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Garcinia mangostana pericarp and α-mangostin normalized the expression of colonic and renal cytochrome P450 genes and abated the expression of renal inflammatory genes in dextran sulfate sodium-induced ulcerative colitis in mice

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ABSTRACT

Ulcerative colitis (UC) causes inflammation and ulceration in the colon and often develops renal manifestation. *Garcinia mangostana* pericarp crude extract (GM) and α-mangostin (MGS), a major bioactive compound, have potentiality to consider as a new complementary therapy for UC due to pharmacological activities, particularly anti-inflammatory activity. However, safety in terms of drug interaction has been neglected. The current study investigated the impacts of GM and MGS on the cytochrome P450 (CYP) profiles in the mouse colon and kidneys, including the inflammatory response in the kidneys. Male ICR mice were orally pre-treated with 40–1,000 mg/kg/day of GM, 30 mg/kg/day of MGS, or 100 mg/kg/day of sulfasalazine daily for 7 days. On days 4–7, 6 g/kg of 40 kDa dextran sulfate sodium (DSS) was orally administrated to induce UC. RT-qPCR was performed to determine the mRNA expressions of CYP and inflammatory genes. DSS suppressed *Cyp1a1, Cyp2b9/10, Cyp2c29, Cyp2d9, Cyp2e1, Cyp3a11*, and *Cyp3a13* expressions, whilst GM and MGS positively adjusted the CYP expression in both organs. Besides, *Tnf-α, Mcp-1*, and *Nf-κb* expressions were up-regulated after UC induction, while they were restored to the level comparable to the control by GM and MGS. Therefore, *G. mangostana* pericarp is a promising candidate to normalize the CYP profiles and reducing the risk of drug interaction, and to revitalize against inflammation.

INTRODUCTION

Ulcerative colitis (UC) is a long-term inflammatory disease of the large intestine and rectum. The character of UC appears as recurrent and transmitting mucosal inflammation beginning in the rectum and spreads to the proximal segment of the colon (Ungaro *et al*., 2017). The typical symptoms of UC include bloody diarrhea, fecal urgency, tenesmus, and lower abdominal pain (Collins and Rhodes, 2006). Chronic symptoms with an improper treatment may develop severity of the disease, and resulting in colorectal cancer (Jang *et al*., 2022). Extraintestinal manifestation (EIM) is frequently associated with UC, affecting organs outside the gastrointestinal tract, such as kidneys (Levine and Burakoff, 2011). Patients with inflammatory bowel disease (4%–23%) had kidney or urination problems (Ambruzs and Larsen, 2018). Kidney EIM includes nephrolithiasis, glomerulonephritis, tubulointerstitial nephritis, and amyloidosis (Levine and Burakoff, 2011). Sulfasalazine (SUL) is the most common treatment for mild to moderate UC (Ungaro *et al*., 2017). However, SUL can result in serious side effects, e.g., interstitial nephritis, tubular atrophy, kidney failure, and renal necrosis (Niknahad *et al*., 2017).

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Garcinia mangostana Linn. (GM) is native to the tropical areas of Myanmar, Malaysia, the Philippines, and Thailand (Pedraza-Chaverri *et al*., 2008). α-Mangostin (MGS) was majorly found among significant xanthones taken from the GM pericarp (Ibrahim *et al*., 2016). GM pericarp extract possesses several beneficial properties such as antitumoral, antibacterial, antifungal, antioxidative, and anti-inflammatory activities. GM pericarp has been widely experimented with in rodent models (Pedraza-Chaverri *et al*., 2008).

Cytochrome P450 (CYP) is a super-enzyme responsible for metabolizing foods, drugs, and xenobiotic in the body. CYP constitutively expresses in various organs, such as the liver, kidneys, and colon. CYP in families 1–3, including *Cyp1a1, Cyp1a2, Cyp2b9/10, Cyp2c29, Cyp2d9, Cyp2e1, Cyp3a11*, and *Cyp3a13*, are majorly responsible for metabolism and biotransformation. Alteration of CYP expression profiles from dextran sulfate sodium (DSS) and GM pericarp might result in a risk of drug-drug and/or herb-drug interaction, following treatment failure or toxic effects (Court, 2013; Malki and Pearson, 2020). Thereby, this study aimed to examine the impacts of GM pericarp and MGS on the CYP expressions and inflammatory status in the colon and/or kidneys in DSS-induced UC mice.

MATERIALS AND METHODS

Chemicals and reagents

MGS (Cas No. 6147-11-1, >98% purity, Batch PR15092126) was obtained from Chengdu Biopurify Phytochemicals (Republic of China). SUL was a product of Sigma Chemicals (Saint Louis, MO). ReverTraAce® was from Toyobo® (Japan). Random primers and ribonuclease inhibitor were provided by Invitrogen® (Carlsbad, CA). Taq polymerase was obtained from Vivantis (Malaysia).

Preparation of the GM pericarp extract

GM was purchased from the Khon Kaen municipal market, Muang Khon Kaen, Thailand (April 2014) and deposited at the Herbarium of Faculty of Pharmaceutical Sciences, Khon Kaen University (KKU). The samples were identified as PANPB-GM 2014-001 by Prof. Waraporn Putalun, Department of Pharmacognosy and Toxicology, KKU, Thailand. GM pericarp was washed 2–3 times and dried at 50°C–60°C before grinding. The powdered GM pericarp was subjected to Soxhlet extraction with ethanol for 3 hours, filtered, evaporated, and lyophilized to achieve the ethanolic GM pericarp extract. MGS content of the extract was determined by a high-performance liquid chromatographic system, which consisted of a C18 column (Phenomenex® Luna 5 µm C18 100 Å, 4.6 × 250 mm, Waldbronn, Germany) coupled with an isocratic mobile phase of 85% acetonitrile in distilled water. The flow rate was 1 ml/minute and the UV detector was set at 244 nm (Tatiya-aphiradee *et al*., 2018). HPLC chromatograms of standard MGS and the extract are depicted in Figure 1. The MGS content of the ethanolic GM pericarp extract was 17.93% ± 0.08% dry weight (Tatiya-aphiradee *et al*., 2021a).

Animals and experimental design

Six-week-old male Institute of Cancer Research (ICR) mice weighing 25–30 g (from NELAC, KKU , Thailand) were acclimated in polycarbonate cages in an animal room of Faculty of Pharmaceutical Sciences, KKU, maintained at 25°C with a controlled 12 hours dark-light cycle under *ad libitum* feeding for 7 days. All animal handling and experimental protocols were implemented in accordance with the Institutional Animal Care and Use Committee of the Northeast Laboratory Animal Center, KKU (Approval No. IACUC-KKU-26/61) under supervision of a certified veterinary.

Mice were randomly divided into seven groups ($N = 9$ each); control, non-treatment, GM40, GM200, GM1,000, MGS, and SUL. UC was induced with intragastric administration of a 40 kDa-DSS solution (6 g/kg/day; 0.25 ml 21% DSS four times per day) for four consecutive days, as shown in Table 1 (Tatiya-aphiradee *et al*., 2020; Tatiya-aphiradee *et al*., 2021a). One day after the last treatment, the mice were euthanized with Zoletil® (100 mg/kg). The colon and kidneys were collected and kept at −80°C for further analysis.

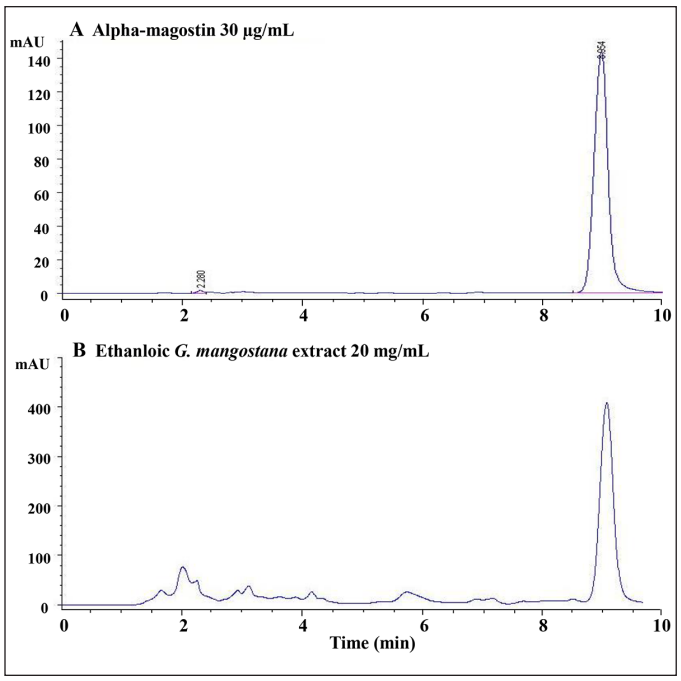

Figure 1. HPLC chromatograms of A, α-mangostin 30 µg/ml and B, ethanolic GM pericarp extract 20 mg/ml.

Table 1. Animal treatment.

Groups	Days 1–7	Days 4–7
Control	0.5% carboxymethyl cellulose	Distilled water
Non-treatment	0.5% carboxymethyl cellulose	DSS 6 g/kg
GM40	40 mg/kg GM pericarp extract	
GM200	200 mg/kg GM pericarp extract	
GM1000	1,000 mg/kg GM pericarp extract	
MGS	30 mg/kg MGS	
SUL	100 mg/kg SUL	

GM, *Garcinia mangostana* pericarp extract; DSS, 40 kDa dextran sulfate sodium.

DSS-induced UC index determination

For disease activity index (DAI) determination, each mouse was placed in a cage without bedding for 15 minutes to examine the stool characteristics (Chassaing *et al*., 2014). Body weight, stool consistency, and the presence of blood in stool were recorded daily. Body weight loss, reduced stool consistency, and bleeding in stools were scored to determine the DAI (Tatiya-aphiradee *et al*., 2020; Xiao *et al*. 2013). One day after the last treatment, colons were collected for colon length measurement (Tatiya-aphiradee *et al*., 2020; Xiao *et al*., 2013) and colon tissue was embedded in a paraffin block and sectioned at 5-µm thickness for alcian blue staining. After the slide was rehydrated, it was soaked in 3% acetic acid at pH 2.5 for 3 minutes, followed by staining with alcian blue at pH 2.5 for 30 minutes and counterstaining with eosin for 5 minutes. All slides were covered with coverslips using a mounting medium (Tatiya-aphiradee *et al*., 2020). Images were collected at 1,000-fold magnification using an Olympus CX23-microscope and EP50 camera (Olympus, Tokyo, Japan).

Determination of mRNA expression by RT-qPCR

Total RNA was procured from the colon or kidney by guanidinium thiocyanate-phenol-chloroform technique (Nopwinyoowong *et al*., 2022) and reverse transcribed to cDNA using ReverTraAce®. cDNA of the CYP and inflammatory-associated genes, as well as the reference gene *Gapdh* was amplified by qPCR with specific primers (Table 2). mRNA expression was normalized to *Gapdh* and relative fold expression was calculated via $^{\Delta\Delta}$Ct technique. The changes in Ct (ΔCt) between the genes of interest and the mean of the reference (*Gapdh*) gene and the changes in $^{\Delta}$Ct between the treatments and the control (ΔΔCt) were calculated. The fold change in expression between samples was calculated from $2^{-(\Delta\Delta Ct)}$ (Chatuphonprasert *et al*., 2020; Livak and Schmittgen, 2001).

Statistical analysis

The results are shown as mean ± standard deviation. One-way analysis of variance was carried out, followed by Tukey's post hoc test (IBM SPSS ver. 26, Armonk, NY). A significance was considered at $p < 0.05$.

RESULTS AND DISCUSSION

DSS determines UC characters by their molecular weight, dosage, and the treatment period. DSS of 500 kDa failed to induce UC, while those lower molecular weights of 5 and 40 kDa for 7 days-treatment induced UC in BALB/c mice

Table 2. Forward and reverse primers for qPCR.

Genes		Forward and reverse primer sequences (5′ → 3′)	Product size (bp)	$T_{annealing}$ (°C)
Cyp1a1	F	GAC ATT TGA GAA GGG CCA CAT C	135	60.0
	R	CCA AAG AGG TCC AAA ACA ATC G		
TaqMan® probe		FAM-CGA GAA TGC CAA TGT CCA GCT GTC A-TAMRA		
Cyp1a2	F	AAG ATC CAT GAG GAG CTG GA	359	48.0
	R	TCC CCA ATG CAC CGG CGC TTT CC		
Cyp2b9/10	F	CTC TTC CAG TGC ATC AC	229	60.0
	R	CAA TGT AGT CGA GGA GTT CC		
Cyp2c29	F	ATC TGG TCG TGT TCC TAG CG	218	50.0
	R	AGT AGG CTT TGA GCC CAA ATA C		
Cyp2d9	F	ATT CTT GTT GCC CCC TCT CC	94	60.4
	R	TGG CAG GAA ACT GCC CTA CA		
Cyp2e1	F	TCC CTA AGT ATC CTC CGT GA	189	50.0
	R	GTA ATC GAA GCG TTT GTT GA		
Cyp3a11	F	TTT GGT AAA GTA CTT GAG GCA GA	134	64.0
	R	CTG GGT TGT TGA GGG AAT C		
Cyp3a13	F	TGT GCT GGC TAT CAC AGA TCC	101	55.0
	R	AAA TAC CCA CTG GAC CAA AGC		
Tnf-α	F	CCG ATG GGT TGT ACC TTG TC	77	68.0
	R	GTG GGT GAG GAG CAC GTA GT		
Mcp-1	F	CAG ATC TCT CTT CCT CCA CCA CTA T	73	68.0
	R	CAG GCA GCA ACT GTG AAC AAC		
Nf-κb	F	GAA ATT CCT GAT CCA GAC AAA AAC	194	60.0
	R	ATC ACT TCA ATG GCC TCT GTG TAG		
Gapdh	F	CCT CGT CCC GTA GAC AAA ATG	124	57.4
	R	TGA AGG GGT CGT TGA TGG C		

Primers and real-time qPCR conditions were modified from Chatuphonprasert *et al*. (2009); Chatuphonprasert *et al*. (2019); Tatiya-aphiradee *et al*. (2021b).

(Kitajima *et al*., 2000). DSS (5 kDa) caused mild UC, whilst DSS (40 kDa) developed more severity (Kitajima *et al*., 2000). Administration of 2%–5% DSS (36-50 KDa) to inbred mice for 4–9 days persuaded acute UC, whereas 15 days-period of 0.5% DSS led to chronic UC (Nishihara *et al*., 2006). Our previous study supported that 6g/kg of 40 kDa DSS for four consecutive days successfully induced UC in ICR mice, demonstrating weight loss, bloody stool, shortened colon, crypt erosion, mucin depletion, and inflammatory and mast cell infiltration (Tatiya-aphiradee *et al*., 2020; Tatiya-aphiradee *et al*., 2021a).

GM pericarp extract protected against DSS-induced UC

The severity of UC was indicated by the DAI score (Xiao *et al*. 2013). The DAI scores were significantly higher after DSS administration for 4 days and all treatments, including GM pericarp extract, MGS, and SUL, reduced the DAI score (Fig. 2A). Likewise, the colons were significantly shortened after DSS induction (Fig. 2B). Interestingly, GM pericarp extract, MGS, and SUL restored the colon length comparable to the control. Distribution of mucin in colon tissue was examined by alcian blue staining (Fig. 2C). A significant pathological feature of DSS-induced UC is goblet cell loss, leading to mucin depletion (Tatiya-aphiradee *et al*., 2021a). The control demonstrated mucin-full crypt cavities (yellow arrows). The administration of DSS depleted the amount of mucin, as seen in the non-treatment group. Treatment with GM pericarp extract (40–1,000 mg/kg) and MGS preserved the colon tissue and restored the amount of mucin, while treatment with SUL was inferior. These findings reveal that GM pericarp extract and MGS potentially possess colon protective effects.

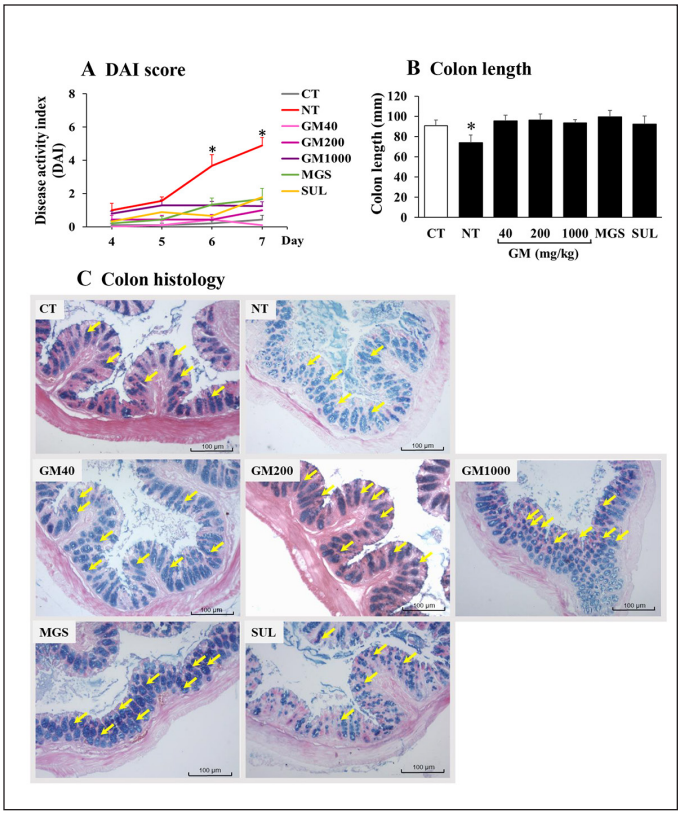

Figure 2. Effects of GM pericarp extract on A, DAI, B, colon length, and C, colon histology. The results are expressed as mean ± SD (n = 9). *p < 0.05 VS CT (control). GM, *Garcinia mangostana* pericarp extract; MGS, α-mangostin; SUL, sulfasalazine.

Effect of the GM pericarp extract and MGS on the mRNA expression of CYPs in the mouse colons

Typically, hepatic CYP enzymes are responsible for metabolism; nonetheless, intestinal CYPs likewise metabolized orally administered drugs and xenobiotics and contributed to the first-pass metabolism of oral medications (Xie *et al*., 2016). Colonic CYP profiles of UC patients were modified; expression of CYP2B6, CYP2E1, and CYP3A4 were slightly induced, while those of CYP2C9 and CYP1A1 were suppressed (Plewka *et al*., 2014).

Figure 1 showed DSS-modified colonic CYP mRNA profiles and the neutralizing effect of the GM pericarp extract and MGS. *Cyp1a1, Cyp2b9/10, Cyp2c29, Cyp2d9, Cyp2e1, Cyp3a11*, and *Cyp3a13* expressions were significantly suppressed after DSS administration (Fig. 3A–G). The GM pericarp extract (40–1,000 mg/kg) up-regulated the CYP profiles to the levels comparable to control, except that of *Cyp2b9/10*. The lowest dose of GM pericarp extract (40 mg/kg) did not restore *Cyp2b9/10* expression (Fig. 3B). MGS and SUL returned the CYP profiles equivalent to the GM pericarp extract.

In addition, Tatiya-aphiradee *et al*. (2021a) reported that DSS-induced UC suppressed mRNA expression of inflammatory-associated genes, namely *Tnf-α, Mcp-1, Tlr-2, Icam-1*, and *Vcam-1*, in mouse colons, by which these were up-regulated by the GM pericarp extract, leading to restoration of inflammatory revival in the colons. These observations suggested a relevance of inflammatory-associated genes and CYP profiles in the colon; up-regulating expression of inflammatory-associated genes down-regulating expression of CYP profiles. Likewise, GM pericarp extract reduced inflammation, causing an increase in CYP expression profiles. These findings revealed that CYP expression was inversely proportional to inflammation. IL-6 down-regulated orphan nuclear receptors, including constitutive androstane receptor (CAR), retinoid X receptor (RXR), and pregnane X receptor (PXR). In general, CAR regulated expression of *Cyp2b9/10, Cyp2c29, Cyp3a11,* and *Cyp3a13* mRNAs, whilst RXR transactivated transcription of *Cyp3a11* and *Cyp3a13* and PXR associated with regulation of *Cyp2c29, Cyp3a11,* and *Cyp3a13* (Down *et al*., 2007; Kusunoki *et al*., 2015). Albeit inflammation is corrected, IL-1β, IL-6, and TNF-α are lessened with meanwhile PXR and CAR normalization reinstated *Cyp2b9/10, Cyp2c29, Cyp3a11,* and *Cyp3a13* expression (Kusunoki *et al*., 2015).

Effect of the GM pericarp extract and MGS on the mRNA expression of CYPs and inflammatory-associated genes in the mouse kidneys

Kidneys comprise a large number of CYPs enzymes; 4%–20% of hepatic CYP protein contents (Gundert-Remy *et al*., 2014). DSS-induced UC caused renal injury and inflammation. Wistar rats daily received 5% DSS for 7 days showed an increase in creatinine, a biochemical parameter of renal function (Rtibi *et al*. 2016). Correspondingly, DSS extensively suppressed expression of renal CYP and inflammatory-associated genes (Fig. 4). Recovery of the CYP profiles was achieved after the GM

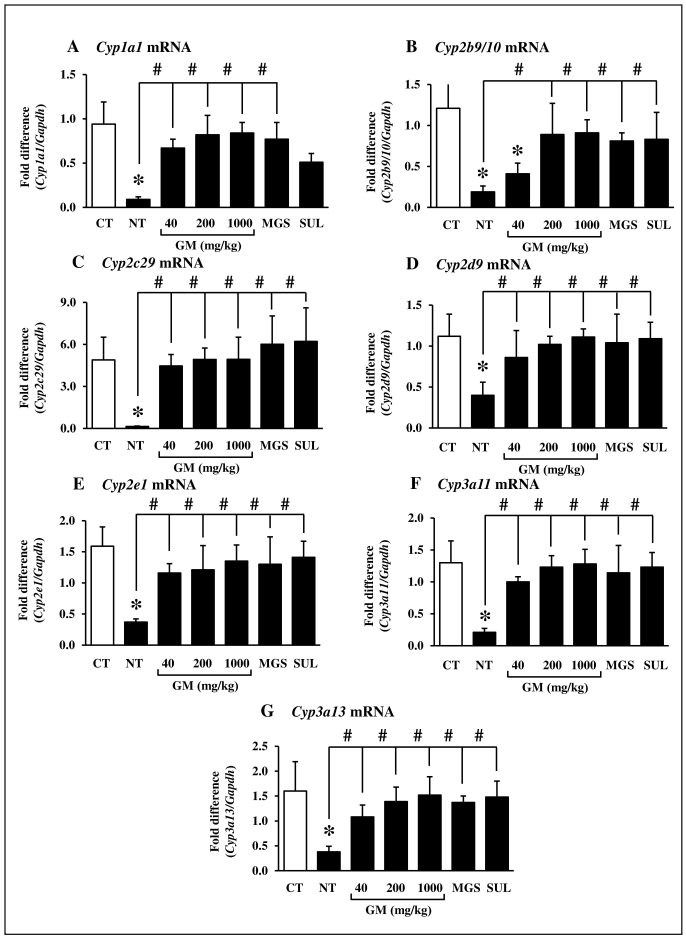

Figure 3. Effects of GM pericarp extract and MGS on the mRNA expression of CYPs in the colons of DSS-induced UC mice. A, *Cyp1a1*; B, *Cyp2b9/10*; C, *Cyp2c29*; D, *Cyp2d9*; E, *Cyp2e1*; F, *Cyp3a11*; G, *Cyp3a13*. The results are expressed as mean ± SD (n = 9). *p < 0.05 VS CT (control), #p < 0.05 VS NT (non-treatment). GM, *Garcinia mangostana* pericarp extract; MGS, α-mangostin; SUL, sulfasalazine.

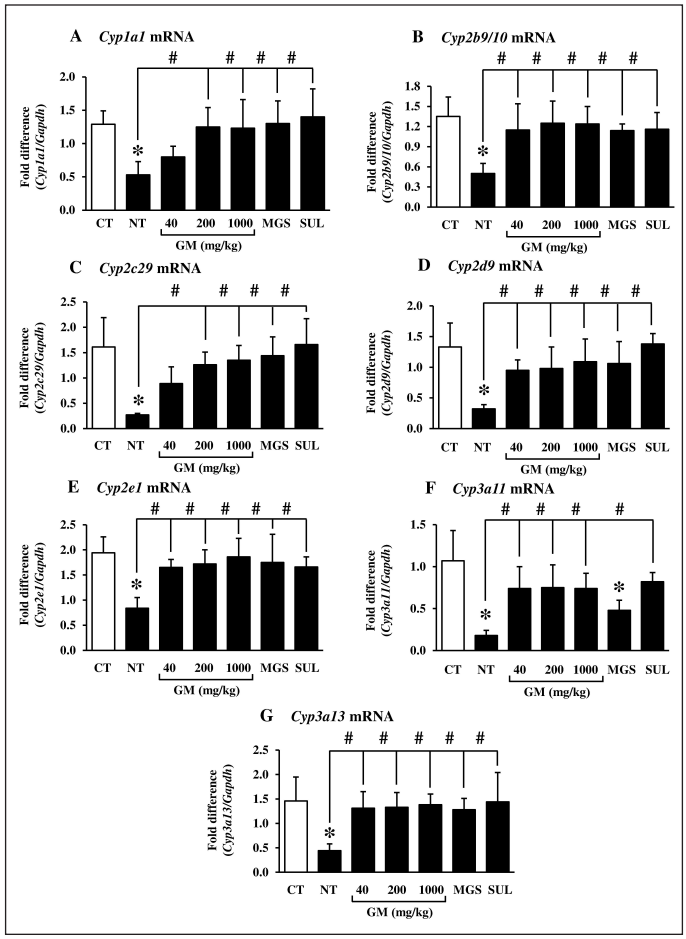

Figure 4. Effects of GM pericarp extract and MGS on the mRNA expression of CYPs in the kidneys of DSS-induced UC mice. A, *Cyp1a1*; B, *Cyp2b9/10*; C, *Cyp2c29*; D, *Cyp2d9*; E, *Cyp2e1*; F, *Cyp3a11*; G, *Cyp3a13*. The results are expressed as mean ± SD (n = 9). *p < 0.05 VS CT (control), #p < 0.05 VS NT (non-treatment). GM, *Garcinia mangostana* pericarp extract; MGS, α-mangostin; SUL, sulfasalazine.

pericarp extract, MGS, and SUL administration (Fig. 4A–E and G), excluding MGS-treated *Cyp3a11* expression (s).

In addition, mRNA expression of inflammatory-associated genes, namely tumor necrosis factor-α (*Tnf-α*), monocyte chemoattractant protein-1 (*Mcp-1*), and nuclear factor kappa b (*Nf-κb*) was significantly induced after DSS administration (Fig. 5). The GM pericarp extract and MGS significantly returned those expressions to the levels comparable to the control. SUL extensively suppressed *Tnf- α* and *Mcp-1* expression (Fig. 5A and B), while that of *Nf-κb* was slightly lessened and even significantly different to the control (Fig. 5C). TNF-α is a pro-inflammatory cytokine generated by T-lymphocyte, macrophage, and natural killer (NK) cell (Jang *et al*., 2021). *Tnf- α* is triggered by a foreign body or immune system, including B and T lymphocytes and fibroblast, to produce various inflammatory cytokines and mediators such as interleukin 1 (IL-1), IL-6, IL-8, and granulocyte monocyte colony-stimulating factor (Jang *et al*., 2021; Shanahan and Clair, 2002). MCP-1, a member of the C-C chemokine family, is induced by inducing cytokines, oxidative stress, or growth factor. *Mcp-1* serves to regulate the migration and infiltration of monocyte, memory T lymphocyte, and NK cell in inflammatory response (Deshmane *et al*., 2009). *Nf-κb* is a transcription factor regulating the expression of critical inflammatory mediators, including IL-1, IL-6, IL-8, IL-12, *Tnf-α*, and cyclooxygenase-2 (*Cox-2*). Moreover, chronic inflammation stimulates *Nf-κb* to generate more inflammatory cytokines (Liu *et al*., 2017). Administration of 3.5% of DSS for 5 days increased neutrophil infiltration in kidney interstitium and induced expression of *Il-6*, interferon γ-induced protein 10 *(Ip-10), Mcp-1*, and *Cox-2* in C57BL/6 mouse kidneys (Ranganathan *et al*., 2013). In consistency, the present study observed up-regulation of *Tnf-α, Mcp-1*, and *Nf-κb* expression, suggesting the occurrence of an inflammatory response.

Conclusively, DSS-induced UC injured kidneys, leading to the alteration of renal CYP profiles and the inflammatory response. These findings suggested that suppression of renal CYP expression profiles resulted from the increased inflammation in the kidneys, by which the GM pericarp extract and MGS help to revive the inflammation. A decrease in the inflammation restored the CYP expression profiles, brought about normalizing CYP functions. Therefore, the GM pericarp extract is a potential candidate to develop as an alternative medicine for UC and kidney EIM therapy with a low risk of herb-drug interaction.

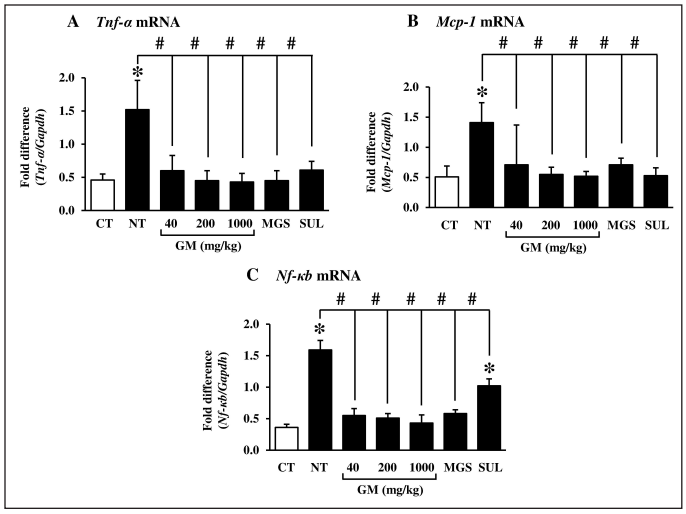

Figure 5. Effects of GM pericarp extract and MGS on the mRNA expression of inflammatory-associated genes in the kidneys of DSS-induced UC mice. A, *Tnf-α*; B, *Mcp-1*; C, *Nf-κb*. The results are expressed as mean ± SD (n = 9). *p < 0.05 VS CT (control), $^{\#}p$ < 0.05 VS NT (non-treatment). GM, *Garcinia mangostana* pericarp extract; MGS, α-mangostin; SUL, sulfasalazine.

CONCLUSION

UC induces EIM by inducing renal inflammation and affecting CYP expression profiles in the kidneys and colon. Promisingly, the GM pericarp extract and MGS down-regulated the expression of inflammatory-associated genes, including *Tnf-α, Mcp-1*, and *Nf-κb* in the mouse kidneys and normalized the expression of CYPs in the mouse kidneys and colon comparable to the standard drug SUL. Hence, it is worthwhile developing the GM pericarp extract for alternative therapy of UC and kidney EIM.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

The Institutional Animal Care and Use Committee of the Northeast Laboratory Animal Center, KKU (Approval No. IACUC-KKU-26/61) under supervision of a certified veterinary.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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