



GASTROPROTECTIVE ACTIVITY OF INHALED CURCUMA RHIZOME ESSENTIAL OIL ON MALE MICE INDUCED BY ACUTE STRESS

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ABSTRACT

Stress is the body's response to physical, emotional, or psychological stress. One of the causes of stress is sound. This study aims to determine the gastroprotective activity of the stomach of male mice given inhalation of curcuma rhizome essential oil and induced acute stress using an ultrasonic modification method. The study was conducted experimentally using male mice divided into 6 groups, namely group 1 as a normal control that was not induced by anything. Group 2 was induced by stress with ultrasonic, group 3 was a positive control given ranitidine 0.8 mg/20 grams of mouse body weight which was given orally and induced stress with ultrasonic. Group 4 was induced by stress and given inhalation of curcuma rhizome essential oil at a concentration of 0.5%, Group 5, was induced by stress and given inhalation of curcuma rhizome essential oil at a concentration of 1% and Group 6, was induced by stress and given inhalation of curcuma rhizome essential oil at a concentration of 2%. Stress was induced using an ultrasonic method, and the parameters measured were the pH of gastric fluid. The results of the study showed that inhalation of curcuma rhizome essential oil provided a gastroprotective effect, indicated by a decrease in the number of gastric ulcers and the severity of gastric ulcers.

Keywords: acute stress; curcuma xanthorrhiza; essential oil; stomach; ultrasonic

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INTRODUCTION

Stress arises when individuals are unable to cope with challenges, affecting biological, psychological, and social functions through environmental pressures, internal responses, and physiological changes (Buenrostro-Jáuregui et al., 2025). One trigger is sound—particularly ultrasonic waves—which, when continuously emitted at high frequencies (10–70 kHz, especially around 22 kHz), can induce stress in mice by disrupting the auditory nerve and suppressing the central nervous system, including the limbic system. This interference inhibits serotonin and norepinephrine release, potentially leading to gastric ulcers (Susan, 2022). In such stress-induced models, ylang-ylang (*Cananga odorata*) essential oil has shown anti-inflammatory and antinociceptive properties that help protect against gastric damage (Berenguel Lossavaro et al., 2024).

Acute stress can disrupt gastric acid secretion, mucosal blood flow, and protective mechanisms, leading to stress-related mucosal damage (SRMD) such as erosion and bleeding (Zhang et al., 2022). Gastric ulcers—lesions affecting the mucosa, submucosa, and muscularis—remain a major global health concern, with prevalence in Indonesia estimated at 6–15%, especially among individuals aged 20–60 years (WHO, 2023). SRMD arises from an imbalance between aggressive factors (e.g., acid, pepsin) and protective factors (e.g., mucus, bicarbonate), and is commonly observed in critically ill patients (Krag et al., 2021). Histamine H₂ receptor antagonists like ranitidine have traditionally been used to reduce acid secretion by inhibiting histamine and gastrin stimulation of parietal cells (Krag et al., 2020). However, recent guidelines recommend stress ulcer

prophylaxis only for high-risk patients, and ranitidine use has declined due to safety concerns (Zhang et al., 2022). The long-term use of synthetic drugs to treat stress-induced gastric disorders can lead to adverse effects such as drug resistance and organ toxicity. As a result, natural therapies are gaining attention, including the use of *Curcuma xanthorrhiza* Roxb. essential oil, which contains bioactive compounds like xanthorrhizol and curcumin known for their antioxidant, anti-inflammatory, and gastroprotective properties. Recent studies have demonstrated that *Curcuma xanthorrhiza* extract, prepared using ethanol and Natural Deep Eutectic Solvent (NADES), significantly reduces ulcer index, increases gastric mucus levels, and maintains gastric pH in mice exposed to ethanol-HCl ulcer induction (Hanifa et al., 2024). Additionally, GC-MS profiling of essential oils from different regions in Yogyakarta revealed high xanthorrhizol content and antibacterial activity, supporting its therapeutic potential (Rahman et al., 2024).

Aromatherapy with essential oils from several plants has been shown to be effective in reducing stress levels and anxiety disorders in patients (Sundara et al., 2023). Previous research has shown that curcuma essential oil can provide therapeutic effects for various health disorders, but studies specifically evaluating its effects on acute stress, particularly through inhalation, are still very limited. Inhaling eucalyptus oil at a dose of 0.5 mL in mice prevented damage to the gastric mucosa after stress induction, with a lower average score for the eucalyptus oil group (Kabrahamun et al., 2022). The mechanism of action of essential oil aromas in the human body occurs through two physiological systems: the circulatory system and the olfactory system. When ingested or applied to the skin, essential oils are absorbed by the body and then carried through the blood and lymphatic circulation through the skin's capillary processes and absorption. Capillary vessels lead to the central nervous system, and the brain will send messages to the affected organs, while the aroma through breathing will enter the nasal cavity through inhalation so that it will be recorded by the brain as a process of smell. Fragrant aromas have been shown to influence a person's psyche, memory, and emotions through a direct olfactory-neural pathway. Odor molecules bind to receptors in the olfactory epithelium, sending signals via the olfactory bulb to the limbic system and hypothalamus, where they are interpreted and translated into emotional and physiological responses (Hanifa & Suryadi, 2024). Based on this background, the authors sought to determine the gastroprotective effects of inhaling curcuma rhizome essential oil on male white mice induced by ultrasonic-modified stress.

METHOD

The study was a quantitative experimental research conducted using a preclinical design with animal models. Male mice were divided into six groups. Group 1 served as a normal control without any induced stress. Group 2 was induced with ultrasound stress. Group 3, a positive control, was administered orally with ranitidine 0.8 mg/20 grams of mouse body weight and induced with ultrasound stress. Group 4 was induced with stress and inhaled with 0.5% curcuma rhizome essential oil. Group 5 was induced with stress and inhaled with 1% curcuma rhizome essential oil. Group 6 was induced with stress and inhaled with 2% curcuma rhizome essential oil. If the data were normally distributed ($p < 0.05$), a parametric one-way analysis of variance (ANOVA) test was performed. Post hoc tests were used to determine whether there were significant differences between the treatment groups. Data on the gastroprotective effect were analyzed quantitatively by measuring gastric pH, the number of gastric ulcers, and the severity of the ulcers, followed by statistical analysis.

RESULT

Table 1. shows the results of the gastroprotective effect test of essential oil rhizome inhalation on gastric pH. The results of the percentage increase in gastric pH in mice when given essential oil inhalation at concentrations of 0.5%, 1%, and 2%.

Table 1.
Results of the percentage increase in gastric pH of mice

Treatment Group	Average body weight	Average pH	%Increase in gastric pH
Normal control	34,40 ± 0,40 ^{bce}	4,40 ± 0,04 ^{bde}	-
Negative control	22,40 ± 0,40 ^{abcd}	5,96 ± 0,05 ^{abcd}	-
Positive control	33,60 ± 0,24 ^b	4,56 ± 0,04 ^{bcd}	23,45 ± 1,14 ^{b,c}
CREO 0,5%	27,60 ± 0,50 ^{cd}	4,98 ± 0,04 ^d	16,42 ± 0,72 ^{a,d}
CREO 1%	32,4 ± 0,40 ^e	4,86 ± 0,04 ^{ae}	18,44 ± 0,45 ^a
CREO 2%	33,2 ± 0,37 ^e	4,76 ± 0,02 ^{ae}	19,98 ± 1,00 ^b

Description: CREO: Curcuma Rhizome Essential Oil

^a significantly different from the positive group

^b significantly different from the 0,5% concentration

^c significantly different from the 1% concentration

^d significantly different from the 2% concentration

^e significantly different from the negative group

^f significantly different from the normal group

The number of gastric ulcers was observed visually in the stomachs of mice that had been dissected on the 14th day after being given curcuma rhizome essential oil inhalation therapy and after gastric pH measurements were taken. The results of the observation of the average number of gastric ulcers for each group can be seen in Table 2 below.

Tabel 2.
Results of the percentage reduction in the number of gastric ulcers

Group	Average	% Reduction in the number of gastric ulcers
Normal control	0,00 ± 0,00 ^e	-
Negative control	1,20 ± 0,20 ^{ad}	-
Positive control	0,20 ± 0,20 ^e	80,00 ± 20,00
CREO 0,5%	0,80 ± 0,27	30,00 ± 37,41
CREO 1%	0,60 ± 0,24	50,00 ± 22,36
CREO 2%	0,40 ± 0,24 ^e	60,00 ± 24,49

Description: CREO: Curcuma Rhizome Essential Oil

^a significantly different from the positive group

^b significantly different from the 0,5% concentration

^c significantly different from the 1% concentration

^d significantly different from the 2% concentration

^e significantly different from the negative group

^f significantly different from the normal group

Gastric ulcer severity was determined by measuring the diameter of the gastric ulcer in the stomachs of mice using a caliper.

Table 3.
Percentage reduction in severity of gastric ulcers

Treatment Group	Average	Ulcer Index	%Reduction in severity of gastric ulcers
Normal control	0,00 ± 0,00 ^{abcde}	10,18	-
Negative control	0,54 ± 0,20 ^{af}	11,74	-
Positive control	0,26 ± 0,20 ^{ef}	10,46	49,14 ± 16,83
CREO 0,5%	0,46 ± 0,37 ^f	11,26	13,71 ± 10,66
CREO 1%	0,44 ± 0,24 ^f	11,04	17,71 ± 7,89
CREO 2%	0,40 ± 0,24 ^f	10,8	22,28 ± 14,52

Description: CREO: Curcuma Rhizome Essential Oil

^a significantly different from the positive group

^b significantly different from the 0,5% concentration

^c significantly different from the 1% concentration

^d significantly different from the 2% concentration

^e significantly different from the negative group

^f significantly different from the normal group

DISCUSSION

The gastroprotective effect of curcuma rhizome essential oil inhalation was observed by calculating the number of ulcers, ulcer severity, and gastric pH in each treatment group. The test animals were weighed beforehand to determine the oral dose of ranitidine administered to the control group. The normal control group was not induced by stress or any other stress induction, while the control group was induced solely by 26,000 Hz ultrasonic sound without any other induction. Treatment group 1 consisted of test animals induced by stress and inhaled curcuma rhizome essential oil at a concentration of 0.5%. Treatment group 2 consisted of test animals induced by stress and inhaled curcuma rhizome essential oil at a concentration of 1%. Treatment group 3 consisted of test animals induced by stress and inhaled curcuma rhizome essential oil at a concentration of 2%. Stress occurs due to ultrasonic induction carried out for 14 days, induced every day for 15 minutes. Ultrasonic stress induction is a stress induction carried out by sound induction with a frequency of 26,000 Hz. On the 14th day after treatment, the mice were sacrificed, then dissected and the stomach organs were taken, to measure the gastric pH, calculate the number of ulcers, and the severity of gastric ulcers. The stomach was cut at the junction of the esophagus (above the cardia) to below the pylorus (the distal part connected to the duodenum) the stomach was opened and washed with NaCl solution to measure the pH of the mice's stomach. Next, the stomach obtained was seen the number of gastric ulcers and the severity of gastric ulcers. Then the data analysis used ANOVA.

Results of the gastroprotective effect test of inhalation of curcuma rhizome essential oil on gastric pH

Based on Table 1, the study on the effect of inhaling essential oil from Javanese curcuma rhizome on the gastric pH of mice exposed to ultrasonically induced stress revealed that pH values varied according to the administered treatment. In rodents, normal gastric pH generally ranges from 3 to 5, but can increase under certain physiological or pathological conditions (Zhang et al., 2022). The negative control group recorded the highest pH (5.96), which, although still acidic, was likely due to their lower body weight compared to other groups. Recent studies indicate a negative correlation between body weight and gastric acid output, where reduced body mass is associated with decreased parietal cell activity and higher gastric pH (Lee et al., 2023). Significant weight loss under stress can impair mucosal perfusion and increase oxidative stress via sympathetic activation, further reducing HCl secretion (Martins et al., 2024). This suggests that the elevated pH in the negative control group is physiologically plausible, reflecting systemic effects of severe stress on gastric acid regulation and nutritional status. In contrast, the normal control group had a gastric pH of 4.40, consistent with healthy gastric function. The positive control group given ranitidine had a pH of 4.56. As a histamine H₂ receptor antagonist, ranitidine inhibits acid secretion by blocking histamine and gastrin stimulation of parietal cells but lacks antioxidant or anti-inflammatory effects (Nogueira et al., 2024). Consequently, under ultrasonic stress, gastric mucosal injury can still occur due to excessive reactive oxygen species (ROS) and inflammation.

This condition may trigger a compensatory physiological response in the form of increased gastric acid secretion, keeping pH relatively low even after ranitidine administration. In contrast, groups receiving curcuma essential oil not only maintained more stable gastric pH but also suppressed oxidative stress and inflammation. Active compounds in curcuma, such as xanthorrhizol and curcumin, possess antioxidant and anti-inflammatory activities that protect the gastric mucosa from further damage (Hanifa et al., 2024). Gastric pH in the 1% and 2% curcuma oil groups tended to be higher than in the positive control group, indicating that mucosal protection depends not only on reduced acid production but also on the ability to counteract stress and inflammation. Although all concentrations showed beneficial effects, the 2% concentration produced results closest to normal conditions. The Shapiro–Wilk normality test statistical results showed that the gastric pH data were not normally distributed ($p < 0.05$), so the analysis was continued with non-parametric methods.

The Kruskal–Wallis test showed a significant difference between groups ($p < 0.05$), indicating that the treatment had an effect on changes in gastric pH. Based on the Kruskal–Wallis test results, $p = 0.005$ ($p < 0.05$) was obtained, indicating that there was a significant difference in gastric pH reduction between treatment groups. This indicates that inhalation of curcuma rhizome essential oil at various concentrations has an effect on the level of gastric acidity in mice induced by acute stress. After the Kruskal–Wallis test, a Mann–Whitney test was continued. The Mann–Whitney test was used to see whether the two groups differed significantly. Overall, curcuma essential oil has the potential as a natural alternative for preventing stress and protecting the stomach from the effects of stress, although its effectiveness is still slightly below ranitidine. These results confirm that the administration of curcuma rhizome essential oil by inhalation can have a significant effect on increasing the gastric pH of mice experiencing acute stress. The percentage increase in gastric pH is an important indicator to assess the effectiveness of treatment in reducing gastric acidity due to stress. From the data obtained, the positive control group showed an increase in pH of $23.45 \pm 1.14\%$, a concentration of 0.5%, an increase in gastric pH was recorded at $16.42 \pm 0.72\%$, while concentrations of 1% and 2% each resulted in a decrease of $18.44 \pm 0.45\%$ and $19.98 \pm 1.00\%$, respectively. The gastroprotective mechanism of curcuma essential oil involves inhibition of excessive gastric acid secretion, particularly under stress or inflammation, by modulating histamine and gastrin release to parietal cells. This reduces HCl production, balancing gastric pH and preventing mucosal damage. Its high antioxidant capacity neutralizes ROS, thereby controlling inflammation, reducing mucosal injury, and supporting recovery (Hanifa et al., 2024).

Results of the gastroprotective effect test of inhalation of curcuma rhizome essential oil on the number of ulcers.

The results of the study show that the number of gastric ulcers is one indicator of mucosal damage due to stress exposure. Based on the statistical data processing in Table 2, the Shapiro–Wilk normality test shows that the data on the number of gastric ulcers is not normally distributed ($p < 0.05$), so the analysis was continued with a non-parametric method. The Kruskal–Wallis test showed a significant difference between groups ($p > 0.05$). As can be seen from the percentage decrease in the number of gastric ulcers, the negative control group had the highest average number of gastric ulcers, namely 1.20 ± 0.20 , indicating that acute stress can cause significant gastric mucosal damage if not given protective treatment.

The positive control group receiving ranitidine therapy showed an average number of gastric ulcers of 0.20 ± 0.20 with a percentage reduction of ulcers reaching $80 \pm 20.00\%$. This indicates that ranitidine can prevent the formation of stress-induced ulcers. In the group given the inhalation of curcuma rhizome essential oil, a decrease in the number of ulcers was seen depending on the concentration. The group with a concentration of 0.5% showed a decrease of $30 \pm 37.41\%$, while the concentrations of 1% and 2% showed a decrease of $50 \pm 22.36\%$ and $60 \pm 24.49\%$, respectively. Based on the results of the study, the effective concentration of curcuma rhizome essential oil in reducing the number of gastric ulcers in mice induced by acute stress was at a concentration of 1%, which resulted in a decrease in the number of ulcers by $50\% \pm 22.36$. This concentration demonstrates a balance between effectiveness and response stability, and indicates a positive concentration-response relationship for gastric mucosal protection. The effectiveness of curcuma rhizome essential oil against gastric ulcers demonstrates a positive concentration-response relationship, where increasing essential oil concentration correlates with increased protective effects. A concentration of 0.5% is not yet effective enough due to its mild effect and unstable results with a large standard deviation value. A concentration of 1% shows a balance between effectiveness and consistency, with a 50% reduction in ulcers and a smaller standard deviation. Meanwhile, a concentration of 2% provides the highest protective effect, but is not the most efficient concentration considering the stability and efficiency of the concentration for long-term use. Therefore, a concentration of curcuma rhizome essential oil at 1% can be considered an effective concentration.

The mechanism by which essential oils improve the number of gastric ulcers is by stimulating the secretion of mucus and bicarbonate on the surface of the gastric mucosa. These two components are crucial in maintaining the mucosal barrier or protective layer against the damaging effects of gastric acid and digestive enzymes. Mucus functions as a physical layer covering gastric epithelial cells, while bicarbonate plays a role in neutralizing hydrogen ions, thus helping to maintain a more neutral microenvironment pH near the mucosal surface, even though the overall pH of the stomach is highly acidic (Kabrahamun et al., 2022). In this way, the gastric mucosa is protected from erosion, inflammation, or ulceration due to excess acid, especially under conditions of stress or inflammation. This mucus and bicarbonate stimulating effect explains the contribution of curcuma essential oil in preventing gastric mucosal damage and supporting the healing process of irritated tissue (Athala, 2021).

Results of the gastroprotective effect test of inhalation of curcuma rhizome essential oil on ulcer severity

The gastric ulcer index in Table 3 reflects the severity of gastric mucosal ulcer lesions caused by stress. The higher the index value, the more severe the mucosal damage. In this study, the negative control group had the highest ulcer index (11.74), indicating that untreated stress significantly damaged the gastric mucosa. Exposure to ultrasonic waves can cause mucosal injury through several mechanisms, including direct mechanical stress on epithelial cells that disrupts tissue integrity, and increased production of reactive oxygen species (ROS) that trigger oxidative stress. These ROS damage cell membranes, proteins, and DNA, leading to cell death and an inflammatory response (Rezvani, 2024). Cellular injury stimulates the release of pro-inflammatory mediators and interleukins, which exacerbate inflammation and tissue destruction. In addition, disruption of the mucus layer and epithelial cells compromises the mucosal barrier, allowing gastric acid and digestive enzymes to penetrate more easily, increasing the risk of erosion and ulceration. Ultrasonic exposure can also impair microcirculation in the gastric mucosa, reducing oxygen and nutrient delivery required for tissue regeneration, thereby slowing the healing process (Popovic et al., 2023).

In contrast, the normal control group showed the lowest index value, namely 10.18, reflecting a healthy stomach condition without stress or treatment. The positive control group receiving ranitidine therapy showed a decrease in the ulcer index to 10.46, with a percentage decrease in severity of $49.14 \pm 16.83\%$. This indicates the effectiveness of ranitidine treatment in reducing the severity of stress-induced ulcers. In the treatment group with curcuma rhizome essential oil inhalation, there was a gradual decrease in the ulcer index as the concentration increased, 0.5%, namely an index of 11.26 (a decrease in severity of $13.71 \pm 10.66\%$), 1% index of 11.04 (a decrease in severity of $17.71 \pm 7.89\%$), 2% index of 10.80 (a decrease in severity of $22.28 \pm 14.52\%$). Although the index values in these three groups were not as effective as the positive control, there was a decrease in the severity of gastric ulcers that was consistent with the increase in concentration. This shows that curcuma essential oil is able to provide protection against gastric mucosa damaged by stress, although at a lower capacity than standard treatment.

Based on statistical data processing of the reduction in gastric ulcer severity, the Shapiro–Wilk normality test showed that the number of gastric ulcers was not normally distributed ($p < 0.05$), so the analysis was continued with a non-parametric method. The Kruskal–Wallis test showed a significant difference between groups ($p > 0.05$). The statistical test results showed that the negative control group had the highest gastric ulcer score (0.54 ± 0.20) and was significantly different from the positive control and normal control ($p < 0.05$). The MART group showed a gradual decrease in ulcer scores as the concentration increased, with the lowest value at MART 2% (0.40 ± 0.24). Although all MART groups were still significantly different from normal controls, these results indicate that curcuma rhizome essential oil has a cytoprotective effect on the stomach, especially at higher concentrations. The gastric ulcer index and the percentage reduction in ulcer severity can be

seen from the 0.5% concentration, which only showed a 13.71% reduction in severity, with a fairly large SD (± 10.66). This indicates that the protective effect is still mild and unstable, and not yet effective enough to prevent complete mucosal damage. The 1% concentration increased protection to 17.71%, with the smallest SD (± 7.89). This indicates a protective effect that is starting to stabilize, with more consistent results between animals. This concentration is the minimum effective concentration that provides a significant protective response. And the 2% concentration provided the highest reduction in severity (22.28%), approaching the positive control. However, the standard deviation value is quite high (± 14.52), indicating that despite the strong effect, the animal response is more variable compared to 1% curcuma rhizome essential oil.

The essential oil from Javanese curcuma rhizome has anti-inflammatory and antioxidant properties that play a key role in reducing the severity of gastric mucosal ulcers. Active compounds in the essential oil, such as xanthorrhizol and curcumin, work by inhibiting the production of inflammatory mediators such as TNF- α , interleukin-1 beta (IL-1 β), and prostaglandin E2 (PGE2), which are typically elevated in gastric inflammation (Simamora et al., 2024). Furthermore, this essential oil can neutralize reactive oxygen species (ROS) generated during the inflammatory process, thereby reducing oxidative stress that can damage cell membranes and exacerbate tissue injury (Liao et al., 2022). By mitigating inflammation and oxidative stress, Javanese curcuma essential oil supports the healing of gastric mucosa and reduces ulcer severity. These findings are consistent with recent studies demonstrating that *Curcuma xanthorrhiza* exhibits gastroprotective effects and modulates inflammatory pathways such as NF- κ B, contributing to mucosal protection and recovery (Syamsi et al., 2025).

CONCLUSION

Inhalation of curcuma rhizome essential oil has gastroprotective activity in the stomachs of mice experiencing acute stress. This was demonstrated by a reduction in the number and severity of gastric ulcers and an improvement in the structure of the gastric mucosa.

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