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Original Research Article

Nephroprotection of *Garcinia mangostana* Pericarp Extract and α-Mangostin Against Oxidative Stress in Renal Manifestation of Ulcerative Colitis in Mice

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ABSTRACT

Garcinia mangostana (GM) pericarp is an herbal medicine in the Thailand National Essential Drug List. GM pericarp and its major active constituent α-mangostin (MGS) exhibit several pharmacological properties, including anti-oxidative activity. Ulcerative colitis (UC) is the consequence of prolonged oxidative stress and inflammation in the large intestine and can result in extraintestinal manifestations (EIM) in other organs. This study evaluated the impact of GM pericarp extract and MGS on oxidant-antioxidant status in the kidneys of UC-induced mice. Six-week-old ICR mice were administered orally GM pericarp extract (40, 200, and 1,000 mg kg^{-1}), MGS (30 mg kg^{-1}), or sulfasalazine (100 mg kg^{-1}) for 7 consecutive days. UC was induced by administering dextran sulfate sodium (40 kDa; 6 g kg^{-1}) on days 4-7. Kidneys were collected to determine the activity and expression of the catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) antioxidant enzymes, lipid peroxidation levels, and glutathione stores. UC induction suppressed expression of *Cat*, *CuZn-Sod*, *Mn-Sod*, and *Gpx* mRNAs and reduced CAT, SOD, and GPx activities in the kidneys, which was followed by an increase in lipid peroxidation. Total GSH and reduced GSH contents decreased, while oxidized GSSG content increased, reducing the GSH/GSSG ratio in the kidneys. GM and MGS improved the oxidative status of the kidneys similar to sulfasalazine by restoring the expression and activity of the antioxidant enzymes and balancing the glutathione stores. GM and MGS are promising nephroprotective antioxidant treatments and are worthy of development as alternative medicines for renal EIMs of UC.

Keywords: Oxidant-antioxidant system, Mangosteen, Antioxidant enzymes, Glutathione stores.

Introduction

Diseases and disorders related to oxidative stress impact human and animal health. Ulcerative colitis is a chronic disease resulting from prolonged inflammation of the large intestine, especially in the colon and rectum. Ulcerative colitis causes discomfort in daily life and undermines health, possibly leading to more severe diseases such as colorectal cancer.[1] Typical clinical signs are bloody diarrhea and melena with fecal urgency, rectal bleeding, pain, depression, and fever also present.[2,3] The empirical pathology is ulcers in the large intestine, the target organ of ulcerative colitis, but ulcerative colitis also causes fascinating and harmful extraintestinal manifestations.[1] The primary disorder eventually leads to diseases in neighboring organs such as the kidneys. Renal manifestations include nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis.[4] Unfortunately, sulfasalazine, the first-line drug for treatment of ulcerative colitis, can cause renal injuries such as renal enlargement, interstitial nephritis, tubular atrophy, and renal necrosis.[5-6]

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Garcinia mangostana Linn. is a tropical fruit, of which *α*-mangostin is the most abundant xanthone found in the pericarp.[7] *G. mangostana* pericarp is listed in the Thailand National Essential Drug List A.D. 2016, Annex 4: List of Herbal Medicine Products. It is traditionally used to treat wounds, skin infections, and amoebic dysentery.[8] *G. mangostana* pericarp possesses several pharmacological properties, including antioxidative, anti-inflammatory, antiallergic, antibacterial, antifungal, antiviral, antiprotozoal, anti-parasitic, and anticancer activities.[8-9] Recently, it was reported to improve ulcerative colitis in ICR mice via suppression of inflammatory and oxidative responses.[10] Oxidative stress is an imbalance in the oxidant-antioxidant system[11] that adversely affects tissues and cell membranes, damages DNA, and causes organ degeneration in many systemic diseases.[12-13] Oxidants, e.g. reactive oxygen species (ROS), are highly active atoms that become more stable through the loss of electron(s).[14] ROS are intermediates of food and xenobiotic metabolism, and cellular respiration. Hence, excessive amounts of ROS can be formed when these processes are upregulated[15] or stimulated by external environmental factors such as UV radiation and toxic chemicals.[16] This study was designed to evaluate the effects of *G. mangostana* pericarp extract and *α*-mangostin on the renal oxidative status in ulcerative colitis-induced mice.

Materials and Methods

Plant material and reagents

G. mangostana (voucher number PANPB-GM-2014-001) was purchased from a market in Khon Kaen, Thailand (April 2014). *G. mangostana* pericarps were washed with water and mashed before Soxhlet extraction with ethanol (50 g powder to 1 L 95% ethanol).

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The extract was concentrated with a rotary evaporator until completely dry and stored at -20°C. α-Mangostin (purity > 98%, Cas no. 6147-11-1) was bought from Chengdu Biopurify Phytochemicals (Sichuan, China). Sulfasalazine, CAT, SOD, GPx, 5,5'-dithiobis-2-nitrobenzoic (DTNB), *L*-glutathione reduced (GSH), *L*-glutathione oxidized (GSSG), glutathione reductase (GR), nicotinamide adenine dinucleotide phosphate (NADPH), sulfosalicylic acid (SSA), and bovine serum albumin (BSA) were obtained from Sigma-Aldrich® (Missouri, USA). ReverTraAce® was supplied by Toyobo® (Osaka, Japan). Taq DNA polymerase was from Vivantis (Selangor Darul Ehsan, Malaysia).

Animal experiment
Five-week-old (25-30 g) male ICR mice were provided by the Northeast Laboratory Animal Center, Khon Kaen University (KKU), Khon Kaen, Thailand. The mice were housed in corncob bedding filled stainless steel cages with a commercial rodent diet and water *ad libitum* in the PS-KKU animal unit B 2559/00015.003 and acclimatized for one week before treatment. The animal unit had a 12-hour-dark/light cycle, a temperature of 25°C, and 45% relative humidity. The protocol was approved by Institutional Animal Care and Use Committee of KKU (Approval no. IACUC-KKU-26/61). After acclimatization, the mice were randomly divided into seven groups (9 mice per group) and treated as described in Table 1.

Table 1: Animal treatment.

Groups	Oral administration on days 1-7
Normal (distilled water) days 4-7	
Control	vehicle
UC Induction (dextran sulfate sodium 40 kDa, 6 g kg^{-1}) days 4-7	
Non-treatment	vehicle
GM40	40 mg kg^{-1} *Garcinia mangostana* pericarp extract
GM200	200 mg kg^{-1} *G. mangostana* pericarp extract
GM1000	1,000 mg kg^{-1} *G. mangostana* pericarp extract
MGS	30 mg kg^{-1} α-mangostin
SUL	100 mg kg^{-1} sulfasalazine

Note. vehicle, 0.5% carboxymethyl cellulose. n = 9 each.

After the last treatment for 24 hours, all animals were sacrificed with 100 mg kg^{-1} Zoletil® Virbac New Zealand (Hamilton, New Zealand). Kidneys were removed and kept in a deep freezer (-80°C) until used.

Determination of protein content
Kidney homogenate was prepared with 3 volumes of 0.01 M phosphate-buffered saline (PBS). The protein content of kidney homogenate was determined by the Bradford method.[17] Absorbance was measured at UV 595 nm using standard BSA (0.0125-0.15 mg mL^{-1}) as a standard.[17]

Assessment of thiobarbituric acid reactive substance (TBARS)
Kidney homogenate was vigorously mixed with 10% trichloroacetic acid (1:1), before centrifugation at 2,291 ×*g*, 4°C for 10 min. The supernatant was added to 0.8% thiobarbituric acid (1:1) and heated at 95-100°C for 15 min, before being moved to an ice-bath to stop the reaction. Fluorescence intensity was measured at 520/590 of excitation/emission, respectively, and compared to standard malondialdehyde (MDA; 5-40 μM).[18]

Determination of superoxide dismutase (SOD) activity
Kidney homogenate was extracted by a mixture of ethanol and chloroform and subjected to centrifugation at 14,000 ×*g*, 4°C for 30 min. The reaction mixture consisting xanthine, ethylenediaminetetraacetic acid, nitroblue tetrazolium, sodium carbonate, BSA, copper (II) chloride was mixed with the supernatant and left at room temperature as previous described. Absorbance was measured at UV 550 nm. SOD activity was calculated by comparing with standard SOD (0.04 units μL^{-1}).[18]

Determination of catalase (CAT) activity
Kidney homogenate was shortly reacted with hydrogen peroxide at 37°C and terminated using ammonium molybdate.[18] Absorbance was measured at UV 405 nm. CAT activity was calculated by comparing with standard CAT as previous described.[18]

Determination of glutathione peroxidase (GPx) activity
Kidney homogenate was mixed with assay buffer containing sodium phosphate buffer, EDTA, and sodium azide as previous described.[19] The reaction was initiated by adding reduced GSH and hydrogen peroxide before termination with sulfosalicylic acid. The mixture was centrifuged at 330 ×*g* for 15 min and the supernatant was incubated with 4-VP for 1 hour. Likewise, standard GPx or reduced GSH were added to the assay buffer, 6 units mL^{-1} GR, 1.5 mg mL^{-1} DTNB, and 0.16 mg mL^{-1} NADPH. Absorbance was recorded at UV 405 nm. GPx activity was determined from the production of GSSG in μmol min^{-1}.[19]

Determination of total glutathione stores
Kidney homogenate was added to 5% w/v SSA before centrifugation at 10,000 ×*g* 4°C for 10 min. The supernatant was mixed with the assay buffer (as used for the determination of GPx activity previously described). Absorbance was recorded at UV 405 nm. The slope of a standard GSH (6.25-50 mg mL^{-1}) curve was used to calculate total GSH.[19] Determination of GSSG content was similar to that of total GSH content, but the sample was pre-incubated with 4-VP at room temperature for 1 hour before performing the reaction and readings were compared with the slope of standard GSSG (5-30 mg mL^{-1}).[19] GSH content was calculated from the difference between total GSH and GSSG.[19]

Determination of mRNA expression by RT/qPCR
Total RNA was prepared from the kidneys using phenol extraction method and reverse-transcribed to cDNA with ReverTraAce enzyme.[10] cDNA was amplified using Taq-buffer, $MgCl_2$, dNTP mixture, forward and reverse primers, and Taq DNA polymerase with CFX96 Touch Real-Time PCR Detection System (CA, USA).
The primer sequences (5′→3′) were as follows: *Cat*, forward (F)-GCA GAT ACC TGT GAA CTG TC and reverse (R)-GTA GAA TGT CCG CAC CTG AG; *CuZn-SOD*, F-AAG GCC GTG TGC GTG CTG AA and R-CAG GTC TCC AAC ATG CCT CT; *Mn-SOD*, F-GCA CAT TAA CGC GCA GAT CA and R-AGC CTC CAG CAA CTC TCC TT; *GPx1*, F-CCT CAA GTA CGT CCG ACC TG and R-CAA TGT CGT TGC GGC ACA CC; glyceraldehyde 3-phosphate dehydrogenase (*Gapdh*), F-CCT CGT CCC GTA GAC AAA ATG and R-TGA AGG GGT CGT TGA TGG C. Relative mRNA expression is presented as the fold-difference value of the target gene to a reference gene *Gapdh*.[10]

Statistical analysis
The results are expressed as mean ± standard deviation. The results were analyzed using one-way analysis of variance (ANOVA), couple with Tukey procedure (IBM SPSS software version 26, Armonk, New York, USA). $p < 0.05$ was considered statistically significant.

Results and Discussion

Ulcerative colitis induction significantly increased the MDA levels in mouse kidneys, indicating an increase in renal lipid peroxidation (Figure 1A). *G. mangostana* pericarp extract dose-dependently reduced formation of MDA in the kidneys, with the highest dose (1,000 mg kg^{-1}) of *G. mangostana* pericarp extract and 30 mg kg^{-1} α-

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mangostin significantly lowering the MDA level to the same level as the control, with effects comparable to sulfasalazine, the first line ulcerative colitis therapy. These observations revealed the potential of *G. mangostana* pericarp extract, α-mangostin, and sulfasalazine to decrease lipid peroxidation in the mouse kidneys.

Oxidative stress is one factor of ulcerative colitis [20] and it is excessive ROS production that leads to tissue damage.[21] Peroxidation of polyunsaturated fatty acids in cell membranes causes cell damage and generates MDA as a by-product, which is a well-known oxidative stress marker.[22] The present findings corresponded to a previous study that showed MDA, myeloperoxidase (MPO), and H_2O_2 levels were elevated in the kidneys of Wistar rats that received 5% dextran sulfate sodium in drinking water for over seven days.[23]

In addition, dextran sulfate sodium-induction of ulcerative colitis drastically reduced the activity of the SOD (Figure 1B), CAT (Figure 1C), and GPx (Figure 1D) antioxidant enzymes in mouse kidneys. *G. mangostana* pericarp extract, α-mangostin, and sulfasalazine significantly elevated SOD, CAT, and GPx activities. Interestingly, *G. mangostana* pericarp extract at the highest dose (1,000 mg kg^{-1}) completely restored both SOD and GPx activities to the similar level as the control and was as effective as the first line therapy sulfasalazine. These results showed a dose-dependent effect of *G. mangostana* pericarp extract to restore antioxidant enzyme activity.

Correspondingly, there was a large down-regulation in mRNA expression of the *CuZn-Sod*, *Mn-Sod*, *Cat*, and *Gpx1* antioxidant enzyme genes observed in the kidneys of dextran sulfate sodium-induced ulcerative colitis mice (Figure 2). *G. mangostana* pericarp extract, α-mangostin, and sulfasalazine effectively returned the mRNA expression of all investigated antioxidant enzymes to a level comparable to the control.

The glutathione system is a non-enzymatic antioxidant mechanism.[24] dextran sulfate sodium-induced ulcerative colitis extensively disturbed the balance of glutathione stores in the mouse kidney. Dextran sulfate sodium treatment greatly reduced total glutathione and GSH contents while sharply increasing GSSG content, resulting in a large reduction in the GSH/GSSG ratio (Table 2). *G. mangostana* pericarp extract successfully improved the glutathione balance in the ulcerative colitis-induced mouse kidneys in a dose-dependent pattern through a significant increase in the GSH/GSSG ratio. α-Mangostin and sulfasalazine also significantly maintained the balance of renal glutathione stores in dextran sulfate sodium-induced ulcerative colitis mice. The antioxidative system is crucial to maintaining an oxidant-antioxidant equivalence. Antioxidant enzymes, including CAT, SOD, and GPx, are the enzymatic elements of the antioxidant system.[25] Cytosolic (*CuZn-Sod*) and mitochondrial (*Mn-Sod*) SODs play essential roles in protecting cells from oxidative stress by converting free radicals to H_2O_2 and oxygen, before H_2O_2 is transformed to water by CAT and GPx. The glutathione system consists of GSH and GSSG, in which GSSG is reduced by GR to active GSH, while GSH converts a critical cellular free radical, H_2O_2, to water and GSSG by GPx.[19]

Current knowledge on the renal antioxidative system in the ulcerative colitis mouse model is insubstantial. The present study supported the observation that dextran sulfate sodium induced an imbalance in the oxidant-antioxidant system by affecting both antioxidant enzymes and non-enzymatic glutathione stores in mouse kidneys. One previous study noted that there was a reduction in the renal intercellular GPx protein level in C3H/HeJ mice that received 5% dextran sulfate sodium (40,000 kDa) for seven days.[26] Antioxidants is generally deficient under oxidative stress. The oxidant dextran sulfate sodium gives rise to an increase in ROS.[27] Antioxidants are consumed to neutralize ROS in an attempt to restore the oxidant-antioxidant balance and lessen oxidative stress and hence a rapid decrement in the amount of antioxidant(s) appears in the early stages of oxidative stress.[28]

G. mangostana pericarp extract and α-mangostin act as potent ROS scavengers and oxidative stress normalizers. A significant increase in the activity of renal SOD, CAT, and GPx enzymes and the expression of *Mn-Sod*, *CuZn-SOD*, *Cat*, and *GPx1* mRNAs, followed by an extensive reduction in MDA levels during treatment with *G. mangostana* pericarp extract or α-mangostin under ulcerative colitis induction conditions were noted in this study. α-Mangostin, a major xanthone in *G. mangostana* pericarp has also been reported to have health benefits due to its antioxidative and anti-inflammatory activities.[10] Oral administration of xanthones from *G. mangostana* pericarp (100 and 200 mg kg^{-1}) increased renal SOD level and delayed inflammation and apoptosis in lead acetate-induced chronic kidney disease in ICR mice.[29,30]

Table 2: Effects of *Garcinia mangostana* pericarp extract and α-mangostin on glutathione stores in the kidneys of UC mice.

Treatments	Glutathione contents (μmol/mg protein)			GSH/GSSG ratio
	Total GSH content	GSSG content	GSH content	
Normal				
Control	226.552 ± 11.920	10.488 ± 1.404	220.031 ± 19.727	21.308 ± 1.771
UC induction				
Non-treatment	52.041 ± 4.507*	19.193 ± 2.567*	37.967 ± 5.006*	2.472 ± 0.521*
GM40	145.235 ± 5.242*#	16.465 ± 2.299*	129.518 ± 2.916*#	8.188 ± 0.843*
GM200	179.804 ± 7.652#	15.353 ± 1.885*#	165.250 ± 7.714#	10.474 ± 0.836*#
GM1000	197.970 ± 7.483#	13.159 ± 1.759#	182.632 ± 13.461#	13.845 ± 1.882*#
MGS	191.770 ± 10.099#	14.187 ± 1.199#	178.237 ± 10.322#	12.481 ± 1.710*#
SUL	198.796 ± 15.475#	11.555 ± 1.721#	196.627 ± 22.788#	19.589 ± 2.180#

Note. The data are presented as mean ± SD. GSH, reduced glutathione; GSSG, oxidized glutathione; UC, ulcerative colitis; GM, *Garcinia mangostana* pericarp extract (40, 200, and 1,000 mg kg^{-1}); MGS, α-mangositn (30 mg kg^{-1}); SUL, sulfasalazine (100 mg kg^{-1}). *$p<0.05$ VS Control, #$p<0.05$ VS Non-treatment. n = 9 each.

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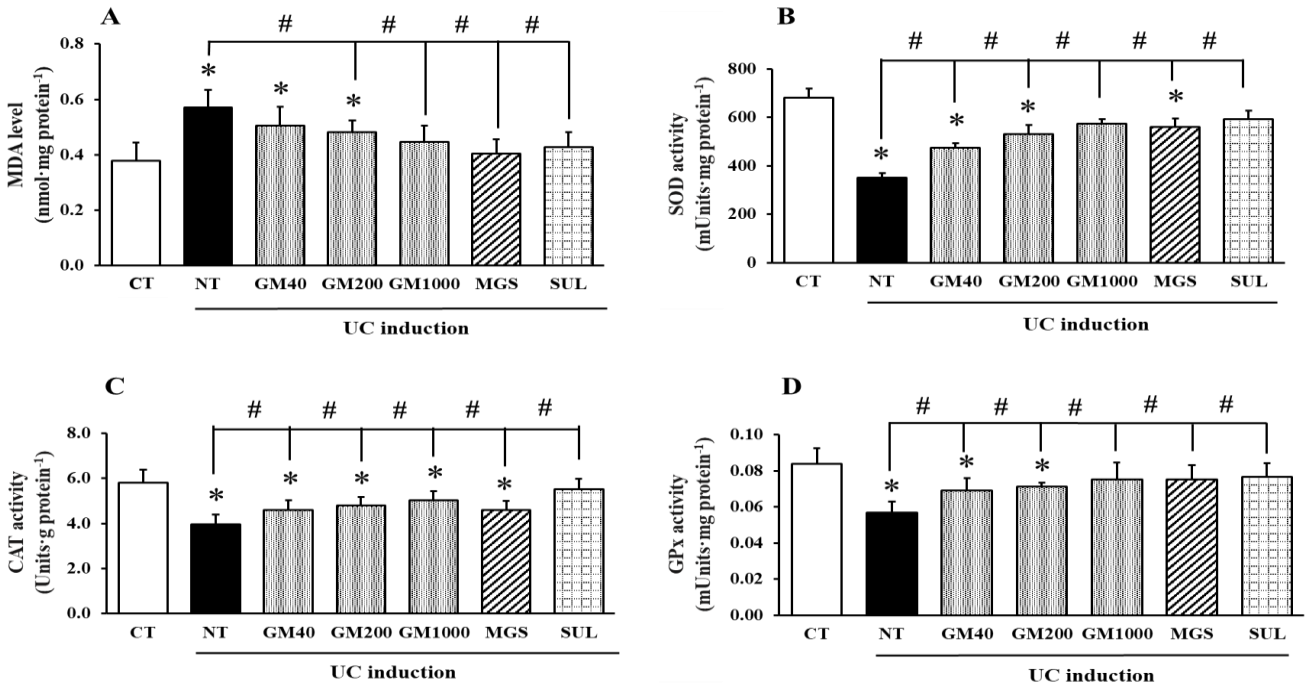

Figure 1 Effects of GM pericarp extract, α-mangostin, and sulfasalazine on (A) MDA level and (B) SOD, (C) CAT, and (D) GPx activities in the kidneys of UC mice.

CT, control; NT, non-treatment; GM, GM pericarp extract; MGS, α-mangostin; SUL, sulfasalazine; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; $^{*}p < 0.05$ versus CT; $^{\#}p < 0.05$ versus NT.

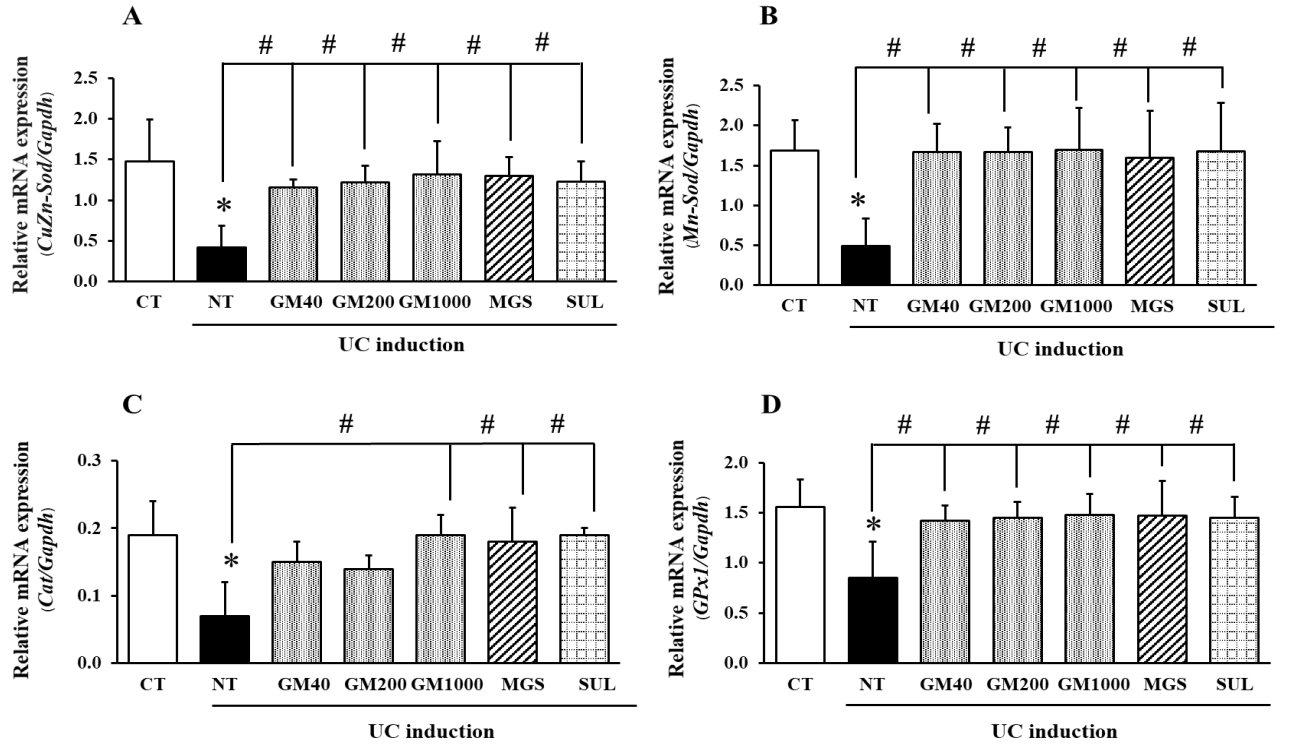

Figure 2: Effects of GM pericarp extract, α-mangostin, and sulfasalazine on mRNA expression of (A) *CuZn-Sod*, (B) *Mn-Sod*, (C) *Cat*, and (D) *GPx1* in the kidneys of UC mice.

CT, control; NT, non-treatment; GM, GM pericarp extract; MGS, α-mangostin; SUL, sulfasalazine. $^{*}p < 0.05$ versus CT; $^{\#}p < 0.05$ versus NT.

Correspondingly, *G. mangostana* pericarp extract (100 and 200 mg kg^{-1}) treatment for one-week improved SOD and CAT contents in the kidneys of streptozotocin-induced ICR mice.[31-32] This is consistent with our recent report emphasizing that dextran sulfate sodium (40 kDa) induction diminished CAT and SOD activities and down-regulated expression of *Cat* and *Sod* in ulcerative colitis mouse colonic tissues and *G. mangostana* pericarp extract and α-mangostin restored those antioxidant enzymes.[10]

The oxidant-antioxidant system is associated with ulcerative colitis. Dextran sulfate sodium induced ulcerative colitis in mice, leading to

an imbalance in the antioxidative system that was followed by oxidative stress not only in the primary organ, the intestine, but also in the kidney. *G. mangostana* pericarp extract exerted antioxidant benefits in this model improving the renal oxidant-antioxidant status in dextran sulfate sodium-induced oxidative stress in mice. The mechanism(s) underlying the effects of *G. mangostana* pericarp extract or α-mangostin on oxidative status is worth further investigation.

Conclusion

Dextran sulfate sodium-induced ulcerative colitis mice showed reduced activity and mRNA expression of SOD, CAT, and GPx antioxidant enzymes and reduced non-enzymatic glutathione stores, which was followed by increased lipid peroxidation in kidneys, indicating oxidative stress. *G. mangostana* pericarp extract and α-mangostin improved the oxidative status by restoring the antioxidant enzyme system and balancing the glutathione stores. Therefore, *G. mangostana* pericarp extract and α-mangostin are promising candidates for protection against kidney extraintestinal manifestation of ulcerative colitis and worthy for further study as an alternative therapy for ulcerative colitis

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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