ORIGINAL RESEARCH REPORT

Immunomodulatory Activity of Ganyong Tuber (*Canna edulis* K.) Extract on Phagocytosis, Leukocytes, and Antibody of Mice against Bacterial Infections

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ABSTRACT

Background: Ganyong tubers (*Canna edulis* K.) are widely consumed by Indonesians as an alternative food source. However, no studies have investigated the pharmacological properties of ganyong tubers, particularly their immunomodulatory activity. **Objective:** This study aimed to evaluate the immunomodulatory effects of ganyong tubers in mice infected with *Staphylococcus aureus*. **Material and Method:** This study used a randomized experimental design involving 30 male BALB/c mice divided into five groups, including a normal control, a negative control (infected with *Staphylococcus aureus*), and three groups treated with ganyong (*Canna edulis* K.) extract at doses of 50, 100, and 150 mg/kg BW. The extract was administered orally for seven days, followed by *S. aureus* injection. Phagocytic activity, leukocyte count, spleen weight, and antibody levels were evaluated using microscopy and ELISA. Data were analyzed using one-way ANOVA and Duncan's post hoc test. **Result:** This study evaluated the immunomodulatory effects of ganyong tuber (*Canna edulis* K.) extract on phagocytosis activity and capacity, leukocyte count, spleen weight, and antibody levels in mice infected with *Staphylococcus aureus*. Phagocytosis activity and capacity were highest in the group receiving 50 mg/kg body weight (BW) extract, with decreasing effects at higher doses. Leukocyte counts were highest in the infected untreated group, while spleen weight was significantly increased in the 50 mg/kg BW treatment group compared to controls. Although the 100 mg/kg BW group showed the highest antibody levels, these differences were not statistically significant. **Conclusion:** Ganyong tuber extract demonstrated immunomodulatory activity by enhancing innate immune responses against *S. aureus* infection.

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Highlights

1. Ganyong tuber exhibits immunomodulatory activity against *Staphylococcus aureus* infection in mice.
2. Ganyong tuber extract increases phagocytic activity, leukocyte count, and spleen weight in infected mice.

BACKGROUND

Microorganisms such as bacteria, viruses, parasites, and fungi can cause infectious diseases (Oktari, et al., 2020). Indonesia experiences a high number of infectious disease cases each year. For example, AIDS and tuberculosis rank second in the world (de Jong, et al., 2018; Ministry of Health of The Republic of Indonesia, 2020). *Staphylococcus aureus* infections are also of concern, with annual deaths in the United States reaching up to 20,000 (Cheung, et al., 2021).

Treatment for infectious diseases commonly involves antibiotics, which have led to resistance in several pathogens—one of the most notable being Methicillin-resistant *Staphylococcus aureus* (MRSA) (Lee, et al., 2018). MRSA infections exacerbate patient conditions and have been linked to increased mortality rates in various regions (Turner, et al., 2019). According to the World Health Organization (WHO), antibiotic resistance occurs in approximately 20% of cases globally, with up to 80% found in Asia (Syahniar, et al., 2020).

The global health crisis caused by bacterial and viral resistance highlights the need for alternative treatments for infectious diseases (Pang, et al., 2019). One such alternative is immune system modulation.

The immune system comprises a series of physiological processes that protect the body against pathogens, such as viruses, bacteria, parasites, and fungi, to maintain homeostasis (Behl, et al., 2021; Haque, et al., 2017; Sindhu, et al., 2021). The spleen is one of the secondary lymphoid organs involved in immunity. It contributes to infection defense by supporting T lymphocyte activation and forming germinal centers for B lymphocyte proliferation and antibody production (Bakir, 2023).

Furthermore, its marginal zone is rich in leukocytes like macrophages and neutrophils, which eliminate pathogens via phagocytosis (Aliyu, et al., 2021; Norris, et al., 2020). Therefore, the interactions between leukocytes, phagocytosis, and the spleen form the foundation of both innate and adaptive immune responses. In infection therapy, monitoring parameters such as leukocyte counts, phagocytic activity, and spleen weight is essential to evaluate the effectiveness of immunomodulator-based treatment.

Maintaining and modulating the immune system is critical in protecting the body from pathogenic attacks (Oktari, et al., 2020). Immunomodulatory compounds can regulate (enhance or suppress) immune responses and optimize both innate and adaptive immunity (Hartati, et al., 2017; Sianipar, 2021). These active compounds include polysaccharides, flavonoids, and terpenoids (Aziz, et al., 2020; Blomquist, et al., 2021; Prahesti, 2019).

Ganyong (*Canna edulis*) is a tuberous plant native to South America and now widely distributed in Asia, Australia, and Africa. In Indonesia, it is mainly cultivated on the islands of Java and Bali (Praseptiangga, et al., 2018). Traditionally, ganyong tubers have been used as an alternative food source, processed into flour, noodles, vegetables, or side dishes, due to their high carbohydrate (22–23%) and protein (~1%) content (Praseptiangga, et al., 2018; Pudjihastuti, et al., 2018).

Ganyong tubers contain various secondary metabolites such as alkaloids, flavonoids, steroids, and phenolics (Putri & Dyna, 2019). More specifically, they include compounds like flavonoids, terpenoids, alkaloids, and polysaccharides (e.g., D-Mannitol, 2-Deoxy-D-ribose, and D-Mannose) (Savira, et al., 2023). These constituents suggest that ganyong tubers have potential as immunomodulatory agents.

According to Chinese Materia Medica (Zhonghua), *Canna edulis* exhibits anti-inflammatory properties (Zhang, et al., 2020). Burhannudin, et al., (2018) also reported its potential in preventing colorectal carcinogenesis due to its high fiber and calcium content. However, no studies have yet investigated the immunomodulatory effect of *Canna edulis* tuber extract in mice infected with *Staphylococcus aureus*.

Therefore, this study aims to evaluate the immunomodulatory activity of ganyong tuber extract by measuring leukocyte count, phagocytic activity, and antibody levels. This research also seeks to identify

alternative natural treatments that can limit the spread of *Staphylococcus aureus*, a major contributor to life-threatening infections.

OBJECTIVE

The purpose of this study was to evaluate the effect of ganyong tubers on phagocytic activity and capacity, spleen weight, leukocyte count, and antibody levels in mice infected with *Staphylococcus aureus*.

MATERIAL AND METHOD

This study employed a randomized experimental design. All procedures adhered to the ethical standards approved by the Ethics Committee of the Faculty of Dentistry, University of Jember (No.1590/UN25.8/KEPK/DL/2022), on 25-07-2022. Phagocytosis activity and leukocyte counts were assessed using an Olympus BX53F2 Optical Microscope (Japan) equipped with CellSens Imaging Software. Serum samples were obtained by centrifugation at 3000 rpm for 20 minutes using an Eppendorf Centrifuge 5810 R. Antibody levels were measured using a Mouse Immunoglobulin G ELISA kit (Bioassay Technology Laboratory, BT Lab), and optical density (OD) was read using a Bio-Rad iMark microplate absorbance reader.

Sample collection

Fresh Ganyong (*Canna edulis* K.) tubers were collected in July 2022 from Tugusari Village, Bangsalsari, Jember, Indonesia. Botanical identification was performed at the Biology Laboratory, Faculty of Mathematics and Natural Sciences, University of Jember. The red ganyong tubers used were 6–8 weeks old, 5–9 cm in diameter, and 10–15 cm in length.

Ganyong (*Canna edulis* K.) extraction

The tubers were washed twice with distilled water, crushed, and macerated with 96% ethanol. Initially, the maceration was carried out for 24 hours. The extract was filtered and dried. The dried material was then soaked in ethanol (1:3 ratio) and shaken for 72 hours (3 × 24 h), with the solvent being replaced every 24 hours. The combined filtrates were evaporated using a vacuum rotary evaporator at 75–80 °C to obtain a solid extract, which was stored for administration at designated doses (Luhurningtyas, et al., 2021).

Animal study and treatments

Thirty adult male BALB/c mice (8–10 weeks old, 25–30 g body weight) were randomly assigned into five groups (n=6 per group): K (normal control), K− (negative control, infected with *Staphylococcus aureus*), P1 (treated with 50 mg/kg BW ganyong extract), P2 (treated with 100 mg/kg BW ganyong extract), and P3 (treated with 150 mg/kg BW ganyong extract). Ganyong extract was administered orally for seven consecutive days. On day 8 and day 22, the mice were intraperitoneally injected with *S. aureus* (0.5 McFarland standard). On day 23, the mice were sacrificed for the collection of intraperitoneal fluid, blood, and serum (Wahyuningsih, et al., 2017).

Phagocytic ability assay

To assess phagocytic activity and capacity, 0.2 mL of *S. aureus* was injected intraperitoneally. After one hour, mice were anesthetized, and 2 mL of 3% EDTA was injected intraperitoneally. Peritoneal fluid (~1 mL) was aspirated. Phagocytosis assessment followed the method by Savira, et al., (2021).

Leukocyte number and spleen weight measurement

Blood samples were applied to a hemocytometer and allowed to stand for 1 minute to lyse erythrocytes. Leukocytes were counted under 40× magnification across 4 large squares. Total leukocytes per mm³ were calculated using the formula:

$$The\ number\ of\ Leukocytes = \frac{1}{64} \times 160 \times 10 \times cells$$

Spleens were collected, rinsed with PBS, and weighed using an analytical balance (Wahyuningsih, et al., 2017).

Antibody level by ELISA

Serum IgG levels were measured using a mouse IgG ELISA kit (BT LAB). Each well received 40 µL of serum, 10 µL of anti-IgG antibody, and 50 µL of streptavidin-HRP. The plate was mixed, sealed, and incubated at 37 °C for 60 minutes. Wells were washed five times with 0.35 mL wash buffer. After drying, 50 µL of substrate solutions A and B were added, followed by a 10-minute dark incubation at 37 °C. The reaction was stopped, and OD was measured at 450 nm using a microplate reader.

Data Analysis

Data were analyzed using one-way ANOVA followed by Duncan's post hoc test using SPSS version 23.0 (IBM Corp., Armonk, NY). A $p<0.05$ was considered statistically significant.

RESULT

Phagocytosis ability

Phagocytosis ability was assessed by evaluating both phagocytic activity and capacity. Phagocytic activity was determined by counting the number of actively phagocytosing cells out of 100 total phagocytes. Active phagocytes were identified by their larger size and brighter cytoplasm compared to inactive cells (Figure 1a). Phagocytic capacity was measured by counting the total number of *Staphylococcus aureus* cells engulfed by 50 active phagocytic cells (Figure 1b) (Wahyuningsih, et al., 2016).

As shown in Figure 2, the P1 group (treated with 50 mg/kg BW of ganyong extract) exhibited the highest mean phagocytic activity among all treatment groups. In contrast, the P2 (100 mg/kg BW) and P3 (200 mg/kg BW) groups showed a dose-dependent decrease in phagocytic activity. The lowest activity was observed in the negative control group (K−). Notably, there was no significant difference in phagocytic activity between the K− and P3 groups.

Phagocytic capacity results were consistent with phagocytic activity trends. As illustrated in Figure 1d, the K− group had the lowest capacity, while the P1 group showed the highest, with an average of approximately 407 *S. aureus* cells phagocytosed by 50 phagocytes.

The number of leukocyte and spleen weight

Based on the results (Table 1), the K− group exhibited the highest mean leukocyte count at 27,563 cells/mm³, while the P3 group had the lowest count at 2,675 cells/mm³.

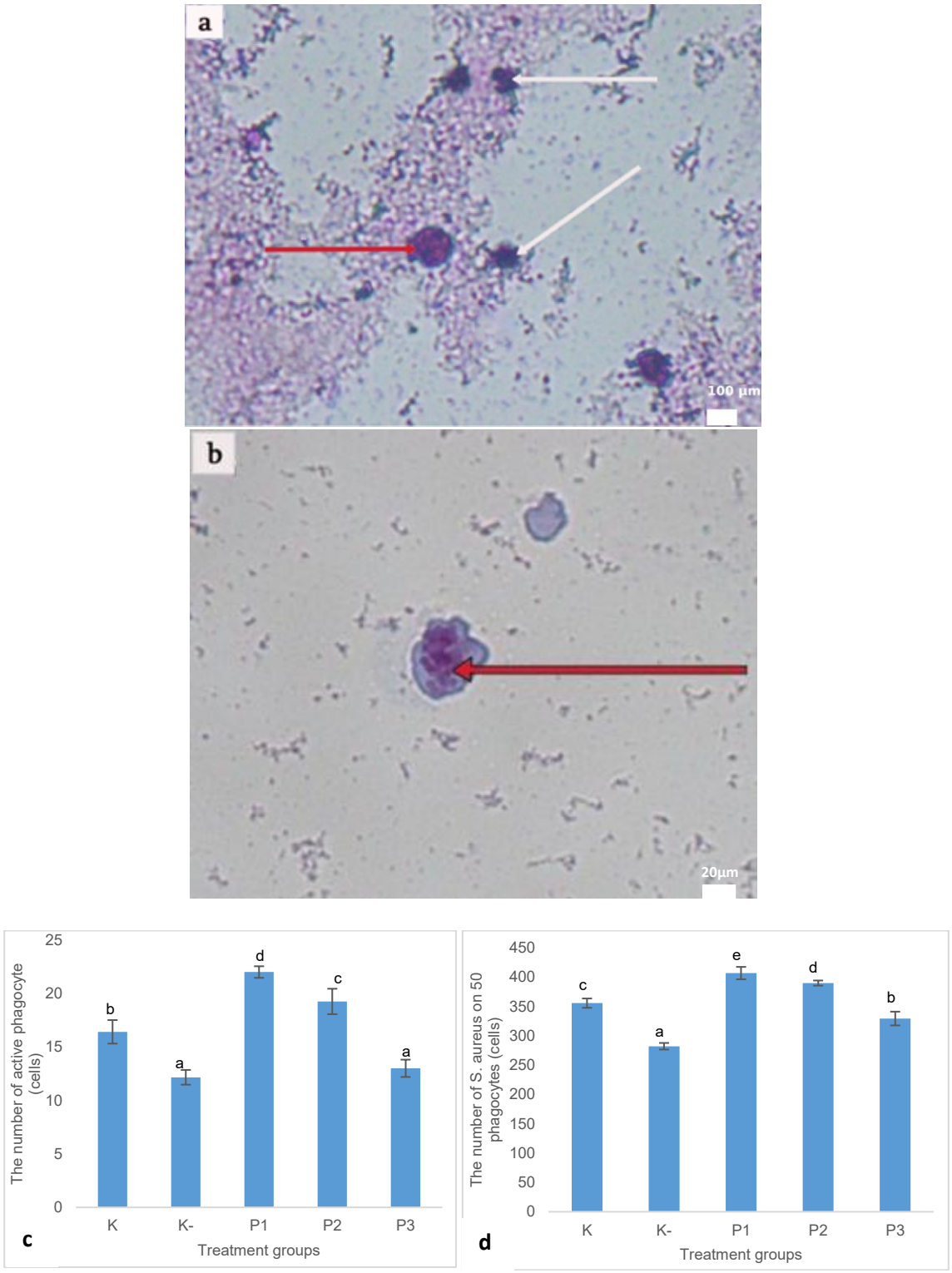
In contrast to the leukocyte count, spleen weight measurements revealed different trends. The P1 group demonstrated the highest spleen weight, which was significantly different compared to both the normal control (K) and negative control (K−) groups. Meanwhile, the P2 group showed the lowest spleen weight, which was comparable to the K group.

Table 1. Effect of ganyong tuber extract on the number of leukocyte and spleen weight.

Treatment groups	Number of leukocyte (cells/mm^3)	Spleen weight (mg)
K	10418.75^{b}	150^{ab}
K-	27,562.50^{d}	170^{b}
P1	11456.25^{bc}	220^{c}
P2	13643.75^{c}	120^{a}
P3	2575.00^{a}	170^{b}

Legends: Diverse letters in each data label indicate statistically significant differences ($P < 0.05$).

The graph in Figure 2 illustrates the antibody level results, with the highest levels observed in the P2 group. However, based on one-way ANOVA analysis, the differences among all treatment groups were not statistically significant.



Legends: Diverse letters in each data label indicate statistically significant differences ($p<0.05$).

Figure 1. Effect of ganyong tuber extract on phagocytosis ability. (a) the different of active phagocyte (red arrow) and non-active (white arrow); (b) *S.aureus* cells on active phagocyte (red arrow); (c) the phagocytosis activity; (d) the phagocytosis capacity.

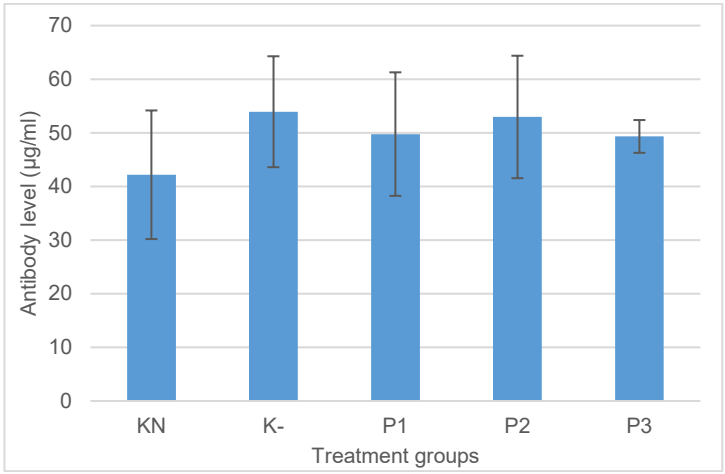


Figure 2. Effect of ganyong tuber extract on antibody level.

DISCUSSION

Ganyong (*Canna edulis* K.) contains several secondary metabolites that are important immunomodulators. According to research by Savira, et al., (2023), ganyong tuber extract contains high levels of 2,3-dihydro benzofuran, a flavonoid compound. Flavonoids possess anti-inflammatory properties by inhibiting the production of pro-inflammatory cytokines by phagocytes (Bayat, et al., 2021; Parubak, 2019). They regulate the function of phagocytes such as macrophages and neutrophils, and have the potential to influence lymphokine production by T cells while stimulating phagocytic cells (Pasaribu & Longdong, 2019).

In addition to flavonoids, ganyong tuber extracts contain three types of polysaccharides: D-mannitol, 2-deoxy-D-ribose, and D-mannose (Savira, et al., 2023). These polysaccharides can induce nitric oxide synthase, leading to the production of nitric oxide (NO), a marker of macrophage activation essential for phagocytosis (Burhannudin, et al., 2018). This is supported by the increased phagocytosis activity observed in the P1 treatment group, which showed the highest mean activity compared to other groups. Polysaccharides are also expected to enhance antibody production for opsonization, thereby increasing phagocytosis capacity. However, in this study, antibody levels did not increase in the ganyong extract-treated groups despite the rise in phagocytosis capacity. The polysaccharides may exert anti-inflammatory effects that normalize leukocyte counts.

Other bioactive compounds in ganyong tuber extract include alkaloids and terpenoids (Savira, et al., 2023). Alkaloids have been shown to act as immunomodulators by inhibiting TNF-α, IL-6, and IL-1β, thus reducing inflammation in both in vitro and in vivo studies (Fan, et al., 2018). Terpenoids modulate the immune response by decreasing pro-inflammatory cytokine production and activating macrophages for bacterial clearance (Yang, et al., 2020).

The secondary metabolites in ganyong tuber extract demonstrate potential as immunomodulators. However, exceeding the effective dose may cause immunogenic intolerance or a decreased immune response (Trihastuty, et al., 2019). One plausible explanation is that high doses could trigger excessive pro-inflammatory cytokine release (e.g., TNF-α, IL-6), which activates compensatory anti-inflammatory pathways (e.g., IL-10, regulatory T cells), resulting in net immunosuppression. This hypothesis requires further validation through cytokine profiling and dose-response studies (Tanaka, et al., 2018). In this study, the P3 group showed reduced phagocytic ability and a sharp decrease in leukocytes, indicating that the effective dose of ganyong extract is 50 mg/kg BW. These findings underscore the need for future research to confirm biphasic effects and elucidate underlying molecular mechanisms.

The increase in leukocyte counts observed in the negative control group should also correlate with spleen weight. The spleen is a site for proliferation of B lymphocytes, macrophages, and T lymphocytes. Wahyuningsih, et al., (2017) demonstrated that increased B lymphocyte proliferation correlates with increased spleen weight. However, B lymphocyte proliferation was not measured in this study. Since B lymphocytes are responsible for antibody production and antibody levels did not increase in the

ganyong-treated groups, it suggests that the polysaccharides and secondary metabolites in ganyong tuber extract primarily modulate innate immune responses against bacterial infection.

Strength and limitations

This study is among the first to investigate the immunomodulatory potential of *Canna edulis* K. (ganyong) tuber extract against *Staphylococcus aureus* infection in vivo, assessing both innate (phagocytic activity, leukocyte count, spleen weight) and adaptive (antibody levels via ELISA) immune responses. The use of a well-controlled experimental design with multiple dosage groups and the measurement of key immunological markers strengthens the validity and reliability of the findings. However, the study has several limitations, including the lack of detailed phytochemical characterization of the extract, the absence of lymphocyte proliferation assays, and the inability to demonstrate significant increases in antibody production. Furthermore, the observed decrease in immune response at higher doses underscores the need for further dose optimization and comprehensive toxicity profiling in future research.

CONCLUSION

Overall, this study indicates that Ganyong (*Canna edulis* K.) tuber extract has potential as an immunomodulator by enhancing phagocytic activity and capacity, increasing spleen weight, and modulating leukocyte counts. However, further phytochemical investigations are necessary to identify the specific chemical compounds responsible for these immunomodulatory effects.

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Conflict of Interest

The authors have no conflict of interest to declare.

Ethic Consideration

Animal welfare and experimental procedures were conducted in accordance with protocols approved by the Ethical Committee of the Medical Research Faculty of Dentistry, University of Jember (No. 1590/UN25.8/KEPK/DL/2022, on 25-07-2022).

Funding Disclosure

None.

Author Contribution

NIIS: contributed to conceptualization, project administration, supervision, methodology, data analysis, writing original draft, and final approval. SSAQ contributed to literature review, data validation, formal analysis, and writing, review & editing. MPM contributed to animal handling, extract preparation, and data curation. ML contributed to Sample collection, lab work, and assistance in leukocyte and spleen data acquisition. EN contributed to provision of laboratory resources (ELISA kit), and manuscript review. MP contributed to scientific consultation on immunological analysis, data interpretation, and critical manuscript revision. AIM contributed to data visualization, and proofreading.

Data Availability

None.

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