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Green Phytochemical-Based Gastroprotection of Glucomannan against Indomethacin-Induced Gastric Ulcers via Cytoprotection and Anti-Apoptotic Effects

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used but frequently induce gastric mucosal injury. Indomethacin disrupts mitochondrial function, promotes cytochrome c release, and activates caspase-3, leading to apoptosis and epithelial damage. Systemic inhibition of cyclooxygenase-1 (COX-1) further reduces prostaglandin synthesis, compromising gastric mucosal defense. Current anti-ulcer therapies show limited efficacy and notable adverse effects, highlighting the need for safer gastroprotective alternatives. Glucomannan, a plant-derived polysaccharide, has demonstrated the ability to enhance COX-1 expression and suppress apoptotic activity. This study aimed to evaluate the protective effects of *Amorphophallus oncophyllus*-derived glucomannan against indomethacin-induced gastric ulceration in Wistar rats and to elucidate its cytoprotective, and anti-apoptotic mechanisms. Thirty male Wistar rats were randomly allocated into five groups (n = 6). Group 1 received vehicle only; Group 2 was administered a single oral dose of indomethacin (50 mg/kg). Groups 3-5 were pretreated orally with glucomannan (40, 80, or 160 mg/kg) for seven consecutive days, followed by indomethacin administration. Macroscopic gastric lesions were quantified, and immunohistochemical analyses for COX-1 and caspase-3 expression were performed. Indomethacin induced marked gastric damage characterized by inflammation, erosion, ulceration, and hemorrhage. Glucomannan pretreatment significantly attenuated these lesions in a dose-dependent manner, with 160 mg/kg exhibiting the strongest protective effect (ulcer inhibition rate: 80%). Glucomannan restored COX-1 expression while markedly reducing caspase-3 activity, demonstrating enhanced mucosal cytoprotection and reduced apoptosis. *Amorphophallus oncophyllus* glucomannan confers potent gastroprotective effects against indomethacin-induced gastric injury, mediated through the upregulation of COX-1 and suppression of caspase-3-dependent apoptosis. These findings suggest its potential as a natural, safe prophylactic agent for NSAID-associated gastric ulceration.

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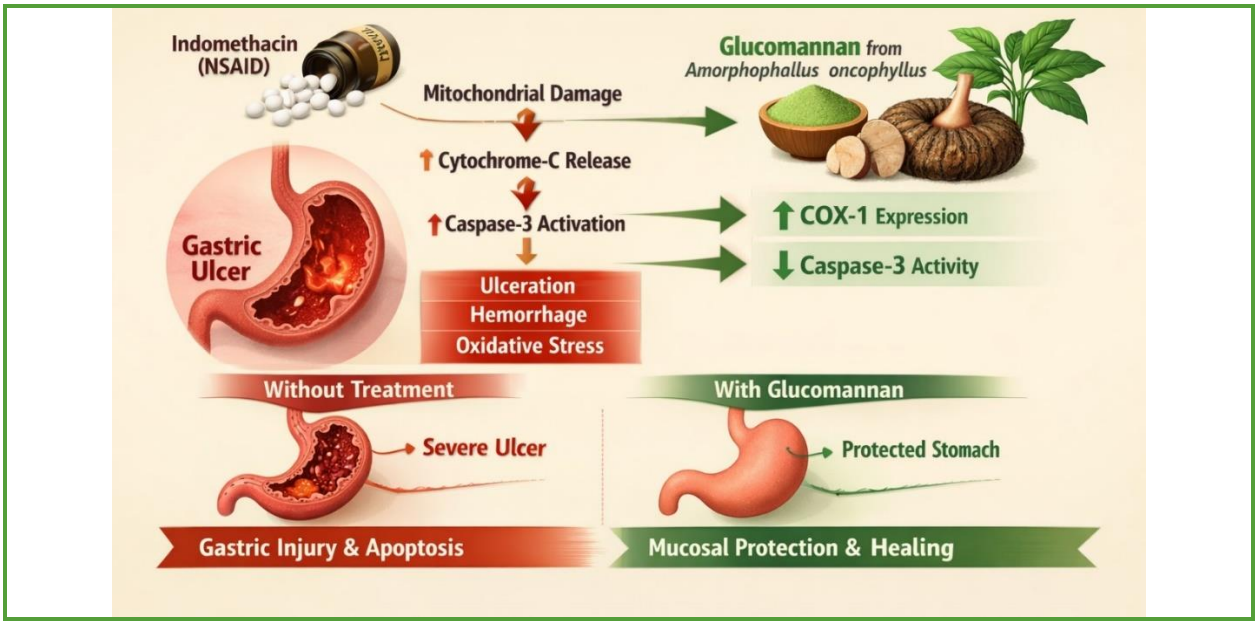
Graphical Abstract



Introduction

Gastric ulcer is a frequent gastrointestinal disease characterized by the disruption of gastric mucosa, resulting in injury ranging from superficial erosion to deep ulceration. The gastric mucosal integrity depends on an equilibrium between protective and aggressive factors [1]. When this equilibrium is disturbed, whether by chemical, infectious, or mechanical stimuli, lesions may develop and impair digestive function, ultimately diminishing quality of life [2]. Peptic ulcer disease impacts approximately 4 million individuals each year and remains a major global health burden due to its risk of complications such as bleeding, perforation, and malignant transformation [3]. Despite *H. pylori* infection and chronic consumption of non-steroidal anti-inflammatory drugs (NSAIDs) being recognized as primary etiological factors, gastric ulcers are more frequently associated with NSAID exposure than with *H. pylori* infection [4,5].

NSAIDs continue to be extensively used around the world for their anti-inflammatory, analgesic and antipyretic effects. Nevertheless, their therapeutic benefits are limited by gastrointestinal toxicity. Indomethacin, a potent non-selective NSAID, is widely used in experimental models due to its strong ulcerogenic potential [6]. It induces gastric injury through both topical and systemic mechanisms. Locally, the weakly acidic nature of indomethacin facilitates ion trapping within gastric epithelial cells, leading to mitochondrial dysfunction, pore transition opening, cytochrome c release, and caspase activation that culminates in apoptosis. Systemically, indomethacin suppresses cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), with COX-1 inhibition reducing prostaglandin synthesis required for mucosal defense, blood flow maintenance, mucus secretion, and epithelial renewal [7].

Although proton pump inhibitors (PPIs) and other anti-ulcer medications are commonly prescribed to mitigate NSAID-induced gastric injury, prolonged use is correlated with adverse effects, including hypomagnesemia, increased infection risk, hypergastrinemia, and impaired

mineral absorption. Moreover, recurrence of gastric ulcers remains frequent despite conventional therapy and eradication of *H. pylori* [8]. These constraints highlight the necessity for innovative gastroprotective approaches, particularly those derived from natural sources with better safety profiles. Plant-derived polysaccharides have gained considerable attention for their therapeutic potential, including antioxidant, anti-inflammatory, immunomodulatory, and gastroprotective properties. Among these, glucomannan a water-soluble, non-ionic polysaccharide found abundantly in several plants, exhibits promising biological effects [9,10]. Previous research has shown that glucomannan from *Cyrtopodium andersonii* and *Aloe vera* can mitigate gastric damage by reducing oxidative stress, inflammatory responses, and apoptotic signaling while enhancing endogenous antioxidant enzymes such as superoxide dismutase and catalase [9,11].

Konjac glucomannan, commonly obtained from *Amorphophallus konjac*, has been extensively studied; however, its availability in Indonesia is limited [12,13]. In contrast, *Amorphophallus oncophyllus* (porang), a native Indonesian species, contains a high concentration of glucomannan and has gained economic and scientific interest as an alternative source [14]. Preliminary studies have demonstrated that porang-derived glucomannan may accelerate healing of gastric inflammation in rat models, suggesting potential anti-ulcer activity [15]. Despite these findings, the molecular processes responsible for its gastroprotective effects—especially on indomethacin-induced gastric ulceration remain insufficiently understood. Given the increasing need for safer anti-ulcer agents and the potential benefits of porang glucomannan, this study investigates its protective effects on indomethacin-induced gastric ulceration in rats. Specifically, its cytoprotective role was evaluated through modulation of COX-1 expression and its anti-apoptotic effect via attenuation of caspase-3 activation. Understanding these mechanisms may support the development of *Amorphophallus oncophyllus* glucomannan as a natural, effective, and locally sourced gastroprotective agent.

Experimental

Experimental animals

Male Wistar rats (12 weeks old, 150–200 g) were obtained from the Animal Facility, Universitas Airlangga, Surabaya, Indonesia. Animals were housed under standard laboratory conditions (temperature 22–24 °C, relative humidity 40–70%, and a 12 h light/dark cycle) with free access to food and water. All procedures were conducted in accordance with ethical standards and approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Airlangga (Ethical Clearance No. 31/EC/KEPK/FKUA/2024).

Experimental design

After a one-week acclimatization period, 30 rats were randomly assigned into five groups (n = 6 per group):

-Group 1 (Normal control): received vehicle only.

-Group 2 (Ulcer control): received a single oral dose of indomethacin (50 mg/kg).

-Groups 3–5 (Treatment groups): pretreated with glucomannan at 40, 80, or 160 mg/kg/day for 7 days, followed by indomethacin administration (50 mg/kg) 1 h after the final glucomannan dose.

All rats were fasted for 24 h before indomethacin treatment, with water available ad libitum. 6 h after indomethacin administration, animals were euthanized using ether anesthesia.

The stomachs were excised, opened along the greater curvature, rinsed with cold saline, and processed for macroscopic and histological assessment [16,17].

Macroscopic assessment of gastric lesions

Each stomach was digitally photographed immediately after dissection. The area of visible lesions (mm^2) was quantified using ImageJ software. Ulcer severity was scored based on lesion length: 0 = no lesions; 1 = min hemorrhagic spots; 2 = lesions < 2 mm; 3 = 2–3 mm; 4 = 3–4 mm; 5 = > 4 mm [8,18]. The ulcer score (US) was calculated for each group (total scores divided by the number of animals). The ulcer index (UI) was obtained by multiplying US by 100. The ulcer inhibition rate (UIR) was determined using Equation 1:

$$UIR\ (\%) = [(UI\_indomethacin - UI\_treated) / UI\_indomethacin] \times 100 \quad (1)$$

Gastric tissues were subsequently sectioned and fixed for histopathological and immunohistochemical analysis.

Immunohistochemistry for COX-1 expression

Fundic stomach tissues were fixed in 10% buffered formalin, dehydrated in graded ethanol, and embedded in paraffin. Sections (4 μm thick) were mounted on poly-L-lysine–coated slides. Immunostaining was performed using a primary antibody against COX-1 (sc-19998, Santa Cruz Biotechnology, USA) and processed with an automated immunostaining system (ScyTeK Laboratories). A blinded pathologist evaluated 20 randomly selected fields per slide (1,500 cells per sample) at 1,000× magnification using an Olympus DX41 microscope equipped with a Panasonic G9 digital camera and Lumix Sync software.

Immunohistochemistry for caspase-3 expression

Caspase-3 expression in gastric tissue was assessed using a specific primary antibody (sc-56053, Santa Cruz Biotechnology, USA). Staining and evaluation procedures followed the same steps described for COX-1 analysis.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Statistical differences among groups were evaluated using one-way analysis of variance (ANOVA) followed by Duncan's post hoc test. Analyses were performed using SPSS version 17.0, with $p<0.05$ considered statistically significant.

Results

Effect of glucomannan on the macroscopic evaluation of indomethacin-induced gastric ulcer

The macroscopic appearance of the gastric mucosa varied distinctly among the experimental groups (Figure 1). Rats in the normal control group exhibited an intact mucosal surface characterized by a smooth texture and uniform light pink coloration, with no visible signs of injury. In contrast, indomethacin administration resulted in extensive mucosal damage, including marked hyperemia, edema, deep erosions, ulceration, and multifocal hemorrhages.

Pretreatment with *Amorphophallus oncophyllus* glucomannan mitigated the severity of gastric lesions in a dose-dependent manner. Rats receiving 40 mg/kg showed noticeable but reduced mucosal injury, with moderate erosions and fewer ulcerative lesions compared to the ulcer control group. Animals pretreated with 80 mg/kg exhibited only mild erosions, minimal ulceration, and isolated hemorrhagic spots. The most pronounced protection was observed in

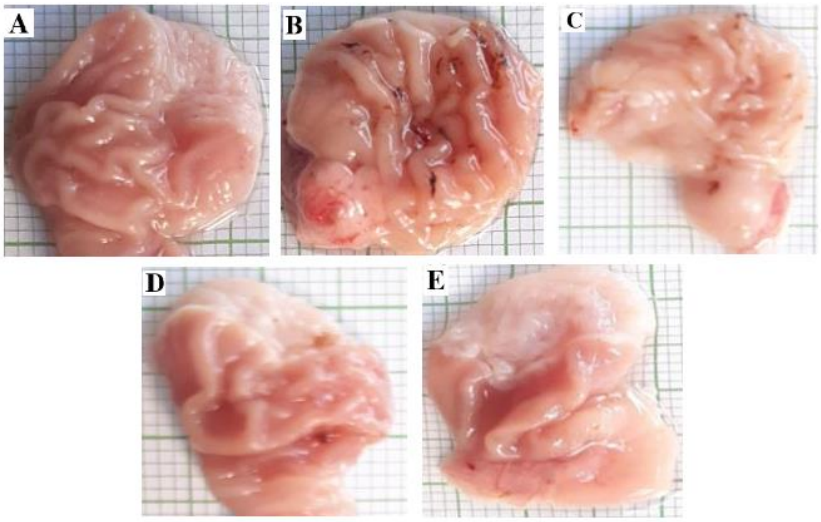


Figure 1. Effects of *Amorphophallus oncophyllus* glucomannan on indomethacin-induced gastric ulcers. Shown are the normal control group (A), indomethacin-treated group (B), and glucomannan-treated groups at doses of 40 mg/kg BW (C), 80 mg/kg BW (D), and 160 mg/kg BW (E)

the 160 mg/kg group, where gastric morphology closely resembled that of the normal control group, with only minute and superficial changes. Ulcer score (US), ulcer index (UI), and ulcer inhibition rate (UIR) further confirmed these macroscopic observations.

Rats in the indomethacin-only group displayed the highest US (6.67 ± 0.52) and UI (667). Glucomannan pretreatment significantly reduced lesion severity: 40 mg/kg: US = 4.50 ± 0.84, UI = 450; 80 mg/kg: US = 1.67 ± 0.52, UI = 167; and 160 mg/kg: US = 1.33 ± 0.52, UI = 133. The highest dose provided the strongest protection, achieving an ulcer inhibition rate of 80%, indicating substantial amelioration of indomethacin-induced gastric damage.

Effect of glucomannan on COX-1 expression in indomethacin-induced gastric ulcer

Immunohistochemical evaluation revealed substantial differences in COX-1 expression across groups. Gastric tissues from the normal control group showed strong COX-1 staining, consistent with normal mucosal cytoprotective activity. Indomethacin markedly suppressed COX-1 expression, indicating disruption of mucosal defense mechanisms. Glucomannan pretreatment enhanced COX-1 expression in a dose-dependent manner. The 40 mg/kg dose produced only a slight increase, not significantly different from the ulcer control group. In contrast, the 80 mg/kg and 160 mg/kg doses markedly restored COX-1 expression, showing staining intensities comparable to the normal control group. The 160 mg/kg dose produced the strongest immunoreactivity, as evidenced by prominent reddish-brown staining in mucosal epithelial cells (Figure 2). These findings suggest that glucomannan effectively counteracts the COX-1 inhibitory effect of indomethacin and strengthens gastric cytoprotection.

Effect of glucomannan on caspase-3 expression in indomethacin-induced gastric ulcer

Indomethacin exposure significantly increased caspase-3 expression in gastric

epithelial cells, demonstrating enhanced apoptotic activity. This elevation was markedly higher than in the normal control group, which exhibited only very mild caspase-3 staining. Glucomannan pretreatment reduced caspase-3 expression in all treated groups. The 40 mg/kg dose resulted in moderate expression, whereas the 80 mg/kg dose substantially decreased caspase-3 levels to near-baseline values. The 160 mg/kg dose produced the lowest caspase-3 staining intensity among the treatment groups, comparable to normal gastric mucosa (Figure 3). These findings demonstrate that *Amorphophallus oncophyllus* glucomannan exhibits a strong anti-apoptotic effect by suppressing caspase-3 activation triggered by indomethacin.

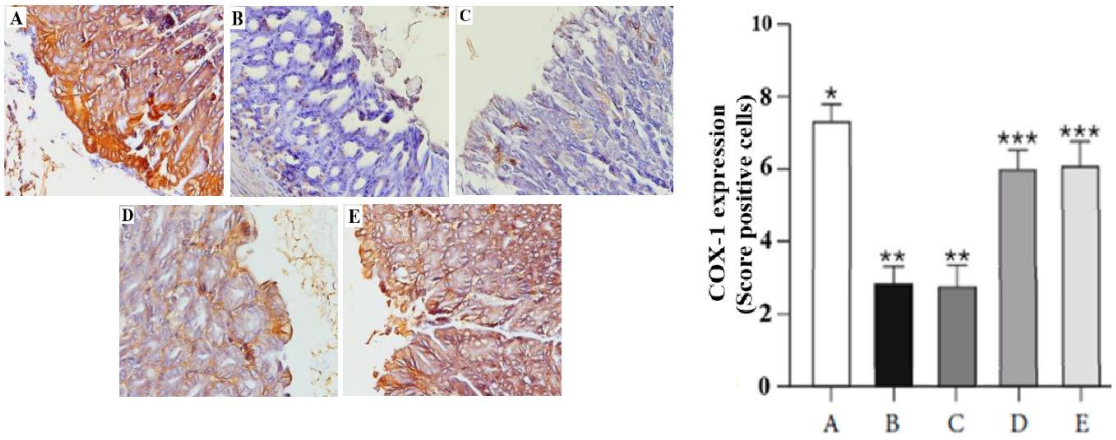


Figure 2. Immunohistochemical analysis showing the influence of Glucomannan on COX-1 expression in indomethacin-induced gastric ulcer. Control group (A); indomethacin-treated group (B); Glucomannan-treated groups at doses of 40 mg/kg BW (C), 80 mg/kg BW (D), and 160 mg/kg BW (E). Bars bearing different superscripts *-*** indicate statistically significant variation ($p < 0.05$). Image magnified ×400

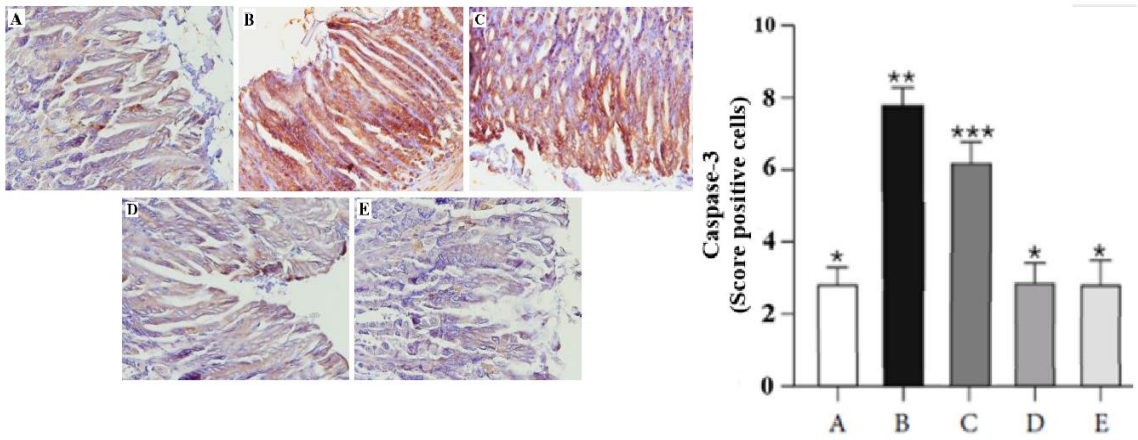


Figure 3. Immunohistochemical analysis showing the influence of Glucomannan on Caspase-3 expression in indomethacin-induced gastric ulcer. Control group (A); Indomethacin-treated group (B); Glucomannan-treated groups at doses of 40 mg/kg BW (C), 80 mg/kg BW (D), and 160 mg/kg BW (E). Bars bearing different superscript *-*** indicate statistically meaningful variation ($p < 0.05$). Image magnified ×400

Discussion

Gastric ulcers remain a major clinical concern due to their high global prevalence and the significant morbidity associated with complications such as bleeding and perforation [3]. While multiple etiological factors contribute to ulcer development, chronic consumption of non-steroidal NSAIDs continues to account for a substantial proportion of gastric ulcer cases [4]. The limitations of existing pharmacological therapies, including risks of long-term adverse effects, incomplete healing, and frequent recurrence underscore the need for safer and more effective gastroprotective agents. In this context, polysaccharides derived from natural sources have gained considerable attention for their biological activities, including cytoprotection, anti-inflammatory effects, and modulation of apoptotic pathways [9]. The present study investigated the gastroprotective potential of *Amorphophallus oncophyllus* glucomannan against indomethacin-induced gastric ulceration in rats. Correlating with previous literature, administration of indomethacin resulted in pronounced mucosal injury characterized by hyperemia, edema, erosions, ulceration, and hemorrhage. These findings align with earlier reports showing that indomethacin induces gastric lesions by disrupting mitochondrial oxidative phosphorylation, promoting mitochondrial permeability transition, and activating caspase-mediated apoptosis [6,7,18,19]. The marked rise in caspase-3 expression observed in the ulcer control group further confirms the pro-apoptotic actions of indomethacin on gastric epithelial cells. Pretreatment with *Amorphophallus oncophyllus* glucomannan markedly attenuated gastric injury in a dose-dependent manner. The highest dose (160 mg/kg) provided the most robust protection, reducing macroscopic lesion severity and achieving an ulcer inhibition rate of 80%. These results are in line with prior research demonstrating that plant-derived mannans can ameliorate gastric damage by enhancing mucosal integrity and modulating oxidative and inflammatory pathways [11,20]. The protective effect observed in this study suggests that porang-derived glucomannan, similar to konjac glucomannan, exerts biological activities relevant to gastric mucosal defense. One of the central mechanisms contributing to indomethacin-induced gastric injury is the inhibition of COX-1, an enzyme essential for maintaining basal prostaglandin synthesis in the stomach. Prostaglandins are key regulators of mucus secretion, bicarbonate production, mucosal blood flow, and epithelial cell turnover [21,22].

The significant reduction of COX-1 expression in the ulcer control group reflects impaired cytoprotective function. Glucomannan pretreatment successfully restored COX-1 expression, particularly at 80 and 160 mg/kg doses, suggesting that enhancement of prostaglandin-dependent defense mechanisms contributes to its anti-ulcer effect. These findings are consistent with previous studies reporting that plant polysaccharides can upregulate COX-1 expression and reinforce gastric mucosal resilience [23]. Apoptosis plays a critical role in maintaining gastric mucosal homeostasis, and excessive activation of apoptotic pathways is strongly associated with NSAID-induced epithelial injury [24]. Caspase-3, a key executioner caspase, serves as an indicator of irreversible apoptotic activity [25]. The substantial increase in caspase-3 expression observed in the indomethacin group confirms the involvement of apoptosis in gastric ulcer pathogenesis. Glucomannan pretreatment, particularly at 80 and 160 mg/kg, significantly reduced caspase-3 activation, demonstrating a potent anti-apoptotic effect. This anti-apoptotic action is consistent with findings from studies

using *Aloe vera* and *turmeric*-derived mannans, which have shown suppression of apoptosis-related pathways and protection against gastric injury [20,23]. The combined ability of *Amorphophallus oncophyllus* glucomannan to enhance COX-1 expression and suppress caspase-3 activation highlights its dual mechanism of gastroprotection: strengthening mucosal defense and preventing epithelial cell death. These complementary actions may explain the substantial reduction in gastric lesions observed in pretreated animals. Furthermore, the results support the potential of porang glucomannan as a viable natural alternative to conventional anti-ulcer therapies, offering both efficacy and safety. Given its abundance in Indonesia, porang-derived glucomannan also presents an economically valuable resource for the development of functional natural products.

Although present research demonstrates substantial insights into the gastroprotective mechanisms of *Amorphophallus oncophyllus* glucomannan, further investigations are warranted. Additional studies exploring its effects on mucin production, prostaglandin levels, inflammatory cytokines and oxidative stress markers would deepen mechanistic understanding. Ultimately, clinical trials will be needed to ascertain the translational relevance of these findings in human populations, particularly in individuals requiring long-term NSAID therapy. Overall, the findings of this study demonstrate that glucomannan from *Amorphophallus oncophyllus* exerts significant gastroprotective effects through cytoprotective reinforcement and inhibition of apoptosis. These results establish a scientific foundation for the development of porang-derived glucomannan as a promising natural agent for preventing NSAID-associated gastric mucosal injury.

Conclusion

This study demonstrates that *Amorphophallus oncophyllus* derived glucomannan confers significant gastroprotection against indomethacin-induced gastric ulceration in Wistar rats. Pretreatment with glucomannan, particularly at a dose of 160 mg/kg, markedly attenuated macroscopic mucosal damage and achieved the highest ulcer inhibition rate, effects that were accompanied by restoration of COX-1 expression and pronounced suppression of caspase-3 activation, indicating enhancement of mucosal cytoprotection and inhibition of apoptosis in gastric epithelial cells. Collectively, these findings suggest that porang-derived glucomannan exerts its protective effects through a dual mechanism involving reinforcement of gastric defense pathways and attenuation of apoptotic signaling. Given its natural origin, favorable safety profile, and biological efficacy, *Amorphophallus oncophyllus* glucomannan represents a promising prophylactic candidate for reducing the risk of NSAID-induced gastric ulceration, although further mechanistic studies and clinical trials are required to confirm its therapeutic potential in humans.

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Conflict of Interest

The authors declare no conflict of interest.

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