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Research Article

Garcinia mangostana and α-Mangostin Revive Ulcerative Colitis-Modified Hepatic Cytochrome P450 Profiles in Mice

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Abstract

Background and Objective: Ulcerative colitis (UC) is inflammation of the large intestine with ulceration but can also cause extraintestinal manifestations (EIM) by damaging surrounding organs such as the liver. *Garcinia mangostana* (GM) pericarp and α-mangostin (MGS) have been reported to have anti-inflammatory activity. This study evaluated the effects of GM pericarp extract and MGS on the expression of hepatic cytochrome P450 (CYP) enzymes as an EIM of UC. **Materials and Methods:** Male ICR mice were orally administered GM pericarp extract (40, 200 and 1000 mg/kg/day), MGS (30 mg/kg/day) or sulfasalazine (SUL) (100 mg/kg/day) daily for 7 days. On days 4-7, UC was induced by dextran sulfate sodium (DSS 40 kDa, 6 g/kg/day). Profiles of CYP mRNA expression were determined by RT/qPCR. Alkoxyresorufin *O*-dealkylation (including ethoxy-, methoxy-, pentoxy- and benzyloxy-resorufin), aniline hydroxylation and erythromycin *N*-demethylation CYP responsive activities were also examined. **Results:** The DSS-induced UC mice showed suppressed expression of *Cyp1a1*, *Cyp1a2*, *Cyp2b9/10*, *Cyp2e1*, *Cyp2c29*, *Cyp2d9*, *Cyp3a11* and *Cyp3a13* mRNAs. The GM pericarp extract and MGS restored expression of all investigated CYPs and their responsive enzyme activities in DSS-induced UC mice to levels comparable to the control and parallel to the effects of the anti-inflammatory control SUL. **Conclusion:** The GM is a promising therapy to restore UC-modified hepatic CYP profiles.

Key words: Cytochrome P450, liver manifestation, mangosteen, dextran sulfate sodium, ulcerative colitis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by prolonged inflammation of the colon, rectum and caecum, which results in the formation of ulcers in the gastrointestinal epithelium and increased gastric peristalsis[1]. The causes of UC are unclear, however, it is associated with various genetic disorders, epithelial disorders, abnormal responses of the immune system, environmental conditions and oxidative status[2]. The UC is a lifelong recurring condition. Bloody diarrhoea is the initial sign of UC, appearing in more than 90% of cases[1], but UC patients experience a range of symptoms including intolerance diarrhoea, abdominal cramps, anaemia, weight loss, weakness and fever[3]. In addition to the primary lesions in the gastrointestinal system, the damage from UC can extend to surrounding organs as extraintestinal manifestations (EIMs). The EIMs are found in 6-46% of IBD patients (both UC and Crohn's disease) and almost all organs are affected[4,5]. The EIMs of IBD are most frequently found in the hepatobiliary tract, with lower incidences in kidneys, lungs, skin, joints and eyes[5,6]. Primary sclerosing cholangitis, fatty liver and autoimmune hepatitis are the main hepatobiliary EIM diseases[7].

Garcinia mangostana Linn. (GM, family Clusiaceae or Guttiferae) is found throughout Southeast Asia, including Thailand. The GM fruit is a rich source of phenolic compounds, mainly xanthones, tannins and proanthocyanidins and α-mangostin (MGS) is the major xanthone found in GM pericarp[8]. The GM pericarp has been shown to possess several potential pharmacological benefits including anti-inflammatory, anti-oxidative, anti-cancer, anti-parasitic and anti-microbial activities[9].

Cytochrome P450 (CYP) is a super-family of enzymes that play a vital role in the biotransformation of many endogenous and exogenous compounds including drugs, xenobiotics, foods and toxins. The primary site of CYP activity is the liver, but it can also be active in other organs including the intestine and kidneys[10]. The major CYP expressed in mouse and human livers are CYP3A, followed by CYP2C, CYP2D, CYP1A, CYP2B and CYP2E, respectively[11]. A study of homology between mouse and human CYP isoforms showed that CYP1A1, CYP1A2 and CYP2E1 were present in both mice and humans, while mouse *Cyp2b10, Cyp3a11* and *Cyp3a13* were homologous with human CYP2B6, CYP3A4 and CYP3A7[12]. Dextran sulfate sodium (DSS)-induction of UC in mice might also modify hepatic CYP expression and activity, which can lead to therapeutic failure, adverse drug reactions, drug-drug interactions and toxicity[10].

The present study evaluated the effects of GM pericarp extract and MGS on the mRNA profiles and responsive enzyme activities of major CYPs, namely *Cyp1a1*, *Cyp1a2*, *Cyp2b9/10*, *Cyp2e1*, *Cyp2c29*, *Cyp2d9*, *Cyp3a11* and *Cyp3a13*, in the livers of DSS-induced UC mice.

MATERIALS AND METHODS

Study area: The study was performed at the animal unit (B 2559/00015.003) and the Research Group for Pharmaceutical Activities of Natural Products using Pharmaceutical Biotechnology, Khon Kaen University, Khon Kaen 40002, Thailand between August, 2020 and May, 2021.

Chemicals: The α-mangostin (CAS No. 6147-11-1, purity >98%, Lot No. PRF15092126) was purchased from Chengdu Biopurify Phytochemicals, Sichuan, China. Sulfasalazine, resorufin, methoxyresorufin, ethoxyresorufin, benzyloxy-resorufin, pentyloxyresorufin, erythromycin and aniline hydrochloride were products of Sigma Chemicals (Missouri, USA). ReverTraAce® was from Toyobo® (Tokyo, Japan). *Taq* polymerase was supplied by Vivantis (Selangor, Malaysia).

Preparation of GM pericarp extract and determination of α-mangostin: The GM fruits were collected from a fresh market, in Khon Kaen, Thailand (April, 2014). The pericarp was cleaned and mashed before Soxhlet extraction with 95% ethanol for 3 hrs, followed by filtration through Whatman® filter paper. The organic solvent was evaporated by a rotary evaporator and the extract was completely dried by a freeze dryer. The content of MGS in the extract was 17.93±0.08% dry weight[13].

Animal handling and treatment: Sixty three male ICR mice at 5 weeks old were provided by the Northeast Laboratory Animal Center of Khon Kaen University, Khon Kaen, Thailand. All mice were raised in stainless-steel cages with corncob bedding and free access to commercial food and water in the animal unit (B 2559/00015.003) at the Faculty of Pharmaceutical Sciences, Khon Kaen University. The atmosphere was controlled at 25°C and 45% relative humidity with 12 hrs-dark/light cycle. The mice were acclimated for 1 week before the treatment. The protocol was approved by Institute Animal Care and Use Committee, Khon Kaen University (Approval No. IACUC-KKU-26/61).

The mice were randomly divided (N = 9 each) into 7 groups. The control (CT) and non-treatment groups (NT) were orally given 0.5% carboxymethyl cellulose for 7 consecutive days. Treatment groups were orally administered GM pericarp extract (40, 200 and 1000 mg/kg/day), MGS (30 mg/kg/day) or sulfasalazine (SUL, 100 mg/kg/day) daily for the same period. The UC was induced in the non-treatment and treatment groups by oral administration of dextran sulfate sodium (DSS 40 kDa, 6 g/kg/day) on days 4-7, while the control was given distilled water for the same period. All mice were euthanized 24 hrs after the last treatment (day 8) with Zoletil® (80-100 mg/kg). The blood was drained through the hepatic portal vein using 1.15% potassium chloride and the livers were collected and kept at -80°C before analysis.

Preparation of hepatic microsomes: Livers were homogenized in 1.15% w/v potassium chloride (in a volume of 3 times the liver weight) with a hand-homogenizer before centrifugation at 10,000×g, 4°C for 10 min. The supernatant was collected and ultracentrifuged at 104,000×g, 4°C for 60 min before the microsome was resuspended in ice-cold distilled water and kept at -80°C[14].

Assessment of alkoxy resorufin-O-dealkylation: Ethoxy- (EROD), methoxy- (MROD), benzyloxy- (BROD) and penthoxy- (PROD) resorufin-*O*-dealkylations were performed as previously described[14]. The reaction was generated by adding 0.5 mM NADPH to a mixture of microsomes and 0.05 mM ER, MR, BR or PR. Fluorescence intensity at excitation and emission wavelengths of 520 and 590 nm, respectively, was measured by a spectrophotometer and compared with a standard resorufin (1 µM).

Assessment of aniline hydroxylation: The 4-aniline hydroxylation (ANH) was performed as previously described[14]. Microsomes were mixed with 100 mM aniline hydrochloride, 50 mM $MgCl_2$, 100 nM nicotinamide and 10 mM NADPH. The mixture was incubated at 37°C for 20 min. Trichloroacetic acid was added before centrifugation at 1,900 rpm. The supernatant was added to 20% Na_2CO_3 and 4% phenol and left to stand for 30 min. Absorbance was measured at 630 nm. ANH activity was calculated by comparison with a standard curve of 4-aminophenol (3.125-31.25 µM).

Assessment of erythromycin N-demethylation: Erythromycin *N*-demethylation (ENDM) was performed as previously described[14]. Microsomes were mixed with 10 mM erythromycin, 150 mM $MgCl_2$ and 10 mM NADPH. The reaction mixture was incubated at 37°C for 20 min. And then 12.5% trichloroacetic acid was added to the mixture, followed by centrifugation at 1,900 rpm for 15 min. The supernatant was mixed with Nash reagent and incubated at 50°C for 15 min. Absorbance was measured at 405 nm. The ENDM activity was calculated by comparison with a standard curve of formaldehyde (0-200 µM).

Determination of mRNA expression by RT-qPCR: Total RNA was extracted as previously described by Tatiya-Aphiradee[15]. Total RNA (1 ng) was converted to cDNA by ReverTraAce® (Toyobo®, Japan) before amplification with specific primers and/or probe (Table 1) by qPCR (CFX96, Bio-rad®, California, USA). The ΔΔCt method was applied to calculate mRNA expression of target genes and expression was compared with the glyceraldehyde 3-phosphate dehydrogenase (*Gapdh*) reference gene[16].

Statistical analysis: The results are expressed as Mean±Standard deviation. One-way ANOVA with Tukey's *post hoc* test was carried out using IBM SPSS Statistics (Ver. 26, Armonk, New York, USA) with a significant difference of $p<0.05$.

Table 1: Primers and probe sequences of the target genes

Genes	Forward primer (5'→3')	Reverse primer (5'→3')	Annealing temperature (°C)
Cyp1a1	GAC ATT TGA GAA GGG CCA CAT C	CCA AAG AGG TCC AAA ACA ATC G	60.0
	[Probe] FAM-CGA GAA TGC CAA TGT CCA GCT GTC A-TAMRA		
Cyp1a2	AAG ATC CAT GAG GAG CTG GA	TCC CCA ATG CAC CGG CGC TTT CC	48.0
Cyp2b9/10	CTC TTC CAG TGC ATC AC	CAA TGT AGT CGA GGA GTT CC	60.0
Cyp2c29	ATC TGG TCG TGT TCC TAG CG	AGT AGG CTT TGA GCC CAA ATA C	50.0
Cyp2d9	ATT CTT GTT GCC CCC TCT CC	TGG CAG GAA ACT GCC CTA CA	60.4
Cyp2e1	TCC CTA AGT ATC CTC CGT GA	GTA ATC GAA GCG TTT GTT GA	50.0
Cyp3a11	TTT GGT AAA GTA CTT GAG GCA GA	CTG GGT TGT TGA GGG AAT C	64.0
Cyp3a13	TGT GCT GGC TAT CAC AGA TCC	AAA TAC CCA CTG GAC CAA AGC	55.0
Gapdh	CCT CGT CCC GTA GAC AAA ATG	TGA AGG GGT CGT TGA TGG C	57.4

RESULTS AND DISCUSSION

Effects of GM pericarp extract and MGS on *Cyp1a1* and *Cyp1a2* expression in the mouse livers: The DSS induction resulted in a significant decrease in EROD (Fig. 1a) and MROD (Fig. 1b) activities, which are responsive reactions for *Cyp1a1* and *Cyp1a2*, respectively, in the mouse livers. Besides, expression of both *Cyp1a1* (Fig. 1c) and *Cyp1a2* (Fig. 1d) mRNAs were extensively suppressed after DSS induction. The GM pericarp extract and MGS raised both EROD and MROD activities comparable to the control. Correspondingly, the expression of *Cyp1a1* and *Cyp1a2* mRNAs was returned to the level similar to the control after GM pericarp extract and MGS treatments. The SUL reassembly demonstrated a consequence as GM pericarp extract and MGS (Fig. 1a-d). These observations were consistent with previous studies[17-19]. Expression of *Cyp1a2* mRNA was lessened in male ICR mice accessed to 3.5% DSS-mixed drinking water for 10 days[17] and a decrease in CYP1A2 activity was noted in 5% DSS-induced acute colitis for 7 days in Sprague-Dawley rats[18]. Nevertheless, aqueous extract of GM pericarp slightly inhibited CYP1A2 expression in commercial pooled human liver microsomes[19].

Regarding aryl hydrocarbon receptor (AhR)-mediated CYP1A regulation, AhR expression has previously been shown to be suppressed in IBD patients[20] and GM has been shown to up-regulate the expression of AhR protein[21]. This suggested that GM can restore the regulation of CYP1A expression.

Effects of GM pericarp extract and MGS on *Cyp2b9/10*, *Cyp2e1*, *Cyp2c29* and *Cyp2d9* expression in mouse livers: The DSS induction significantly reduced PROD (Fig. 2a) and BROD (Fig. 2b) activities, which are the responsive reactions for *Cyp2b9/10*, in the mouse livers. Correspondingly, the expression of *Cyp2b9/10* mRNA was significantly down-regulated by DSS induction (Fig. 2c). The GM pericarp extract and MGS extensively increased both the activities of PROD and BROD and the expression of *Cyp2b9/10* as effectively as SUL, to levels comparable to the control (Fig. 2a-c). The ANH activity, the responsive reaction for *Cyp2e1*, was extensively lessened after DSS induction (Fig. 3a), which accords with the decline in DSS-induced *Cyp2e1* expression (Fig. 3b). Both ANH activity and *Cyp2e1* mRNA expression was restored to control levels by GM pericarp extract, MGS and SUL. Finally, the expression of *Cyp2c29* (Fig. 3c) and *Cyp2d9* (Fig. 3d) was extensively suppressed after DSS induction and restored to levels comparable to the control by all treatments, namely GM pericarp extract, MGS and SUL.

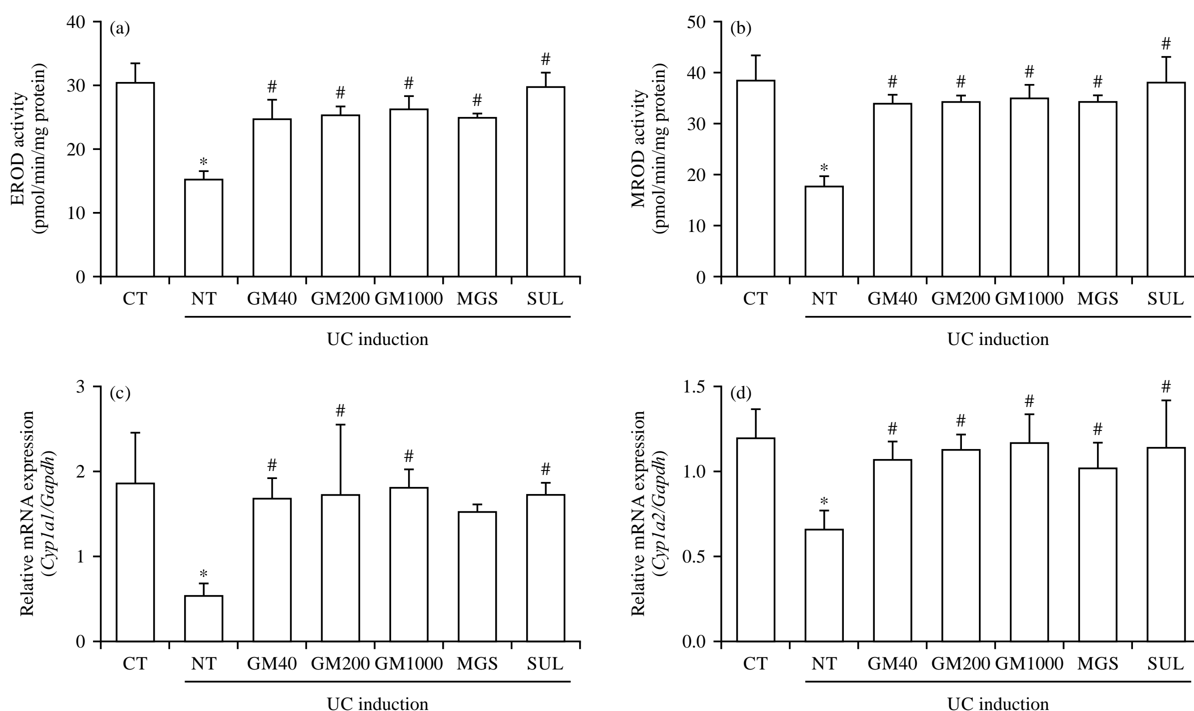

Fig. 1(a-d): Effect of GM pericarp extract and MGS on (a) ethoxyresorufin *O*-deethylase (EROD), (b) methoxyresorufin *O*-demethylase (MROD) activity and relative mRNA expression of (c) *Cyp1a1/Gapdh* and (d) *Cyp1a2/Gapdh* in dextran sulfate sodium-induced ulcerative colitis (UC) in mouse livers

CT: Control, NT: Non-treatment, GM: GM pericarp extract, MGS: α-mangostin, SUL: Sulfasalazine, *p<0.05 vs. CT and #p<0.05 vs. NT

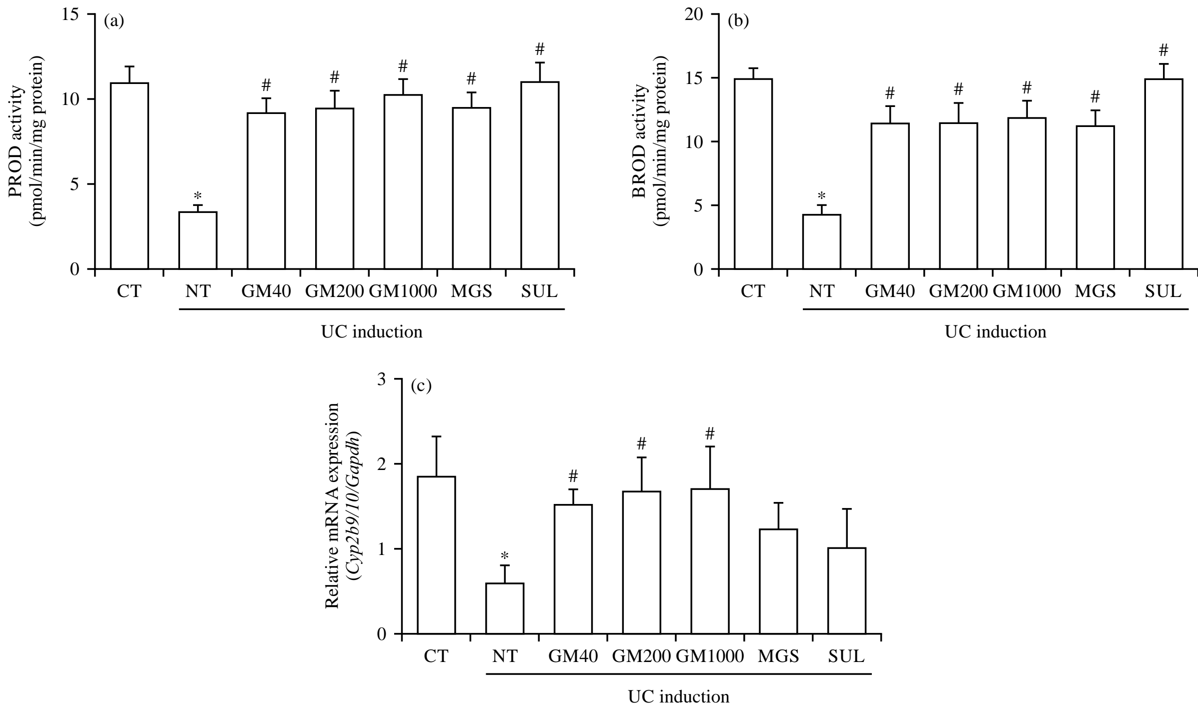

Fig. 2(a-c): Effect of GM pericarp extract and MGS on (a) penthoxyresorufin *O*-dealkylase (PROD), (b) benzyloxyresorufin *O*-dealkylase (BROD) activity and relative mRNA expression of (c) *Cyp2b9/10/Gapdh* in dextran sulfate sodium-induced ulcerative colitis (UC) in mouse livers

CT: Control, NT: Non-treatment, GM: GM pericarp extract, MGS: α-mangostin, SUL: Sulfasalazine, *p<0.05 vs. CT and #p<0.05 vs. NT

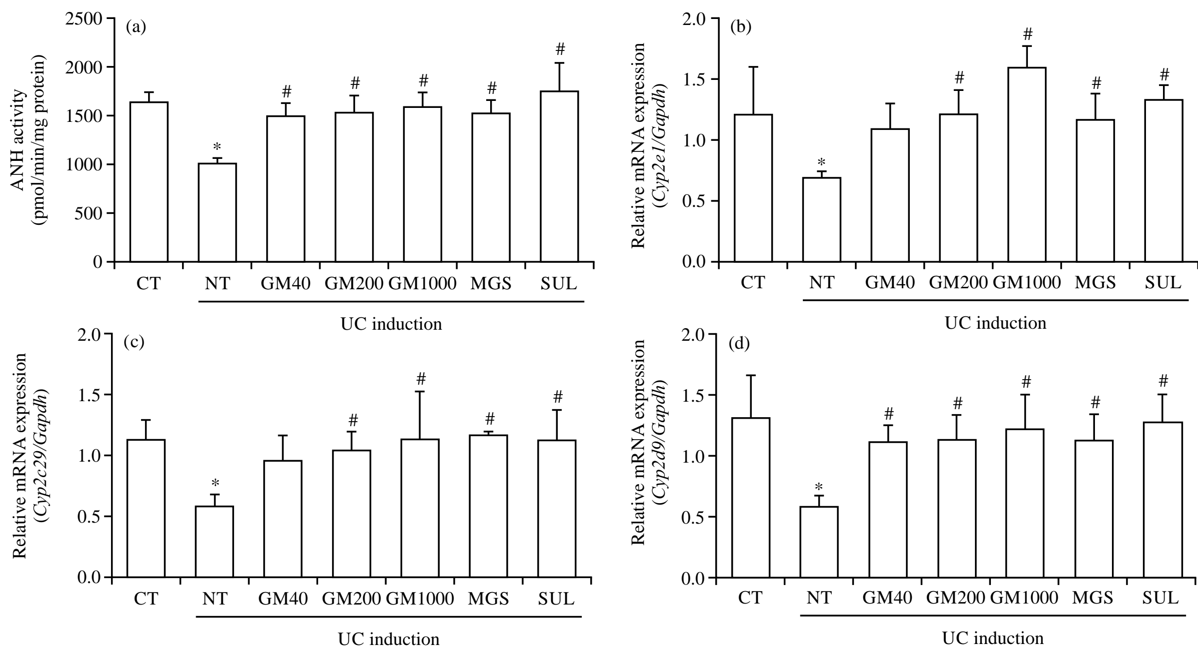

Fig. 3(a-d): Effect of GM pericarp extract and MGS on, (a) aniline hydroxylase activity (ANH) and relative mRNA expression of (b) *Cyp2e1/Gapdh*, (c) *Cyp2c29/Gapdh* and (d) *Cyp2d9/Gapdh* in dextran sulfate sodium-induced ulcerative colitis (UC) in mouse livers

CT: Control, NT: Non-treatment, GM: GM pericarp extract, MGS: α-mangostin, SUL: Sulfasalazine, *p<0.05 vs. CT and #p<0.05 vs. NT

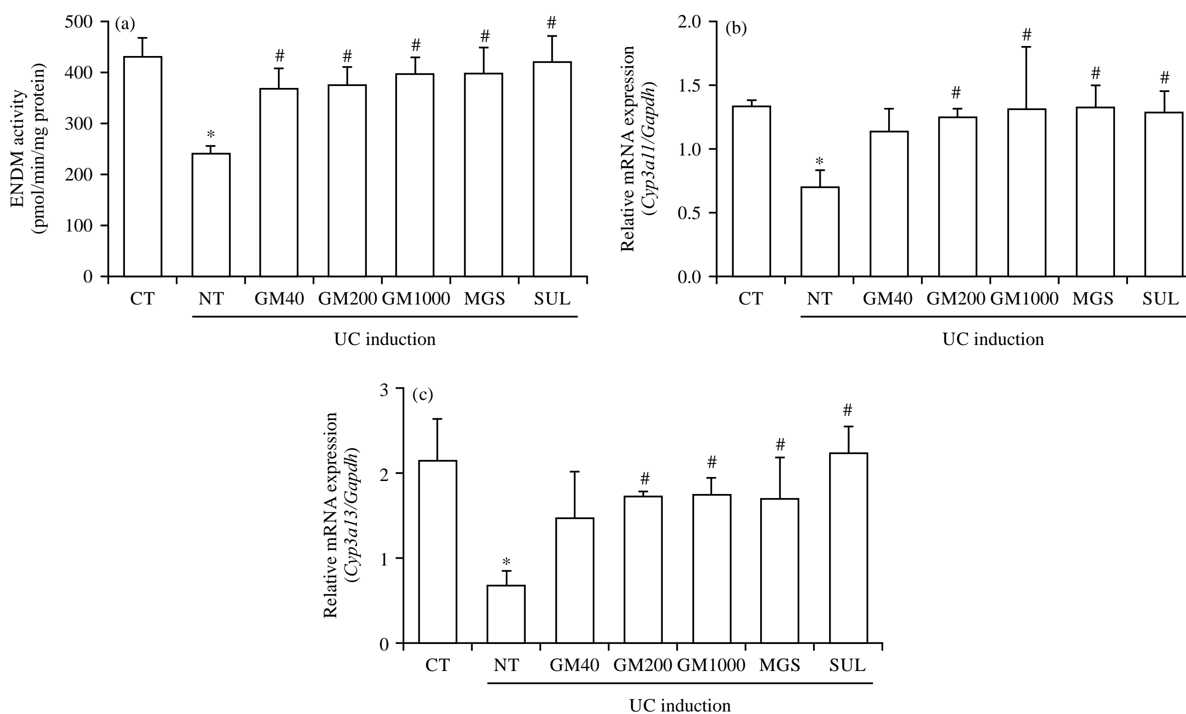

Fig. 4(a-c): Effect of GM pericarp extract and MGS on (a) erythromycin *N*-demethylase (ENDM) activity and relative mRNA expression, (b) *Cyp3a11/Gapdh* and (c) *Cyp3a13/Gapdh* in dextran sulfate sodium-induced ulcerative colitis (UC) in mouse livers

CT: Control, NT: Non-treatment, GM: GM pericarp extract, MGS: α-mangostin, SUL: Sulfasalazine, *$p<0.05$ vs. CT and $^{\#}p<0.05$ vs. NT

These findings correspond to previous reports showing the down-regulation of *Cyp2c29*, *Cyp2d9* and *Cyp2e1* expression in ICR mice given 3.5% DSS-drinking water[17] and the suppression of *CYP2B1*, *CYP2C6/11* and *CYP2E1* mRNAs in Sprague-Dawley rats with 5% DSS-induced acute UC[18]. In humans, patients with severe mucosal inflammation were previously found to have lower levels of CYP2E1 mRNA expression[22], whilst GM pericarp extracts improved expression of CYP2D6 and CYP2E1 in pooled human liver microsomes[19].

The DSS causes inflammation in the liver[15,17,23]. Up-regulation of inflammatory cytokines, namely tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6, was seen in the livers of male ICR mice receiving 3.5% DSS-drinking water, indicating hepatic inflammation[17]. In turn, the IL-1β and IL-6 inflammatory cytokines suppressed transcriptional regulation of CYP2C11 mRNA in male Sprague-Dawley rat hepatocytes[24] and IL-6 was also shown to down-regulate the constitutive androstane receptor (CAR), the nuclear receptor that regulates mouse Cyp2b9/10 and *Cyp2c29* expression[25]. Hepatic inflammation has also been reported to reduce levels of Hepatocyte Nuclear Factor-4α (HNF-4α), HNF-1α and HNF-3β in rat livers and HNF-4α and HNF-1α are known to activate *Cyp2d9* and *Cyp2e1* transcription, respectively[24]. Hence, DSS-mediated inflammation down-regulated the expression of murine hepatic CYP mRNAs via several nuclear receptor-related pathways[17,18].

The GM pericarp extract and MGS have been shown to lessen inflammation by suppressing TNF-α and IL-1β inflammatory cytokines via inhibition of NF-κB activation and down-regulation of mitogen-activated protein kinase (MAPK) pathways[15,26,27]. The NF-κB is an important transcription factor existing in a cytoplasmic complex with its inhibitor protein IκB before activation[28]. Phosphorylation of IκB activates nuclear translocation of NF-κB, thereby inducing transcription of a series of inflammatory genes[29,30]. The GM pericarp extract and MGS suppressed NF-κB in DSS-induced UC and reduced inflammation[26,27]. MAPK responds to pro-inflammatory cytokines to induce transcription and translation of other inflammatory mediators to increase inflammation[31,32]. The GM also suppressed the MAPK inflammatory pathway in DSS-induced UC to decrease inflammation[15,27]. A study of DSS-induction of UC in ICR mice found that during a 10 days

period, DSS treatment elevated IL-1β, IL-6 and TNF-α expression, suppressed *Cyp2c29*, *Cyp2d9* and *Cyp2e1* expression and reduced nuclear translocation of the PXR and CAR receptors, indicating inflammation. Replacement of DSS with purified water then rapidly reduced expression of those pro-inflammatory cytokines, gradually increased *Cyp2c29, Cyp2d9* and *Cyp2e1* expression and normalized nuclear localization of PXR and CAR over a 40 days time period[17]. Therefore, the reduction of inflammation by GM pericarp extract and MGS potentially restored DSS-induced suppression of *Cyp2c29*, *Cyp2d9* and *Cyp2e1* expression in mouse livers. However, a study of any correlation between GM pericarp extract and MGS activity and the nuclear receptors CAR and PXR is unavailable to date.

Effects of GM pericarp extract and MGS on *Cyp3a11* and *Cyp3a13* expression in mouse livers: The ENDM activity is the responsive enzyme reaction for *Cyp3a11* and *Cyp3a13* in mouse livers. The UC induction with DSS significantly reduced ENDM activity (Fig. 4a). Correspondingly, the expression of *Cyp3a11* (Fig. 4b) and *Cyp3a13* (Fig. 4c) was significantly suppressed after UC induction. The GM pericarp extract and MGS extensively increased ENDM activity and restored *Cyp3a11* and *Cyp3a13* expression to levels similar to those seen for SUL and the control.

Suppression of *Cyp3a11* mRNA expression has been observed in C57BL/6 mice receiving 5% DSS mixed-drinking water for 7 days[33] and ICR mice administered 3.5% DSS for 10 days[17]. In addition, a reduction in CYP3A1 and CYP3A2 activities was noted in DSS-treated Sprague-Dawley rats[18]. Patients with violent mucosal inflammation demonstrated a decrement in *CYP3A4* expression[22] and suppression of CAR and RXR (retinoid X receptor) mediated expression of *Cyp3a11* and *Cyp3a13* was observed in C57BL/6 mouse livers following induction of IL-6 in human hepatocytes[25,34]. In addition, the immunosuppressive drug cyclosporin that is recommended to treat severe UC is a substrate of CYP2C9, CYP3A4 and CYP3A5. The GM pericarp extract and MGS restored *Cyp3a11* and *Cyp3a13* expression through a decrease in inflammatory cytokines, inhibition of NF-κB activation and down-regulation of the MAPK pathway[15,26,27]. Hence, following GM pericarp extract and MGS-receded inflammation, the AhR, CAR, PXR and RXR nuclear receptors could be restored, which was subsequently associated with conventional CYP regulation.

CONCLUSION

The DSS modified the major CYP profiles in the liver, an EIM of UC. The GM pericarp extract and MGS restored the mRNA expression of all investigated CYPs and their responsive enzyme activities in the livers of DSS-induced UC mice to levels comparable to the control and parallel to the effects of the anti-inflammatory control SUL. Therefore, GM pericarp extract and MGS are worthy of development as novel alternative health supplements for UC therapy.

SIGNIFICANCE STATEMENT

This study discovered that besides the intestine, DSS caused lesions in the liver, an EIM of UC. The mRNA profiles of major CYPs, namely *Cyp1a1*, *Cyp1a2*, *Cyp2b9/10*, *Cyp2c29*, *Cyp2d9*, *Cyp2e1*, *Cyp3a11* and *Cyp3a13*, were down-regulated, in accord with their responsive enzyme activities, CYP1A1, CYP1A2, CYP2B9/10, CYP2E1 and CYP3A, respectively, after the UC induction. The GM pericarp extract and MGS completely restored both the mRNA level and the enzyme activity to levels comparable to the control and parallel to the effects of the anti-inflammatory control SUL. Therefore, GM is a promising therapy to restore UC-modified hepatic CYP profiles.

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