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## **Comparative efficacies of 2 cysteine prodrugs and a glutathione delivery agent in a colitis model.**

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### **Abstract**

Oxidant-mediated injury plays an important role in the pathophysiology of inflammatory bowel disease (IBD). Recently, antioxidants were shown to modulate colitis in mice. In this study, the protective effects of L-cysteine and glutathione (GSH) prodrugs are further evaluated against progression of colitis in a murine model. ICR mice were fed compounds incorporated into chow as follows: Group (A) received chow supplemented with vehicle. Group (B) was provided 2-(RS)-n-propylthiazolidine-4(R)-carboxylic-acid (PTCA), a cysteine prodrug. Group (C) received D-ribose-L-cysteine (RibCys), another cysteine prodrug that releases L-cysteine. Group (D) was fed L-cysteine-glutathione mixed sulfide (CySSG), a ubiquitous GSH derivative present in mammalian cells. After 3 days, the animals were further provided with normal drinking water or water supplemented with dextran sodium sulfate (DSS). Mice administered DSS developed severe colitis and suffered weight loss. Colonic lesions significantly improved in animals treated with PTCA and RibCys and, to a lesser extent, with CySSG therapy. Hepatic GSH levels were depleted in colitis animals (control vs DSS,  $P < 0.001$ ), and normalized with prodrug therapies (control vs treatments,  $P > 0.05$ ). Protein expressions of serum amyloid A and inflammatory cytokines [interleukin (IL)-6, IL-12, tumor necrosis factor-alpha (TNF-alpha), osteopontin (OPN)] were significantly increased in colitis animals and improved with therapies. Immunohistochemistry and Western blot analyses showed significant upregulation of the macrophage-specific markers, COX-2 and CD68, which suggests macrophage activation and infiltration in the colonic lamina propria in colitis animals. These abnormalities were attenuated in prodrug-treated mice. In conclusion, these data strongly support the novel action of the PTCA against colitis, which further supports a possible therapeutic application for IBD patients.

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