METHODS

Experimental research with posttest control group design. Subjects were male Wistar rats aged 12-14 weeks weighing 200-300gram obtained from the Animal Laboratory Unit of the Pharmacology Unit of the Faculty of Medicine, Udayana University. The study was conducted for 8 weeks, from June to August 2019. A total of 20 rats were divided into 2 groups to be induced with a d-galactose dose of 100 mg/kg/day orally and intraperitoneal injection. The use of animals is carried out according to the rules of research ethics and obtaining ethical clearance from the ethical commission and scientific research coordinator in the field of health at the Faculty of Medicine, Udayana University. Furthermore, the Y maze test for 5 minutes at the end of week 8 to assess the exploration ability and motor activity of rats from the total number of rats entered the arm.

## RESULTS

Statistical analysis showed that the average locomotor activity after d-galactose administration in the injection group (5.5+0.341) was lower compared to the oral group (6.5+0.268). The Shapiro-Wilk normality test shows that the data are normally distributed with  $p > 0.05$ . Independent t-test results obtained a significant difference in locomotor activity between the injection and oral groups with  $p = 0.034$  ( $p < 0.05$ ). The analysis results are presented in Table 1.

The use of d-galactose in inducing aging in experimental animals has been carried out over the past two decades.<sup>1</sup> In this study, it was found that administration of d-galactose resulted in decreased locomotor activity in both treatment and control groups. This result is in line with Cardoso et al. (2015) who administered d-galactose to 4-week-old Wistar rats at a dose of 300 mg/kg for 8 weeks intraperitoneally. Systemic exposure to d-galactose results in biochemical changes and morphological aging in several organs, including the central

nervous system.<sup>8</sup> Mice that receive 50-500 mg/kg injection of d-galactose daily intraperitoneally for 6-8 weeks, physiologically and pathologically resembles rats aged 16-24 months in control mice.<sup>10</sup> The aging model method with d-galactose administration has the advantage of low cost, high life rate during administration, low tumor incidence and easy use.<sup>10</sup> Some other unsuccessful studies in conducting the aging model by administering d-galactose, it has variations regarding the types of experimental animals, the route of administration, duration of administration, and also the dosage.<sup>1,6</sup>

In this study, the mean spatial memory score after d-galactose administration in the injection group (5.5+0.341) was lower than the oral group (6.5+0.268). Lin et al. suggested that administration of d-galactose by intraperitoneal injection significantly increased the A $\beta$  level in rat hippocampus. An earlier study also stated that the administration of d-galactose by intraperitoneal injection could increase aggregation and deposition of A $\beta$  in the brain, and this process subsequently results in a cellular cascade of neuronal loss and dementia.<sup>8</sup> A study comparing chronic administration of d-galactose systemically with oral shows that oral administration routes can improve cognitive deficits in streptozotocin-induced AD model mice in which the protective effect of d-galactose depends on the concentration or route of administration. There is still controversy surrounding the use of d-galactose by this oral route.<sup>9</sup>

The difference in locomotor activity between the injection and oral groups in this study was assessed using the independent t-test obtained  $p = 0.034$  with a significance level of  $p < 0.05$ . The results of this study can be concluded that there are significant differences in locomotor activity in rats induced by oral d-galactose and intraperitoneal injection. This is in line with the research of Zhang et al. which uses an open field test to measure the decline in motor function of mice due to the reduction of Purkinje cells that occur mostly in the aging and neurodegenerative processes and can measure motor activity in a relevant way to assess pathology in the cerebellum.<sup>11</sup> In aging that occurs due to d-galactose administration, there are a decrease in locomotor and exploration activities in open field tests.<sup>9</sup>

## CONCLUSION

Based on the results of this study, it was concluded that there were differences in locomotor activity in rats induced by oral d-galactose and intraperitoneal injection. The locomotor activity appears to be lower in administering d-galactose by intraperitoneal injection than oral administration.

**Table 1** Average locomotor activity after administration of d-galactose

Group	Mean group of spatial memory scores	P
Oral	6.5+0,268	0.034
Injeksi	5.5+0.341	

Further research needs to be done with a longer d-galactose administration time to increase the success of accelerating aging in the cerebellum. Further research needs to be carried out on the effect of antioxidant administration on locomotor activity by assessing oxidative stress markers and changes in mitochondrial function in cerebellum aging by administering d-galactose.

### ETHICAL CONSIDERATION

Ethics consideration has been obtained from the Ethics Committee, Faculty of Medicine, Universitas Udayana, Bali, Indonesia prior to the study being conducted.

### CONFLICT OF INTEREST

None.

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### AUTHORS CONTRIBUTION

All of the authors are equally contributed to the study from the conceptual framework, data gathering, data analysis, until reporting the results of the study.

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