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Antidepressant Activity of *Curcuma heyneana*

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Abstract

BACKGROUND: The resistance to depression therapy remains high, and therapy failure leads to suicide. Curcuma heyneana (*C. heyneana*) is a plant of Zingiberaceae. Conventionally, the rhizome has been used as an anxiolytic and sedative. However, the activity as antidepression has never been conducted.

AIM: Therefore, this research was aimed to investigate the antidepressant activity of C. heyneana rhizome.

METHODS: This research was conducted using male mice aged 2–3 months. Chronic mild stress for 14 days was used to induce depression, followed by administration of the extract at 50, 100, and 200 mg/kg for 10 days. Evaluation of antidepression was carried out using tail suspension test (TST), forced swim test (FST), open field test (OFT), and blood glucose and injury of gastric. Sertraline at the dose of 6.5 mg/kg was used as a positive control.

RESULTS: The result revealed that stress induction for 14 days causes decreasing in locomotor activity and increased immobility. The extract administration at the doses of 100 and 200 mg/kg showed increased locomotor activity, which can be seen from the elevation of the central square and cross in the OFT ($p < 0.05$). The extract also decreased immobility in the tail suspension and FSTs ($p < 0.05$). Furthermore, the extract also prevents increases in blood glucose and gastric irritation.

CONCLUSION: Extract of *C. heyneana* rhizome at the doses of 100 and 200 mg/kg has antidepressant activity by increasing locomotor activity, decreasing immobility time, and preventing elevation of blood glucose and gastric injury.

Introduction

Depression is a mental disorder caused by the depletion of serotonin, norepinephrine, and/or dopamine levels in the central nervous system [1]. This condition is characterized by several symptoms such as emotional symptoms (feeling sad, loss of interest in usual activities, loss of pleasure, sleep disturbances, appetite disturbances, loss of sexual interest, and gastrointestinal and cardiovascular complaints); intellectual symptoms (decreased concentration, poor memory, confusion, and indecision); and psychomotor disorders (slow physical movement) [2].

The prevalence of depressive disorder in the world is about 5%–10% per year and mainly occur in the productive age that is 25–44 year. There are several groups of antidepressants such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors, which are claimed to be effective and better tolerated than older agents [2]. However, those existing antidepressants remain to have some limitations such as various side effects, lower response, and the onset of action, which lead to non-compliance of the patients [3]. Besides, according to the sequenced treatment alternatives to relieve depression, about 50%–66% of patient with depression was not cured fully with an existing antidepressant. Inadequate treatment for depression patients may lead to suicide and death [4]. Therefore, a new antidepressant with minimal side effects and high potency is necessary to be found.

Curcuma heyneana is a pseudo-trunked annual shrub that can grow wild in gardens and fields on moist soil and belongs to the Zingiberaceae family. The tropics, notably Indonesia, are home to this plant. It is one of the medicinal plants that have many benefits, traditionally used to treat anxiety, heart palpitations, reduce obesity, remove body odor, dysentery, constipation, slimming agent, sedative, skin disease medicine, worm medicine, wound healing, urinary tract infection, gastric infection, liver protector, and also used for beauty [5], [6], [7]. This plant contains curcumin

which can help manage oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia [8].

Several studies mention the activity of *C. heyneana,* including analgesic, hepatoprotective, anti-ageing, antibacterial, and antiviral [9], [10], [11], [12]. The rhizome of *C. heyneana* contains curcumin compounds, essential oils, starch, resins, fats, tannins, saponins, and flavonoids [13]. Curcumin compounds include polyphenolic compounds, namely, flavonoids, which are known to have various activities, including antidepressants, and can affect multiple physiological and biochemical functions in the body [14], [15]. Several studies related to curcuminoids reveal their activity to increase the neurotransmitter that is responsible for relieving depression [16], [17], [18]. Therefore, this research was aimed to determine the antidepressant activity of *C. heyneana* with immobility time and locomotor activity method.

Methods

Plant material

C. heyneana rhizome was harvested in Brastagi, North Sumatera, and authentication was done in Herbarium Medanense, Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara. The certificate number: 5077/MEDA/2020 mentioned that the sample is *C. heyneana* Val. and V.

Extraction

The rhizomes were washed and dried in a drying cabinet and afterward grounded into a coarse powder. The extraction was conducted using the maceration method. The dry rhizome, as much as 956.61 g, was soaked in 9.6 L ethanol (1:10 ratio) for a couple of days, stirred, and filtered every day. The residue was re-macerated until the filtrate was clear and colorless. The entire filtrate was collected, and the solvent evaporated using a rotary evaporator. The thick extract gained was 89 g from 956.61 dry rhizomes (the yield was 9.3%).

Animals

The animals used were Swiss albino male mice, 3 months old (weighing 20-35 g), purchased from Animal House of the Faculty of Pharmacy, Universitas Sumatera Utara, Medan, Indonesia. All animals were put in a plastic cage and allowed 2 weeks of acclimatization. The animals had free access to dry rodent pellets and drinking water and were exposed to a 12-h dark/12-h light cycle, room temperature 25°C ± 2°C, and relative humidity 55–60%. They were handled according to standard protocols for the use of laboratory animals. The experimental protocol was approved by Ethics Committee of the Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara, Number: 00515/KEPH-FMIPA/2020.

Chemicals

Chemicals used were sertraline (PT. Guardian Pharmatama, Indonesia), carboxymethyl cellulose sodium (Merck, Germany), and ethanol (Merck, Germany).

Characterization and determination of secondary metabolites

The dry rhizome of *C. heyneana* is characterized by water content, total ash content, water-soluble content, ethanol-soluble content, and acid insoluble ash content. Extract of *C. heyneana* is characterized by water content, total ash content, and acid insoluble ash content [19]. Determination of secondary metabolites carried out toward alkaloids, glycosides, flavonoids, saponins, tannins, and steroids/triterpenoids [20].

Antidepressant activity

The antidepressant activity of the extract was evaluated by the tail suspension test (TST), open field test (OFT), and forced swimming test. The mice were divided into six groups (n = 6). Before the experiment, all of the mice were induced with chronic mild stress (CMS) that were given different stressors every day for 7 days with a total duration of 14 days, as presented in Table 1 [21].

Table 1: Stress induction schedule

Stressor	Day						
	1	2	3	4	5	6	7
Fasting for 12 h (only water allowed)	■		■				
Predator voice (cat and dog voice for 4 h)		■		■		■	
Cage shaking for 15 min			■		■		
Wet bedding filled with soil, pebble, leaves flakes, and mud		■				■	
The dark and light cycle abruptly	■				■		■
Reduce bedding				■		■	

The design of the experiment is based on the research of Rahman *et al*. (2020), with a slight modification is shown in Table 2 [22].

Tail suspension test

The antidepressant activity of the extract was carried out according to the method described by Steru *et al*. (1985) with slight modification. The test was carried out after 10 days of treatment (on the 24th day), as described in Table 2. After 45 min of treatment, each mouse was suspended on the 30 cm long stick with adhesive. The space between the mouse head and the floor was about 10 cm. The observation was carried out

Table 2: Research design

Group	Treatment
Negative control	Stress induction for 14 days followed by administration of carboxymethyl cellulose sodium 1% (10 mL/kg) orally to the mice for 10 days
Dose of 50 mg/kg	Stress induction for 14 days followed by administration extract at the dose of 50 mg/kg orally to the mice for 10 days
Dose of 100 mg/kg	Stress induction for 14 days followed by administration of the extract at the dose of 100 mg/kg orally to the mice for 10 days
Dose of 200 mg/kg	Stress induction for 14 days followed by administration of the extract at the dose of 200 mg/kg orally to the mice for 10 days
Positive control	Stress induction for 14 days followed by administration of sertraline at the dose of 6.5 mg/kg orally to the mice for 10 days
Normal control	No induction

on the mobility of the mice until they stopped for the first time (immobile) and recorded with a video camera. The observation was conducted for 6 min [23].

Open field test

The test was conducted based on the method described by Gould *et al*. (2009) with slight modification. After 45 min of treatment, the mice were put in the 40 cm × 40 cm × 35 cm box without a cover. The observation was conducted on a bare floor with grid marking. The observation carried out in 5 min covered Central Square, crossing, and grooming [24], [25], [26].

Forced swimming test

The test was conducted based on the method described by Porsolt *et al*. (1977). After 45 min of treatment, the mice were put in the glass box (25 cm × 15 cm × 25 cm) filled with water. The observation is carried out toward immobility time when mice maintain their head above the water for the first time. The duration of observation was 7 min [27].

Blood glucose

The blood of mice was withdrawn from the tail at the end of treatment, and the blood glucose was measured using a portable blood glucose analyzer.

Macroscopic and microscopic gastric

At the end of the research, the gastric was taken and analyzed toward injury by histopathology study. The injury in the gastric is classified as follows: Normal gastric (score zero), ulcer spot (score one), and bleeding (score two).

Statistical analysis

The values are presented as mean ± standard error mean and analyzed using one-way analysis of variance (ANOVA) SPSS version 23 followed by *post-hoc* least significant difference (LSD). The antidepressant effect was considered to be significant at $p < 0.05$.

Results

Secondary metabolites and characteristics of Curcuma heyneana

The result of secondary metabolites and characteristics of dry rhizome and extract of *C. heyneana* is shown in Table 3.

Table 3: Secondary metabolites and characteristics of dry rhizome and extract of *Curcuma heyneana*

Parameters	Result			
	Dry rhizome	Reference	Extract	Reference
Secondary metabolites				
Alkaloids	NA		NA	
Glycosides	NA		NA	
Saponins	+		+	
Flavonoids	+		+	
Tannins	NA		NA	
Triterpenoids/steroids	+		+	
Characteristics of *Curcuma heyneana* (%)				
Water content	3.98	≤ 10	4.63	≤ 10
Water soluble content	18.99	≥ 13		
Ethanol soluble content	17.52	≥ 14.9		
Total ash content	5.51	≤ 9.8	5.8	≤ 9.9
Acid insoluble content	0.53	≤ 6.6	0.57	≤ 0.6
Curcuminoid content			5.33	

Reference used was Indonesian herbal pharmacopoeia, 2nd edition (2017). NA: Not available, +: available.

Subjective observation and bodyweight profile of mice in the antidepressant test

The behavior of mice and body weight can be used as parameters to see the condition of depression. The result is shown in Table 4.

From Table 4, more than 75% of mice become passive or immobile after induction with CMS. On day 24 or after administration of the extract, the mice undergo changing their behavior from immobile and passive become normal, at least 75% population. In contrast, 100% of mice undergo passive and immobile in the negative control group. The change in body weight can also be observed to know the condition of depression in mice. The result is shown in Figure 1.

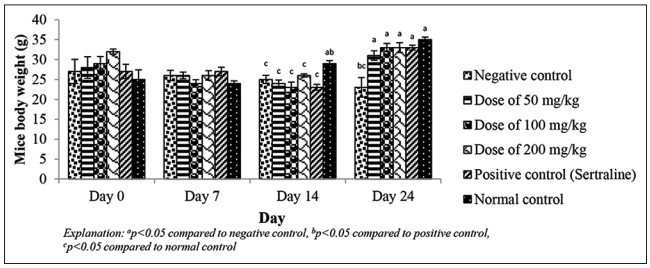

Figure 1: Mice body weight

On day 14, after CMS, the body weight of mice in all groups decreased and significantly different from the normal control group ($p < 0.05$) and also significantly

Table 4: The behavior of mice

Subjective observation	Percentage (%)																	
	Negative control			Dose of (50 mg/kg)			Dose of (100 mg/kg)			Dose of (200 mg/kg)			Positive control (sertraline)			Normal control		
	Days																	
	0	14	24	0	14	24	0	14	24	0	14	24	0	14	24	0	14	24
Passive	25	100	100	0	75	25	0	100	0	0	100	0	0	100	0	0	0	0
Normal	75	0	0	50	25	75	75	0	75	75	0	75	75	0	75	75	100	100
Aggressive	0	0	0	50	0	0	25	0	25	25	0	25	25	0	25	25	0	0

Every group consists of four mice.

different from the body weight on day 0 ($p < 0.05$). On day 24, after administration of the extract, the body weight of mice in the group doses of 50, 100, and 200 mg/kg increased and significantly different from the negative control group ($p < 0.05$) and the same as normal control group ($p > 0.05$). The extract administration reversed the decrease in body weight caused by stress. Furthermore, extract can also normalize food consumption. Therefore, the body weight turns to normal weight.

Tail suspension test

The result of the TST is shown in Figure 2.

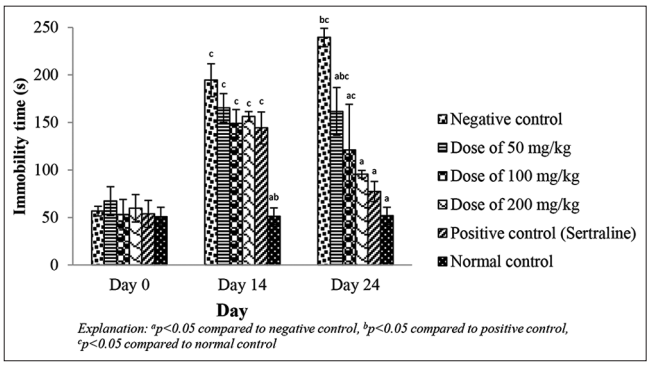

Figure 2: Immobility time of mice in tail suspension test

On day 14, the duration of immobility in mice increased and significantly different from the normal control group ($p < 0.05$). It means depression in mice has already occurred. On day 24, the duration of immobility decreased with the administration of the extract. Extract at the dose of 200 mg/kg reversed immobility condition to the normal state.

Forced swim test

The result is shown in Figure 3.

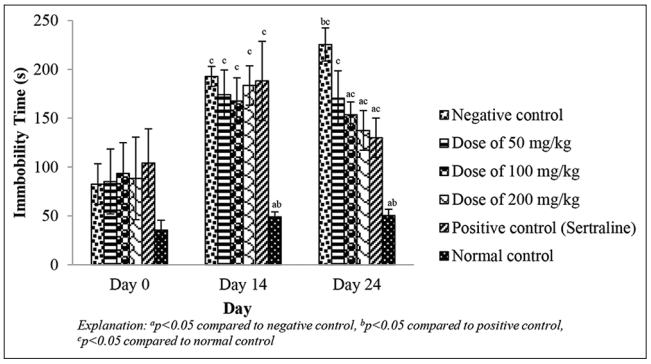

Figure 3: Immobility time of mice in forced swim test

On day 14, the duration of immobility in mice increased and significantly different from the normal control group ($p < 0.05$). It means depression in mice has already occurred.

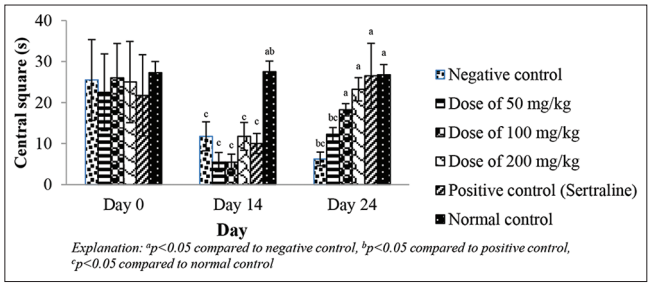

Figure 4: Duration of the Central Square in open field test

On day 24, the duration of immobility decreased with the administration of the extract except for the group at the dose of 50 mg/kg. On the other hand, the immobility time of the negative control group remains increased even though the induction has been stopped.

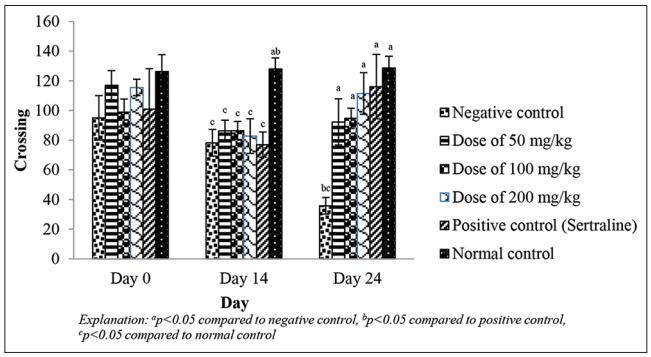

Figure 5: Amount of crossing in open field test

Open field test

Parameters that are observed in OFT are Central Square, crossing, and grooming. The results are shown in Figures 4-6.

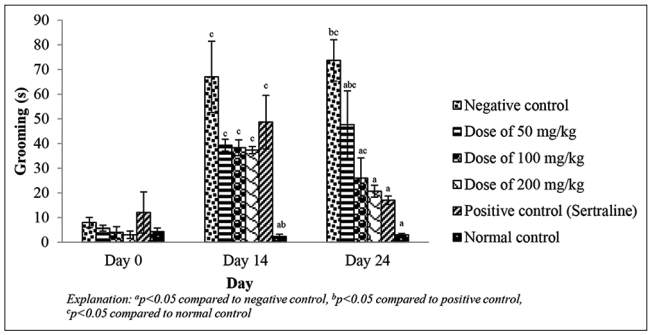

Figure 6: Duration of grooming in open field test

From Figures 4 and 5, induction of CMS decreased the duration of Central Square and amount of crossing of mice which is significantly different from the normal control group ($p < 0.05$). This condition indicates that the animal has experienced depression. However, the administration of the extract, especially at the doses of 100 and 200 mg/kg, reversed the condition to the normal state. From Figure 6, induction of CMS increased the duration of grooming, and administration of extract decreased the grooming, especially in the group at the dose of 200 mg/kg that returned the condition to the normal state.

Blood glucose

The result of blood glucose is shown in Table 5.

Table 5: Blood glucose of mice

Group	Average of blood glucose ± SEM (mg/dl)
Negative control	229.50 ± 24.47[b,c]
Dose of 50 mg/kg	165.00 ± 1.29[a]
Dose of 100 mg/kg	160.25 ± 5.62[a]
Dose of 200 mg/kg	158.00 ± 10.92[a]
Positive control (sertraline)	151.25 ± 9.25[a]
Normal control	144.50 ± 12.80[a]

[a]$p < 0.05$ compared to the negative control, [b]$p < 0.05$ compared to the positive control, [c]$p < 0.05$ compared to normal control. SEM: Standard error of mean.

On day 24, mice that were given extract at the doses of 50, 100, and 200 mg/kg for 10 days had blood glucose lower than the negative control ($p < 0.05$) and the same as normal control ($p > 0.05$).

Macroscopic and microscopic of gastric

The result of macroscopic and microscopic of gastric is shown in Figures 1 and 2.

From Figure 7, the gastric mucosa injury can be scored as listed in Table 6.

Based on Table 6, gastric mucous in negative control mice undergo bleeding and ulcer as much as 13.00 ± 0.71 spots. Administration of extract at the doses of 50, 100, and 200 mg/kg decreased the number of ulcer spots in the gastric mucosa and significantly different from the negative control ($p < 0.05$). The higher the dose, the more the protective effect of the extract on the stomach. The injury of the gastric was also confirmed with microscopic observation. The result is shown in Figure 8.

Based on Figure 8, the result of microscopic is in line with the injury of gastric mucosa as shown in Figure 7. Administration of extract at the doses of 50, 100, and 200 mg/kg reduced the injury of gastric.

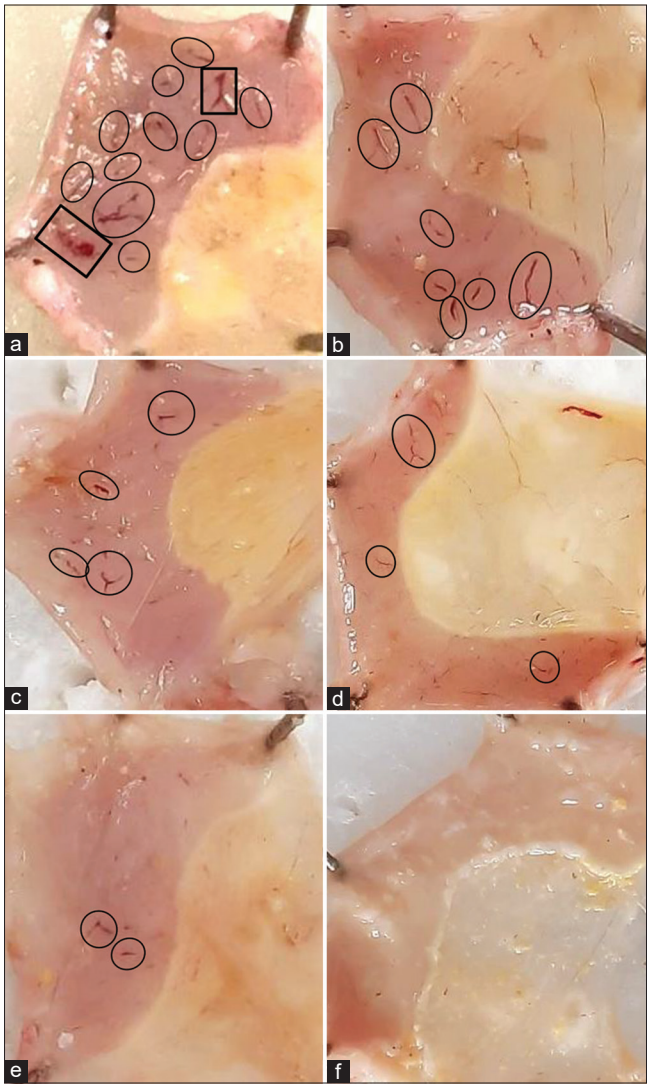

Figure 7: *Macroscopic of gastric; (a) negative control; (b) dose of 50 mg/kg; (c) dose of 100 mg/kg; (d) dose of 200 mg/kg; (e) positive control; (f) normal control. Explanation: ▭ = bleeding; ⬭ = ulcer spot*

Discussion

Depressive disorder can be observed from specific symptoms, namely, gloom, and withdrawal from the social environment. In the animal model, depression can be evaluated by increasing immobility time and decreasing locomotor activity. In this research, the duration of induction for 14 days has emerged the condition of depression, which is characterized by increasing the immobility duration in forced swim test (FST) and OFT. The duration of immobility is the duration of the mice stop trying to escape from the given stressor. The longer the duration of immobility, the more severe the level of depression in mice. In addition, there was also a decrease in locomotor activity, which was marked by a decrease in the duration of the central square and the number of crossings because anxious/

Table 6: Score of gastric injury

Group	The score of gastric injury on day 24
Negative control	13.00 ± 0.71[b,c]
Dose of 50 mg/kg	8.00 ± 0.63[a,b,c]
Dose of 100 mg/kg	5.00 ± 0.58[a,b,c]
Dose of 200 mg/kg	2.00 ± 0.43[a,c]
Positive control (sertraline)	2.00 ± 0.63[a,c]
Normal control	0.00 ± 0.00[a,b]

[a]$p < 0.05$ compared to the negative control, [b]$p < 0.05$ compared to the positive control, [c]$p < 0.05$ compared to normal control.

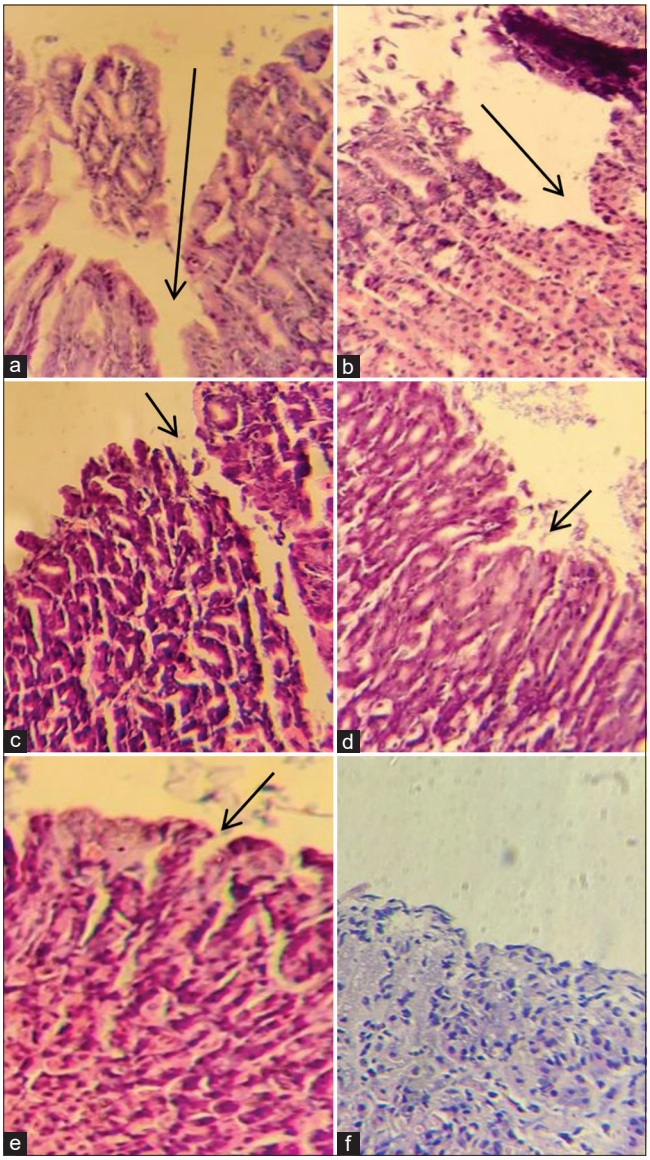

Figure 8: Microscopic of gastric mucosa; (a) negative control; (b) dose of 50 mg/kg; (c) dose of 100 mg/kg; (d) dose of 200 mg/kg; (e) positive control; (f) normal control. Explanation: The erosion of gastric mucosa pointed with a black arrow

stressed mice were more likely to spend some time sitting still near the wall than doing activities in the middle of the box [24].

In addition, there was also a significant decrease in body weight in depressed animals. This happens because exposure to chronic stress can cause a decrease in food intake [28]. Stress conditions can also increase the speed of metabolism and nitrogen excretion so that endogenous proteins and fat reserves in the body are broken down into energy sources [29]. This is consistent with depressive symptoms [2].

In depressive conditions, there is a metabolic disorder of the neurotransmitter biogenic amines, which results in a decrease in the amount of noradrenaline (NE), serotonin (5-HT), and dopamine (DA) signaling [30]. In addition, there was also a decrease in brain-derived neurotrophic factors (BDNF) [31].

In this research, the administration of *C. heyneana* extract for 10 days provided a good antidepressant effect that can be seen in the increase in body weight, decreased immobility time, and increased locomotor activity. In this study, although the number of neurotransmitters was not measured directly, the antidepressant effect could be seen directly from changes in their behavior.

In addition, depression can also cause an increase in blood glucose levels and gastric ulcers. In this research, there was no increase in blood glucose and no injury of the gastric mucosa of the animals given the extract. This result indicated that the animal recovered from a depression state toward a normal state. Some researchers mentioned that in depression conditions, atrophy of the hippocampus occurs associated with excessively increased cortisol or abnormally low concentration of BDNF. This condition is associated with diseases in the peripheral nervous system, including peptic ulcers and diabetes [31], [32], [33]. Although cortisol did not measure as a parameter of depression in this study, the impact of cortisol on diabetes and peptic ulcers can be seen in blood glucose levels, mucosal injury, and gastric microscopic.

The antidepressant effect of the *C. heyneana* extract is suggested by various chemical components contained in it. Based on this research, it is known that the rhizome of *C. heyneana* contained saponins, flavonoids, and steroids/triterpenoids. Curcuminoid is one of the flavonoid compounds, and in this rhizome, the curcuminoid concentration is about 5.33%. Flavonoids show various pharmacological activities, including as antidepressants and affect various physiological and biochemical functions in the body, namely: (a) increasing BDNF; (b) modulating the monoaminergic system by increasing levels of serotonin, norepinephrine and dopamine, namely, by interacting with presynaptic 5-HT1A receptors, 5-HT2 noradrenergic α2, and dopaminergic D1, D2, and D3 receptors [34], [35] also, by inhibiting the monoamine oxidase enzyme activity [27], [36], [37]; (c) protecting neurons; (d) also, the involvement of the HPA axis [36].

In addition, curcumin can inhibit the process of gluconeogenesis in the liver so that it can reduce blood glucose levels, and curcumin can protect the gastric mucosa by increasing mucus secretion and has a vasodilator effect and with several mechanisms, including directly blocking histamine H2 receptors, inhibiting gastrin receptors, and explicitly inhibiting cyclooxygenation (COX)-2 [38].

Conclusion

The ethanol extract of *C. heyneana* at the doses of 100 and 200 mg/kg shows antidepressant activity

by decreasing immobility time, increasing locomotor activity, inhibiting blood glucose increase, and inhibiting gastric mucosal damage. Further study that needs to be addressed is to test the activity of *C. heyneana* on the animal model that undergoes depression genetically.

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