Borneo Journal of Pharmacy
Vol 8 Issue 4 November 2025
Pages 388 – 397

https://journal.umpr.ac.id/index.php/bjop/article/view/10233
DOI: https://doi.org/10.33084/bjop.v8i4.10233
e-ISSN: 2621-4814

Research Article

The Protective Effect of *Amorphophallus oncophyllus* against Indomethacin-Induced Duodenal Mucosal Injury in Rats via Inhibition of Inflammatory Cell Infiltration

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Keywords:
Amorphophallus oncophyllus
Anti-inflammatory
Glucomannan
Indomethacin
Non-communicable disease

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) can cause significant gastrointestinal mucosal injury, particularly in the duodenum. This damage is often initiated by localized erosion of the duodenal mucosa, which triggers a subsequent inflammatory cascade. The porang tuber (*Amorphophallus oncophyllus*) is a promising candidate for mitigating this injury due to its rich composition of bioactive compounds, including flavonoids, alkaloids, tannins, and glucomannan, all of which possess known anti-inflammatory properties. This study investigated the protective effect of an ethanolic *A. oncophyllus* extract on the duodenal mucosa in an indomethacin-induced rat model. Thirty Wistar white rats (*Rattus norvegicus*) were randomly assigned to five groups: a vehicle control, a model group receiving indomethacin, and three treatment groups that were pretreated with *A. oncophyllus* extract at doses of 50, 100, and 200 mg/kg, respectively, for seven days before a single dose of indomethacin. Our findings demonstrated that the *A. oncophyllus* extract, particularly at a dose of 200 mg/kg, effectively reduced duodenal mucosal injury caused by indomethacin. This protective effect is likely attributable to the extract's phytochemical profile, which contains flavonoids, tannins, saponins, terpenoids, and alkaloids. In conclusion, this research confirms that *A. oncophyllus* extract has the potential to protect the duodenal mucosa from NSAID-induced damage.

Received: July 3rd, 2025
1st Revised: August 8th, 2025
Accepted: October 16th, 2025
Published: November 30th, 2025

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are globally utilized for their analgesic, antipyretic, and anti-inflammatory properties[1]. However, their chronic use is significantly associated with severe upper gastrointestinal side effects, including erosion, ulceration, bleeding, and perforation[2]. Peptic ulcer disease, particularly when complicated by hemorrhage and perforation, remains a severe health burden; perforation is the most common indication for emergency surgery and accounts for approximately 40% of all ulcer-related fatalities, demanding substantial financial resources for treatment[3]. The underlying mechanism involves NSAID inhibition of the cyclooxygenase (COX)-1 enzyme, leading to a decrease in protective prostaglandin synthesis, subsequent reduction in gastrointestinal mucosal defense, and resultant

How to cite: Setiawati Y, Kurnijasanti R, D'Arqom A, Nugraha J, Illiandri O, Sudjarwo SA. The Protective Effect of Amorphophallus oncophyllus against Indomethacin-Induced Duodenal Mucosal Injury in Rats via Inhibition of Inflammatory Cell Infiltration. Borneo J Pharm. 2025;8(4):388-97. doi:10.33084/bjop.v8i4.10233

tissue damage[4]. Furthermore, NSAIDs exacerbate gastrointestinal injury by increasing levels of pro-inflammatory factors such as TNF-α, IL-1, IL-8, ICAM-1, leukotrienes (LT-B_4), and free radicals, which drive neutrophil infiltration and intense local inflammation[5]. Given its known gastrointestinal toxicity, Indomethacin is frequently employed as an agent to induce experimental ulcer models in rats[6].

Currently, the most effective therapeutic approaches for gastric and duodenal ulcers involve reducing gastric acid secretion through agents like proton pump inhibitors, histamine H_2 receptor blockers, and antacids, alongside the use of gastroprotective factors[7]. Despite their efficacy, many synthetic antiulcer drugs are associated with serious side effects, including hypomagnesemia, hypergastrinemia, hypocalcemia, bone fractures, and unwanted cardiovascular events, frequently leading to patient non-compliance[8]. Consequently, there is an urgent and ongoing need for new, safe therapeutic agents with minimal side effects and ready accessibility[9].

Although synthetic drugs have long dominated ulcer therapy, global interest in traditional medicine has experienced a resurgence in recent years[2]. Natural products offer a rich source of bioactive compounds that can mitigate reactive oxygen species (ROS) production and suppress inflammatory factors[10]. Plant-derived secondary metabolites such as flavonoids and tannins offer significant therapeutic potential. Flavonoids, in particular, exhibit diverse effects within the gastrointestinal tract, including anti-inflammatory, antispasmodic, antisecretory, antidiarrheal, and antiulcer properties[11,12]. Similarly, tannins are known for their anti-inflammatory, antioxidant, and antiulcer activities[13]. Furthermore, alkaloids possess various biological activities, including antioxidant, anti-inflammatory, antipyretic, and gastro-/hepatoprotective effects[14].

The Porang tuber (*Amorphophallus oncophyllus*) is a disti nctive tuber widely cultivated in Indonesia, resulting in its increasing abundance[15,16]. Phytochemical screening confirms that *A. oncophyllus* contains several key bioactive compounds, including flavonoids, alkaloids, and tannins[17]. Importantly, *A. oncophyllus* is notable for its high concentration of glucomannans, comprising approximately 55% of its composition[18]. Glucomannans are recognized for their anti-obesity, anticancer, antioxidant, anti-inflammatory, and gastrointestinal-protective properties[19]. While research on *A. oncophyllus* as a gastrointestinal protectant remains limited, one prior study indicated that an A. oncophyllus flour solution could alleviate gastric inflammation induced by acetic acid by 25%. It was effective in treating gastric wounds in Wistar rats within seven days[18]. Based on its established phytochemical profile and preliminary findings, it is hypothesized that *A. oncophyllus* tuber extract has the potential to reduce the degree of inflammation, erosion, and ulceration associated with gastrointestinal mucosal injury, such as duodenal mucosal damage.

MATERIALS AND METHODS

Materials

The plant material, *A. oncophyllus* tubers, was collected from Trenggalek, East Java, Indonesia. The identity of the plant was formally confirmed by the Biological Services Unit, Faculty of Science and Technology, Universitas Airlangga. The tubers were first peeled, washed, and sliced, then air-dried and weighed before being reduced to a coarse powder using a grinder. Following the methodology described by Kurnijasanti and Candrarisna[20], *A. oncophyllus* tuber powder was further processed by grinding and sieving through a 60-mesh sieve. A total of 0.8 kg of this refined powder was subjected to extraction via maceration using 5 L of 96% ethanol (Molindo Raya Industrial). Maceration was conducted over a period of three 24-hour intervals, with daily stirring to ensure maximum compound dissolution. After the third day, the mixture was filtered to separate the macerate, which was subsequently evaporated using a rotary evaporator at 50 rpm and 45°C until a thick extract was obtained. The 96% ethanol extract of *A. oncophyllus* was prepared at the Pharmacology Laboratory, Universitas Airlangga.

A cohort of 30 male Wistar white rats (*Rattus norvegicus*), aged 10–12 weeks and weighing between 150–200 g, was procured from the Experimental Research Center in the Faculty of Veterinary Medicine, Universitas Airlangga. The animals were provided with standard pellet feed and water ad libitum, and were maintained under standard housing conditions with optimal humidity and room temperature. They were subjected to a 12-hour light/dark cycle in separate cages throughout the experiment. All procedures conducted within this study received comprehensive approval from the Ethical Clearance Committee for Preclinical Research, Faculty of Veterinary Medicine, Universitas Airlangga (Ethical Clearance No. 1.KE.094.10.2020).

Methods

Animal experiment

The anti-ulcerogenic activity of the extract was evaluated using Wistar white rats. Before the experiment, the rats underwent a 7-day acclimatization period. Thirty animals were randomly assigned to five experimental groups, with six rats in each group. Group 1 served as the vehicle control, receiving only 1 mL/kg of 1% CMC-Na and 1 mL/kg of distilled water. Group 2, the disease model group, received 1 mL/kg of 1% CMC-Na and the ulcerogenic agent, indomethacin (50 mg/kg). Groups 3, 4, and 5 received *A. oncophyllus* extract orally at escalating doses of 50, 100, and 200 mg/kg, respectively[21,22]. The *A. oncophyllus* extract was administered orally once daily for seven consecutive days. Indomethacin, purchased from Sigma Aldrich (St. Louis, MO, USA), was administered orally once on the seventh day, specifically one hour after the final dose of the *A. oncophyllus* extract. Six hours after the administration of indomethacin on the seventh day, all subjects were humanely sacrificed[23]. All animals were fasted for 24 hours before sacrifice, although they had free access to drinking water.

Phytochemical screening

Qualitative phytochemical screening was performed on both the simplicia powder and the wet extract samples to identify the presence of alkaloids, flavonoids, terpenoids/steroids, tannins, and saponins using standard laboratory procedures[24,25].

Saponin: 2 mL of the A. oncophyllus extract was mixed with 3 mL of distilled water, boiled in a water bath with 20 mL of water, and then filtered. The filtrate was vigorously shaken and allowed to stand for 5 minutes. The formation of stable foam indicated a positive result for saponins.

Tannin: To the saponin filtrate, three drops of 1% $FeCl_3$ solution were added. The appearance of a greenish-brown or blackish-blue coloration indicated the presence of tannins.

Flavonoid: 2 mL of the extract was combined with one tablespoon of Mg powder, three drops of concentrated HCl, and three drops of alcohol. A positive reaction was confirmed by a color change from reddish-yellow to orange.

Alkaloid: The presence of alkaloids was tested using three common reagents: Wagner's Reagent: 2 mL of extract was treated with three drops of Wagner's reagent; a positive result was the formation of a brown precipitate; Mayer's Reagent: 2 mL of extract was treated with three drops of Mayer's reagent solution; the formation of a white or yellow lumpy precipitate indicated a positive reaction; Dragendorff's reagent: 2 mL of extract was treated with three drops of Dragendorff's reagent solution; the formation of a red precipitate indicated a positive reaction.

Steroid/terpenoid: 2 mL of extract was combined with three drops of acetic acid and three drops of concentrated H_2SO_4. A change to a green-blue color indicated the presence of steroids, while a change to a red-purple color indicated the presence of triterpenoids.

Histopathology

For histological assessment of the duodenum, the preparation was first cut along the midline to yield a rectangular section. Duodenal samples from each rat were immediately fixed in 10% buffered formalin and subsequently embedded in paraffin blocks. Sections were then cut to a thickness of 5 mm and stained with Hematoxylin and Eosin (H&E). Duodenal histopathological observations were conducted at 100x and 400x magnification. The specific variables assessed included inflammatory cell infiltration, erosion, and ulcers. The severity of these conditions was scored on a scale from 0 to 4, where 0 represented normal tissue, 1 was minimal (<25%), 2 was mild (25–35%), 3 was moderate (36–50%), and 4 indicated severe damage (>51%)[26].

Data analysis

All resulting data from this research were meticulously entered and processed using the SPSS version 21.0 software. The statistical variation observed among the different experimental groups was initially assessed using the Kruskal–Wallis test. This non-parametric test was chosen to determine if significant differences existed across the multiple groups. Following the detection of a significant overall difference, the Mann–Whitney U test was subsequently employed as a post-hoc analysis for pairwise comparisons between specific groups. For all analyses performed, a probability value of $p < 0.05$ was established as the criterion for statistical significance.

RESULTS AND DISCUSSION

Research on *A. oncophyllus* and its potential therapeutic applications is still in its early stages of development, resulting in a limited number of scientific publications. Previous studies have indicated the presence of key bioactive substances, including flavonoids, alkaloids, polyphenols, and tannins. To expand on this knowledge, phytochemical screening was conducted on the 96% ethanol extract of *A. oncophyllus*. The results, summarized in **Table I**, confirmed the presence of several secondary metabolites: flavonoids, tannins, saponins, terpenoids, and alkaloids. Secondary metabolites are chemical compounds synthesized by plants primarily for adaptation under stress conditions, and they are widely recognized for their applications in human nutrition and disease treatment. The extraction process serves to isolate and concentrate these valuable compounds, harnessing their benefits.

Table I. Phytochemical screening tests of *A. oncophyllus* 96% ethanol extract.

Bioactive compound	Description	Result
Flavonoid	The color changes to yellow	(+)
Tannin	The color changes to black	(+)
Saponin	Foam forms for 10 minutes; foam does not disappear with the addition of 1 drop of HCl	(+)
Steroid/Terpenoid	Steroid: No color	(-)
	Terpenoid: The color change to purple	(+)
Alkaloid	Dragendorff's: Orange precipitate	(+)
	Mayer's: No precipitate	(-)
	Wagner's: Brown precipitate	(+)

The presence of flavonoids, tannins, saponins, terpenoids, and alkaloids in the *A. oncophyllus* extract suggests a strong potential to ameliorate duodenal mucosal injury. Histopathological observations demonstrated an apparent dose-dependent protective effect in Wistar rats induced with indomethacin. The highest mean rank values for inflammatory cell infiltration, erosion, and ulceration were observed in the model group, with values progressively decreasing across the treatment groups (Groups 3, 4, and 5) toward the control group (**Table II**). Notably, the results of the Mann-Whitney test indicated that the highest dose group (Group 5, 200 mg/kgBW) was not significantly different from the control group across all histological variables.

Table II. Mean rank values for all white rat duodenal histopathological observation variables at five field of view.

Group	n	Inflammatory cell infiltration (Neutrophil)	Erosion	Ulcer
1 (Control)	6	$4.90^{a} \pm 0.063$	$5.50^{a} \pm 0.000$	$5.70^{a} \pm 0.040$
2 (Model)	6	$19.30^{c} \pm 0.279$	$20.60^{c} \pm 0.075$	$20.10^{c} \pm 0.102$
3 (50 mg/kgBW)	6	$18.30^{c} \pm 0.319$	$16.70^{c} \pm 0.147$	$18.00^{c} \pm 0.075$
4 (100 mg/kgBW)	6	$13.40^{bc} \pm 0.228$	$14.10^{bc} \pm 0.141$	$14.50^{bc} \pm 0.141$
5 (200 mg/kgBW)	6	$9.10^{ab} \pm 0.147$	$8.10^{ab} \pm 0.049$	$6.90^{ab} \pm 0.049$

Note: ^{a,bc} Different superscript within each column indicate a significant difference between the means ($p < 0.05$).

The administration of *A. oncophyllus* extract demonstrated a significant anti-inflammatory effect, reducing the inflammatory process in the indomethacin-induced duodenal mucosa. This was evidenced by a dose-dependent decrease in the infiltration of inflammatory cells (neutrophils) from the model group to Group 5 (**Figure 1**). Indomethacin, by inhibiting COX-1, reduces the production of protective prostaglandins, leading to gastrointestinal mucosal irritation. This irritation can manifest as epithelial detachment, erosion, and ulceration[27]. In inflammatory states, excessive proteolytic activity causes tissue destruction, resulting in erosion or more severe ulcer damage[28]. The 96% ethanol extract of *A. oncophyllus* significantly reduced the severity of both erosion and ulceration in a dose-dependent manner (**Figure 2**).

Phytochemical screening is a crucial preliminary step for identifying secondary metabolites in natural ingredients[29]. The qualitative screening, performed via color reactions with specific reagents, revealed positive results for flavonoids, tannins, saponins, terpenoids, and alkaloids in the 96% ethanol extract of *A. oncophyllus*. This finding is more comprehensive than a previous study that reported only flavonoids, tannins, and alkaloids[18]. Plants produce these compounds as a defense mechanism against environmental stressors, and numerous studies have confirmed their beneficial effects on human health[30].

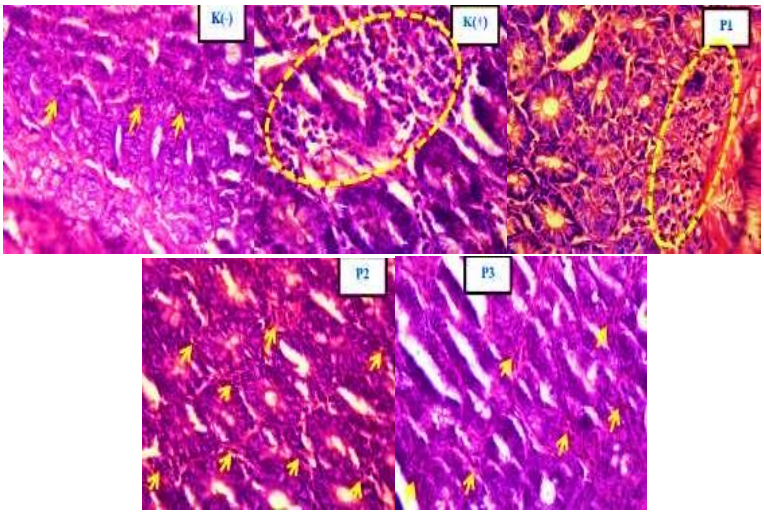

Figure 1. Inflammatory cell infiltration variable on duodenal histopathological observations. H&E color with 400x magnification using Optilab ® viewer. (K-) There is no inflammatory cell infiltration. (K+) Many inflammatory cell infiltrates can be observed. (P1) There are still many inflammatory cell infiltrates. (P2) There are fewer inflammatory cell infiltrates. (P3) There is little (lowest) inflammatory cell infiltration. Arrows and yellow circles indicate the presence of leukocyte (neutrophil) cells.

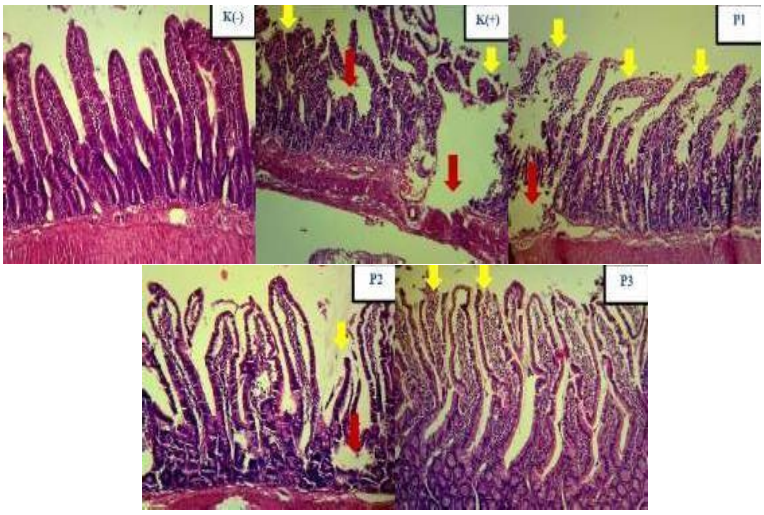

Figure 2. Epithelial erosion and ulceration duodenal variable on histopathological observations. H&E color with 100x magnification using Optilab ® viewer. (K-) There is no damage to the epithelium. (K+) Many erosions and ulcers are visible. (P1) There are many erosions and fewer ulcers. (P2) There are fewer erosions and fewer ulcers. (P3) There is a small epithelial erosion. Yellow arrows indicate epithelial erosion with partial thickness loss of mucosa. Red arrows indicate mucosal ulcers that appear to have lost the entire thickness of the mucosal layer and penetrated the deepest layer.

The tests confirm the therapeutic relevance of these metabolites: Flavonoids, identified by a color change to yellow following the reduction of glycosidic bonds, are polyphenols known for their widespread bioactivities, including anti-inflammatory, antioxidant, and gastroprotective effects[31]. Tannins, identified by the formation of a black color upon the addition of $FeCl_3$ (indicating the presence of phenol groups), are known for their astringent, anti-inflammatory, antioxidant, and gastrointestinal protective properties[32]. The foam test confirmed the presence of Saponins; these glycosidic compounds are recognized for their emulsifying and stabilizing properties, and they exhibit anti-inflammatory, antioxidant, and gastroprotective effects[33,34]. The positive result for Terpenoids suggests the presence of non-phenolic secondary metabolites with anti-inflammatory and gastroprotective potential[35,36]. Finally, the presence of Alkaloids, indicated by precipitate formation with Wagner's and Dragendorff's reagents, is significant given their reported antioxidant, anti-inflammatory, anti-ulcer, and gastroprotective activities[14].

The proven anti-inflammatory effect of *A. oncophyllus* is likely due to a synergistic action of these bioactive compounds. The extract's ability to reduce inflammatory cell infiltration, erosion, and ulcer severity after one week of preventive administration is further supported by the high content of glucomannans (approximately 55%) previously found in *A.*

oncophyllus[18]. Glucomannans are reported to have anti-inflammatory benefits through the inhibition of the transcription factor Nuclear Factor kappa B (NF-κB) expression[37]. NF-κB is a central regulator of inflammatory responses, and its activation leads to the production of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6. The inhibition of NF-κB prevents the release of TNF-α, which reduces the activation and aggregation of neutrophils, thereby decreasing inflammatory cell infiltration[38]. This mechanism aligns with previous findings showing that oral glucomannan reduced the production of TNF-α and the number of inflammatory cell infiltrations in mice with atopic dermatitis[39].

The protective effect against indomethacin-induced injury involves countering the damage mechanism. Indomethacin inhibits COX-1, thereby reducing the synthesis of protective prostaglandins, which leads to decreased mucus secretion and a weakened duodenal mucosal barrier[40]. The induction of inflammation by indomethacin is also linked to the generation of reactive oxygen species (ROS) and the subsequent activation of NF-κB[36]. The antioxidant properties of the *A. oncophyllus* extract, possibly through glucomannans, likely suppress free radicals, inhibiting NF-κB activation and reducing the expression of TNF-α. Reduced TNF-α production subsequently decreases neutrophil activation and the release of destructive protease enzymes, thus preventing tissue damage, erosion, and ulceration[41,42]. The overall decrease in all three histopathological variables (inflammation, erosion, and ulceration) from the model group to Group 5 strongly supports the 200 mg/kgBW dose as the effective prophylactic dose. Furthermore, the combination of various bioactive substances is thought to exert a synergistic anti-inflammatory effect, a phenomenon supported by studies on combined phytochemicals, such as flavonoids, alkaloids, and saponins, which act on different inflammatory targets and pathways[43-45].

The limitations of this study include the reliance on qualitative phytochemical testing and the absence of molecular marker examinations, such as ELISA-based quantification of pro-inflammatory cytokines (TNF-α, IL-1, IL-6). Additionally, the extract was administered for a short duration (less than a week). These areas are identified as the focus for further research to provide more robust evidence for the extract's anti-inflammatory mechanisms.

CONCLUSION

The ethanolic extract of *A. oncophyllus* was conclusively shown to possess significant protective effects on the duodenal mucosa of Wistar white rats following ulcer induction with indomethacin. A specific dose of 200 mg/kgBW was determined to be the most effective in mitigating mucosal damage. These findings strongly suggest the therapeutic potential of *A. oncophyllus* as a natural gastroprotective agent against non-NSAID-induced enteropathy.

ACKNOWLEDGMENT

The authors sincerely thank the pharmacology laboratory staff of Universitas Airlangga for their dedicated support, which was essential to the execution and successful completion of this research.

AUTHORS' CONTRIBUTION

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Writing - review & editing: Yuani Setiawati, Rochmah Kurnijasanti, Annette D'Arqom, Jusak Nugraha, Oski Illiandri, Sri Agus Sudjarwo

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest related to this research.

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