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Mango (*Mangifera indica* L.) polyphenols reduce IL-8, GRO, and GM-SCF plasma levels and increase *Lactobacillus* species in a pilot study in patients with inflammatory bowel disease

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Abbreviations:

5-ASA; 5-aminosalicylic acid

AMPK; AMP-activated protein kinase

AUC; area under the curve

CD; Crohn's disease

CRP; C-reactive protein

COX-2; cyclooxygenase-2

DSS; dextran sulfate sodium

E. coli; Escherichia coli

ELISA; enzyme-linked immunosorbent assay

GM-CSF; granulocyte macrophage colony-stimulating factor

GMP; Good Manufacturing Practices

GRO; monocyte growth-regulated oncogene

HPLC-PDA; high performance liquid chromatography equipped with photodiode array detector

IBD; Inflammatory bowel disease

IL-1β; interleukin-1 beta

IL-6; interleukin-6

IL-7; interleukin-7

IL-8; interleukin-8

IL-10; interleukin-10

IL-17A; interleukin-17A

IND; Investigational New Drug

IP-10; interferon gamma-induced protein-10

L. lactis; Lactococcus lactis

L. plantarum; Lactobacillus plantarum

L. reuteri; Lactobacillus reuteri

MCP-1; monocyte chemoattractant protein-1

MIP-1β; macrophage inflammatory protein-1 beta

qPCR; quantitative PCR

rRNA; ribosomal RNA

SCCAI; Simple Clinical Colitis Activity Index

SCFAs; short-chain fatty acids

SIBDQ; Short Inflammatory Bowel Disease Questionnaire

TNF-α; tumor necrosis factor alpha

UC; ulcerative colitis

Abstract

Inflammatory bowel disease (IBD) characterized by chronic intestinal inflammation and intestinal microbial dysbiosis present a major risk factor in the development of colorectal cancer. Previously, dietary polyphenols from mango (*Mangifera indica* L.) such as gallotannins and gallic acid have been shown to mitigate intestinal inflammation and carcinogenesis, as well as modulate intestinal microbial composition. To further translate findings from preclinical models, we hypothesized that mango polyphenols possess anti-inflammatory and microbiome-modulatory activities and may improve symptoms of IBD, reduce biomarkers for inflammation and modulate the intestinal microbiome when administered as an adjuvant treatment in combination with conventional medications in patients with mild to moderate IBD. In this study, ten participants received a daily dose of 200-400 g of mango pulp for 8 weeks (NCT02227602). Mango intake significantly improved the primary outcome Simple Clinical Colitis Activity Index (SCCAI) score and decreased the plasma levels of pro-inflammatory cytokines including interleukin-8 (IL-8), growth-regulated oncogene (GRO) and granulocyte macrophage colony-stimulating factor (GM-CSF) by 16.2% (p=0.0475), 25.0% (p=0.0375) and 28.6% (p=0.0485), all factors related to neutrophil-induced inflammation, respectively. Mango intake beneficially altered fecal microbial composition by significantly increasing the abundance of *Lactobacillus spp., Lactobacillus. plantarum*, *Lactobacillus. reuteri* and *Lactobacillus. lactis,* which was accompanied by increased fecal butyric acid production. Therefore, enriching diet with mango fruits or potentially other gallotannin-rich foods seems to be a promising adjuvant therapy combined with conventional medications in the management of IBD via reducing biomarkers of inflammation and modulating the intestinal microbiota.

Keywords: Mango polyphenols, inflammatory bowel disease, translational human clinical trial, inflammatory cytokines, fecal microbiota

1. Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory disorders of the digestive tract [1]. Previous studies indicate that IBD affects 1.5 million individuals in the USA, 2.2 million people in Europe, and many more in other countries [2]. IBD presents a major risk factor in the development of gastrointestinal malignancies [3] and can develop to colorectal cancer over a period of 10-15 years. This offers an extended window of opportunity for preventive measures [4].

Multiple studies have demonstrated the intestinal health benefits of naturally occurring phytochemicals in fruits and vegetables including polyphenols [5]. Polyphenols, such as quercetin, flavone, curcumin and tea polyphenols have been shown to exert anti-inflammatory activities but also influence endogenous antioxidant enzyme activity, suppress proliferation and enhance apoptosis in the colon *in vitro* and *in vivo* studies where intestinal inflammation or colon carcinogenesis were prevented [6-9]. Our previous investigations indicate that polyphenols from pomegranate, mango and other fruits prevent chemical-induced intestinal inflammation and carcinogenesis [10-13]. However, only few human clinical studies have examined the mitigating activities of dietary polyphenols in IBD. A previous study with patients suffering from IBD investigated anti-inflammatory effects of the oral intake of curcumin where a total of 99 patients indicated curcumin co-administered with mainstream therapy (sulfasalazine or mesalamine derivatives or corticosteroids) improved patients' symptoms and allowed a decrease in the dosage of corticosteroids or 5-aminosalicylic acid (5-ASA) derivatives, or even stopping the

medication [14]. Co-administration of curcumin with conventional drugs was considered effective, well tolerated and safe in maintaining remission, preventing relapse and improving clinical activity indices [15].

Polyphenols identified in the edible part of mango (*Mangifera indica* L.) have been previously characterized and include flavonoids such as quercetin and kaempferol glycosides, phenolic acids, predominantly gallic acid, galloyl glycosides, in part polymerized, and in some varieties mangiferin [16]. Overall, previous studies have demonstrated that mango polyphenols possess anti-inflammatory, anti-obesogenic and anti-cancer activities [17-21], indicating their potential in modulating risk factors for intestinal disease. In preclinical studies, mango beverage intake attenuated inflammation in rats with dextran sulfate sodium (DSS)-induced colitis, possibly attributable to the production of pyrogallol, a major microbial metabolite of gallotannins that has been found to modulate inflammatory biomarkers via the AMP-activated protein kinase (AMPK)-associated pathways [12, 19, 21].

Intestinal microbial dysbiosis and its associated changes in immune response are considered major factors in the pathogenesis of IBD. Alterations of intestinal microbiota in human studies reveal that patients with IBD exhibited lower microbial diversity and abundance of *Firmicutes* and *Bacteroides*, and higher abundance of *Gammaproteobacteria* compared with healthy individuals [22, 23]. Some groups of intestinal microbiota may protect the host from mucosal inflammation via the production of short-chain fatty acids (SCFAs), such as *Lactobacillus, Bifidobacterium* and *Faecalibacterium* [24, 25], whereas the pathogenic bacteria *Escherichia coli* (*E. coli*) exacerbated intestinal disease activity [26]. Therefore, alteration of the

microbial signatures of IBD patients may improve associated intestinal inflammation. Unveiling the role of polyphenols in the manipulation of intestinal microbiota may benefit the application of polyphenols as a therapeutic strategy in reducing intestinal inflammation associated with IBD. In rats with colitis, the intake of mango beverage induced the production of SCFAs by increasing the abundance of the SCFAs-producing intestinal microbiota [12]. However, translation of promising preclinical findings into clinical therapies seems to be limited based on the lack of evidence in human clinical trials with IBD patients. In this study, mango polyphenols were administered as an adjuvant therapy with commonly used medications for IBD including mesalamine, balsalazide and olsalazine so that study participants would not have to deviate from their drug regimen.

In this study, it was hypothesized that mango polyphenols may reduce symptoms of IBD, biomarkers of inflammation and modulate the intestinal microbiome when administered as an adjuvant treatment in combination with conventional medications in patients with IBD. The objective of this pilot study was to investigate the anti-inflammatory activities and modulation of the intestinal microbiome by the daily consumption of mangos in a population with mild-moderate IBD.

2. Methods and materials

2.1. Study participants

Participants, aged 18-75 years, exhibiting IBD (mild or moderate CD or UC) were recruited at the Ertan Digestive Disease Center or Texas A&M University for this study. The

inclusion criteria included: Current or previous (past 6 months) treatment with IBD medications; currently being on a stable drug-regiment for at least 3 weeks before the beginning of this study's treatment phase. The exclusion criteria included: history of recurrent hospitalizations within the last 6 months; known lactose intolerance, gluten sensitivity or celiac disease; planned or scheduled IBD-related surgery; current IBD-related intestinal stricture; binge drinking; smoking; current pregnancy or lactation; allergy against mangos. Approval for human subject research was obtained from the Texas A&M University Institutional Review Board (2016-0223F and 2013-0541F). The protocol was registered at clinicaltrials.gov (NCT02227602) and informed consent was obtained from participants before any intervention. In order to use mango fruits as adjuvant therapy with other commonly used drugs in the treatment of IBD, an Investigational New Drug (IND) registration with the FDA was required and IND# 111797 was assigned to this study.

2.2. Study design and dietary intervention

Mangos (cv. Keitt) were allowed to fully ripen to ripening stage 4 and processed according to Good Manufacturing Practices (GMP) in the Department of Nutrition and Food Science, Texas A&M University. Briefly, mangos were peeled and deseeded. 400 g of mango pulps were vacuum-sealed in food storage bags and frozen at -20 ºC within 4 hours of processing until use [27]. Total phenolic content was quantified to be 190.36 mg of pro-gallic acid polyphenols including gallotannins, gallic acid and monogalloyl glucose in 400 g of mango pulp. A representative HPLC chromatogram was reported in our previous study [10, 11].

Participants were asked to include 200-400 g of mango pulp every day into their diets for 8 weeks. Participants were advised to increase their mango consumption slowly over the first week. Participants received a scale to weigh how much mango they consumed each time and were asked to record the exact amount consumed each day. Participants consumed their regular diet but reduced the intake of plant-based dietary supplements, which contain secondary plant compounds such as resveratrol, quercetin, tannins, and also reduced their carbohydrate-derived energy by the same amount supplied by mango pulp. Blood and stool samples were collected on the first and last study days. Dietary intake was assessed by a 3-day food record, performed on the first and last week of the study. Participants were asked to log all food and drinks they consume for three days. Data were analyzed using iProfile 3.0 (http://iprofile.wiley.com) and calculated as calories, fat, carbohydrates, dietary fiber and protein [18].

2.3. Assessment of the severity of IBD

In this study, the primary endpoint was defined as improvement of Simple Clinical Colitis Activity Index (SCCAI) [28] at end of treatment. Improvement of Short Inflammatory Bowel Disease Questionnaire (SIBDQ) [29] and biomarkers for inflammation in plasma were secondary endpoints. During all study visits, the severity of symptoms was assessed using the SIBDQ and SCCAI. Survey entries were compared, before and after the nutritional intervention for each participant.

2.4. Blood sample preparation and analysis

On the first and last study days (Week 0 and Week 8), 10 mL of fasting blood was collected, centrifuged and stored at -80 ºC until analysis. Plasma levels of inflammatory biomarkers were quantified using xMAP Multiplex Assay (Luminex 200, Luminex Corporation, Austin, TX) with magnetic beads acquired from EMD Millipore (Billerica, MA) according to the manufacturer's instructions [18]. These analytes included: interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), granulocyte macrophage colony-stimulating factor (GM-CSF), eotaxin, interleukin-8 (IL-8), interleukin-17A (IL-17A), interferon gamma-induced protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), growth-regulated oncogene (GRO), interleukin-7 (IL-7), and macrophage inflammatory protein-1 beta (MIP-1β).

2.5. Plasma endotoxin analysis

Plasma endotoxin concentration was measured using an Endpoint Chromogenic LAL Assay kit (Lonza, Walkersville, MD) according to the manufacturer's instructions. Samples were heated at 37 °C for 10 min to inactivate plasma proteins. And then, a substrate solution was added to the samples at 37 °C for 6 min. To remove background, negative controls of each sample without adding the substrate were prepared. After adding the stop reagent, the absorbance was measured at 410nm. The value of each negative control was subtracted from sample values [30].

2.6. Composition of fecal microbiota – Quantitative PCR assay

Quantitative PCR (qPCR) targeting 16S ribosomal RNA (rRNA) genes is a useful tool for quantifying very low concentrations of bacterial targets in fecal samples [31]. Bacterial DNA was extracted from 200 mg of fecal samples using a commercial DNA extraction kit (QIAGEN, Germany) according to the manufacturer's instructions [31]. qPCR assays for screening selected bacterial groups were performed (**Table 1**). Especially, *Lactobacillus plantarum* (*L. plantarum*) and *Lactococcus lactis* (*L. lactis*) were selected because they are well-known producers of tannase [32]. In addition, for creating standard curves, PCR was performed for getting the CT values of 10-fold dilutions of each DNA template (10 ng/ul), and the bacterial DNA templates were extracted from the specific bacteria obtained from the USDA-Agricultural Research Service. The qPCR results are expressed as log amount of DNA (pg of DNA template) for each particular bacterial group [34].

2.7. Fecal short-chain fatty acid (SCFA) analysis

SCFAs were analyzed by a high-performance liquid chromatography equipped with photodiode array detector (HPLC-PDA) system using an Aminex HPX-87H strong cation-exchange resin column (300 × 7.8 mm) fitted with an ion exchange microguard refill cartridge (Bio-Rad, Hercules, CA). The HPLC-PDA system consists of a Water 2695 Separation Module (Waters, Milford, MA) equipped with a Water 2996 PDA. Samples (20 μL) were eluted isocratically with 5 mM sulfuric acid at 0.6 mL/min, and the column temperature was held at 50 °C. Sodium butyrate, acetate, propionate, and valerate were identified and quantified by comparing retention time and UV-Visible spectral data to standards [33].

2.8. Statistical analyses

Data were analyzed using Graphpad Prism 7.04 (GraphPad Software, Lo Jolla, CA). Normality test was performed: if data were normally distributed, a paired two-tail Student's *t* test was used; if data were non-normally distributed, a Wilcoxon signed-rank test was used. Data were considered statistically significant at $p < 0.05$. Results of biochemical parameters are presented as means ± SD, whereas results of assessment of IBD, SCFA and endotoxin levels are presented as means ± SE.

3. Results

3.1 Demographic characteristics and dietary intake

Out of 14 participants initially recruited in this study, ten participants (5 males and 5 females, 30.9 ± 11.0 years) completed the study, including 3 participants with CD and 7 with UC, and 4 participants dropped out due to time constraints or relocation (**Fig. 1.** and **Table 2**).

Participants' dietary intake of calories, carbohydrates, protein, fat and dietary fiber assessed by the 3-day food record is shown in **Table 3**. Daily mango intake seemed to have been associated with a significantly decreased fat intake (decreased by 22.6%, p=0.0403), also reflected in calorie intake (decreased by 11.9%, p=0.0391). No change was observed for other macronutrients and dietary fiber in this study **(Table 3)**.

3.2 Assessment of IBD and biochemical parameters

SIBDQ and SCCAI scores were evaluated during each study visit. Results showed 8 weeks of mango intake had no significant effect on SIBDQ scores in this study **(Fig. 2A).** Mango intake for 8 weeks significantly decreased the SCCAI score from 4.4 to 2.8 (p=0.0447) **(Fig. 2B)**, indicating alleviated severity of UC symptoms.

Levels of inflammatory biomarkers were assessed at Week 0 and Week 8 **(Table 4)**. The production of pro-inflammatory cytokines including IL-8, GRO and GM-CSF were significantly lowered by 16.2% (p=0.0475), 25.0% (p=0.0375) and 28.6% (p=0.0485), respectively, after 8 weeks of mango intake **(Table 4)**.

3.3 Fecal microbial composition, SCFA production and endotoxin levels

qPCR analysis for screening selected bacterial groups was performed to examine the changes in fecal microbial composition by mango intake **(Supplemental Fig. S1)**. At the genus level, eight weeks of mango intake increased levels of *Lactobacillus* **(Fig. 3A)** (p=0.0391). *Lactobacillus* species mitigated inflammation through enhancing the production of SCFAs by fermenting carbohydrate end-products [34]. At the species level, increased abundance was observed for tannase-producing bacteria including *L. plantarum* (p=0.0039) and *L. lactis* (p=0.0098) that can break down mango-derived gallotannins and release free gallic acid and pyrogallol [35], as well as *L. reuteri* (p=0.0371) **(Fig. 3A)**.

SCFAs are metabolites produced from undigested carbohydrates, fibers and polyphenols by intestinal microbiota [36]. In this study, after 8 weeks of mango intake, increased level of butyric acid (p=0.0472) was detected in fecal samples while no statistical significance was

observed for other SCFAs **(Fig. 3B)**. Systemic and intestinal inflammatory diseases are associated with increased LPS permeability and damaged epithelial barrier. LPS was identified as one causative factor in the pathogenesis of IBD [37]. Eight weeks of mango intake caused a trend towards lowered production of LPS in plasma (p=0.0808) but not significantly (p=0.05) **(Fig. 3C)**.

4. Discussion

This study investigated if mango polyphenols can be used as an adjuvant treatment in combination with conventional medications in patients with IBD. Findings in this study showed that 8 weeks of mango intake exert beneficial effects in slowing the progression and reducing the severity of IBD, some biomarkers for inflammation and had microbiome-modulatory activities. Therefore, our study hypothesis was partially confirmed.

In this study, daily mango intake seemed to have been associated with a slightly decreased calorie and fat intakes. In previous human clinical trials, only one study reported that 6 weeks of mango intake significantly lowered dietary intake of lean participants [18] while others reported mango intake induced a decreased trend of calorie intake of obese, as well as constipated participants [38, 39]. This calorie intake-lowering effect by polyphenol-rich food intake might be partly due to their ability in increasing hepatic fat oxidation that delivers signals to the appetite-regulating center of the brain in response to changes in liver energy status [40]. Dietary assessment by self-reported 3-day food record is a frequently used tool that is known for its limited reliability and validity [41]. These dietary intake data should be interpreted carefully

and there's a crucial need for high-quality study to assist in investigating the influence of dietary factors on food intake.

SIBDQ is a disease-specific questionnaire that measures quality of life in 4 domains, including bowel syndrome, emotional health, systemic systems and social functions, to define health status in participants with IBD [42]. Results showed 8 weeks of mango intake had no significant effect on SIBDQ scores**.** SCCAI is a validated score to help assess the severity of participants with UC. In addition, this score was also applied to participants with Crohn's disease [43], as this score can be used to evaluate patient-reported symptoms based on the disease status without requiring the assessment of biopsies. Criteria for this evaluation instrument include bowel frequency, stool consistency, abdominal pain, anorexia, nausea/vomiting, extracolonic manifestations and important clinical signs (e.g., body temperature and blood in stool) [28]. Decreased SCCAI has been associated with decreased severity of UC [44, 45]. Mango intake for 8 weeks significantly improved the SCCAI score, but had no effect on SIBDQ score, indicating alleviated severity of UC symptoms. The effect of mango intake on the Crohn's disease seemed to be limited and remained to be investigated in future studies in participants with Crohn's disease only.

Levels of inflammatory biomarkers including IL-8, GRO and GM-CSF were significantly lowered after 8 weeks of mango intake. These cytokines are associated with neutrophil-induced inflammation and have been shown to increase in individuals with inflammatory bowel disease [46-48]. Mucosal *E. coli* found in IBD promotes the release of IL-8 from colon epithelial cells, which can contribute to the pathological process of gastrointestinal inflammation and

malignancies [46, 47]. In line with the findings from the current study, mango intake for 6 weeks significantly lowered the plasma area under the curve (AUC) of IL-8 in obese participants [18]. GRO is an oncogenic-related peptide that plays a key role in the pathogenesis of IBD and is believed to involve in the development of colon cancer in IBD patients and to be correlated to C-reactive protein (CRP) and IL-6 in patients with IBD [49]. Additionally, both IL-8 and GRO are involved in neutrophil attraction through binding to the receptor, CXCR2 [50]. In a previous study, blocking of CXCR2 by tea polyphenols showed therapeutic effects in reducing neutrophil concentration in intestinal inflammation [51]. GM-CSF is considered a biomarker reflecting improvement and remission of IBD in clinical trials [52] and has been associated with delayed clearance of neutrophils in inflamed intestinal tissue [48, 53]. Gallic acid, a major polyphenol in mango fruits, decreased inflammation and tissue damage mediated by neutrophil activation *in vitro* [54]. Reducing the production of IL-8, GRO and GM-CSF by mango polyphenols might be a therapeutic strategy in reducing neutrophil-induced inflammation, therefore, the alleviation or treatment of IBD. Further understanding of the role of IL-8/GRO/GM-CSF signaling in IBD and the modulatory effects exerted by mango polyphenols may provide novel adjuvant therapies in the treatment of IBD.

Mango intake beneficially altered fecal microbial composition by significantly increasing the abundance of *Lactobacillus spp., Lactobacillus. plantarum*, *Lactobacillus. reuteri* and *Lactobacillus. lactis,* which was accompanied by increased fecal butyric acid production. Both gallic acid and pyrogallol have shown potent anti-inflammatory activities in reducing inflammation in animals with chemical-induced colitis [10, 55]. In addition, *L. plantarum*, *L. reuteri* and *L. lactis* are known to possess anti-inflammatory activity in the treatment of colitis by

down-regulating the secretion of TNF-α and cyclooxygenase-2 (COX-2) and up-regulating IL-10 [56, 57]. SCFAs including acetic acid, propionic acid, butyric acid and valeric acid are metabolites produced when dietary fiber is fermented in the colon [36]. Compelling evidence has shown that some SCFAs, particular butyric acid, exert a protective role in maintaining the mucosal barrier in the colon, therefore helping restore the mucosal permeability in IBD [58]. This has contributed to the discovery of new therapy beyond conventional drugs in the treatment of IBD [59]. In this study, 8 weeks of mango intake significantly increased fecal level of butyric acid, which may result in enhanced mucosal barrier function.

Although the improvement of SCCAI was statistically significant, it is important to consider if it is also clinically meaningful. It is accepted that a remission score of <2.5 at the endpoints is considered to be clinically relevant [60]. However, in this study, the average SCCAI score after 8-week mango intake was 2.8. Therefore, the results should be interpreted with caution. Potential weaknesses of this pilot study include the low number of participants (n=10) that may result in lower statistical power and findings remain to be confirmed in a larger scale human clinical trial. However, even in this small pilot study, several biomarkers and disease status seem to have been significantly affected by the study treatment and this provides encouraging data for future, larger human clinical studies. Overall, the total amount of calories reported by participants was hypocaloric for most participants at 1721 kcal-1516 kcal over the 8 week-intervention period; however, there were no changes in body weight observed. Underreporting of caloric intake on food frequency questionnaires has previously been discussed and is a known limitation of assessing dietary intake in study participants [61]. Increased SCFAs production achieved by increased fiber intake contained in mango fruits may have contributed to the

modulation of SCFA production. However, limited evidence regarding the efficacy and safety of dietary fiber alone in the management of IBD is currently available [62, 63] and fiber treatment is known to cause adverse effects in individuals with IBD [64]. Initially, the planned design for this study included a fiber-placebo group in a randomized, open label, cross-over design. However, when most interested patients indicated that they would not consent to any fiber-treatment arm due to anticipated adverse effects, and enrollment was significantly hampered, the fiber arm was eliminated from this pilot-study. Future clinical studies are planned including a suitable control-arm. Additionally, fecal calprotectin as an indicator of mucosal inflammation and colonoscopic endpoints as key indicators of mucosal healing would increase clinical relevance of future study designs [65].

In conclusion, findings in this study indicate that 8 weeks of mango intake exert beneficial effects in slowing the progression and reducing the severity of IBD by lowering the SCCAI score associated with improved quality of life. Additionally, mango intake mitigates intestinal inflammation by reducing the production of pro-inflammatory cytokines (IL-8, GRO and GM-CSF) that are associated with neutrophil-induced inflammation, increasing the abundance of beneficial bacteria that may enhance the production of SCFAs, particularly butyric acid. A gallotannin-enriched diet may serve as a novel adjuvant therapy in combination with conventional therapies that would ameliorate symptoms and improve the outcomes of patients with IBD.

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Table 1. Primers used for quantitative PCR analysis targeting specific fecal microbiota.

Target	Forward sequence	Reverse sequence	Reference
Bacteroidetes	CCGGAWTYATTGGGTTTAAAGGG	GGTAAGGTTCCTCGCGTA	*Muhling et al. (2008)*
Firmicutes	TGAAACTYAAAGGAATTGACG	ACCATGCACCACCTGTC	*Bacchetti De Gregoris et al. (2011)*
Bifidobacterium Spp.	TCGCGTCYGGTGTGAAAG	CCACATCCAGCRTCCAC	*Malinen et al. (2005)*
Faecalibacterium Spp.	GAAGGCGGCCTACTGGGCAC	GTGCAGGCGAGTTGCAGCCT	*Garcia-Mazcorro et al. (2012)*
Lactobacillus spp.	AGCAGTAGGGAATCTTCCA	CACCGCTACACATGGAG	*Malinen et al. (2005)*
Akkermansia muciniphila	CAGCACGTGAAGGTGGGGAC	CCTTGCGGTTGGCTTCAGAT	*Collado et al. (2007)*
Butyrivibrio Fibrisolvens	ACACACCGCCCGTCACA	TCCTTACGGTTGGGTCACAGA	*Klieve et al. (2003)*
Clostridium butyricum	GTGCCGCCGCTAACGCATTAAGTAT	ACCATGCACCACCTGTCTTCCTGCC	*Bartosch et al. (2004)*
Clostridium leptum	GCACAAGCAGTGGAGT	CTTCCTCCGTTTTGTCAA	*Matsuki et al. (2004)*
Crostridium coccoides	AAATGACGGTACCTGACTAA	CTTTGAGTTTCATTCTTGCGAA	*Matsuki et al. (2002)*
E. coli	CATGCCGCGTGTATGAAGAA	CGGGTAACGTCAATGAGCAAA	*Huijsdens et al. (2002)*
Faecalibacterium prausnitzii	GATGGCCTCGCGTCCGATTAG	CCGAAGACCTTCTTCCTCC	*Bartosch et al. (2004)*
Lactococcus lactis	TGAAGAATTGATGGAACTCG	CATTGTGGTTCACCGTTC	*Achilleos et al. (2013)*
Lactobacillus plantarum	CTCTGGTATTGATTGGTGCTTGCAT	GTTCGCCACTCACTCAAATGTAAA	*Matsuda et al. (2009)*
Lactobacillus reuteri	ACCTGATTGACGATGGATCACCAGT	CCACCTTCCTCCGGTTTGTCA	*Kwon et al. (2004)*
Streptococcus gallolyticus	CAATGACAATTCACCATGA	TTGGTGCTTTTCCTTGTG	*Sasaki et al. (2004)*

Table 2. Study demographics.

Parameter	Population (n = 10)
Gender	5 males; 5 females
Age (years)	30.9 ± 11.0
Weight (kg)	74.5 ± 28.6
BMI (kg/m^2)	25.9 ± 10.0
Mango Intake (g/day)	289.07 ± 60.96
Disease	Crohn's disease n=3 Ulcerative colitis n=7

All data are expressed in mean ± SD.

Table 3. Dietary intake assessed by a 3-day food record.

Variable		Week 0	Week 8	Delta	*p*-value[a]
Calories	Mean	1721	1516	-204.7	**0.0391***
(kcal)	SD	589.7	503.1		
Carbohydrates	Mean	185.6	184.4	-1.19	0.9421
(g)	SD	49.41	50.46		
Protein	Mean	68.05	57.9	-10.14	0.1099
(g)	SD	30.75	19.07		
Fat	Mean	74.19	57.43	-16.76	**0.0403***
(g)	SD	36.27	29.52		
Dietary fiber	Mean	17.95	17.19	-0.7619	0.6418
(g)	SD	5.042	4.959		

All data are expressed in means ± SD. [a] p-values were obtained from paired Student's *t*-tests. * indicates significant difference ($p < 0.05$) between mean change (n=10).

Table 4. Levels of inflammatory biomarkers at Week 0 and Week 8.

Variable (pg/mL)		Week 0	Week 8	Delta	p-value[a]
IFN-γ	Mean	339.4	310	-29.39	0.3125[b]
	SD	878.4	790		
IL-1β	Mean	0.7405	0.8974	0.1569	0.0770
	SD	0.4451	0.6182		
IL-6	Mean	1	1.148	0.1476	0.4401
	SD	0.8502	1.021		
IL-8	Mean	49.37	41.36	-8.005	**0.0475***
	SD	86.66	77.82		
IL-10	Mean	26.22	25.28	-0.9404	0.7078
	SD	29.51	28.11		
TNF-α	Mean	1.389	1.97	0.5807	0.0979
	SD	1.176	1.724		
IL-7	Mean	36.65	55.32	18.67	0.3652
	SD	82.98	137.4		
IL-17A	Mean	34.9	40.21	5.316	0.5101
	SD	78.25	99.56		
Eotaxin	Mean	110.6	102.7	-7.962	0.6253
	SD	82.42	101.5		
MIP-1β	Mean	135.6	121.4	-14.26	0.2997
	SD	333.8	298		
IP-10	Mean	389.4	290.2	-99.13	0.3720
	SD	202.3	176.9		
MCP-1	Mean	200	279.4	79.39	0.9999[b]
	SD	94.51	371.3		
GRO	Mean	1264	947.7	-316.2	**0.0375***
	SD	524.3	398.9		
GM-CSF	Mean	133	94.94	-38.03	**0.0485***
	SD	222.4	181.6		

All data are expressed in means ± SD. [a] p-values were obtained from paired Student's *t*-tests or [b] Wilcoxon matched-pairs test. * indicates significant difference ($p < 0.05$) between mean change (n=10).

Figure legends

Fig. 1. CONSORT diagram for participation.

Fig. 2. Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and Simple Clinical Colitis Activity Index (SCCAI) in participants with inflammatory bowel disease at Week 0 and Week 8. (A) SIBDQ and (B) SCCAI scores of study participants. Mango intake for 8 weeks significantly decreased the SCCAI score (p=0.0447). Values are means ± SE. Data were considered statistically significant at $p < 0.05$ (Paired Student's *t*-tests; n = 10).

Fig. 3. Intestinal microbial composition, short chain fatty acids production and lipopolysaccharide levels in plasma in participants with inflammatory bowel disease at Week 0 and Week 8. (A) Quantitative real-time PCR results for selected bacterial groups. Mango intake significantly increased levels of *Lactobacillus* spp. (p=0.0391), *L. plantarum* (p=0.0039), *L. lactis* (p=0.0098) and *L. reuteri* (p=0.0371). Results are expressed as log amount of DNA (pg of DNA template). The whiskers are representative of the min-max range. Data were considered statistically significant at $p < 0.05$ (Wilcoxon matched-pairs test; n = 10). (B) Short chain fatty acids production including acetic acid, proprionic acid, butyric acid and valeric acid before and after 8 weeks of mango intake in participants with inflammatory bowel disease. Mango intake increased the fecal level of butyric acid (p=0.0472). Results are expressed in mmol/g of fecal dry contents. (C) Lipopolysaccharide levels in plasma. Results are expressed in EU/ml. Values are means ± SE. Data were considered statistically significant at $p < 0.05$ (Paired Student's *t*-tests; n = 10).

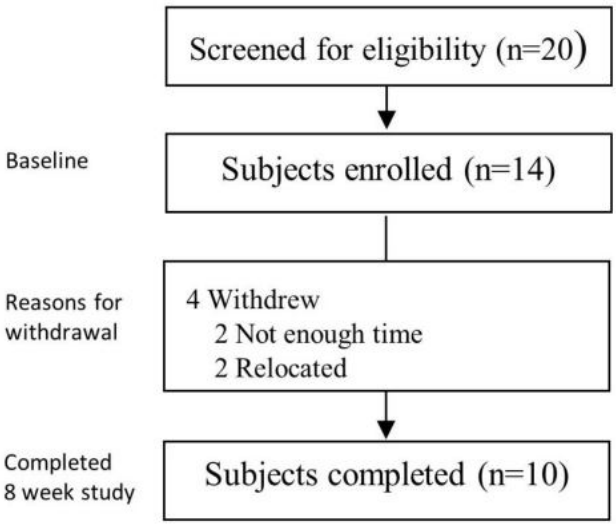

Fig. 1.

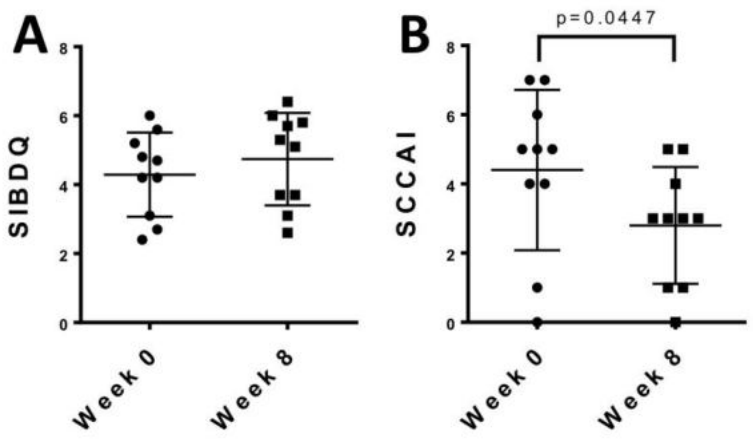

Fig. 2.

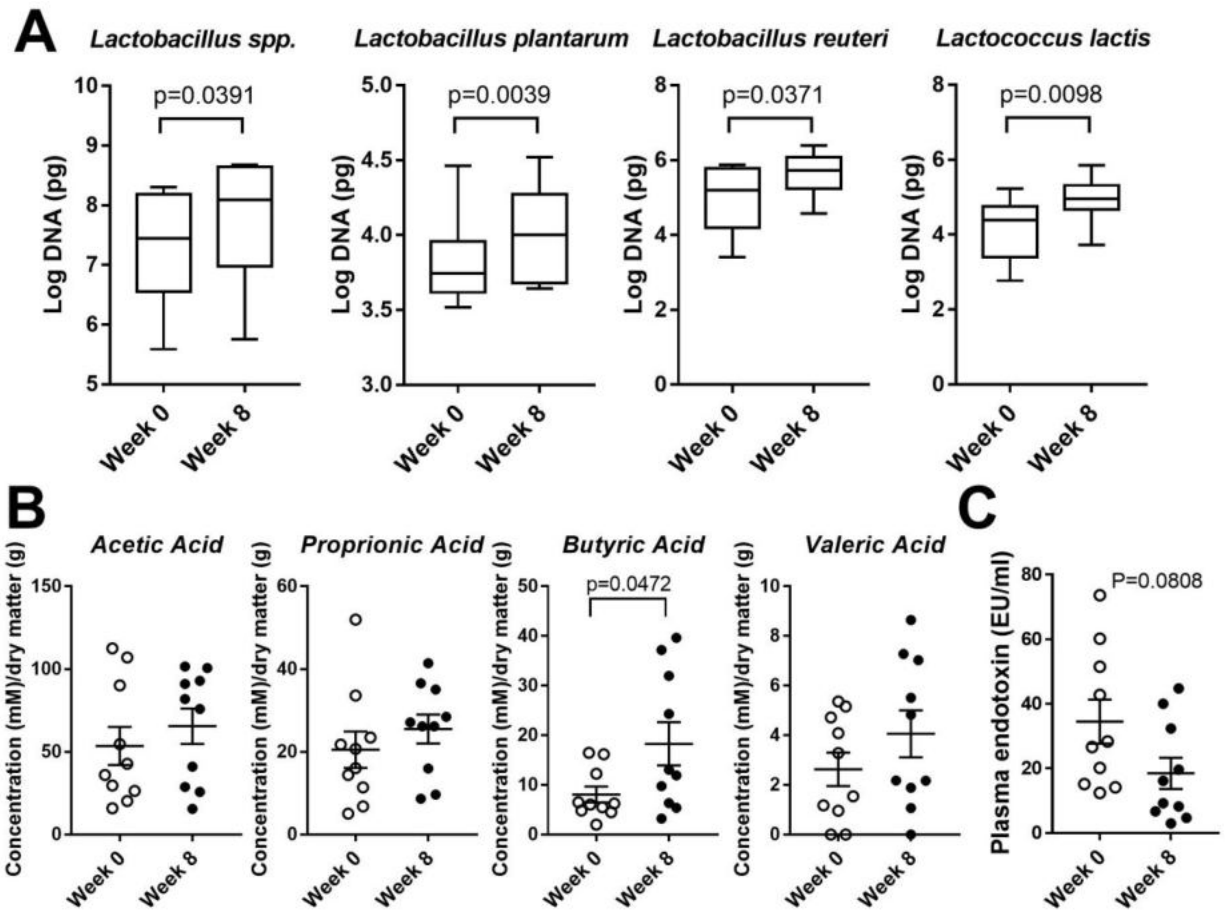

Fig. 3.

Author statement

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Highlights

- Ten patients with mild to moderate Inflammatory bowel disease (IBD) received a daily dose of mango pulp for 8 weeks, and the gallotannin-enriched diet may serve as a novel adjuvant therapy in combination with conventional therapies that may ameliorate and improve symptoms of patients with IBD.
- Mango intake significantly improved the Simple Clinical Colitis Activity Index (SCCAI) score and decreased the production of pro-inflammatory cytokines including interleukin-8 (IL-8), growth-regulated oncogene (GRO) and granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with IBD.
- Mango intake beneficially altered intestinal microbial composition by significantly increasing the abundance of *Lactobacillus spp., Lactobacillus. plantarum, Lactobacillus. reuteri and Lactobacillus. lactis* in patients with IBD.