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ORIGINAL RESEARCH

The Gastroprotective Effect of Hydrogen-Rich Coral Calcium in a Mouse Model of Peptic Ulcer Disease

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Introduction: Peptic ulcer disease (PUD), including gastric and duodenal ulcers, is primarily caused by *Helicobacter pylori* infection and non-steroid anti-inflammatory drugs, with additional contributors like stress, certain foods, and alcohol. Proton pump inhibitors (PPIs) are effective but with adverse effects, prompting the exploration of alternative therapies. Hydrogen-rich coral calcium (HRCC) is a novel antioxidative agent that exerted anti-oxidative and anti-inflammatory activities; however, the effects of HRCC on PUD were still obscure.

Methods: The gastroprotective effects of HRCC were investigated in a mouse model of PUD, and macroscopic score was used to investigate the effects of HRCC on PUD. In addition, the expression of the pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), C-C motif chemokine ligand 2 (Ccl2), and interleukin-6 (IL-6) by real-time quantitative polymerase chain reaction. In addition, Western blots were used to evaluate the expressions of anti-oxidative enzymes, including catalase, glutathione peroxidase-1 (GPx), and superoxide dismutase (SOD).

Results: HRCC attenuated ulcer severity induced by ethanol and hydrogen chloride ex vivo (n = 6). In addition, long-term treatment of HRCC for seven-day reduced ethanol and hydrogen chloride-induced ulcer formation (n = 6). Moreover, we found that HRCC treatment decreased immune cell infiltration, the gene expressions of pro-inflammatory cytokines (n = 6), and enhanced antioxidative enzyme levels (n = 3) in stomach of the animals in vivo.

Conclusion: HRCC has potential as a gastroprotective agent with anti-oxidative and anti-inflammatory activities, and its application may provide an alternative for treating PUD.

Keywords: antioxidant, anti-inflammation, gastric ulcer, gastroprotection, hydrogen-rich coral calcium

Introduction

Peptic ulcer disease (PUD) including gastric ulcers and duodenal ulcers, which are highly prevalent worldwide. The primary causes are largely associated with non-steroidal anti-inflammatory drugs, and alcohol consumption.[1] Although it was known that these factors lead to destruction of the gastric mucosa and disruption of protective mechanisms, the therapeutic strategies and medication for PUD were still scarce.

Proton pump inhibitors (PPIs) are currently the most effective medication. However, prolonged PPI use has been associated with some adverse effects, such as *Clostridium difficile* infection, hypergastrinemia, malabsorption of minerals and vitamins, kidney disease, drug-related lupus, dementia, and pneumonia.[2,3] Therefore, seeking alternative therapies or supplements to reinforce or assist long-term PPIs use can be beneficial for individuals prone to recurrent PUD.

Gastrointestinal mucosa is constantly exposed to reactive oxygen species (ROS), generated by infectious pathogens, alcohol and non-steroidal anti-inflammatory drugs. Prolonged excessive oxidative stress and inflammation are two important risk factors for PUD. Thus, supplements with potent anti-oxidant and anti-inflammatory activities have been tested in PUD models to evaluate their therapeutic potential.[4] It was known that hydrogen gas eliminates free radicals in

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the body and reduces cell damage,[5] and many manufacturers began infusing hydrogen into water using methods like electrolysis, creating water enriched with hydrogen molecules, known as hydrogen water. Several studies suggested that diabetic patients who consume hydrogen water experience significant reductions in blood low-density lipoprotein cholesterol and oxidative stress.[6] Additionally, liver cancer patients consuming hydrogen water showed significant improvements in appetite loss and taste disorders caused by radiation therapy, leading to a significant increase in their quality of life.[7] Moreover, in experimental mice, hydrogen water improved non-alcoholic fatty liver induced by high-fat diet.[8] Furthermore, in terms of alcoholic fatty liver, hydrogen water effectively reduced alcohol-induced fatty liver and liver inflammation in experimental animals.[9] However, the actual hydrogen concentration in various hydrogen water products remains unknown, posing challenges for academic research and casting doubt on the efficacy of hydrogen water.

In response, novel technologies have been developed to utilize the porous structure of coral calcium, which can effectively chelate hydrogen molecules, achieving hydrogen concentrations of up to 14.72 ppm in water.[10] Additionally, coral calcium, with its high solubility, offers increased surface area in contact with gastric acid facilitating absorption in the intestines.[11] Furthermore, one study revealed that hydrogen-rich coral calcium (HRCC) exhibited activities against alcohol-induced hepatoxicity and intoxication.[12] We also found that consumption of HRCC protected mice from methionine and choline deficiency-induced liver injury through changes of gut microbiome.[13] Although HRCC might exert beneficial effects on human health, the effects of HRCC on PUD were still unknown. Thus, the present study aimed to develop new therapeutic approaches by evaluating the effects of HRCC using a mouse model of PUD.

Materials and Methods

Animals

All the animal experiments were performed according to National Institutes of Health guide for the care and use of laboratory animals and were approved by National Cheng Kung University Institutional Animal Care and Use Committees (IACUC No: 111-255). Eight-week-old C57BL/6 male mice were purchased from the Laboratory Animal Center, College of Medicine at National Cheng Kung University, and housed in the environment with a temperature of 23 ± 2°C, humidity 60 ± 10% and alternative light and dark every 12 hours (lights on at 07:00AM). The mice were randomly assigned to four groups (n = 6 for each group), including (1) mice treated with 210 mg/kg porous coral calcium dissolved in 3% carboxymethyl cellulose (CMC; Sigma-Aldrich, St. Louis, MO, USA) (CTL group) via oral gavage; (2) 0.4 M hydrochloric acid/60% EtOH (HCl/EtOH)-induced gastric ulcer mice treated with 210 mg/kg porous coral calcium (CH group); (3) HCl/EtOH-induced gastric ulcer mice treated with 105 mg/kg HRCC (Low-dose group; LH); and (4) HCl/EtOH-induced gastric ulcer mice treated with 210 mg/kg HRCC (High-dose group; HH). The optimal sample size was calculated using resource equation method to test the hypothesis.[14]

Ex vivo Gastric Injury Model

After an eight-hour fasting, each group of the mice was sacrificed after anesthesia, and the stomachs were isolated. The pylorus was ligated using silk suture material around the junction between the pylorus and the duodenum. The stomach was then inflated by injecting one mL saline containing different doses of HRCC or porous coral calcium as control group. After incubation for 30 minutes, saline containing HRCC or porous coral calcium was drained, and one mL HCl/EtOH solution was then injected into the stomach to induce the gastric injury. After a one-hour treatment, the stomach tissues were emptied, and one mL of 1% formalin solution was then used to fix the tissues for 10 min. The tissue was opened along with the greater curvature, and the area of hemorrhagic lesions that had developed in the stomach was measured under a digital camera to calculate the damage score.

Gastric Injury Model

In addition to ex vivo model, the animals were oral gavaged with 210 mg/kg HRCC or porous coral calcium for 30 minutes, prior to intragastric administration of HCl/EtOH solution once daily for consecutive seven days to examine the long-term effects of HRCC on gastric injury in vivo. After an eight-hour fasting, the stomach tissues of each group of the mice were collected for further experiments after the induction of gastric ulcer for one hour.

Hematoxylin and Eosin Stain

At the end of the experiments, the stomach tissues of each group of the mice were removed, and the fix by 10% formalin. Five-μm thick sections were deparaffinized and then stained with hematoxylin for 3–8 minutes and eosin solution for another 1–3 minutes. After dehydration, the sections were sealed and then observed under a light-field microscope. The processed sections were evaluated by pathologists in a blinded fashion for qualitative assessment of morphological details in terms of cellular outline, nuclear and cytoplasmic features, and overall morphology.

Western Blot Analysis

The protein samples from stomach tissues were extracted and mixed with radioimmunoprecipitation lysis buffer (VWR Chemical solon, OH, USA), containing protease inhibitors (Sigma-Aldrich, St. Louis, MO, USA). After centrifuge at 13,000 rpm in 4°C for 10 minutes, the supernatant was collected, and the protein concentration was determined by bicinchoninic acid assay kit (Visual Protein, Taipei, Taiwan). The proteins were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and then transferred to polyvinylidene difluoride membrane (Biomate, Taipei, Taiwan). The membranes were blocked with 10% skim milk for one-hour at room temperature, and then incubated with a 1:1000 dilution of primary antibodies, including superoxide dismutase [Cu-Zn] (SOD1), glutathione peroxidase-1 (GPx), catalase (Abcam, Cambridge, UK), or actin (Millipore, Billerica, MA, USA) at 4°C overnight. After the membranes had been washed with TBS-T (10 mM Tris (pH 7.6), 150 mM NaCl, and 0.05% Tween 20), and then the blots were incubated with a 1:5000 dilution of horseradish peroxidase-conjugated secondary antibodies at room temperature for one-hour. The protein bands were detected using Immobilon (Millipore), and the signal intensity was quantified by ImageJ software.

Real-Time Quantitative Polymerase Chain Reaction

The gene expressions of inflammatory cytokines, including interleukin-6 (*Il6*), tumor necrosis factor-alpha (*Tnfa*), and the C-C motif chemokine ligand 2 (*Ccl2*) in the mouse stomach were examined using real-time quantitative polymerase chain reaction. The following primer pairs were used: Forward, 5-CCC TCA CTC AGA TCA TCT TCT-3 and reverse, 5-GCT ACG ACG TGG GCT ACA G-3 for *Tnfα*; forward, 5-AGT TGC CTT CTT GGG ACT GA-3 and reverse, 5-TCC ACG ATT TCC CAG AGA AC-3 for *Il6*; forward, 5-TCA GCC AGA TGC AGT TAA CGC-3 and reverse, 5-TCT GGA CCC ATT CCT TCT TGG-3 for *Ccl2*; forward, 5-CTG CGA CTT CAA CAG CAA CT-3 and reverse, 5-GAG TTG GGA TAG GGC CTC TC-3 for *Gapdh* as internal control. Briefly, the RNAs from each sample were extracted using GENEzol reagent (Geneaid Biotech, New Taipei City, Taiwan), according to the manufacturer's instruction. Reverse transcription was performed to generate complementary DNA using MMLV Reverse Transcription Kit (Protech, Placentia, CA, USA), and the real-time fluorescence quantitative polymerase chain reaction instrument (StepOnePlus Real-Time PCR Detection System, Applied Biosystems, Foster City, CA, USA) was used to quantify of relative mRNA expression levels with the $2^{-\Delta\Delta ct}$ method.

Statistics

Graphpad prism 8 was used for illustration and statistical analyses. The data were presented with mean ± standard error (SEM). Student's *t*-test or one-way ANOVA followed by Tukey's post hoc test were used. Statistically significance was defined as $p < 0.05$.

Results

Administration of HRCC Improves HCl/Ethanol-Induced Gastric Ulcer in Mice

To investigate the direct effects of HRCC on the protection of PUD, we first used an ex vivo gastric injury model. As shown in Figure 1, the stomach of the control group appeared normal in size without any signs of bleeding, whereas after infusion with HCl/EtOH solution significantly induced gastric ulcers with bleeding. Pretreatment with HRCC effectively prevented the formation of these ulcers upon subsequent exposure to the HCl/EtOH solution in both LH and HH groups (Figure 1), implying HRCC had a potential against PUD in vivo.

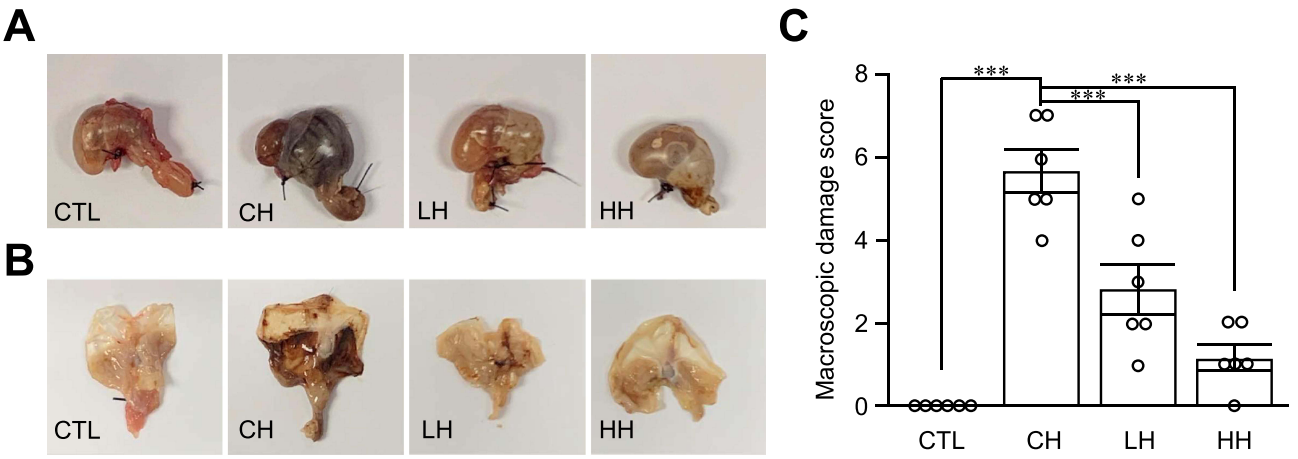

Figure 1 Hydrogen-rich coral calcium consumption protects gastric mucosa from the damage of HCl/EtOH solution ex vivo. Isolated gastric stomach was inflated with 1 mL saline containing 210 mg/kg hydrogen-rich coral calcium (HRCC) (Low dose group, ML), 420 mg/kg HRCC (High dose group; MH), or HCl/EtOH solution supplemented with coral calcium group (CH) and control group (CTL). After the pre-treatment for 30 minutes, the stomach was emptied and refilled with HCl/EtOH solution for another one-hour (**A** and **B**). At the end of the experiments, the stomach was explored and scored with macroscopic damage scoring system (**C**). N = 6 for each group of the mice; ***$p < 0.001$ as compared with indicated groups.

Consumption of HRCC Decreases Immune Cell Infiltration and Mucosa Destruction HCl/Ethanol-Induced Gastric Ulcer in Mice

We then investigated the in vivo effects of HRCC after a long-term treatment. After the treatment of HCl/EtOH solution, the gastric mucosa defect was developed and visible hemorrhagic lesions, necrosis, and burning damage were observed. In addition, the immune cell infiltration was significantly increased in HCl/EtOH solution-treated group. After the pretreatment of HRCC for seven-day, HRCC attenuated ulcer severity and maintained the integrity of the gastric mucosa, as well as the decrement in immune cell infiltration (Figure 2).

Long-Term Consumption of HRCC Decreases Pro-Inflammatory Cytokine Expressions in HCl/EtOH-Induced Gastric Ulcer in Mice

Among the different groups, pro-inflammatory cytokine expressions were significantly elevated in HCl/EtOH-treated group ($p < 0.01$). Either *Tnfa* (Figure 3A), *Ccl2* (Figure 3B), and *Il6* (Figure 3C) gene expression was significantly decreased in both the group pretreated with low dose and high dose of HRCC. At different doses of HRCC, higher dose of HRCC reduced the gene expressions of pro-inflammatory cytokines in the stomach significantly, as compared with low dose-treated group (Figure 3).

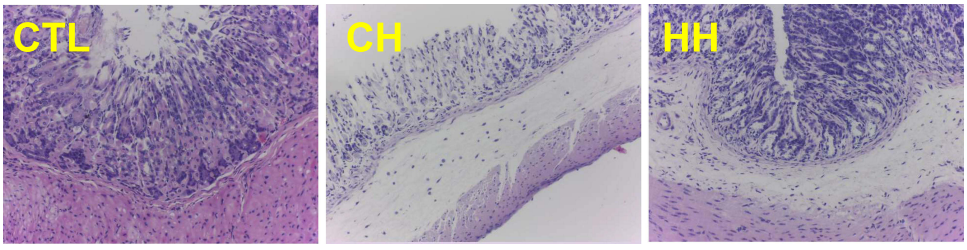

Figure 2 Long-term consumption of HRCC decreases immune cell infiltration and mucosa destruction in HCl/EtOH solution-induced gastric ulcer in mice. Mice were gavage with 420 mg/kg hydrogen-rich coral calcium (HRCC) (High dose group; HH), or coral calcium (control group; CTL). After the pre-treatment of HRCC for 30 minutes, the animals were oral-gavage with HCl/EtOH solution once daily for seven-day (CH). At the end of the experiments, the stomach tissues were collected to perform H&E staining.

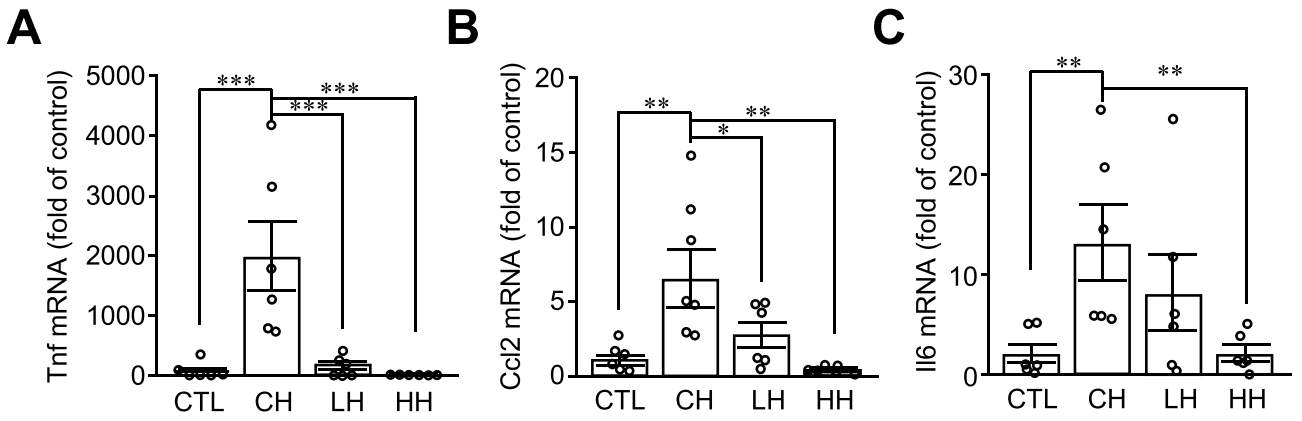

Figure 3 Consumption of HRCC decreases pro-inflammatory cytokine expressions in HCl/EtOH solution-induced gastric ulcer in mice. Mice were gavage with 210 mg/kg HRCC (Low dose group, LH), 420 mg/kg hydrogen-rich coral calcium (HRCC) (High dose group; HH), or coral calcium (control group; CTL). After the pre-treatment of HRCC for 30 minutes, the animals were oral-gavage with HCl/EtOH solution once daily for seven-day (CH). At the end of the experiments, the stomach tissues were removed for the determination of tumor necrosis factor-α (TNF-α) (**A**), C-C motif chemokine ligand 2 (Ccl2) (**B**), and interleukin-6 (IL-6) (**C**) gene expressions by quantitative-polymerase chain reaction. N = 6 for each group of the mice; *p < 0.05; **p < 0.01; ***p < 0.001 as compared with indicated groups.

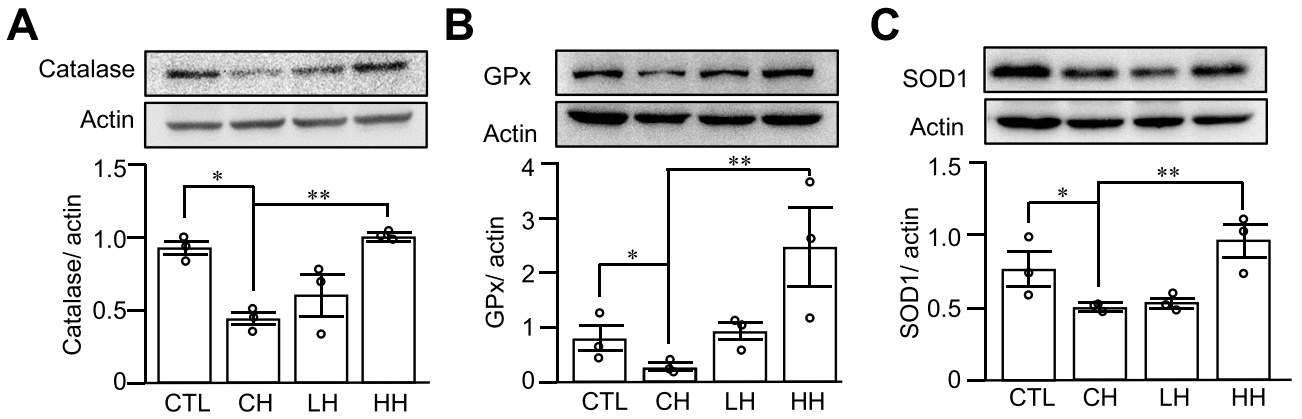

Figure 4 Consumption of HRCC restores the gastric expressions of antioxidative enzymes in HCl/EtOH solution-induced gastric ulcer in mice. Mice were gavage with 210 mg/kg HRCC (Low dose group, LH), 420 mg/kg hydrogen-rich coral calcium (HRCC) (High dose group; HH), or coral calcium (control group; CTL). After the pre-treatment of HRCC for 30 minutes, the animals were oral gavage with HCl/EtOH solution (CH) once daily for seven days. At the end of the experiments, the stomach tissues were removed for the determination of catalase (**A**), glutathione peroxidase-1 (GPx) (**B**), and superoxide dismutase (SOD1) (**C**) protein levels by Western blots. N = 3 mice for each group; *< 0.05; **p < 0.01 as compared with indicated groups.

Long-Term Consumption of HRCC Increases Gastric Antioxidative Enzyme Expressions in HCl/EtOH-Induced Gastric Ulcer in Mice

Antioxidative enzymes, including GPx (Figure 4A), catalase (Figure 4B), and SOD1 (Figure 4C) were significantly decreased in stomach after exposing to HCl/EtOH solution. After pretreatment with HRCC, the expressions of anti-oxidative enzymes were restored. Furthermore, as the HRCC dose increases, the restorative effect became more pronounced (Figure 4).

Discussion

Although some gases, such as H_2S, CO, and NO, have been proven to improve alcohol- and stress-induced ulcers;[15] however, clinical use of gases requires more specialized equipment. Hydrogen has been underutilized due to past inconveniences in its application, and using oral capsules in this study is more suitable for clinical applications. In the present study, HRCC has a gastroprotective effect, and consumption of HRCC increased anti-oxidative enzyme levels and decreased inflammatory cytokine expressions to against HCl/EtOH-induced PUD. Although it was known that

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hydrogen gas showed beneficial effects on PUD by anti-oxidation and anti-inflammation activities, HRCC might broaden the application of hydrogen medicine in PUD.

Although PPIs are currently the main treatment for ulcers,[16] gastroprotective supplements still make potential for future development, especially for some treatment-resistant peptic ulcers or considering the side effects of PPIs.[17,18] In addition to PPI-based anti-secretory therapy, strengthening gastric mucosal protection mechanisms is another approach. Previous studies have found that *Pistacia lentiscus* fatty oil reduces the inflammatory response to improve alcohol-induced ulcers in rodents.[19] In addition, natural xanthones regulate anti-oxidative signaling pathway to achieve mucosal protection benefits.[20] Also, hydrogen sulfide has been found to increase the secretion of protective bicarbonate and mucus in order to prevent gastric acid from damaging the duodenal mucosa.[21] Thus, anti-inflammation and anti-oxidation are promising strategies to improve PUD.

With regard to improve oxidative stress markers such as GPx, SOD, and catalase while reducing blood concentrations of TNF-α and IL-6, alcohol-induced acute ulcers can be alleviated by Manuka Honey.[22] The NFκB family of inducible transcription factors is activated in transcriptional responses to TNFα, and activation of NF-κB by TNFα triggers downstream signals to induce inflammatory responses.[23] It was known that hydrogen gas inhibits NFκB signaling pathway and inflammatory activities to against lung injury.[24] Regarding the decreased TNFα expressions by HRCC, NFκB activities might also be decreased after HRCC treatment in PUD mice model. In addition to NFκB, cyclooxygenase (COX) might also be mediated HRCC-improved PUD. Since COX produces prostaglandins, which are key mediators of inflammation, and hydrogen reduced COX expression and suppressed inflammatory cytokines (IL-6 and TNFα).[25] However, the roles of COX and NFκB in HRCC-improved PUD still need further studies to investigate. This corroborates our findings that HRCC improved conditions leading to acute ulcers induced by HCl/EtOH solution, and HRCC might be synergistically used as a supplement against PUD with PPIs regarding its anti-secretory property.

Conclusion

HRCC can reduce ulcer formation through its antioxidant and anti-inflammatory effects, and these effects are enhanced with increased dosages. HRCC shows promising gastroprotective activity in mice; further mechanistic and clinical studies are required.

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Disclosure

The authors declare no conflicts of interest in this work.

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