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Department of Nutrition and Food Science

Anti-inflammatory Effects of Mango Polyphenolics in Inflammatory Bowel Disease

Final Report

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Executive Summary

Inflammatory bowel disease (IBD) presents a major risk factor for colon cancer [1] and the most common forms of this disorder are the inflammatory Crohn's disease and ulcerative colitis [2].

Preliminary data indicate the strong anti-inflammatory activities of mango relevant to intestinal inflammation.

For this reason, a consumption study with patients with inflammatory bowel disease was performed.

Overall, results from this study show the following:

- Most patients involved in this study suffered from mild to moderate ulcerative colitis
- Symptoms of intestinal colitis were significantly reduced
- Several biomarkers associated with inflammation were decreased after 8 weeks of mango consumption
- GRO – a molecule associated with colon cancer growth was significantly reduced
- Intestinal Lactobacilli and other beneficial probiotic bacteria were significantly increased after the consumption of mango
- Certain short-chain fatty acids, that are essential for a healthy intact intestinal tract were significantly increased
- High endotoxin levels are not only associated with intestinal inflammation but also with other chronic inflammatory diseases. After 8 weeks of mango consumption, high endotoxin levels in plasma were significantly decreased.
- Despite a relatively small subject number, this study yielded significant findings and several biomarkers would have been significantly reduced with a higher subject number.
- All subjects who completed the study declared that they will continue to consume mangos regularly and that they will recommend this to others who suffer from IBD and also their physicians.

Benefits to the Mango Industry:

- Intestinal Bowel Disease is steadily increasing in the U.S. and this study clearly shows that the regular consumption of mango can reduce symptoms
- Results clearly demonstrate the ameliorating effects of mango consumption on inflammatory bowel disease and also indicates the potential to prevent intestinal inflammation.
- Additionally, the consumption off mango may help patients to avoid the intake of drugs with severe side effects, such as immune-suppressants and corticosteroids.

Publications:

Abstracts and Oral Presentations

1. Kim H, Banerjee N, Ivanov I, Prudhomme K, Bisson W, Talcott S, Mertens-Talcott SU. Comparison of anti-inflammatory effects of Mango (Mangifera Indica L.) and Pomegranate (Punica Granatum L.) in rat colitis model. International Conference on Polyphenols and Health 2015, Tours, France
2. H Kim, Y Minamoto, ME Markel, J Suchodolski, S Talcott, SU Mertens-Talcott. Effects of Mango and Pomegranate Polyphenolics in the Modification of Microbiota and Short Chain Fatty Acids in Rat Colitis Model. American Institute for Cancer Research 2014, Washington DC
3. Kim H, Banerjee N, Ivanov I, Talcott S, Mertens-Talcott SU. Comparison of Anti-inflammatory Mechanisms of Mango (Mangifera Indica L.) and Pomegranate (Punica Granatum L.) in DSS-induced Colitis. Experimental Biology, San Diego, 2014
4. Kim H, Banerjee N, Talcott S, Mertens-Talcott SU. Mango polyphenolics reduce inflammation in Intestinal Colitis - Potential Involvement of the miR-126/PI3K/AKT/mTOR pathway in vitro and in vivo. Society of Toxicology 2013, San Antonio

Peer Reviewed Manuscripts

1. Kim H, Banerjee N, Barnes RC, Pfent CM, Talcott ST, Dashwood RH, **Mertens-Talcott** SU. Mango polyphenolics reduce inflammation in intestinal colitis-involvement of the miR-126/PI3K/AKT/mTOR axis in vitro and in vivo. Mol Carcinog. 2017 Jan;56(1):197-207.
2. **Kim** H, Banerjee N, Ivanov I, Pfent CM, Prudhomme KR, Bisson WH, Dashwood RH, Talcott ST, **Mertens-Talcott** SU. Comparison of anti-inflammatory mechanisms of mango (Mangifera Indica L.) and pomegranate (Punica Granatum L.) in a preclinical model of colitis. Mol Nutr Food Res. 2016 Sep;60(9):1912-23
3. Kim H, Craig C, Venancio V, Barnes R, Talcott S, Mertens-Talcott SU. Consumption of Mango Attenuates Biomarkers for Inflammation and Symptoms in Individuals with Ulcerative Colitis, in preparation for Mol. Nutr. Food Res. 2017

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Introduction

Inflammatory bowel disease (IBD) presents a major risk factor for colon cancer [1] and the most common forms of this disorder are the inflammatory Crohn's disease and ulcerative colitis [2]. 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 [3]. The American Cancer Society estimates 134,490 new cases of colorectal cancer, responsible for 49,190 deaths in the USA in 2016 [4]. Colorectal cancer can develop from precursor lesions or polyps over periods of 10-15 years, which provides an extended time for preventive measures [5].

Polyphenolics in Mango: Polyphenolics identified in the edible part of mango (*Mangifera indica*) have been previously characterized and include flavonoids such as quercetin and kaempferol glycosides, phenolics acids, predominantly gallic acid, galloyl glycosides, in part polymerized, and in some varieties mangiferin [6] (Figure 1). Overall, the cytotoxic [7] and anti-inflammatory effects [8] of polyphenolics from mango have

been investigated, however a comparison of several mango varieties in their cytotoxic activities in different cancer cell lines by our research group demonstrated the colon-cancer-cytotoxic and anti-inflammatory activities in vitro [9].

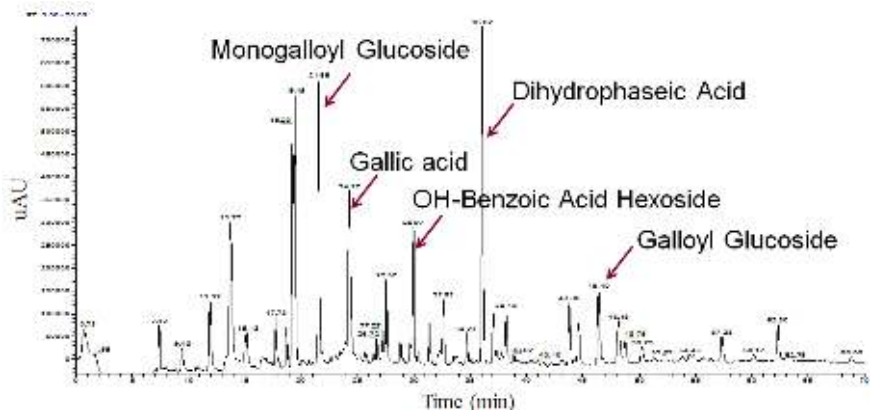

Figure 1. Representative chromatographic profile of phenolic compounds in mango juice.

Polyphenolics in Colon Cancer and Intestinal Inflammation. Multiple studies have demonstrated the health benefits of secondary plant compounds in fruits and vegetables including pomegranate, citrus, and curcuminoids, as reviewed by the director of our botanical core [10]. Polyphenolics have been found to reduce inflammatory processes in many chronic diseases, such as cardiovascular disease, cancer [11], and inflammatory bowel diseases [12]. It was previously demonstrated that polyphenolics, such as quercetin, anthocyanins, and grapefruit polyphenolics influence endogenous antioxidant enzyme activity, suppress proliferation and enhance apoptosis in the colon and have anti-inflammatory effects in vitro and in animal studies where inflammation and colon-carcinogenesis was prevented [13-15]. Our preliminary data indicate that polyphenolics from pomegranate, mango and other fruits prevent chemical-induced intestinal inflammation, as well as chemical-induced carcinogenesis [16-20]. Few human clinical studies using polyphenolics in the treatment of inflammatory bowel disease have been conducted. A previous study with patients suffering from IBD investigated the effects of curcumin; 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-ASA derivatives, or even stopping medication [21]. Overall, it was demonstrated that co-administration of curcumin with conventional drugs was effective, well-tolerated, and safe in maintaining remission, preventing relapse, and improving clinical activity indices [22]. During the process of obtaining an Investigational New Drug Registration (IND) for mango treatment, the United States Food & Drug Administration suggested the use of mangos as adjuvant therapy with commonly used drugs to determine the anti-inflammatory effects instead of testing it by itself in this clinical trial.

Objectives: The objective of this research was to assess the effects of mango consumption as an adjuvant treatment to conventional therapy in Intestinal Bowel Disease (IBD). Our goal was to support the National Mango Board to identify the health benefits associated with the intake of mango fruit in human health, allowing the organization to best market this food. This research also lays vital groundwork towards obtaining legal and marketing claims relating to the health benefits of mango

consumption. We recognize that these foundations are critical to build a strong working case for the goal.

Significance: Bioactive compounds from mango are bioavailable and their anti-inflammatory efficacy has been demonstrated in animals and humans. However, the efficacy of mangoes has not previously been compared with respect to mild inflammatory bowel disease. To justify future pharmacokinetic and pharmacodynamic analyses in human clinical trials, assessing efficacy in preventing or resolving IBD is a necessary step. Therefore, we aimed at determining the clinical relevance of mango as an adjuvant treatment to conventional therapy in IBD. The effects of mango with common drug treatment in mild-moderate IBD will be compared to the drug treatment alone. If mango or any other polyphenolic-rich food could be identified as helpful in shortening or reducing severity of episodes of inflammatory bowel disease, the addition of polyphenolics to conventional drug treatment in IBD would have a significant impact on public health.

Study Approach

This human clinical trial was designed in collaboration with Dr. David Binion, MD, University of Pittsburgh, and was performed in the Department of Nutrition and Food Science, at Texas A&M University, College Station, TX. Data from one subject comes from the Ertan Digestive Disease Center, Memorial Hermann Hospital, Houston, TX. This clinical study was designed as a controlled clinical trial in subjects with mild-moderate active Crohn's disease (CD) or mild-moderate ulcerative colitis (UC).

The study was carried out after approval by the Institutional Review Boards (IRB) at University of Texas, Houston, TX and Texas A&M University, and was registered at www.Clinicaltrials.gov.

Subject Population and Recruitment: Male or female, 18-to-79-years-old subjects with IBD (CD or UC) were recruited at Ertan Digestive Disease Center or Texas A&M University. Informed written consent was obtained by the research personnel before the study began. Inclusion criteria involved: 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. Exclusion criteria involved: history of acute cardiac event, seizures, stroke, or cancer within the last 6 months; recurrent hospitalizations (2 or more hospitalizations within the last 6 months); drug treatment for any of the listed conditions within the last 6 months; abuse of alcohol or substances within the last 6 months; currently smoking more than 1 pack/week; liver or renal dysfunction; current pregnancy or lactation (at the time of screening or at any time during the study); allergy against mangos; hepatitis B, C, or HIV; regular exercise (>60 minutes, ≥ 5 times/wk); known lactose intolerance, gluten sensitivity, or celiac disease; planned or scheduled IBD-related surgery (not including endoscopies); current IBD-related intestinal stricture; current infection with *C. difficile*; previous bowel resection.

Mango treatments: Commercially available mangos of the variety Keitt were obtained. These mangos have been imported from Mexico as commercial produce and gone

through USDA inspection. Upon arrival, mangos were stored in a fruit-storage at the Department of Horticulture, Texas A&M University, until ripe. Upon ripening, mangos were processed according to Good Manufacturing Practices (GMP) defined by the Department of Nutrition and Food Science, Texas A&M University. In brief, intact mangos underwent a wash in bleach solution, were deseeded, peeled, cut and frozen under vacuum in food storage bags (250-400 g) within 6h of deseeding. Bags were stored at -30 ºC. Temperature was monitored daily.

Study treatment: Subjects were asked to include 200-400 g of frozen mango every day on their diets. Subjects were advised to increase their mango consumption slowly over the first week. Since the tolerability of large amounts of fiber-rich fruit varies between subjects and for each patient over time, this study allows subjects to consume mango within a range rather than a fixed amount. This range went from 200g (splitted in two portions throughout the day) to 400g (divided as three equal portions a day). Subjects received a scale to weight how much mango they consumed each time and were asked to record the exact amount consumed each day. Subjects were allowed to skip their mango consumption or reduce it to accommodate any possible digestive issues they may experience. Subjects consumed their regular diet but reduce 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 which is supplied through their mango consumption. The mango treatment started either on their first study day, or as soon as subjects could be classified within the inclusion and exclusion criteria. Subjects that underwent an endoscopy before the beginning of this study needed to wait at least one week before the study treatment could be started. The treatment phase of this study lasted 8 weeks. Subjects were asked to donate blood and stool samples on the first and last study day. The dietary intake of each subject was evaluated by a 72-hour food record, performed on the first and last week of the study. Subjects were asked to log all food and drinks they consume for three days. The data was analyzed using iProfile 3.0 (http://iprofile.wiley.com) and calculated as calories, fat, carbohydrates, dietary fiber, and protein.

Assessment of the severity of IBD episodes: During all study visits, the severity of symptoms was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) [23] and the Simple Clinical Colitis Activity Index (SCCAI) [24]. The results were compared for each subject, before and after the nutritional intervention.

Plasma preparation and analysis: On the first and last study days (week 1 and week 8), a 10-mL blood sample was collected using Vacutainer® systems and K_2EDTA tubes (Becton Dickinson, Franklin Lakes, NJ, USA). For the plasma preparation, tubes were centrifuged at 1,500 × g for 10 minutes at 4 ºC. Plasma samples were then stored at -80 ºC until analysis. Inflammatory biomarkers were assessed in plasma samples from the treated subjects according to the methodologies described below.

Levels of inflammatory cytokines in the plasma of subjects: The levels of several inflammatory markers were quantified in plasma by xMAP Multiplex Assay (Luminex 200, Luminex Corporation, Austin, TX, USA) using magnetic beads acquired from EMD

Millipore (Billerica, MA, USA) and following the manufacturer's protocol. The 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).

Serum endotoxin analysis: Serum endotoxin concentration was measured using ELISA kits from Lonza (Lonza, USA) [25]. To remove noise, the expression of each negative controls was subtracted to the values for the consideration of background fluorescence.

Microbiota composition – Quantitative PCR assays: qPCR targeting 16S rRNA genes is a useful tool for quantifying very low concentrations of bacterial targets in fecal samples [26]. Bacterial DNA (200mg) was extracted from fecal samples using a commercial DNA extraction kit (QIAGEN, Germany) according to the manufacturer's instructions [26]. qPCR assays for selected bacterial groups were performed: total bacteria (341F, 518R), *Lactobacillus spp., Lactobacillus plantarum, Lactobacillus reuter, Lactococcus lactis,* which are well-known producers of tannase [27]. The qPCR data was expressed as log amount of DNA (fg) for each particular bacterial group [28].

SCFA analysis: SCFAs were analyzed by an HPLC-PDA system using an Aminex HPX-87H strong cation-exchange resin column (300 × 7.8 mm) and fitted with an ion exchange microguard refill cartridge (Bio-Rad, Hercules, CA, USA). The HPLC-PDA system consisted of a Water 2695 Separation Module (Waters, Milford, MA), which was equipped with a Water 2996 Photodiode Array detector (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, acetic acid, propionate, and valerate were identified and quantified by comparing retention time and UV-Visible spectral data to standards [29].

Statistical analysis: A paired two-tail Student's *t* test was performed for dietary intake, IBD scores, inflammatory markers, and serum endotoxin. The Wilcoxon test was used for microbiota composition and SCFA analyses. Data were considered different when $p < 0.05$.

Results

Recruitment:

Medical personnel evaluated more than 80 subjects based on medical records. More than 450 interested patients have been pre-screened by our research nurse. Subjects qualified have been called and underwent further screening.

Enrollment:

22 subjects were enrolled and did not complete the study based on:

- mental conditions, changes in disease severity before starting the mango treatment,
- Dislike of fiber treatment and Scheduling difficulties

Completed:
A total of 20 subjects participated in the study (including screening and any of the study days)
A total of 14 subjects completed the study (including completion to 4 and week study day)

Table 1: Study demographics.

Parameter	**Population (*n* = 14)**
Gender	6 males; 8 females
Age (years)	37 ± 17
Weight (kg)	78.8 ± 29.4

Dietary profile: The food intake (calories, fat, cholesterol, carbohydrates, dietary fiber and protein) data, assessed by food questionnaires (72-h food record), is shown in **Table 2**. The addition of mango fruits led to a significant decreased fat intake, reflecting on the calorie intake by the subjects.

Table 2: Daily intake obtained in 72-hour food questionnaire

Variable		Baseline	8 weeks	Delta	p-value
Calories	Mean	1781.4	1623.0	-158.4	**0.0454***
(kcal)	SD	799.3	772.3		
Fat	Mean	78.5	63.5	-15.0	**0.0212***
(g)	SD	41.6	41.5		
Carbohydrates	Mean	192.3	197.6	-5.3	0.7067
(g)	SD	82.0	74.7		
Dietary fiber	Mean	17.7	17.9	0.2	0.9025
(g)	SD	4.8	5.9		
Protein	Mean	70.8	62.3	-8.5	0.0813
(g)	SD	38.1	33.8		

*SIBDQ or SCCAI scores*The Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and Simple Clinical Colitis Activity (SCCAI) scores were evaluated during each study visit. Data is presented on Figure 2. Results show the nutritional intervention with mangos decreased the Colitis Index throughout the study duration. SCCAI is a validated score to help assessing the severity of subjects suffering from ulcerative colitis. Criteria for this score include bowel frequency, stool consistency, abdominal pain, anorexia, nausea/vomiting, extracolonic manifestations, and important signs (such as body temperature and blood in stool) [24]. Decreased SCCAI has been associated with decreased severity of ulcerative colitis [30, 31]. The SIBDQ is mostly used for Crohn's Disease, however, most subjects enrolled in this study suffered from ulcerative colitis, therefore the SCCAI scores are relevant to this study

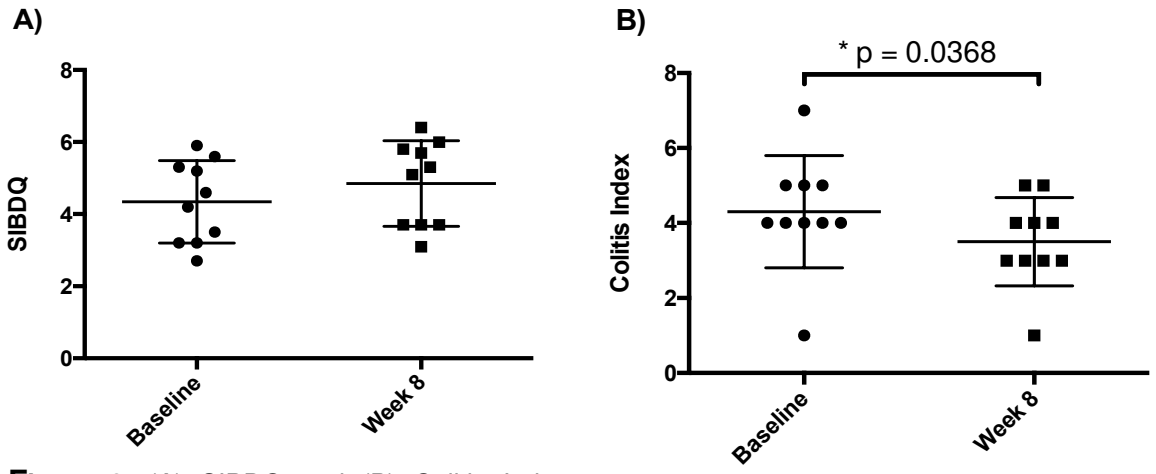

Figure 2. (A) SIBDQ and (B) Colitis Index scores of study subjects.

Table 3 shows the levels of inflammatory biomarkers at baseline and after 8 weeks of nutritional intervention. Statistical analysis found that the 8-week nutritional intervention with mangos led to decreased levels of granulocyte macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), and growth-regulated oncogene (GRO).

Table 3. Changes in inflammatory biomarkers at baseline and 8 weeks of the program participation.

Variable (pg/mL)		Baseline	8 weeks	Delta	p-value
IL-1β	Mean	0.77	0.85	0.08	0.0518
	SD	0.41	0.47		
IL-6	Mean	1.00	1.25	0.25	0.1542
	SD	0.75	0.93		
IL-10	Mean	24.98	25.43	0.45	0.8421
	SD	26.22	24.79		
TNF-α	Mean	1.382	1.699	0.32	0.1622
	SD	1.038	1.391		
GM-CSF	**Mean**	**120.6**	**88.54**	**-32.06**	**0.0444***
	SD	197.4	160.5		
Eotaxin	Mean	97.96	91.21	-6.75	0.5975
	SD	77.45	92.75		
IL-8	Mean	40.57	39.17	-1.40	0.4034
	SD	82.09	85.28		
IL-17A	Mean	31.24	35.86	4.62	0.5150
	SD	74.02	94.04		
IP-10	Mean	465.8	350.5	-115.3	0.2075
	SD	367.6	296.1		
MCP-1	**Mean**	**225.9**	**165.5**	**-60.4**	**0.0199***
	SD	71.80	60.80		
GRO	**Mean**	**1247**	**959.6**	**-287.4**	**0.0177***
	SD	599.4	511.6		
IL-7	Mean	31.22	45.46	14.24	0.3818
	SD	74.07	123.0		
MIP-1β	Mean	112.0	99.94	-12.06	0.2645
	SD	298.6	266.7		

IL-1β: interleukin 1 beta, IL-6 interleukin 6, IL-10: interleukin 10, TNF-α: tumor necrosis factor alpha, G-CSF: granulocyte-colony stimulating factor, IL-8: interleukin 8, IL-17A: interleukin 17A, (IP-10): interferon gamma-induced protein 10, MCP-1: monocyte chemoattractant protein-1, GRO: growth-regulated oncogene, IL-7: interleukin 7, MIP-1β: macrophage inflammatory protein 1-beta.

Several biomarkers were recently recognized as biomarkers for assessing the severity of IBD in humans. GM-CSF have been associated with IBD, since higher levels of this marker have been found in mucosal lesions of Crohn's disease or ulcerative colitis patients [32, 33]. Therefore, GM-CSF has been used as a biomarker of improvement and remission of IBD in clinical trials [34]. MCP-1 is involved in the recruitment of monocytes, granulocytes, lymphocytes, and macrophages from the bloodstream through the endothelium into the colon mucosa, leading to chronic inflammation and higher susceptibility to IBD [35]. The higher the expression of MCP-1 in the mucosa of ulcerative colitis (UC) subjects, the higher is considered their disease activity [36]. Growth-regulated oncogene (GRO) also plays a role in the pathogenesis of IBD. Considering the effects of GRO as an oncogene-related peptide, researchers believe this cytokine may be involved in the development of cancer by IBD patients [37]. Increased levels of GRO were found in the serum of subjects with ulcerative colitis [38] and other authors consider GRO an important marker of IBD activity [37].

Arrays for selected bacterial groups were performed to measure the changes in gut microbiota composition by mango beverage intake. The increased levels of tannase-producers *L. plantarum*, *L reuter* and *L. lactis* act as tannin-metabolizing probiotics by breaking down gallotannins to release free gallic acid, which is then further degraded into pyrogallol, its decarboxylated form [39]. In addition, *L. plantarum*, *L reuter* and *L. lactis* are known to have anti-inflammatory activity in the treatment of colitis [40, 41]. At the genus level, 8 week mango consumption in the IBD patients showed an increasing tendency on the level of *Lactobacillus* (p=0.1749). At the species level, the abundances of *L reuter* among the tannase-producing bacteria increased after 8 week mango consumption (p=0.0496, Wilcoxon test) (**Figure 3**).

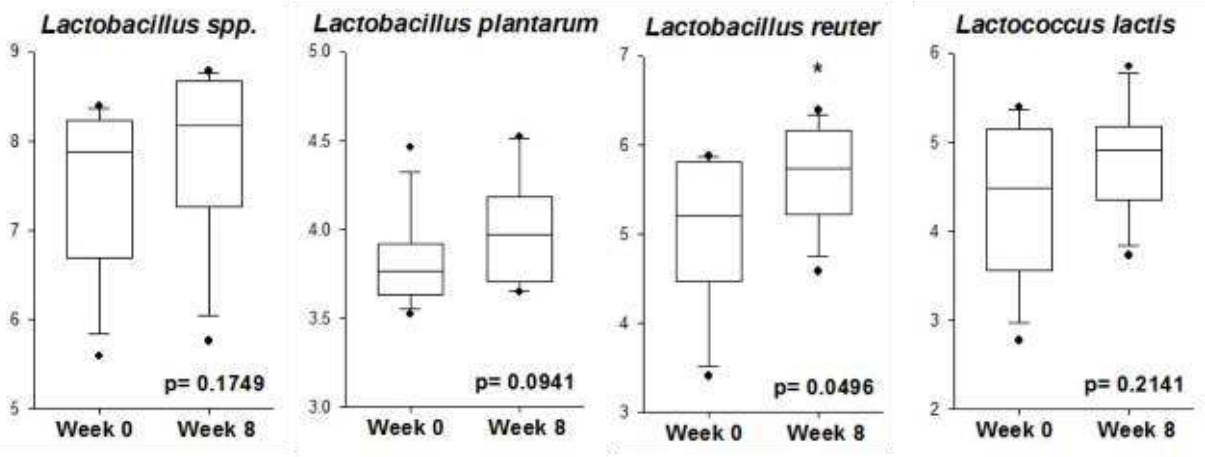

Figure 3. Effects of 56 days of mango consumption on microbiota composition in IBD patients. Quantitative real-time PCR results for selected bacterial groups. Relative log amount were normalized by DNA. Asterisks denote a significant increase in relative proportions observed between groups (n = 12; Wilcoxon test; $p<0.05$).

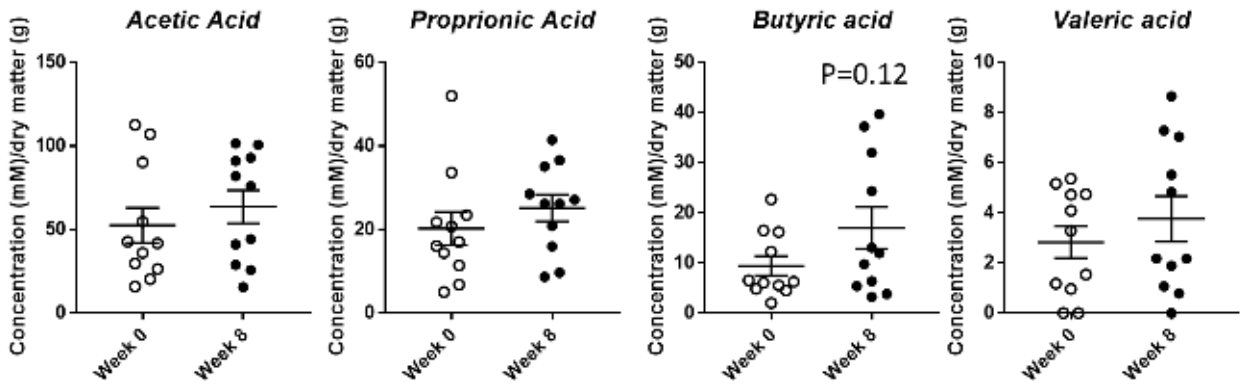

Figure 4. Short chain fatty acid production by 56 days of mango consumption in IBD patients. Results are expressed in mmol/g of fecal dry contents (n = 12).

Lactobacillus species have been shown to have anti-inflammatory effects through the production of short-chain fatty acids (SCFAs) [42]. SCFAs are metabolites produced from undigested carbohydrates, fibers, and polyphenols by gut microbiota [43]. However, no SCFAs exhibited any significant changes. Only 8 week mango consumption showed an increasing tendency in the level of butyrate (p=0.12, Wilcoxon test) (Figure 4).

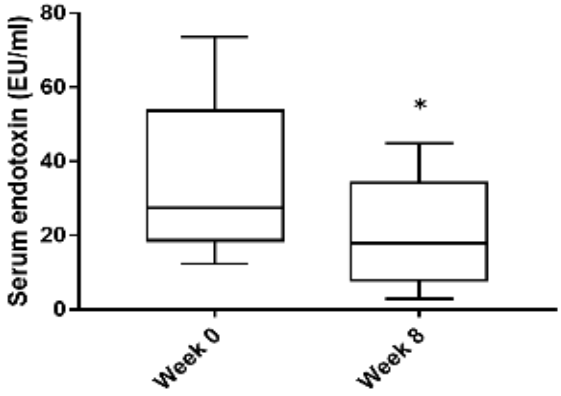

Figure 5. lipopolysaccharide levels in serum from IBD patients with 56 days of mango consumption. Results are expressed in EU/ml. Asterisks denote a significant increase between groups (n = 12; t-test: p=0.04).

It has long been suggested that intestinal and systemic inflammatory diseases are associated with increased LPS permeability and damaged epithelial barrier and this leads to increased endotoxin levels in blood and other tissues. Also, disturbances in fecal flora suggested a role of LPS in the pathogenesis of inflammatory bowel disease [70]. The concentration of LPS in serum was significantly decreased after 8 week mango consumption (p=0.04) and this indicates that the activity of inflammation-associated bacteria in the intestine was reduced or that the consumption of mango significantly improved intestinal integrity and prevent leaking of molecules from the intestines (**Figure 5**).

Conclusion

Taken together, our results indicate mango intake exerted beneficial effects in the progression and severity of the IBD, by decreasing the severity of the disease (SCCAI score), and reducing the levels of IBD-relevant molecules in plasma after 8 weeks of nutritional intervention.

Additionally, mango consumption may mitigate inflammation in part by improving the composition of the intestinal microbiota and decreasing serum endotoxin level.

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