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Enhanced Gastric Ulcer Recovery: Synergistic Therapeutic Benefits of Cabbage (*Brassica oleracea*) and Honey in Indomethacin-Induced Wistar Rats

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Abstract

Peptic Ulcer Disease (PUD) remains a major global health concern due to its significant morbidity and mortality. Although Proton Pump Inhibitors (PPIs) are commonly used for treatment, they are often costly and associated with adverse effects. This study evaluated the therapeutic efficacy of combining cabbage (*Brassica oleracea*) extract and stingless bee honey in healing indomethacin-induced gastric ulcers in albino Wistar rats. Twenty-four male rats were randomly assigned to six groups (four treatment, one negative and one positive control groups (n = 4 per group). The four treatment groups received cabbage extract (300 mg/kg bw), stingless bee honey (0.6 g/kg bw), their combination, or omeprazole (20 mg/kg bw) for seven days. Ulcer healing was assessed by measuring ulcer index, gastric juice volume, total and free acidity, and gastric pH. All treatment groups showed significant improvements ($p < 0.05$) compared to the ulcer control group. The combination therapy resulted in the greatest reduction in ulcer index and acidity parameters and the highest increase in gastric pH. These findings suggest that co-administration of cabbage extract and stingless bee honey may offer a natural, cost-effective alternative to conventional anti-ulcer therapy.

Keywords: Indomethacin-induced ulcers; cabbage; stingless bee honey; gastroprotection effect; natural therapy

Introduction

Peptic ulcer disease (PUD) remains a prevalent and significant gastrointestinal disorder, affecting approximately 5–10% of the global population (Sung et al. 2009). In Tanzania, PUD is in the top ten most commonly diagnosed diseases, with it ranking 5th most frequent diseases or conditions for which patients visit the outpatient department for diagnosis and treatment and the 6th common condition that results in admissions into hospitals (Ministry of Health 2024). The condition is characterized by mucosal erosion primarily due to an imbalance between gastric defensive mechanisms and aggressive factors such as *Helicobacter pylori* infection, non-steroidal anti-inflammatory drug (NSAID) use, alcohol consumption, smoking, and stress (Pahwa et al. 2010; Narayanan et al. 2018). The common symptoms include epigastric pain, weight loss, poor appetite, nausea, vomiting, and signs of gastrointestinal bleeding such as melena or hematemesis (Malik et al. 2023).

The primary etiological agents of PUD are *Helicobacter pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs), the latter accounting for over 90% of non-*H. pylori*-related ulcers (Narayanan et al. 2018). NSAID-induced ulcers result from multiple mechanisms, including impaired mucosal protection through inhibition of prostaglandin synthesis via cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)

suppression (Wallace 2008). NSAID-induced gastric damage is also associated with increased gastric permeability, oxidative stress, reduction in epithelial repair through epidermal growth factor (EGF), inflammatory cytokine release, and increased leukocyte infiltration (Somasundaram et al. 2000; Amirshahrokhi and Khalili 2016).

Proton pump inhibitors (PPIs) remain the main treatment method as they are effective in acid suppression and treating NSAID-induced mucosal damage (Scheiman 2013). However, they are associated with high costs, prolonged treatment duration, and a growing list of adverse effects ranging from infections and nutrient malabsorption to potential links with renal, hepatic, and cognitive disorders (Fossmark et al. 2019, Kavitt et al. 2019, Kuna et al. 2019). Furthermore, growing evidence indicates that prolonged PPI use may carry significant adverse effects, including increased risk of chronic kidney disease, micronutrient deficiencies, cardiovascular events, bone fractures, and gut microbiota imbalance (Vaezi et al. 2017, Kinoshita et al. 2018, Maideen 2023, Tian et al. 2023). These limitations have driven the search for safer, affordable, and more effective alternatives, especially from natural products with anti-ulcer properties.

Cabbage (*Brassica oleracea*) is widely recognized for its nutritional and therapeutic value and has shown promising anti-ulcer activity in animal models, attributed to its phytochemicals such as glutamine, flavonoids, vitamins C and K, and various polyphenols (Carvalho et al. 2011, Oguwike et al. 2014, Sharifi-Rad et al. 2018). These compounds contribute antioxidant and anti-inflammatory effects, aiding mucosal protection and repair. Honey, particularly stingless bee honey, has demonstrated wound healing, antimicrobial, and anti-inflammatory activities, making it a candidate for gastroprotective interventions (Samarghandian et al. 2017, Saranraj and Sivasakthi 2018, Rezaei et al. 2019, Setiawan et al. 2024). Its flavonoid content, acidity, and hygroscopic properties collectively contribute to bacterial inhibition, reduction of reactive oxygen species (ROS), and enhancement of tissue regeneration (Vallianou et al. 2014, Rysha et al. 2022, Stavropoulou et al. 2022). Similar findings of the honey to facilitate mucosal regeneration by modulating cytokine levels and promoting epithelial repair have been previously reported (Palma-Morales et al. 2023).

Despite evidence supporting the individual benefits of cabbage and honey, limited studies have evaluated their synergistic effects on ulcer healing. The present study was designed to investigate the potential synergistic gastroprotective activity of cabbage extract and stingless bee honey in a rat model of indomethacin-induced ulcers. By comparing their effects with omeprazole, and assessing parameters such as ulcer index, gastric acidity, and pH, the study aimed to determine whether this natural combination offers a safer, more holistic alternative to conventional pharmacotherapy.

Materials and Methods

Ethical approval

All procedures involving animals were conducted following the University of Dar es Salaam (UDSM) Research Policy and Operational Procedures, in compliance with national and institutional guidelines for the care and use of laboratory animals. Ethical clearance was granted by the UDSM Animal Ethics Committee.

Experimental animals

Twenty-four healthy male albino Wistar rats (8-10 weeks, weighing 150-200 g) were obtained and housed under standard laboratory conditions (22 ± 2°C, 12 h light/dark cycle, 60–70% humidity). Animals were fed on standard commercial chow (Guinea Feeds, Tanzania) and had access to water ad libitum. Acclimatization was done for one week prior to the experiment. Animal handling, housing, and experimental design followed the OECD guidelines for the testing of chemicals (OECD, 2001) and previous protocols on NSAID-induced ulcer models with some modifications (El-Komy and Mouafi 2016).

Experimental design and grouping

The 24 rats were randomly assigned into six groups (n = 4 per group). Group 1

(Negative Control, NEG) received 1 mL of 0.9% saline orally. Group 2 (Positive Control, POS) was administered indomethacin (20 mg/kg bw) once to induce gastric ulcers. Group 3 (Cabbage, CBG) received indomethacin (20 mg/kg bw), followed by cabbage extract (300 mg/kg bw) twice daily for 7 days. Group 4 (Stingless bee honey, SBH) was treated with stingless bee honey (0.6 g/kg bw) after indomethacin administration. Group 5 (CBG+SBH) received indomethacin and was co-treated with both cabbage extract and honey (300 mg/kg + 0.6 g/kg bw). Group 6 (Omeprazole, OMP) served as the standard treatment group and received indomethacin followed by omeprazole (20 mg/kg bw). All treatments were administered via oral gavage twice daily for 7 days, and the animals were sacrificed on day 8 for analysis (Figure 1).

The sample size of 4 rats per group was determined through a priori power calculations, informed by previous indomethacin-induced ulcer studies (El-Komy and Mouafi 2016), which reported significant reductions in ulcer parameters. Using one-way ANOVA, a large effect size (Cohen's f = 0.8) was assumed based on the anticipated strong anti-ulcer effects of cabbage and honey (Carvalho et al. 2011, Rezaei et al. 2019). Calculations indicated that 4 rats per group could detect differences in key outcomes (e.g., ulcer index, gastric pH) with 80% power and $\alpha = 0.05$. This sample size aligns with the 3Rs principle (replacement, reduction, refinement), minimizing animal use as per the University of Dar es Salaam Animal Ethics Committee guidelines, while practical constraints (e.g., rat availability, laboratory resources) supported the choice. Standardized protocols and the well-characterized ulcer model reduced variability, and significant results ($p < 0.05$) across endpoints validated the sample size. Future studies could use larger samples to explore additional effects.

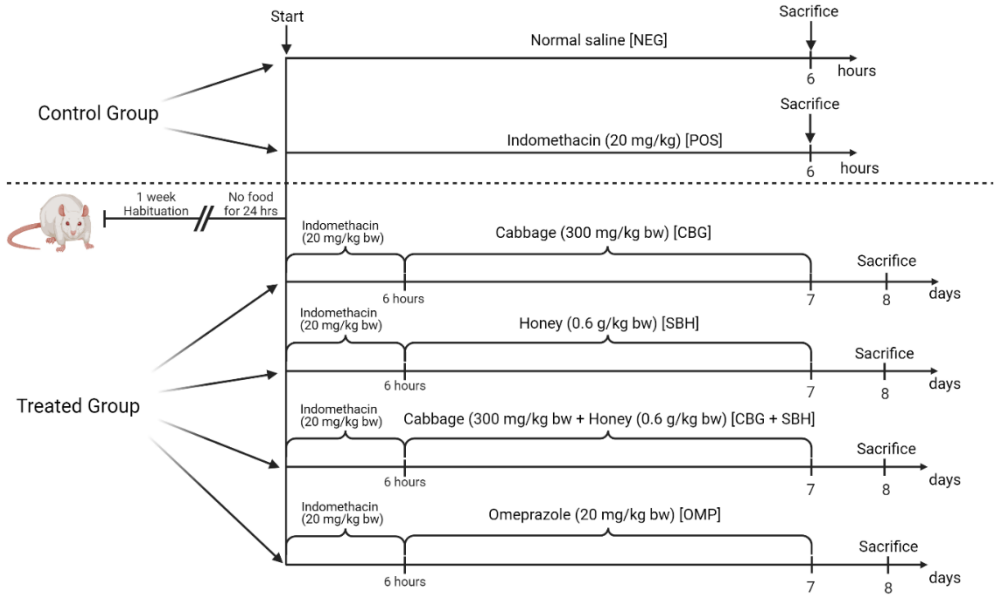

Figure 1: Schematic representation of the experimental design

Preparation of aqueous *B. oleracea* extract

Fresh cabbages obtained in Dar es Salaam were washed and crushed using a mechanical blender. Following a modified method of Carvalho et al. (2011), 250 g of cabbage were homogenized with 500 mL of distilled water, agitated for 4 hours, and left overnight at 4°C. The filtrate was evaporated at 40°C in a hot air oven. The dried extract was reconstituted to 300 mg/kg bw in distilled water immediately prior to administration. Dosing was calculated based on the average body weight of the rats and administered orally via gavage at a volume of 1 mL/200 g body weight.

Administration of stingless bee honey

Crude stingless bee honey was obtained from a certified local apiary. A dose of 0.6 g/kg bw was prepared fresh daily in distilled water and administered via oral gavage. This dosage was selected based on previously published studies evaluating the gastroprotective and antioxidant effects of honey (Porcza et al. 2016, Rao et al. 2016, Ahmed et al. 2017).

Gastric ulcer induction and evaluation

Gastric ulcers were induced using indomethacin (20 mg/kg bw). After euthanasia, stomachs were removed, opened along the greater curvature, rinsed in saline, and pinned for gross examination. Ulcerated and total mucosal areas were measured using ImageJ software. The ulcer index was calculated following the standard method described by Ganguly (1969), based on total lesion area per gastric surface area.

Gastric juice analysis

Gastric juice was collected by ligating the pylorus and inserting a polyethylene cannula into the duodenum. The oesophagus was clamped, and the stomach contents were collected and centrifuged at 5000 × g for 5 minutes. The supernatant volume was expressed in mL/100 g bw. The pH was measured using a digital pH meter. Total and free acidity were determined by titration with 0.01 N NaOH using Topfer's reagent and phenolphthalein as indicators.

Histopathological examination

Stomach tissues were fixed in 10% neutral buffered formalin, dehydrated in graded ethanol, cleared in xylene, and embedded in paraffin. Sections of 4–6 µm were prepared and stained with haematoxylin and eosin (H&E). Microscopic examination was performed to evaluate mucosal integrity, inflammation, and glandular architecture.

Statistical Analysis

Data were analysed using GraphPad Prism 9.5.0. Results are presented as mean ± SEM. One-way ANOVA was used to determine whether there were statistically significant differences in ulcer-related outcomes across all treatment groups, followed by Tukey's post hoc test to compare each treatment with the positive control, and between treatments themselves to determine which interventions were statistically superior. Statistical significance was considered at $p < 0.05$.

Results

Macroscopic mucosal morphology, histopathology and ulcer index

After seven days of treatment, notable differences in gastric mucosal appearance were observed across groups. Macroscopic examination revealed extensive haemorrhagic lesions in the positive control (POS) group, indicating severe mucosal damage due to indomethacin administration. In contrast, all treatment groups showed reduced ulceration, with the combination of cabbage and honey (CBG+SBH) displaying the most intact mucosa (Figure 2).

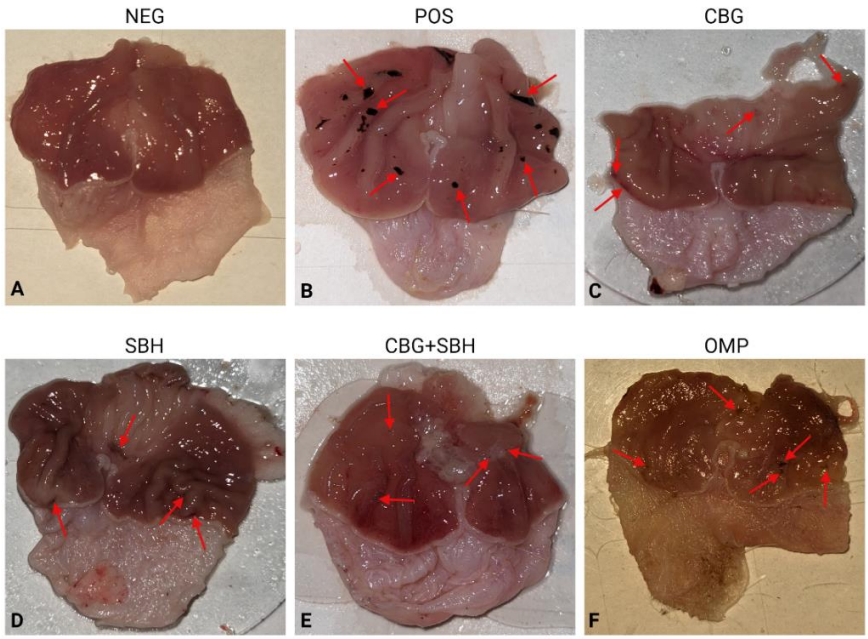

Figure 2: Macroscopic evaluation of gastric mucosa following treatment. (A) NEG: Normal gastric tissue with intact mucosa. (B) POS: Extensive haemorrhagic ulcerations observed post-indomethacin treatment. (C) OMP: Moderate healing with reduced ulceration. (D) CBG: Cabbage extract-treated group showing reduced mucosal lesions. (E) SBH: Stingless bee honey-treated group with visible lesion reduction. (F) CBG+SBH: Most intact mucosal surface, with minimal to no ulceration. Red arrows indicate ulcer sites. All treatment groups showed a marked decrease in ulcer number and size compared to POS.

Histological analysis supported the gross findings. Gastric tissues from the POS group showed deep mucosal ulcerations, oedema, neutrophilic infiltration, and vascular congestion, confirming severe injury. Tissues from the cabbage (CBG), honey (SBH), and omeprazole (OMP) groups showed moderate improvement, while the CBG+SBH group exhibited well-preserved mucosal architecture with minimal inflammation, suggesting accelerated healing (Figure 3a, 3b).

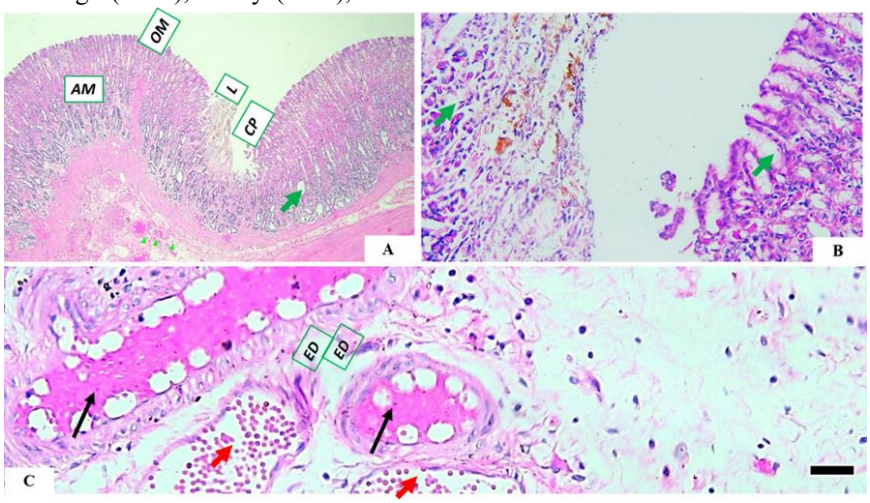

Figure 3(a): Histopathological analysis of gastric tissues stained with haematoxylin and eosin (H&E). POS group at 10×, 20×, and 40× magnification shows severe mucosal ulcerations (green arrows), epithelial disruption, oedema (ED), blood vessel occlusion (black arrows), and neutrophilic infiltration (red arrows). CP = Clotted Precipitate, AM = Ulcerated Mucosa, L = Lumen, OM = Outer Mucosa.

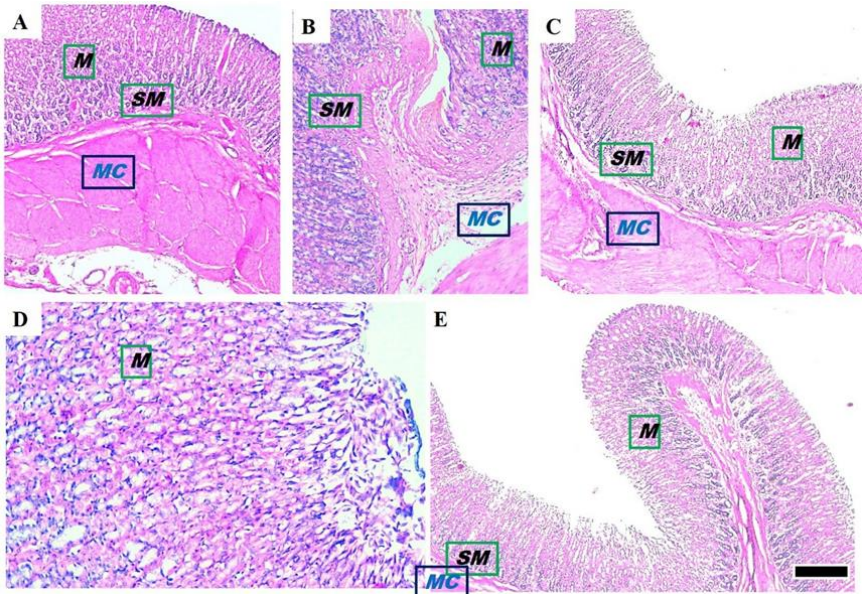

Figure 3(b): Representative photomicrographs at 40× magnification: (A) NEG group with normal histoarchitecture; (B) OMP group showing moderate epithelial preservation; (C) CBG group with partial epithelial restoration; (D) SBH group with mild inflammation; (E) CBG+SBH group showing near-normal mucosal lining. All scale bars = 100 μm. M = Mucosa, SM = Submucosa, MC = Muscularis.

Quantitative analysis of ulcer index revealed significant differences among groups. The POS group exhibited the highest ulcer index (0.775 ± 0.05; mean ± SEM), indicating severe mucosal damage. Treatment with CBG (0.325 ± 0.03), SBH (0.25 ± 0.03), CBG+SBH (0.1 ± 0.03), and OMP (0.475 ± 0.05) all significantly reduced the ulcer index compared to POS ($p < 0.001$). The CBG+SBH group showed the most pronounced reduction ($p < 0.01$ vs CBG; $p < 0.0001$ vs OMP). These findings suggest the combination therapy was more effective than CBG monotherapy or standard treatment (Table 1).

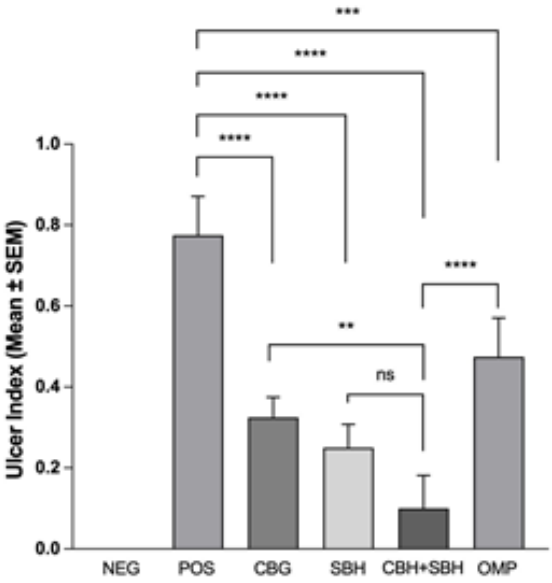

Figure 4: Effect of treatments on ulcer index in indomethacin-induced gastric ulcers. The ulcer index was significantly higher in the POS group compared to the NEG group. All treatment groups demonstrated a marked reduction in ulcer index, with the cabbage and honey combination (CBG+SBH) showing the greatest improvement. Data expressed as mean ± SEM (n = 4); ns = no significant, **p < 0.01, ***p < 0.001, and ****p < 0.0001 vs POS.

Table 1: Turkey's multiple comparison test of the different treatment groups

Comparison Groups	Below threshold	Adjusted P Values
CBG vs SBH	No	0.6806
CBG vs CBG+SBH	Yes	0.0036*
CBG vs OMP	No	0.0765
SBH vs CBG+SBH	No	0.0765
SBH vs OMP	Yes	0.0036*
CBG+SBH vs OMP	Yes	< 0.0001*

* Indicates the statistical significance of all p values <0.05.

Gastric juice volume

Indomethacin administration significantly elevated gastric juice volume in the POS group (1.21 ± 0.06 mL/100 g bw, mean ± SEM) compared to the negative control (NEG) group (0.32 ± 0.04 mL/100 g; $p < 0.0001$). All treatment groups significantly reduced this volume (CBG: 0.51 ± 0.04, SBH: 0.48 ± 0.05, CBG+SBH: 0.39 ± 0.03, OMP: 0.56 ± 0.06 mL/100 g; $p < 0.0001$ vs POS). The CBG+SBH group showed the lowest volume, suggesting effective suppression of gastric secretion. Although not statistically different from the CBG ($p = 0.997$) and SBH ($p = 0.074$) groups, the reduction aligns with improved mucosal protection (Figure 5).

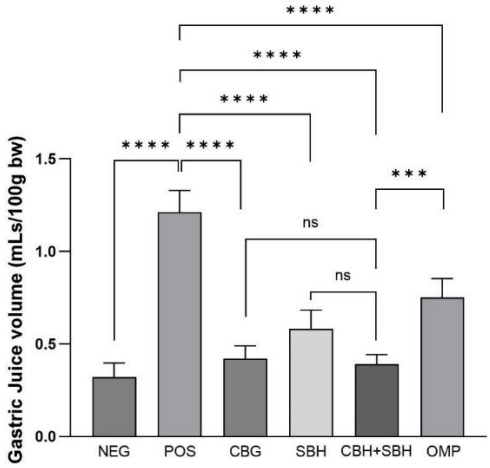

Figure 5: Effect of treatments on gastric juice volume in indomethacin-induced ulcerated rats. All treatment groups significantly reduced gastric juice volume compared to POS. Data expressed as mean ± SEM (n = 4); ns = no significant, ***p < 0.001, and ****p < 0.0001 vs POS.

Gastric pH

The POS group demonstrated significantly decreased gastric pH (2.16 ± 0.20, mean ± SEM) compared to NEG (4.25 ± 0.04; p < 0.0001). Treatment with CBG, SBH, CBG+SBH, and OMP significantly restored pH levels (CBG: 3.62 ± 0.09, SBH: 3.91 ± 0.12, CBG+SBH: 4.56 ± 0.03, OMP: 5.34 ± 0.08; p < 0.0001 vs POS). The CBG+SBH group was significantly higher than CBG (p < 0.01), SBH (p < 0.05), and OMP (p < 0.001) indicating better acid neutralisation (Figure 6).

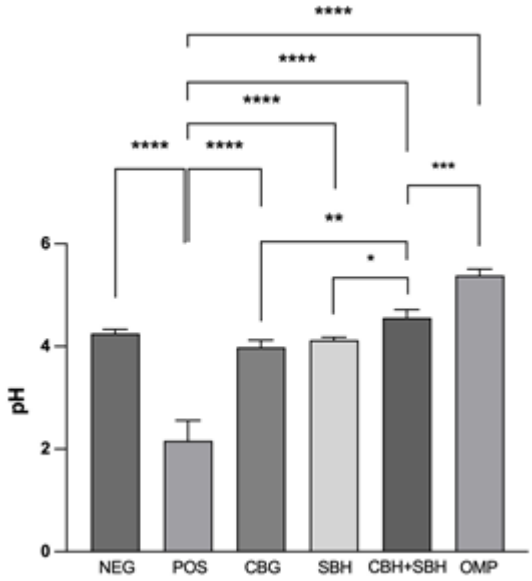

Figure 6: Effect of treatments on gastric pH. POS group had significantly lower pH than NEG. Treatments significantly increased pH, with CBG+SBH showing higher pH than

CBG and SBH alone. Data expressed as mean ± SEM (n = 4); *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 vs POS.

Total and free acidity

The POS group exhibited elevated total acidity (132.75 ± 3.99 mEq/L, mean ± SEM), significantly higher than the NEG group (41.88 ± 0.58 mEq/L; p < 0.0001). All treatments significantly reduced total acidity (CBG: 56.18 ± 2.12, SBH: 47.29 ± 2.54, CBG+SBH: 37.00 ± 1.96, OMP: 65.25 ± 3.37 mEq/L; p < 0.0001 vs POS), with the CBG+SBH group showing the lowest level, statistically lower than OMP (p < 0.0001) but similar to the NEG group (p = 0.688; Figure 7a).

A similar trend was observed for free acidity. The POS group exhibited the highest levels (94.16 ± 3.17 mEq/L/100 g), while CBG+SBH treatment significantly lowered free acidity (20.00 ± 1.11), which was lower than OMP (58.21 ± 1.81; p < 0.0001), and statistically comparable to the NEG (18.67 ± 1.22; p = 0.274; Figure 7b).

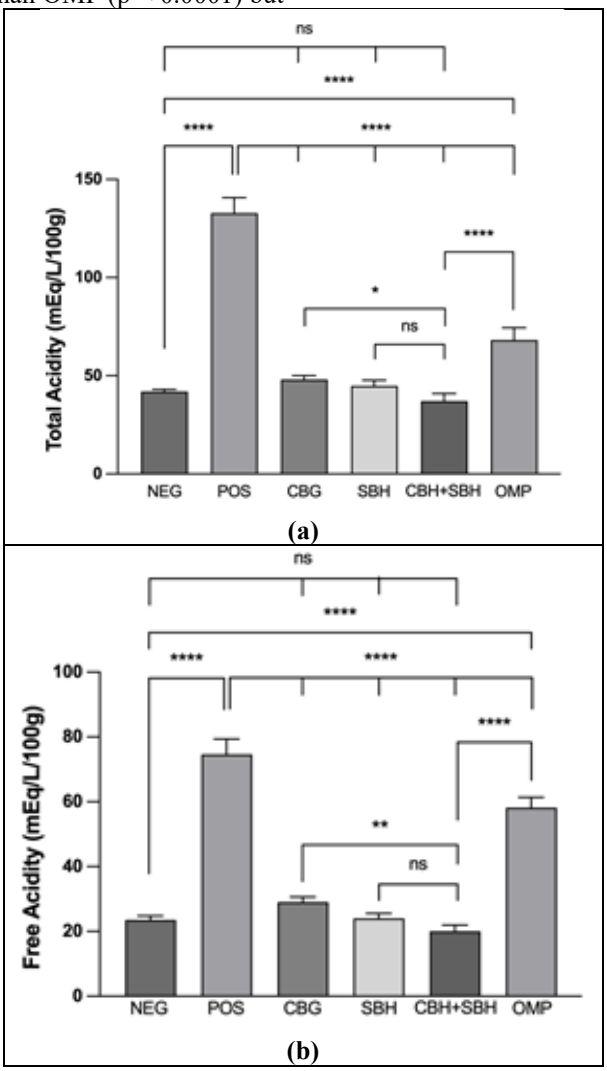

Figure 7: (a) Total acidity and (b) free acidity in gastric juice across groups. POS group exhibited elevated acidity levels, while all treatments significantly reduced both

parameters. The CBG+SBH group had values similar to the NEG group. Data expressed as mean ± SEM (n = 4); ns = no significance, *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001vs POS.

Discussion

This study investigated the gastroprotective effects of combining cabbage extract and stingless bee honey in a rat model of indomethacin-induced peptic ulcers. The results demonstrated that this combination significantly improved healing outcomes compared to individual treatments or standard omeprazole therapy, as evidenced by improvements in ulcer index, gastric juice volume, total and free acidity, and gastric pH. These findings suggest that co-administration of cabbage and honey exerts a synergistic gastroprotective effect. Cabbage extract and stingless bee honey individually showed moderate protective effects, but when combined, they restored gastric mucosal architecture more effectively, as confirmed by both macroscopic and histological assessments.

The positive control group exhibited typical features of NSAID-induced gastric damage, including elevated ulcer index, increased gastric juice volume and acidity, and decreased pH. These findings are consistent with earlier reports showing that NSAIDs like indomethacin compromise mucosal integrity through prostaglandin inhibition, oxidative stress, and leukocyte infiltration (Somasundaram et al. 2000, Wallace 2008). The observed mucosal damage supports the role of reactive oxygen species (ROS) and inflammatory mediators in ulcer pathogenesis, aligning with established models of NSAID-induced gastropathy (Amirshahrokhi and Khalili 2016).

Both cabbage extract and stingless bee honey demonstrated significant healing potential, corroborating previous findings on their individual anti-ulcer activities (Carvalho et al. 2011, Saranraj and Sivasakthi 2018, Rezaei et al. 2019). The enhanced effect observed in the combination group suggests a synergistic mechanism. Cabbage is rich in glutamine, flavonoids, and vitamins C and K compounds known to enhance mucosal repair, modulate inflammation, and promote antioxidant defence (Carvalho et al. 2011, Sharifi-Rad et al. 2018). Honey, particularly from stingless bees, contributes antimicrobial, anti-inflammatory, and antioxidant properties, supporting mucosal defence, regeneration and promote angiogenesis and re-epithelialization (Vallianou et al. 2014, Rezaei et al. 2019, Palma-Morales et al. 2023). The observed superiority of the combination therapy over omeprazole suggests additive or synergistic effects that extend beyond acid suppression.

The significant reduction in ulcer index and acidity, along with improved pH and histological findings, in the combination group indicates multi-modal gastroprotection. This may be attributed to prostaglandin stimulation, ROS scavenging, and enhancement of mucosal blood flow and epithelial regeneration. These mechanisms are supported by earlier studies that demonstrated polyphenol-mediated protection of the gastric mucosa (Vallianou et al. 2014, Beiranvand 2022).

Interestingly, while omeprazole restored pH more effectively, it was less potent in reducing ulcer index and improving histopathology compared to the natural combination. This observation highlights the limitations of acid-suppressing drugs, which do not address oxidative and inflammatory pathways involved in ulceration (Fossmark et al. 2019).

Despite promising findings, this study is limited by its small sample size and lack of molecular analyses. Biomarkers of inflammation, oxidative stress, or healing (e.g., cytokines, antioxidant enzymes, or growth factors) were not evaluated. In addition, only male rats were used, precluding sex-based analyses. These limitations suggest caution in generalizing the findings.

Future studies should expand on these findings by exploring dose–response relationships, chronic ulcer models, and molecular mechanisms.

The combined use of cabbage extract and stingless bee honey offers a compelling

alternative to conventional ulcer therapy. Their synergistic action addresses multiple aspects of ulcer pathophysiology, including acid suppression, mucosal defence, and tissue repair, presenting a holistic approach to ulcer management.

Conclusion

This study provides evidence that the combined administration of cabbage extract and stingless bee honey exerts significant gastroprotective effects against indomethacin-induced peptic ulcers in rats. Compared to individual treatments or standard omeprazole therapy, the combination therapy led to superior improvements in ulcer index, gastric juice volume, acidity, and mucosal histology. These findings highlight the potential of natural product-based interventions as effective and safer alternatives in ulcer management.

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