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Immunomodulatory potential of galing (*Cayratia trifolia* L. Domin) plant on IgM antibody and monocytes in *Salmonella typhi*-infected rats

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ABSTRACT

Typhoid fever remains a health problem that requires support from both humoral and cellular immune responses. Therefore, the search for natural immunomodulators is important. Galing plant (*Cayratia trifolia* L. Domin) contains bioactive compounds such as flavonoids, alkaloids, and saponins, which are thought to have the potential to enhance immune responses. This study aimed to evaluate the immunomodulatory effects of ethanol extracts of galing leaves and stems on immunoglobulin M (IgM) levels and monocyte counts in male white rats induced with *Salmonella typhi*. The research hypothesis was that ethanol extract of galing plant could increase IgM levels and monocyte counts. This study used a randomized posttest-only control group design with seven treatment groups: normal control, negative control, positive control, leaf extract at doses of 400 and 500 mg/kg BW, and stem extract at doses of 400 and 500 mg/kg BW. IgM levels were measured using the ELISA method, while monocyte counts were analyzed using a hematology analyzer. The results showed that administration of ethanol extract of galing plant significantly increased IgM levels and monocyte counts compared with the negative control ($p<0.05$). The leaf extract group at a dose of 500 mg/kg BW showed the highest IgM level of 22.94 ± 2.00 ng/mL and the highest monocyte count of 8.44 ± 0.11%. A positive correlation was found between IgM levels and monocyte counts ($p<0.05$). Ethanol extract of galing plant has the potential to be developed as a natural immunomodulator to enhance immune responses against infection.

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1. Introduction

The immune system is a defense mechanism that protects organisms from exposure to pathogenic microorganisms, such as bacteria, viruses, fungi, and parasites. One important component of the immune response is immunoglobulin or antibody, which is produced by B cells. Immunoglobulin M (IgM) is the first antibody produced by the body following antigen exposure and plays an important role in the early phase of infection (Aris, 2023). IgM is able to recognize antigens, activate the complement system, and support pathogen elimination through phagocytosis and other immune responses (Mahdi and Zangana, 2024; Keyt et al., 2020). In addition to IgM, monocytes also play an important role in the innate immune system. Monocytes function to recognize, engulf, and destroy pathogens and can differentiate into macrophages in tissues to strengthen the immune response against infection (Ha et al., 2026).

Typhoid fever remains a major health problem in Indonesia. The prevalence of typhoid fever in Indonesia is estimated to reach 350 to 810 cases per 100,000 population, with approximately 600,000 to 1,500,000 cases annually. This disease is caused by *Salmonella typhi* infection, which is generally transmitted through contaminated food or beverages. The infection may cause symptoms such as high fever, abdominal pain, diarrhea, and serious complications if not properly treated (Kemenkes RI, 2006). In response to *S. typhi* infection, the body requires a humoral immune response through antibodies, including IgM, as well as a cellular immune response involving monocytes and macrophages to help eliminate bacteria, particularly because *S. typhi* is able to survive within host cells (Prasetyaningsih et al., 2020; Ilyas et al., 2022a).

The high incidence of typhoid fever indicates the need for efforts to enhance the body's defense system. One approach that can be used is the administration of immunomodulators (Shukla et al., 2022). Immunomodulators are compounds capable of regulating or enhancing immune responses, either specifically or nonspecifically. The use of synthetic immunomodulators still has several limitations, including the risk of side effects, relatively high cost, and

dependence on imported products for some preparations. Therefore, the development of natural product-based immunomodulators is important as a more affordable alternative with potentially fewer side effects (Malik et al., 2022; Ilyas et al., 2025b).

One plant with potential to be developed as an immunomodulator is galing (*Cayratia trifolia* L. Domin). This plant belongs to the family Vitaceae and has been traditionally used to treat various health disorders (Yusuf et al., 2019; Ilyas et al., 2026b) Galing leaves have been reported to exhibit biological activities, including antioxidant, antidiabetic, antibacterial, anti-inflammatory, immunomodulator, antitumor, antiulcer, larvicidal, and hepatoprotective activities (Yusuf et al., 2018; Ilyas et al., 2021; Ilyas et al., 2025a; Ilyas et al., 2026b). These activities are thought to be related to the presence of secondary metabolites, such as flavonoids, alkaloids, polyphenols, terpenoids, steroids, saponins, stilbenes, and linoleic acid (Ilyas et al., 2026b). Several of these compounds, particularly flavonoids, are known to have potential as immunostimulants because they can influence the activity of immune cells, including macrophages and lymphocytes (Yusuf et al., 2019; Ilyas et al., 2025a).

Previous research has shown that galing plant extract can significantly increase the phagocytic activity of macrophage cells in Balb/C mice, and increase various functions of immunocompetent cells in the innate and adaptive immune systems (Yusuf et al., 2019; Ilyas et al., 2025a; Ilyas et al., 2026c). However, studies on the immunomodulatory activity of ethanol extract of galing plant on IgM levels and monocyte cell expression, particularly under conditions of *S. typhi* infection, remain limited. Based on this background, this study aimed to determine the immunomodulatory activity of ethanol extract of galing plant (*Cayratia trifolia* L. Domin) on IgM levels and monocyte cell expression in male white rats induced with *S. typhi*. The hypothesis of this study was that ethanol extract of galing plant has immunomodulatory activity that can increase IgM levels and monocyte cell expression in male white rats.

2. Materials and methods

2.1. Materials

The materials used in this study included galing plant (*Cayratia trifolia* L. Domin), male white rats, *Salmonella typhi* ATCC 13311, 96% ethanol, EDTA, 0.5% Na-CMC, 0.9% physiological NaCl, nutrient agar (NA), Rat IgM ELISA kit, and commercial meniran extract (Stimuno®). All chemicals used were of pro analysis grade.

2.2. Sample preparation and determination

The galing plant sample was first identified at the Research Laboratory of the Faculty of Pharmacy, Halu Oleo University, to confirm the species identity used in this study. The samples were then collected, separated from impurities and damaged plant parts, and weighed to determine the fresh simplicia weight. The samples were washed under running water, drained until free from residual water, and then chopped to accelerate the drying process. The samples were dried under sunlight while covered with black cloth. After drying, sorting was performed again, and the simplicia were weighed and ground to obtain simplicia powder.

2.3. Extraction

The leaf and stem extracts of galing plant were obtained by maceration using 96% ethanol. Leaf simplicia (700 g) and stem simplicia (3.6 kg) were macerated separately at a ratio of 1:10 (w/v) for 3×24 h. The macerate was then concentrated using a rotary vacuum evaporator at 60°C until a thick extract was obtained (Yusuf, et al., 2018).

2.4. Preparation of test bacteria

All instruments were sterilized before use. Instruments and media that were not resistant to dry heat were sterilized using an autoclave at 121°C for 15 min, whereas heat-resistant glassware was sterilized using an oven at 180°C for 30 min. Nutrient agar medium was prepared by dissolving 3 g of NA in 50 mL of distilled water, heating until dissolved, transferring into test tubes, and sterilizing by autoclaving. *Salmonella typhi* was rejuvenated on slanted NA medium by aseptic inoculation using an inoculating loop and incubated at 37°C for 24 h. The bacterial suspension was prepared by taking a 24h culture and suspending it in 10 mL of sterile 0.9% NaCl until homogeneous. The turbidity of the suspension was adjusted to the 0.5 Mc.Farland standard, prepared from a mixture of 9.95 mL of 1% H_2SO_4 and 0.05 mL of 1% $BaCl_2$, equivalent to a bacterial concentration of 1.5×10^8 CFU/mL (Yusuf et al., 2020; Suci et al., 2022).

2.5. Acclimatization and treatment of test animals

Male white rats were acclimatized for 7 days before treatment to adapt to the cage environment. During acclimatization, the animals were provided with pellet feed and drinking water ad libitum and maintained at a temperature of 23 ± 3°C (Ilyas et al., 2023; Ilyas et al., 2025a). The number of test animals was determined using Federer's formula, resulting in a minimum of four rats per group. In this study, 35 male white rats were divided into seven groups, each consisting of five rats. Briefly, after meeting the inclusion criteria and completing the acclimatization period, each rat was assigned an identification number and randomly allocated to one of the seven experimental groups using a simple randomization method based on random drawing of the identification numbers. The treatment groups consisted of a normal untreated group (KN), a negative control group administered 0.5% Na-CMC (K-), a positive control group administered Stimuno® forte at a dose of 0.922 mg/kg BW (K+), galing leaf extract at a dose of 400 mg/kg BW (K1), galing leaf extract at a dose of 500 mg/kg BW (K2), galing stem extract at a dose of 400 mg/kg BW (K3), and galing stem extract at a dose of 500 mg/kg BW (K4) (Yusuf et al., 2018; Yusuf et al., 2019). This study has received ethical clearance for the use of laboratory animals from the Halu Oleo University Health Research Ethics Committee, No. 1507/UN29.20.12/PG/2025.

The test preparations were made by suspending the ethanol extract of galing plant in 0.5% Na-CMC. Na-CMC 0.5% was also used as the negative control. The comparator preparation, Stimuno®, was suspended in 0.5% Na-CMC and administered at a dose of 0.922 mg/kg BW. All experimental groups, except for the normal control group (KN), were administered the respective treatments orally once daily for 10 consecutive days, with the dosing volume adjusted according to the body weight of each animal (Dewi et al., 2023; Ilyas et al., 2026a).

2.6. Immunomodulatory effect test on IgM levels and monocyte count

On day 11, all rats, except those in the normal control (KN) group, were orally infected with *Salmonella Typhi* at a dose of 1.5×10^8CFU/mL, with 0.5 mL of the bacterial suspension administered to each animal. Blood was collected intracardially after anaesthesia with ketamine HCl through the rat heart and placed into vacutainer tubes containing EDTA. Blood samples for IgM examination were centrifuged at 3,500 rpm for 15 min to obtain plasma. IgM antibody

maceration duration, and the content of compounds soluble in the solvent (Do et al., 2025).

3.3. Effect of galing plant extract on IgM antibody levels

Administration of ethanol extract of galing plant showed immunomodulatory activity on humoral and cellular immune responses. This was demonstrated by increased IgM antibody levels and monocyte percentages in the treatment groups compared with the negative control. IgM is the first antibody produced when the body is exposed to an antigen; therefore, increased IgM levels may indicate stimulation of the immune system during the early phase of infection. Meanwhile, monocytes play a role in innate immune responses through phagocytosis, antigen presentation, and differentiation into macrophages in tissues. The increase in both parameters indicates that galing plant extract has the potential to enhance the immune response against *Salmonella typhi* infection (Ulfah et al., 2018).

The results of IgM antibody level measurement (Fig. 1) showed that the mean IgM levels in the normal control, negative control, and positive control groups were 2.98 ± 0.83 ng/mL, 6.73 ± 1.46 ng/mL, and 19.82 ± 1.42 ng/mL, respectively. In the treatment groups, IgM levels increased to 18.66 ± 1.32 ng/mL in the group treated with galing leaf extract at a dose of 400 mg/kg BW (K1), 22.94 ± 2.00 ng/mL in the group treated with galing leaf extract at a dose of 500 mg/kg BW (K2), 15.68 ± 1.37 ng/mL in the group treated with galing stem extract at a dose of 400 mg/kg BW (K3), and 19.66 ± 1.19 ng/mL in the group treated with galing stem extract at a dose of 500 mg/kg BW (K4) (Fig. 1).

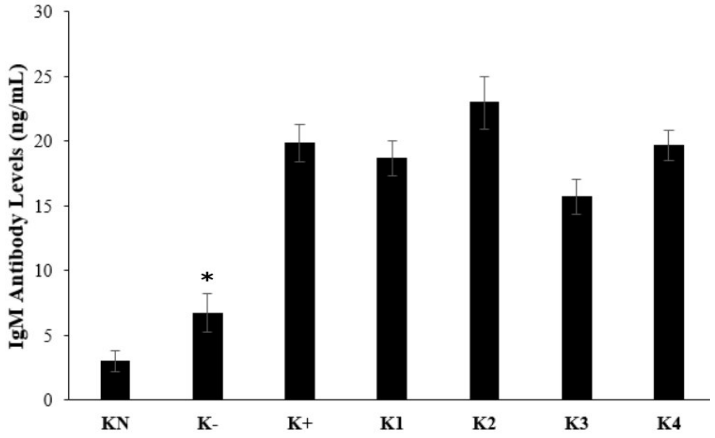

Fig. 1. Comparison of mean IgM antibody levels among treatment groups. Data are presented as mean ± SD (n=5). (*p<0.05=post hoc LSD test significantly different from the negative control group). KN=normal control; K-=negative control; K+=positive control; K1= ethanol leaf extract 400 mg/kg BW; K2= ethanol leaf extract 500 mg/kg BW; K3= ethanol stem extract 400 mg/kg BW; K4= ethanol stem extract 500 mg/kg BW.

Statistical analysis showed that administration of ethanol extracts of galing leaves and stems had a significant effect on IgM antibody levels (*p<0.05). All extract-treated groups showed higher IgM levels than the negative control group. Compared with the positive control group, IgM levels in the groups treated with galing leaf extract at 400 mg/kg BW (K1) and galing stem extract at 500 mg/kg BW (K4) were not significantly different (*p>0.05). In contrast, galing leaf extract at 500 mg/kg BW (K2) and galing stem extract at 400 mg/kg BW (K3) showed significant differences compared with the positive control group (*p<0.05). Descriptively, galing leaf extract at a dose of 500 mg/kg BW (K2) produced the highest IgM level

among all groups, indicating the greatest potential to enhance the IgM antibody response in male white rats.

3.4. Effect of galing plant extract on monocyte cells counts

The results of monocyte percentage measurement (Fig. 2) showed that the mean monocyte percentages in the normal control, negative control, and positive control groups were 4.86 ± 0.53%, 3.50 ± 0.35%, and 12.56 ± 1.88%, respectively. In the treatment groups, the monocyte percentages increased to 6.70 ± 0.21% in the group treated with galing leaf extract at a dose of 400 mg/kg BW (K1), 8.44 ± 0.11% in the group treated with galing leaf extract at a dose of 500 mg/kg BW (K2), 5.70 ± 0.29% in the group treated with galing stem extract at a dose of 400 mg/kg BW (K3), and 7.62 ± 0.44% in the group treated with galing stem extract at a dose of 500 mg/kg BW (K4). The highest monocyte percentage was observed in the positive control group, while among the galing plant extract groups, the highest value was shown by the leaf extract at a dose of 500 mg/kg BW (K2).

Statistical analysis showed that all extract-treated groups had significantly higher monocyte percentages than the negative control group (*p<0.05). Although the monocyte percentages in the extract-treated groups were still significantly different from those in the positive control group (*p<0.05), the observed increase indicated that galing plant extract was able to stimulate the monocyte response, particularly in the group treated with galing leaf extract at a dose of 500 mg/kg BW, which produced the highest monocyte percentage among the extract-treated groups.

3.5. Relationship between IgM levels and monocyte percentage

The results of the correlation analysis between IgM antibody levels and monocyte percentage are presented. The Pearson correlation coefficient value of r= 0.676 with *p=0.001 indicates a strong positive correlation between the two parameters. This suggests that an increase in IgM antibody levels tends to be followed by an increase in monocyte percentage.

The immunomodulatory activity of galing plant extract is thought to be associated with its secondary metabolite content, particularly flavonoids, alkaloids, tannins, saponins, and triterpenoids. Flavonoids are known to act as immunostimulants by enhancing the activation of effector cells, such as lymphocytes and macrophages, which subsequently produce and release cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α) (Siregar et al., 2021; Ilyas et al., 2026b). B lymphocyte activation plays a role in antibody formation, including IgM. In addition, flavonoids and alkaloids have also been reported to increase the production of proinflammatory cytokines involved in enhancing monocyte phagocytosis and endocytosis. These cytokines can increase monocyte and macrophage activity against infection by stimulating lysosomal enzymes and enhancing receptor activity on the surface of phagocytic cells (Sartika and Indradi, 2021). Tannins are also known to stimulate phagocytic cell activity and exhibit antibacterial activity (Yusuf et al., 2019; Ilyas et al., 2025b).

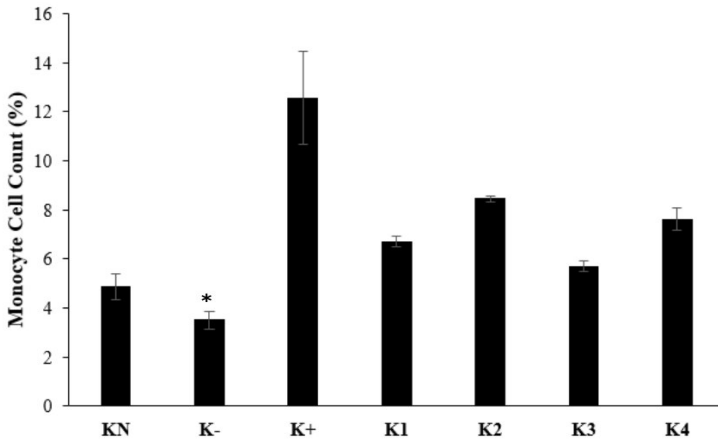

Fig. 2. Comparison of mean monocyte percentages among treatment groups. Data represented as mean ± SD (n = 5). (*p<0.05=post hoc LSD test significantly different from the negative control group). KN=normal control; K-=negative control; K+=positive control; K1= ethanol leaf extract 400 mg/kg BW; K2= ethanol leaf extract 500 mg/kg BW; K3= ethanol stem extract 400 mg/kg BW; K4= ethanol stem extract 500 mg/kg BW.

The group treated with galing leaf extract at a dose of 500 mg/kg BW (K2) showed the highest IgM levels and monocyte percentage among the extract-treated groups. This indicates that the leaves have greater potential than the stems in enhancing immune responses. This difference in response is thought to be related to the higher content or greater extractability of secondary metabolites in the leaves compared with the stems. Leaves are plant organs actively involved in the biosynthesis of various secondary metabolites, and therefore may provide stronger biological activity. In addition, increasing the dose of active compounds such as flavonoids may enhance the activity of phagocytic leukocytes against bacteria, allowing more bacteria to be destroyed and digested by immune cells (Ilyas et al., 2025a; Ilyas et al., 2026b).

The positive control group showed high IgM levels and monocyte percentages because it was administered Stimuno®, an immunomodulatory preparation derived from meniran extract (*Phyllanthus niruri* L.). Meniran is known to contain flavonoid compounds, such as quercetin, quercitrin, isoquercitrin, astragalin, and rutin, as well as tannins, which play a role in enhancing immune responses (Perdana, 2022; Kurniawan et al., 2025). IgM levels in the groups treated with galing leaf extract at 400 mg/kg BW (K1) and galing stem extract at 500 mg/kg BW (K4), which were comparable to the positive control, indicate that these treatments had immunomodulatory effects approaching those of the comparator preparation. However, for the monocyte parameter, all extract-treated groups still showed values that differed from the positive control, although they remained higher than the negative control.

The positive relationship between IgM levels and monocyte percentage indicates an association between humoral and cellular immune responses in male white rats induced with *S. typhi*. IgM plays a role in the early phase of the immune response by recognizing antigens and activating the classical complement pathway. Complement activation produces fragments such as C3b and iC3b, which can bind to complement receptors on monocytes, thereby increasing activation and phagocytosis against pathogens (Liu et al., 2025). Thus, increased IgM levels may support monocyte activation in the bacterial elimination process. The positive correlation obtained supports the hypothesis that increases in both parameters occur in the same direction as part of the body's defense mechanism against infection. However, it should be emphasized that the increases in IgM antibody levels and monocyte counts observed in this study should not be interpreted as direct evidence

of enhanced bacterial killing. Rather, these changes reflect an immune response elicited by exposure to the pathogen.

The results of this study are consistent with previous research reporting that galing plant extract can increase macrophage phagocytic activity, thereby strengthening the assumption that secondary metabolites in this plant contribute to immune response stimulation. However, this study has several limitations, including the limited number of test animals, the use of only two dose variations, and the absence of quantitative identification of active compound levels in the leaf and stem extracts. In addition, the immune parameters observed were limited to IgM and monocytes, and therefore did not fully represent the overall immune response. Further studies are needed with larger sample sizes, broader dose variations, quantitative phytochemical analysis, and measurement of other immune parameters, such as IgG, cytokines, phagocytic activity, and lymphocyte profiles. Practically, the findings of this study indicate that galing plant, particularly the leaves at a dose of 500 mg/kg BW, has potential to be developed as a natural immunomodulator candidate to support enhanced immune responses against infection.

4. Conclusion

Based on the results of this study, ethanol extracts of galing leaves and stems (*Cayratia trifolia* L. Domin) were proven to have immunomodulatory activity in male white rats induced with *Salmonella typhi*. This activity was demonstrated by increased IgM antibody levels as a humoral immune response and increased monocyte percentage as a cellular immune response. The leaf extract at a dose of 500 mg/kg BW showed the greatest potential in increasing both parameters. The positive correlation between IgM levels and monocyte percentage indicates that the enhancement of humoral immune response is in line with the enhancement of cellular immune response. These findings support the use of galing plant, particularly the leaves, as a natural immunomodulator candidate in the development of plant-based medicinal materials.

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Conflict of interest

The authors declare no conflict of interest in this research.

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