Gastroprotective Effects of *Curcuma zedoaria* in Ethanol-Induced Gastric Ulcers of Experimental Rats

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ABSTRAK

Sutardi LN, Mustika AA, Andiyanto, Handharyani E, Winarto A, Rahma A, Nabilah AS, Rahman FA. 2024. Efek gastroprotektif dari *Curcuma zedoria* terhadap kejadiaan gastritis ulcerative pada tikus yang diinduksi dengan etanol. JITV 29(2):97-102. DOI: http://dx.doi.org/10.14334/jitv.v29i2.3183.

Gastritis merupakan salah satu masalah kesehatan global. Kejadian ulkusa dapat dikarakterisasi dengan melihat adanya inflamasi pada lapisan epitel mukosa lambung. Kerusakan di lambung dapat terjadi karena kelebihan sekresi asam lambung, pepsin, dan kehadiran *Helicobacter pylori*, stress, kebiasaan merokok, meminum alcohol, pola makan yang tidak teratur. Infeksi. Dan akibat penggunaan *non-steroidal anti-inflammatory drugs*. Penelitian ini bertujuan untuk mengetahui efek gastroprotektif infusa *Curcuma zedoaria* pada tikus yang mengalami kerusakan mukosa lambung akibat diinduksi HCl/ethanol. Sebanyak 16 tikus Sprague Dawley dibagi menjadi 4 kelompok secara acak: kelompok kontrol negatif (tanpa pemberian terapi), kelompok kontrol positif (terapi dengan omeprazol), P1 (infusa temu putih 30%), dan P2 (infusa temu putih 60%). Parameter penelitian yang dievaluasi adala lesio mukosa lambung, degenerasi sel, kerusakan intraseluler, dan nilai pH. Skor ulkus dan kerusakan mukosa lambung dievaluasi melalui inflamasi mukosa lambung dan pemeriksaan histopatologi. Pemberian infusa temu putih dapat menurunkan indeks ulkus secara signifikan ($P<0.05$) melalui pencegahan terjadinya lesion mukosa lambung, erosi, degenerasi seluler, dan nilai pH juga naik secara signifikan. Hasil penelitian ini menunjukkan bahwa infusa temu putih memiliki efek gastroprotektif yang dapat digunakan untuk mendukung penggunaan obat tradisional.

Kata Kunci: *Curcuma zedoria*, Gastritis, Temu Putih

ABSTRACT

Sutardi LN, Mustika AA, Andiyanto, Handharyani E, Winarto A, Rahma A, Nabilah AS, Rahman FA. 2024. Gastroprotective effects of *Curcuma zedoaria* in ethanol-induced gastritis ulcers of experimental rats. JITV 29(2):97-1021. DOI: http://dx.doi.org/10.14334/jitv.v29i2.3183.

Gastritis is one of the most common health problems of humans in the world. Gastric ulcer is mostly characterized by inflammation of the epithelial cells lining the gastric mucosa. Stomach injury may occur due to excessive secretion of stomach acid, pepsin, *Helicobacter pylori*, stress, smoking habit, alcohol consumption, irregular eating pattern, infection, and the use of non-steroidal anti-inflammatory drugs. This study aimed to explore the gastroprotective effects of *Curcuma zedoaria* infusion (CZI) on HCl/ethanol-induced gastric mucosal damage in rats. A total of 16 Sprague Dawley rats were randomly divided into 4 groups: negative control (without treatment), positive control (treated with omeprazole), P1 (CZI 30%), and P2 (CZI 60%). Several endpoints were evaluated, including gastric mucosal lesions, cellular degeneration, intracellular damage, and pH value. The gastric mucosal injury and ulcer score were determined by evaluating the inflamed gastric mucosa and by histopathological examination. After the treatment animal with CZI significantly ($P<0.05$) decreased the ulcer index by preventing gastric mucosal lesions, erosion, and cellular degeneration, and the value of pH value was increased ($P<0.05$). These results demonstrate that CZI has significant gastroprotective properties which support its use in traditional medicine.

Key Words: *Curcuma zedoaria*, Gastritis, White Turmeric

INTRODUCTION

Gastritis is one of the most common health problems in the human population. Gastritis is an inflammatory disorder that may be caused by various factors. Necrosis and desquamation of epithelial cells of the stomach may appear and may further lead to stomach ulcers ((Beiranvand & Bahramikia 2020)). Stomach constructive factors are the secretion of mucin, peptide, prostaglandin, and vascularization. Stomach destructive factors are the secretion of stomach acid and peptides, *Helicobacter pylori*, stress, smoking habit, alcohol,

irregular eating pattern, infection, and non-steroidal anti-inflammatory drugs (Chiou et al. 2010); Beiranvand & Bahramikia 2020)).

According to the World Health Organization (WHO), the prevalences of gastritis incidence are as follow: Canada (35.0%), China (31.0%), France (29.55%), England (22.0%), and Japan (14.5%). Gastritis in Indonesia is on the sixth place with the number of cases being 33,580 (60.86%) for inpatients, and on the seventh place with the number of cases 201,083 for outpatients. The gastritis case prevalence in Indonesia for several cities are: Medan reaches 91.6%, Jakarta 50%, Denpasar 46%, Palembang 35.5%, Bandung 32%, Aceh 31.7%, Surabaya 31.2%, and Pontianak 31.2% (Mustakim et al. 2022). The disease may affect family economy value due to relatively high expenses for gastritis treatment (Joish et al. 2005).

Many studies have been conducted to develop a suitable drug to control gastritis problems. Herbal medicines are known as an alternative approach to treat gastric ulcer. Several herbal preparates have been investigated recently, such as *Origanum syriacum L.*, *Gardnia jasminoides Ellis,* Korean red ginseng, *Kalopanax pictus*, *Curcuma zedoria* and other such plants (Lee et al. 2009; Oyagi et al. 2010; Afify et al. 2012; Sohn et al. 2015; Gozali et al. 2022). *Curcuma zedoaria*, also known as white turmeric, is a traditional herb in Indonesia (Gozali et al. 2022). The plant is known to be effective to treat gastrointestinal disorders, such as nausea, gastroparesis, and gastric atony. It also prevents gastric ulceration caused by stress and HCl (Kimura et al. 2013).

The purpose of this study was to evaluate the gastroprotective effects of white turmeric infusion for acute gastritis through the assessment of inhibitory effects on stomach mucosal lining cell damage, irritated by HCl/ethanol as well as the anti-inflammatory activity in stomach tissue. This research used acute gastritis animal models in vivo. Finally, it is expected to provide scientific information on the efficacy of white turmeric infusion as a gastroprotective agent for gastritis alternative treatment. This information could also be used as the basis of standardized herbal drug development from white turmeric infusion in controlling gastritis.

MATERIALS AND METHODS

Curcuma zedoaria rhizomes were used in this research as an infusion and were obtained from Tropical Biopharmaca Research Center, IPB University, Bogor. Chemicals and reagents included ethanol 60%, HCl 0.3 M, omeprazole, male *Sprague Dawley* (DW) rats (Laboratory Animal Management Unit, School of Veterinary Medicine and Biomedical Sciences, IPB University), ketamine (Ket A 100®, Peru), xylazine *(Dormi-Xyl*®2, Peru), pH universal strop test*,* graduated alcohol (PT. Brataco, Indonesia), xylol (Merck, German*)*, buffered neutral formalin (BNF) 10% (Delta Lab, Indonesia), Hematoxylin-Eosin (HE) (Merck, Germany), Phosphate Buffer Saline (PBS) (Sigma-Aldrich, American), distilled water (PT. Brataco, Indonesia), and gum. Laboratory equipment was rodent cages (UPHL FKH IPB, Indonesia), scale (Camry, Indonesia), automatic tissue processor *(Sakura*®, USA), rotary microtome, and light microscope (Olympus®, Japan).

Preparation of white turmeric infusion

The infusion was produced by washing and slicing fresh white turmeric rhizomes, followed by boiling in an infusion pan with the ratio between white turmeric and distilled water being 1:10. Boiling was performed at 90°C for 15 minutes until a final concentration of an infusion at 10% was obtained. The white turmeric rhizomes infusion was then diluted to 30% and 60% concentrations.

Gastritis induction in rats

The animals used in this experiment were male Sprague Dawley rats weighing 180-200 grams. The animal feed followed a standard nutrition content according to the Indonesian Food and Drug Authority (Badan Pengawas Obat dan Makanan Republik Indonesia-BPOM RI). Drinking water was provided *ad libitum*. Rats were kept in a normal living environment at 25-28°C and 35-60% humidity. The rats were acclimatized for 14 days.

Sixteen rats were randomly assigned to four groups, 4 rats in each, and fasted for 18h prior to oral dosing with the normal saline solution (negative group/KN), omeprazole (a standard treatment control at a dose of 20 mg/kg bw; positive group/KP), and CZI at concentration 30% (P1) and 60% (P2). Ninety minutes later, all the rats were orally administered 5 ml/kg bw of a mixture of ethanol 60% and 0.15 M HCl solution. All rats were then anesthetized with ketamine and xylazine to reduce pain. Rats were killed by cervical dislocation 90 minutes after the administration of HCl/ethanol solution. The stomach was quickly removed and fixed in 10% neutral formalin solution for 1h, opened by an incision along the greater curvature (Al-Quraishy et al. 2017; Nam & Choo 2021).

Macroscopic lesions of the stomach mucosal lining cells

All rats were necropsied for pathological examination and tissue collection of the stomach. The

stomachs were released from the abdomen and incised to measure the acidity of stomach fluid content using a pH universal strip test (merck universal pH indicator). The stomachs were then washed with physiological NaCl to observe the stomach mucosal lining cells. The stomachs were then fixed in buffer-neutral formalin 10% for histopathological examination. The macroscopic evaluation score was based on gastric mucosa hemorrhage, hyperemic, and loss of rugae (score 0-3; 0 no lesions, 1 mild, 2 moderates, 3 severe).

Microscopic examination

The fixed tissues of the stomach were trimmed at the corpus (glandular) region and set into a tissue cassette. The samples were dehydrated and cleared in an automatic tissue processor with graduated alcohol and xylol. The tissues were put in a paraffin block, cut by rotary microtome, and attached to the object glass. Rehydration was performed followed by staining with hematoxylin and eosin. The slides were examined under the microscope and assessed for histopathological changes such as congestion, mucosal erosion, and inflammation (score 0-3; 0 no lesions, 1 mild, 2 moderate, 3 severe).

Data analysis

The data analysis process of this study included two stages. The first stage included a descriptive analysis to describe the distribution of the data. The second stage included hypothesis testing with ANOVA.

Animal ethics approval

Ethical approval for this study was obtained from The Animal Ethics Committee, School of Veterinary Medicine and Biomedical Sciences, IPB University under certificate Number: 020/KEH/SKE/VII/2022.

RESULTS AND DISCUSSION

The stomach is characterized by folded villi mucosae known as the rugae. The mucosae of the stomach are formed by 3 layers including the epithelial, propria, and muscular layers. The administration of ethanol to rats may cause mucosal damage to the stomach. The injury of stomach mucosae is commonly followed by lowering the pH level of the stomach content, where the normal pH value of the stomach is around 6.5 (Beiranvand & Bahramikia 2020). The present study shows that the negative control was the most acidic stomach content among all treatment groups. The pH value of stomach content (Table 1) are as follows: the negative control (KF) is 1.5, the positive control dosed with omeprazole (KP) is 5.25, the white turmeric 30% infusion (P1 30%) is 3, and the white turmeric 60% infusion (P2 60%) is 3.75. Omeprazole is a drug often used to increase the pH value of the stomach and is regarded as an effective drug to treat stomach acid (Mahdayana et al. 2020; Lazebnik et al. 2021). Omeprazole works by inhibiting the acid-activated proton pump so that it then forms covalent bonds with H+, K+, and ATPase via disulfide bonds which in turn inhibits acid pump enzymes (Shin & Kim 2013). The same mechanism is thought to occur in the use of white turmeric which is known to contain curcumin. Because curcumin can act as a secretion of gastric acid through inhibition of H+/K+ATPase in gastric parietal cells, resulting in a decrease in gastric pH in rats (Kim et al. 2005; Mei et al. 2009; He et al. 2015). Table 1 shows that the white turmeric infusion was effective to control stomach acid problems.

Macroscopically shows that stomach ulcer, congestion, and hemorrhage were not found in the positive control and omeprazole group (Figure 1). The negative control showed congestion, hemorrhage, and ulcer formation on the surface of the stomach mucosa (Figure 1). The stomach of the P1 group was suffering from general hyperemia without hemorrhage, and only a few hyperemias were seen in the P2 group. The rugae of the KN group showed fewer rugae and flattened stomach mucosal. On the other hand, many stomach rugae were noted in the omeprazole group (KP group) and P2 group (*Curcuma zedoria* infusion in 60%), although the P2 group did not have as much a positive control. Identical damage was observed macroscopically in the stomach that did not receive treatment (KN) (Fig. 1a). The stomach of KN rats had the lowest pH value and the highest macroscopic damage of 5.50±1.00 (Table 1). The data supported microscopically (Figure 2) shows that hyperemia and massive infiltration of inflammatory cells in the mucosal region followed by desquamation of mucosae epithelial cells were found in the negative control group with the score 8.67±0.58. Based on Table 1, it is known that macroscopically through assessing the severity of the incidence of hemorrhage, hyperemia, and loss of mucosal folds, it is known that giving CZI 30% compared to giving CZI 60% or treatment using omeprazole, not significantly different ($P<0.05$). Further microscopic observations revealed that giving a CZI of 60% had a better effect compared to rats given a CZI of 30%. It seems that the treatment of stomach ulcers depends on the concentration of white turmeric infusion where a higher concentration of white turmeric infusion was dosed will lead to a better condition of stomach recovery.

The local defense of stomach mucosae is an important factor that protects the mucosa cells from irritants. Several components of mucosal defense are the mucosal blood flow, mucus and bicarbonate secretion,

Table 1. Results of gastric pH, macroscopic and microscopic observations

Kelompok	pH	Skor Makro	Skor Mikro
KN	1.50±0.58^{c}	5.50±1.00^{a}	8.67±0.58^{a}
KP	5.25±0.50^{a}	4.25±1.89^{ab}	4.33±0.58^{bc}
P1	3.00±0.00^{b}	2.50±1.29^{b}	5.00±1.00^{b}
P2	3.75±0.96^{b}	3.00±1.16^{ab}	3.00±0.00^{c}

Gastric macroscopic is assessed by parameters of hemorrhage, hyperemia, loss of mucosal folds (score 0-3; 0 no lesio, 1 mild, 2 moderate, 3 severe). Gastric microscopy was assessed by parameters of congestion, erosion, and inflammation (score 1-3; 1 mild, 2 moderates, 3 severe). Different superscript letters show significant differences (P<0.05)

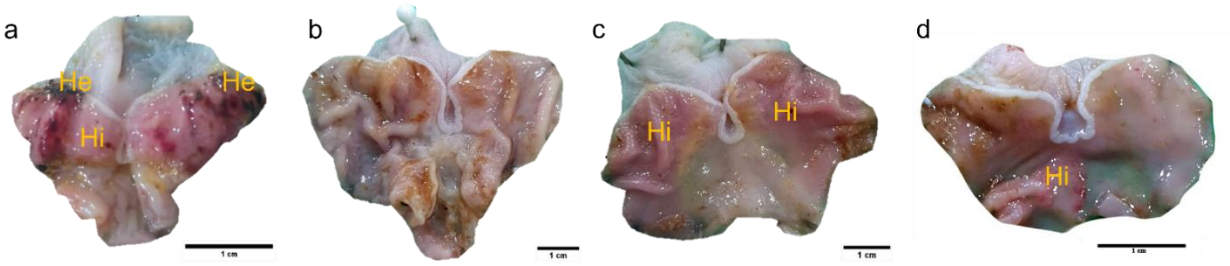

Figure 1. Gross pathology. The effect of white turmeric (*Curcuma zedoaria*) infusion on *Sprague Dawley* (SD) rat stomach suffering from gastritis on treatment groups: a). negative control b). positive control (omeprazole), c). infusion 30%, d). infusion 60%. He: hemorrhage, Hi: hyperemia

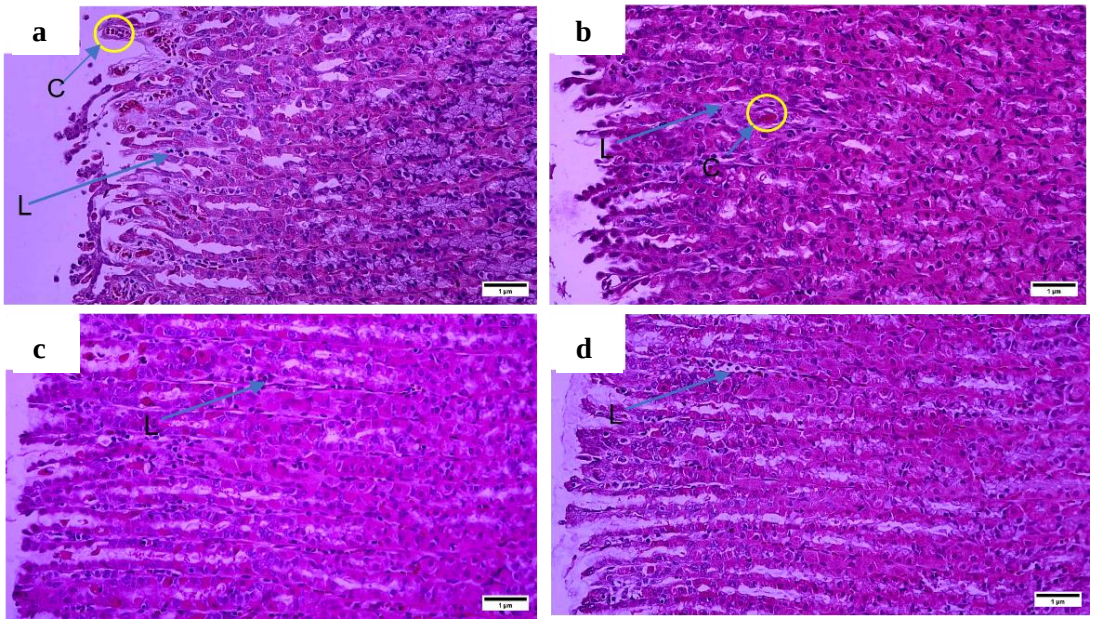

Figure 2. Histopathology of white turmeric (*Curcuma zedoaria*) infusion on the stomach of Sprague Dawley (SD) rats suffering from gastritis, in treatment groups: a). negative control, b). positive control (omeprazole), c). infusion 30%, d). infusion 60%. (staining: HE, magnification: objektive 20x). C: congestion, L: lymphocyte

prostaglandin, and the proliferation of mucosal cells (Laine et al. 2008). If this mucosal defense mechanism is affected followed by the presence of an irritant agent such as ethanol, stomach mucosal damage may occur.

Ethanol is known to cause severe effects in the stomach, such as acute mucosal inflammation, mucosal hyperemia, edema, bleeding, erosion, and stomach mucosa ulceration. Alcohol dehydrogenase found in the stomach can catalyze ethanol into acetyl aldehyde, and oxidation xanthine which would catalyze ethanol into free radicals. The free radicals will then increase the production of reactive oxygen species (ROS) that triggers endothelial cell damage (Chen et al. 2019). The combination of HCl and ethanol may stimulate stomach acid secretion, necrosis, and apoptosis of stomach mucosa through the destruction of the local mucosa

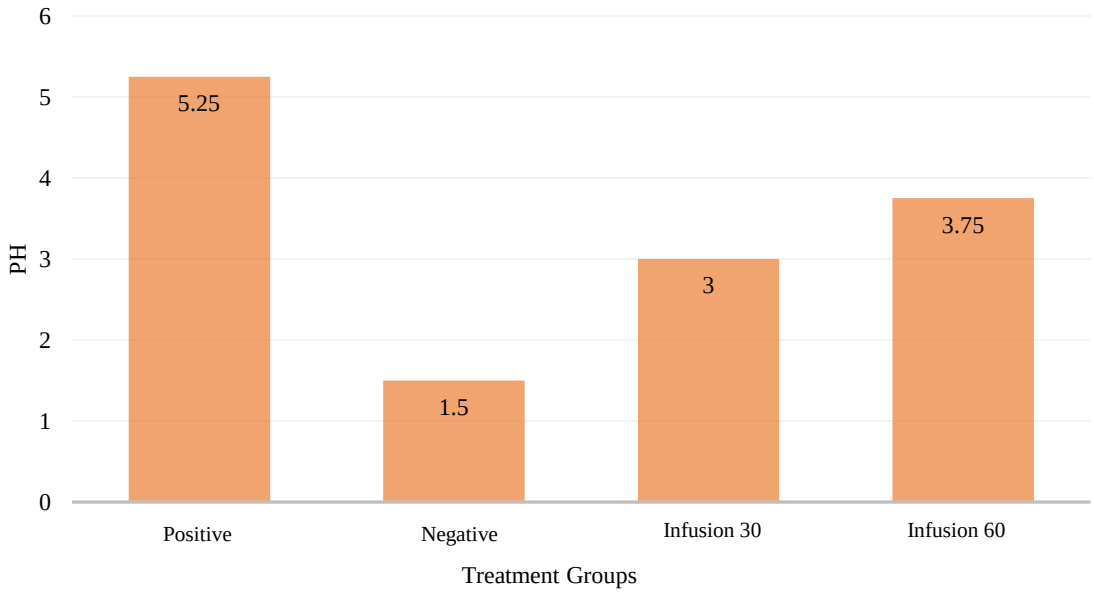

Figure 3. Rat Stomach pH Value

defense system (Bujanda 2000; Sohn et al. 2015). The high number of lymphocyte cells microscopically indicates the inflammation of the stomach. The results of the microscopic assessment carried out sequentially for negative, and positive controls, CZI 30% and CZI 60% were 8.67±0.58, 4.33±0.58, 5.00±1.00, and 3.00±0.00.

Curcuma zedoaria is reported to contain several bioactive including tannins, flavonoids, saponins, alkaloids, terpenoids, carbohydrates, and steroids (Azam et al. 2017). The flavonoid compound in white turmeric acts as an antioxidant containing hydroxyl radicals and superoxide which protect the lipid membrane and prevents cell damage (Czekaj et al. 2018; Gozali et al. 2022). The flavonoid compound, quercetin, contained in white turmeric could also possibly have a protective effect on the mucosa by lowering oxidative stress and increasing the activity of the antioxidant enzyme (Coşkun et al. 2004). The curcumin content in *Curcuma zedoaria* also has anti-inflammatory activity by inhibiting the production of NO and expression of iNOS induced by LPS, as well as the expression and activation of cyclooxygenase-2 (COX-2) (Pan et al. 2000; Hong et al. 2004). These could be the reasons that few inflammations were noted in rats given white turmeric infusion prior to gastritis induction.

CONCLUSION

Curcuma zedoaria can inhibit the stomach-damaging effect of ethanol and HCl administration. Based on the macroscopic and histopathological features of rat stomachs given white turmeric infusion, it was found that stomach injuries decreased along with the increase of white turmeric concentration that was given.

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