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Evaluating the effects of goat's milk on inflammatory responses in rat model with gastritis

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ABSTRACT

Introduction: Gastritis is a health issue that can lead to various complications, including chronic atrophic gastritis, gastric metaplasia/dysplasia, iron deficiency anaemia, gastric bleeding, gastric perforation, and gastric cancer. Goat's milk contains bioactive ingredients, particularly proteins, that offer significant health benefits. This study aimed to examine the potential of goat's milk as an anti-inflammatory agent in gastritis rat models. **Methods:** This research used a pre-clinical experimental design. A total of 25 rats were divided into five groups (n=5 per group): three groups received goat's milk at doses of 0.5 ml, 1 ml, and 1.5 ml daily for 30 days, followed by ethanol administration (80%, 1 ml) for three consecutive days; one group received no treatment and was not exposed to ethanol; and one group received ethanol without prior goat's milk administration. Interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), and interleukin-10 (IL-10) cytokines were analysed using the Luminex Multiplex Bead Assay. **Results:** Administering 1.0 ml and 1.5 ml of goat's milk for 30 days increased IL-10 and inhibited the increase in IL-6 and TNF-α in gastritis rat models compared with administering 0.5 ml of goat's milk. Histological examination revealed a marked improvement in integrity of gastric mucosal layer, with reduced signs of cellular damage, less infiltration of inflammatory cells, and an increase in thickness of mucosal layer. These histological findings correlated with observed cytokine changes, suggesting that goat's milk exerts a protective effect on gastric mucosa, potentially through immunomodulatory mechanisms. **Conclusion:** Goat's milk showed protective and anti-inflammatory effects in a rat model of gastritis, indicating its potential as a supportive dietary component for gastric health, pending further research.

Keywords: cytokines, ethanol, gastritis, goat milk, inflammatory

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INTRODUCTION

Gastritis is an inflammatory condition that occurs when the stomach lining becomes irritated due to a lack of protective mucus. This inflammation can manifest as either sudden (acute) or long-lasting (chronic) (Sylvia, 2013). If acute gastritis is not properly treated, it can progress to a chronic state and lead to various complications, such as chronic atrophic gastritis, gastric metaplasia or dysplasia, iron deficiency anaemia, gastric bleeding, gastric perforation, and gastric cancer.

One of the common causes of gastritis is the imbalance between aggressive and defensive/protective factors, in which the first factor is dominant over the latter. Aggressive factors include stomach acid, pepsin, biliary reflux, ethanol, Non-steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, *Helicobacter pylori* (*H. pylori*), and free radicals. Meanwhile, defensive factors encompass mucosal microcirculation, surface epithelial cells, prostaglandins, phospholipids, mucus, bicarbonate, and digestive tract motility (Silva & de Sousa, 2011). Alcohol (ethanol) ingestion can lead to gastric cell necrosis and blood vessel injury, resulting in ulceration. This occurs due to the formation of hydroperoxyl free radicals and superoxide anions produced during ethanol metabolism in the body (Baratawijaya, 2018). Additionally, ethanol administration disrupts the balance of pro-inflammatory cytokines and affects the nitric oxide pathway. On the other hand, goat's milk contains beneficial bioactive substances, particularly proteins. Some of these proteins include casein (α, β, γ), α-lactalbumin, β-lactoglobulin, immunoglobulin A, immunoglobulin M, immunoglobulin G, lactoferrin, lactoperoxidase, and lysozyme. Notably, α-lactalbumin and lactoferrin function as immunomodulators (Cross & Gill, 2000; Lamothe *et al.,* 2007).

Goat's milk influences inflammatory cytokines, such as TNF-α, IL-6, and IL-10, which play a role in gastritis. Its potential to regulate inflammatory cytokine levels suggests it could serve as an adjunct therapy to support gastric mucosal healing. In this context, goat's milk could offer benefits as a natural immunomodulator, directly reducing gastric inflammation through decreased levels of interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), while promoting tissue repair through increased interleukin-10 (IL-10) (De Ciucis *et al.*, 2023; Albenzio *et al.*, 2021; Lima *et al.*, 2017). This approach underlines how findings on the effect of goat's milk on cytokine regulation may provide a promising new guideline for developing nutrition-based therapies in the supportive treatment of gastritis.

One of the primary reasons for favouring goat's milk over cow's milk is its digestibility. Goat's milk has smaller fat globules and higher levels of medium-chain fatty acids, such as caprylic and capric acids, which are easier for the digestive system to process. This structure makes goat's milk more easily broken down in the stomach, reducing the likelihood of digestive discomfort often associated with cow's milk, particularly in individuals with lactose sensitivity. Additionally, the protein structure of goat's milk differs from cow's milk. Goat's milk contains less α_{s1}-casein, the protein in cow's milk most commonly linked to allergies, making it generally less allergenic and more tolerable for sensitive individuals (Nayik *et al.*, 2022; Rahmatalla, Arends & Brockmann, 2022).

Another factor that highlights goat's milk as a beneficial choice for digestive health is its anti-inflammatory potential. Goat's milk contains various bioactive compounds, including oligosaccharides, that possess anti-inflammatory properties, which can help soothe the gastrointestinal tract. These oligosaccharides function as prebiotics, supporting the growth of beneficial gut bacteria and promoting a balanced gut microbiome. A healthy microbiome plays a critical role in digestive health, as it aids in nutrient absorption, immune function, and protection against pathogens (Leong *et al.*, 2019; Mecocci *et al.*, 2020).

In addition to these benefits, goat's milk has a rich nutrient profile, providing significant amounts of essential vitamins and minerals such as calcium, phosphorus, magnesium, and vitamin A. These nutrients contribute to overall gut health by supporting the structural integrity and function of the gastrointestinal mucosa, which is essential in preventing and repairing damage caused by conditions such as gastritis or peptic ulcers. The presence of bioavailable minerals in goat's milk also enhances its absorption, meaning the body can more effectively utilise these nutrients compared to those in cow's milk (Singh *et al.*, 2021).

This study aimed to evaluate the effects of goat's milk administration on the levels of inflammatory cytokines (IL-6 and TNF-α) and anti-inflammatory cytokine (IL-10) in rat models with gastritis. Additionally, this study sought to assess the gastroprotective potential of goat's milk for gastric mucosal health through immunomodulatory mechanisms. Based on previous studies indicating the anti-inflammatory effects and digestibility of goat's milk, the hypothesis of this study was that administering goat's milk will decrease the levels of pro-inflammatory cytokines IL-6 and TNF-α and increase the levels of the anti-inflammatory cytokine IL-10 in rats with gastritis, indicating the potential of goat's milk as a gastroprotective agent (ALKaisy *et al.*, 2023; Paikray *et al.*, 2024; Panta *et al.*, 2021).

Comparison with cow's milk

a. *Lactose content and digestibility.* Goat's milk has a slightly lower lactose content than cow's milk, as well as a protein structure that is more easily digested. Goat's milk contains smaller and finer protein molecules, making it more bioavailable and easier for the body to absorb. Studies showed that individuals who are intolerant to cow's milk may find goat's milk easier to digest, making it a suitable alternative for those sensitive to lactose or the protein casein found in cow's milk (Lima *et al.*, 2017; Singh *et al.*, 2021).

b. *Fat content.* Goat's milk contains higher amounts of short- and medium-chain fatty acids (MCFAs), such as caproic acid and caprylic acid, which are more readily digested and have anti-inflammatory effects. In contrast, cow's milk tends to have higher levels of long-chain fatty acids, which can be more difficult to digest, especially for those with digestive issues. The MCFAs in goat's milk also have a proven effect on reducing inflammation in the digestive tract (Kompan, 2012).

c. *Anti-inflammatory potential.* Goat's milk is richer in polyunsaturated fatty acids and vitamin A compared to cow's milk, both of which help support the repair and health of the gastric mucosa. This makes goat's milk more effective in promoting healing and reducing inflammation in the digestive system, particularly in conditions like gastritis (Sonu & Basavaprabhu, 2020; Singh *et al.*, 2021).

Comparison with sheep's milk

While sheep's milk is rich in protein and fat, it is often more difficult to digest compared to goat's milk. Goat's milk contains less of the allergenic alpha-S1 casein, which can trigger allergic reactions in some individuals, whereas sheep's milk contains higher levels of alpha-S1 casein, which can be more taxing on digestion. Additionally, goat's milk has more short- and medium-chain fatty acids, which enhance metabolism and possess stronger anti-inflammatory effects, while sheep's milk contains more saturated fats that may provoke inflammation in certain individuals (Ballabio *et al.*, 2011).

MATERIALS AND METHODS

Goat's milk

Fresh Etawa crossbred goat's milk sourced from a farm in Ciamis, West Java, was used. The goats were fed a standard diet consisting of fermented chopped corn stalks aged 65 days. The milk was administered in three different doses: 0.5 ml, 1 ml, and 1.5 ml, using a gastric probe. The maximum dose of 1.5 ml was determined based on the stomach volume capacity of the rat models.

Test animal

The test animals were male Sprague-Dawley rats aged 12-20 days, weighing 200-250 grams, obtained from the National Agency of Drug and Food Control. The rats were housed in a controlled environment with a 12-hour light/dark cycle and had free access to food and water. The number of rats used was determined using Federer's formula, resulting in 25 rats divided into five groups: (i) control: Rats received no treatment (no ethanol 80% induction and no goat's milk administration); (ii) ethanol (EtOH) 80%: Rats were induced with 1 ml of 80% EtOH for three consecutive days with no goat's milk administration; (iii) EtOH 80% + GM 0.5: Rats received 0.5 ml of goat's milk once a day for 30 days, and 1 ml of 80% EtOh for three consecutive days; (iv) EtOH 80% + GM 1: Rats were given 1 ml of goat's milk once a day for 30 days, and 1 ml of 80% EtOH for three consecutive days; (v) EtOH 80% + GM 1.5: Rats received 1.5 ml of goat's milk once a day for 30 days, and 1 ml of 80% EtOH for three consecutive days.

The experimental protocols used in this research were approved by the Health Research Ethics Committee of the Faculty of Medicine, University of Indonesia, with protocol number: KET-1019/UN2.F1/ETIK/PPM.00.02/2022 and were conducted in accordance with ethical guidelines for animal use.

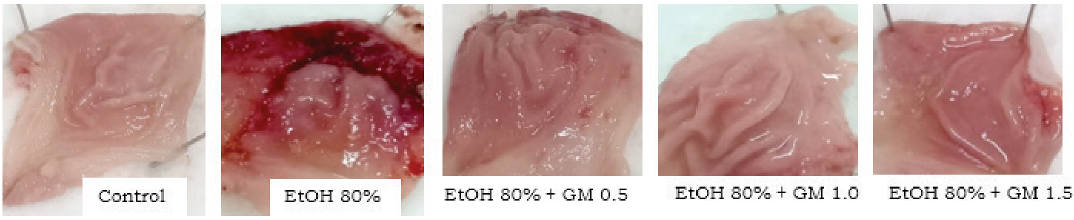
Histological analysis of gastritis rat models

The rats were induced with 1.0 ml of 80% ethanol for three consecutive days and then euthanised using ketamine-xylazine. Their stomachs were removed and fixed in a 10% formalin solution. The tissue was dehydrated with ethanol, cleared in xylene, and embedded in paraffin wax. It was then stained with Haematoxylin and Eosin (H&E) and examined microscopically for morphological changes. The evaluated parameters included erosion, oedema, and inflammatory cell infiltration.

Cytokine analysis

IL-6, TNF-α, and IL-10 cytokines were analysed using the Luminex Multiplex Bead Assay with serum samples. Analyte-specific antibodies were pre-coated onto magnetic microparticles embedded with fluorophores at a defined ratio for each analyte. Standards and samples were pipetted into wells, allowing the immobilised antibodies to bind to the desired analytes. After removing unbound substances, biotinylated antibodies specific to the analytes were added to each well. Following another wash to remove unbound biotinylated antibodies, streptavidin-phycoerythrin conjugate (Streptavidin-PE), which binds to biotinylated antibodies, was

Macroscopic observation results



(a) (b) (c) (d) (e)

Figure 1. Rat's stomach without ethanol 80% induction and without treatment of goat's milk (a); Rat's stomach after being induced with ethanol 80% of 1 ml for three consecutive days (b); Rat's stomach in treatment group 1 (given 0.5 ml goat's milk for 30 days then induced with 80% ethanol 1.0 ml once/day for 3 days) (c); Rat's stomach in treatment group 2 (given 1.0 ml goat's milk for 30 days then induced with 80% ethanol 1 ml once/day for 3 days) (d); Rat's stomach in treatment group 3 (given 1.5 ml goat's milk for 30 days then induced with 80% ethanol 1 ml once/day for 3 days) (e).

added. A final wash removed unbound Streptavidin-PE and the microparticles were suspended in a buffer and analysed using a Luminex (Djoba Siawaya *et al.*, 2008).

Statistical analysis

Data from IL-10, IL-6, and TNF-α tests were first assessed for normality using the Shapiro-Wilk test. Following that, the effects of goat's milk administration between groups were investigated in comparison to the negative control group using one-way analysis of variance (ANOVA) with GraphPad Prism version 9.0 (GraphPad Software Inc., California, USA). In this study, the Tukey post-hoc test was used following ANOVA analysis to compare differences between groups with p-value <0.05 set as statistical significance.

RESULTS

Results of the histological analysis of gastritis rat models

Macroscopic observation results

Macroscopic observations were done through observing colour and consistency. Based on observations of the stomachs of Sprague-Dawley rats, they had the same colour, namely pink. As for stomach consistency, all of them had a soft consistency. In the group of rats that were given 1 ml of 80% EtOH induction for three consecutive days, damage occurred and bleeding appeared. However, in the group of rats that were induced with 80% EtOH and previously given 1.5 ml of goat's milk for 30 days, their stomachs appeared pink and clean.

Microscopic observation results

Microscopic images of the stomachs of Sprague-Dawley rats in the control group showed normal stomach wall layers. The mucosa, submucosa, muscularis and serosa layers were visible. In the treatment group that was given 1 ml of 80% EtOH induction for three consecutive days, this group showed inflammatory cells and mucosal erosion. Histopathology of the gastric epithelium of rats induced by 1 ml of 80% EtOH for three consecutive days showed desquamation, erosion, lamina propria, lymphocyte cells, polymorphonuclear leukocyte (PMN) cells, and epithelial cells.

Pro-inflammatory cytokine

The differences in the effect of giving goat's milk on IL-6 and TNF-α are shown

Microscopic observation results

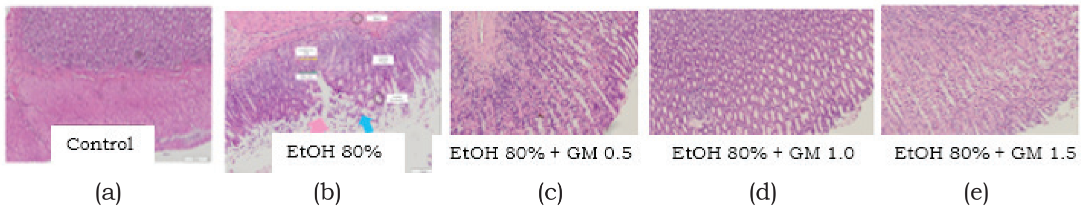


Figure 2. Rat's stomach without ethanol 80% induction after being stained using hematoxylin-eosin. Rat's stomach without ethanol 80% induction and without treatment goat's milk (a); Rat's stomach with ethanol 80% induction of 1 ml for three consecutive days, where erosion presents (b); Rat's stomach in treatment group 1 (given 0.5 ml goat's milk for 30 days then induced with 80% ethanol 1.0 ml once/day for 3 days) (c); Rat's stomach in treatment group 2 (given 1.0 ml goat's milk for 30 days then induced with 80% ethanol 1 ml once/day for 3 days) (d); Rat's stomach in treatment group 3 (given 1.5 ml goat's milk for 30 days then induced with 80% ethanol 1 ml once/day for 3 days) (e).

in Figures 3 and 4. There was a decrease in IL-6 and TNF-α in the groups given 1 ml and 1.5 ml of goat's milk compared to those given 0.5 ml of goat's milk.

The study included several groups of rats for comparison. Statistical analysis revealed the following when comparing the negative control group to other groups. The comparison between the negative control and control group resulted in $p<0.001$. The negative control group and the rat group that received 0.5 ml of goat's milk had $p=0.344$, indicating no significant difference. The negative control group and the rat group administered with 1 ml of goat's milk had $p=0.014$, showing a significant

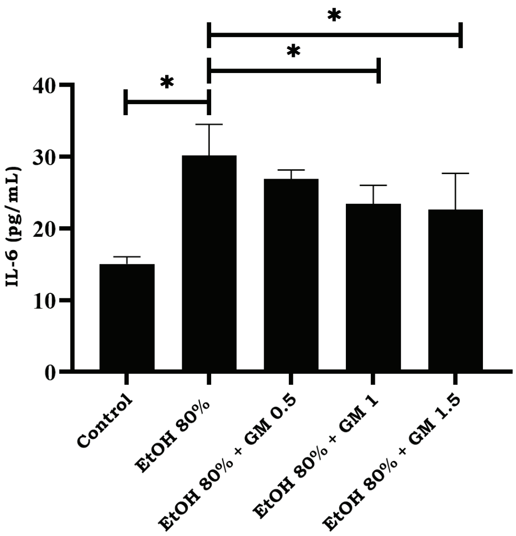


Figure 3. Results of interleukin-6 (IL-6) testing on gastritis rat models with ethanol 80% induction.
EtOH 80% = Ethanol 80%, GM 0.5 = 0.5 ml of goat's milk, GM 1 = 1 ml of goat's milk, GM 1.5 = 1.5 ml of goat's milk. *$p<0.05$

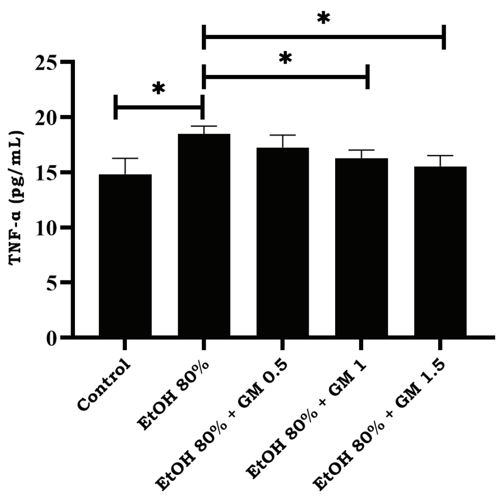


Figure 4. Results of tumour necrosis factor-α (TNF-α) testing on gastritis rat models with ethanol 80% induction.
EtOH 80% = Ethanol 80%, GM 0.5 = 0.5 ml of goat's milk, GM 1 = 1 ml of goat's milk, GM 1.5 = 1.5 ml of goat's milk. *$p<0.05$

difference. The negative control group and the rat group that received 1.5 ml of goat's milk had *p*=0.006, indicating a significant difference. Notably, the rat groups that received 1 ml and 1.5 ml of goat's milk showed a significant decrease in IL-6 levels, suggesting that these dosages had a substantial impact on reducing inflammation.

Tumour necrosis factor-α (TNF-α)

Statistical analysis revealed several important comparisons between the negative control group and the various treatment groups. Firstly, negative control and control group had $p<0.001$, indicating a significant difference between these two groups. Comparison between the negative control group and the rat group administered with 0.5 ml of goat's milk had *p*=0.213, demonstrating no significant difference between these two groups. When comparing the negative control group with the rat group administered with 1 ml of goat's milk, *p*=0.011, indicating a significant difference between these groups. Comparison between the negative control group and the rat group administered with 1.5 ml of goat's milk yielded a *p*=0.001, indicating a significant difference between these groups. This suggested a potential therapeutic effect of these dosages in reducing inflammation.

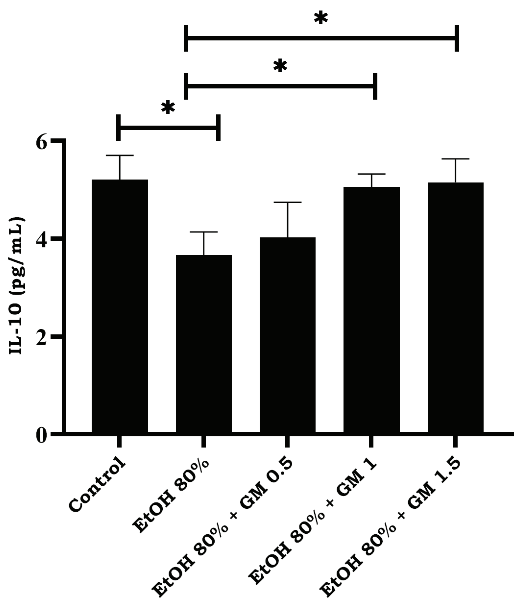


Figure 5. Results of interleukin-10 (IL-10) testing on gastritis rat models with ethanol 80% induction.
EtOH 80% = Ethanol 80%, GM 0.5 = 0.5 ml of goat's milk, GM 1 = 1 ml of goat's milk, GM 1.5 = 1.5 ml of goat's milk. *$p<0.05$

Anti-inflammatory cytokine

The difference in the effect of giving goat's milk on IL-10 is shown in Figure 5. There was an increase in IL-10 in the group given 1 ml and 1.5 ml of goat's milk compared to giving 0.5 ml of goat's milk.

Interleukin-10

A $p<0.001$ was obtained when comparing the negative control and control group. In contrast, the comparison between the negative group and the rat group administered with 0.5 ml of goat's milk resulted in a *p*=0.633, indicating no significant difference. However, there was a notable difference between the negative control group and the rat group administered with 1 ml of goat's milk, with a *p*=0.001. Similarly, the comparison between the negative control group and the rat group administered with 1.5 ml of goat's milk yielded a *p*=0.001, suggesting a significant difference. Notably, the rat groups receiving 1 ml and 1.5 ml of goat's milk showed a significant increase in IL-10 levels, indicating a potential therapeutic effect at these dosages in reducing inflammation.

DISCUSSION

Goat's milk contains several bioactive compounds known to modulate the immune system and influence cytokine production, potentially reducing inflammation and promoting a balanced immune response. Some of the key compounds in goat's milk that affect cytokine levels include:

1. Short-chain fatty acids (SCFAs)
Goat's milk contains SCFAs, such as acetic acid, propionic acid, and butyric acid, which are products of fermentation in the digestive system. SCFAs have been shown to have anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines like TNF-α and IL-6, while also promoting the production of anti-inflammatory cytokines like IL-10. SCFAs stimulate regulatory T cells, which help control immune responses and reduce inflammation. SCFAs can enhance IL-10 production, an anti-inflammatory cytokine that reduces excessive immune reactions (Lima *et al.*, 2017; *Panta et al.*, 2021; Kompan, 2012).

2. Bioactive proteins (e.g., lactalbumin and lactoglobulin)
Goat's milk is rich in bioactive proteins, such as lactalbumin and lactoglobulin, which have the potential to modulate cytokine expression. Research indicates that these proteins can influence both pro-inflammatory and anti-inflammatory cytokines. Lactalbumin and lactoglobulin can reduce pro-inflammatory cytokines (TNF-α, IL-6) and enhance the production of anti-inflammatory cytokines like IL-10. These proteins interact with immune cells, such as macrophages, to balance cytokine production during inflammation *(Selvaggi et al.*, 2014; Zhu *et al.*, 2016).

3. Bioactive peptides
The digestion or fermentation of goat's milk proteins produces bioactive peptides, which can influence cytokine activity. These peptides have been shown to inhibit free radical production and play a role in immune regulation. Bioactive peptides, such as caseinophosphopeptides (CPP), and peptides from casein may reduce inflammation by suppressing the expression of inflammatory cytokines. These peptides also enhance overall immune activity, promoting a more controlled response towards infection or inflammation (Guha *et al.,* 2021).

4. Vitamins and minerals
Goat's milk is a source of essential vitamins and minerals, such as vitamins A and D, as well as selenium, which support the immune system. Vitamin D, in particular, is known to regulate cytokine balance by increasing IL-10 production and reducing pro-inflammatory cytokines like IL-6 and TNF-α. Vitamin D has anti-inflammatory effects by increasing IL-10 and decreasing TNF-α, IL-6, and other pro-inflammatory cytokines. Selenium also plays a role in reducing inflammation by lowering pro-inflammatory cytokine levels and enhancing the body's ability to combat free radicals (Gallo *et al.*, 2023; Sommer & Fabri, 2015; Ghaseminejad *et al.*, 2023; Barragan, Good & Kolls, 2015).

5. Essential amino acids
Goat's milk contains essential amino acids that are involved in protein synthesis and tissue repair. Amino acids like glutamine and arginine can influence cytokine production by enhancing immune cell functions, such as macrophages and T lymphocytes. Glutamine promotes IL-10 production and reduces inflammation, while arginine can enhance immune cell activity and reduce TNF-α synthesis during inflammatory conditions (de Oliveira *et al.*, 2016; Thomson, 2011; Li *et al.*, 2023; Cruzat *et al.*, 2018).

6. Cholesterol and phospholipids
Goat's milk also contains cholesterol and phospholipids, which can influence

cell membranes and immune responses. Phospholipids, in particular, play a role in modulating T cell activation and cytokine production, as well as stimulating the immune system's response to infection or inflammation. Phospholipids in goat's milk can stimulate immune responses and regulate cytokine balance, leading to reduced inflammation (Lima *et al.*, 2017; Kompan, 2012).

Below are the quality control steps applied to goat's milk in this study to ensure compliance with Good Manufacturing Practices (GMP):

1. Selection of the source of goat's milk

The initial quality control step involved selecting a reliable source of goat's milk that met strict hygiene and health standards. The milk used in this study was sourced from a large farm in Ciamis Regency, West Java, Indonesia. This farm complies with applicable animal health regulations, ensuring the goats are disease-free and given safe, nutritious feed. The goats are fed silage made from 65-day-old chopped and fermented corn stalks, which are free from harmful chemicals, pesticides, or antibiotics, to produce high-quality milk.

2. Milk collection process

Milk was collected under sanitary conditions, using equipment such as pumps and bottles that were always new, dry, clean, and sterilised to prevent bacterial contamination. Milk collection was performed at the same time each day in the late afternoon and was done promptly to prevent contamination or quality degradation.

3. Milk storage

After collection, the goat's milk was immediately stored under suitable refrigeration conditions, between 2°C and 8°C, to minimise the risk of bacterial growth and preserve milk quality. It was stored in tightly sealed containers to avoid cross-contamination from other materials. The milk was stored for 24-48 hours, after which fresh milk was collected for the next day. Temperature and storage duration were carefully monitored to ensure consistency, and milk was maintained at the appropriate temperature throughout transport to the research facility.

CONCLUSION

The anti-inflammatory efficacy of goat's milk was demonstrated through decreased levels of IL-6 and TNF-α, as well as increased levels of IL-10, in gastritis rat models. The study has been restricted to Etawa crossbreed goat's milk, specifically. However, it would be beneficial to conduct comparative research to evaluate the potential of alternative types of goat's milk or even cow's milk. The findings of this study suggested that goat's milk exhibits promise as an anti-inflammatory agent for gastritis. To delve deeper into this subject, it would be worthwhile to isolate the active compounds present in goat's milk and conduct clinical trials involving human subjects. Furthermore, assessing the effectiveness of goat's milk in combating gastritis caused by *H. pylori* could might also be valuable.

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Authors' contributions

Farihatun A, researcher, designed and conducted the study, analysed and interpreted data, prepared and revised the manuscript; Kusmardi K, Estuningtyas A, Salleh MN, reviewed the manuscript and provided critical inputs.

Conflict of interest

The authors declare no conflict of interest.

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