Agave tequilana Fructans Versus *Psyllium plantago* for Functional Constipation

Randomized Double-blind Clinical Trial

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Goal: The aim of this study was to evaluate the efficacy of supplementation with *Agave tequilana* Weber blue variety fructans (Predilife) in the improvement of symptoms in functional constipation.

Background: Fiber supplementation is the first-line treatment for constipation. Fibers-like fructans have a known prebiotic effect.

Materials and Methods: A randomized, double-blind, study comparing agave fructans (AF) against *psyllium plantago* (PP). Four groups were randomized. Group 1: AF 5 g (Predilife), group 2: AF 10 g (Predilife), group 3: AF 5 g (Predilife)+10 g maltodextrin (MTDx), and group 4: PP 5 g+10 g MTDx. The fiber was administered once daily for 8 weeks. All fibers were similarly flavored and packaged. Patients kept their usual diet and fiber sources were quantified. Responders were defined as ≥ 1 complete spontaneous bowel movement from baseline to 8 weeks. Adverse events were reported. The study was registered in Clinicaltrials.gov with registration number NCT04716868.

Results: Seventy-nine patients were included (group 1: 21, group 2: 18, group 3: 20, and group 4: 20), of which 62 (78.4%) were women. The responders were similar across groups (73.3%, 71.4%, 70.6%, and 69%, $P > 0.050$). After 8 weeks, all groups significantly increased complete spontaneous bowel movements, showing the greatest increase in spontaneous bowel movements in group 3 ($P = 0.008$). All groups improved in symptoms, stool consistency, and quality of life. Diet and fiber intake were similar between groups. Adverse events were mild and similar between groups.

Conclusions: AF (Predilife) are as effective at different doses and combined with MTDx as PP and are a feasible option for the treatment of functional constipation.

Key Words: functional constipation, randomized clinical trial, fiber, agave fructans

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Constipation is a common gastrointestinal disorder that affects individuals globally, with an estimated prevalence of 14%.[1] The ROME III criteria have defined functional constipation (FC) as the presence of symptoms for > 6 months before diagnosis and symptoms in the last 3 months, meeting at least 2 or more of the following criteria in 25% of cases: increased straining, hard stools (consistency), obstruction/blockage sensation during the evacuation, use of digital maneuvers, incomplete evacuation sensation, and decreased evacuation frequency (< 3/wk).[2] FC can negatively impact the quality of life (QOL) of patients, and also imposes an economic burden on health care providers and health systems.[3,4]

Lifestyle modifications and an increase in dietary fiber intake are the first lines of treatment.[5,6] Fiber supplements have shown beneficial effects on symptoms related to FC.[7]

There are numerous gastrointestinal benefits to fiber supplementation, including a prebiotic effect,[8] a bolus effect, and a reduction in transit times in healthy individuals.[9,10] The American Gastroenterological Association recommends a daily dietary fiber intake of 20 to 30 g.[5] However, fiber intake in adults from food is below the world health organization recommendation (16 to 18 vs. 25 g/d), so a strategy to meet the proposed requirements for the improvement of constipation symptoms is fiber supplementation.[11]

A systematic review that evaluated fiber supplementation in patients with constipation concluded that the provision of soluble fiber, including *psyllium plantago* (PP), is useful in managing constipation symptoms, but the evidence was less for insoluble fiber.[12]

A randomized, controlled clinical trial showed that a plum-derived fiber demonstrated an equal effect in improving FC symptoms compared with PP.[13] More recently, another randomized study tested the noninferiority of a mixed fiber compared with PP with a 75% response in both interventions for the treatment of FC.[7]

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There are different types of fiber available in the market, but most lack scientific evidence and more studies are required to prove the efficacy and safety profile of these supplements.

The fructans of *Agave tequilana* Weber blue variety are highly fermentable and are classified as soluble fiber[14] and have been associated in preliminary studies, both in vitro,[15] and in vivo, with increased populations of *Bifidobacterium* and *Lactobacillus* when compared with placebo, and in vivo studies have shown an increase in the frequency of bowel movements in healthy volunteers.[16] There is no data about the efficacy and safety of fructans of *A. tequilana* Weber supplementation for the treatment of constipation.

We aimed to evaluate the efficacy and safety of the consumption of fructans from the *A. tequilana* Weber blue variety using PP as a standard of reference for the treatment of FC.

MATERIALS AND METHODS

A double-blind randomized clinical trial was carried out in a period from May 2016 to October 2019. The study was approved by the Ethics Committee of the National Institute of Medical Sciences and Nutrition Salvador Zubirán, México City, México. All participants voluntarily signed the informed consent. The study was registered in Clinicaltrials.gov with registration number NCT04716868. All authors had access to the study data and reviewed and approved the final manuscript. The study was submitted to COFEPRIS, being approved and registered in the National Registry of Clinical Trials with number 183300410A0034.

Study Design

Patients of both gender between 18 and 75 years old diagnosed with FC according to the ROME III criteria were recruited. All participants recruited were free from chronic treatment or were only taking occasional laxatives. Recruitment was conducted by advertising in our institution. For subjects older than 50 years, a recent colonoscopy (< 3 y) was required to be included. Exclusion criteria were pregnancy or lactation, continuous use of laxatives, prebiotics or probiotics in the last month, other causes of secondary constipation, abdominal surgeries (except for appendicectomy and cholecystectomy), and meeting criteria for irritable bowel syndrome (IBS). Also, patients were excluded if they were under continuous treatment or failed to a trial of osmotic laxatives or fiber supplementation and were considered to be unresponsive for these interventions. Patients who voluntarily accepted and signed the informed consent were evaluated in detail. Each subject was randomized to receive 1 of 4 treatments: group 1: agave fructans (AF) 5 g (Predilife); group 2: AF 10 g (Predilife); group 3: AF 5 g (Predilife)+10 g of maltodextrin (MTDx); and group 4: PP 5 g+MTDx 10 g MTDx was used in arm 3 to equalize dosage of MTDx used in PP formulation. Participants were advised that all would receive a fiber supplementation but neither the participants nor the investigators were told which fiber they would receive. Patients attended for initial visit and for their follow-up visit at week 8 of the intervention. Participants in each group recorded the number of their bowel movements for 1 week before starting the study intervention and 1 week before finishing the follow-up at week 8. Also, the intensity of push effort, and the sense of complete evacuation were recorded. Randomization was performed by an independent investigator not involved in protocol procedures and used an online randomization sequence (www.randomizer.com) using block randomization, with a 1:1 ratio between groups.

Intervention

The fiber administered was in the form of flavored powder with 4 different flavors, to be dissolved in 250 mL of water. Each of the powders was packaged in envelopes with a similar presentation.

The patient was instructed to consume 1 pack per day during fasting for 8 weeks, 30 minutes before the first meal. To assess treatment compliance, the patient was asked to return the empty envelopes at final visit (week 8). Treatment adherence was considered if > 80% of the prescribed packs had been taken. Sennosides were given as a rescue measure, 1 tablet of 15 mg orally in case the patient did not have a spontaneous bowel movement (SBM) after 72 hours.

Evaluation of Response to the Intervention

A diary for bowel movements and symptoms was used for 1 week before randomization and for the final week, where patients recorded bowel movement frequency, SBMs, complete spontaneous bowel movements (CSBMs), and stool consistency (Bristol stool scale form). Pain during defecation, excessive straining, sense of incomplete evacuation, <3 bowel movements per week and bloating were evaluated using a Likert scale: 0 = no, 1 = mild, 2 = moderate, 3 = severe. The primary objective was the percentage of patients with an increase of ≥ 1 CSBM over baseline and that sustained response was presented at week 8. The secondary endpoints were the total increase in the frequency of CSBM and SBM comparing baseline versus final. In addition, the improvement in pain during defecation, excessive straining, sense of incomplete evacuation, <3 bowel movements per week and bloating were evaluated by presenting a decrease of at least 1 point on the Likert scale for each symptom when comparing their baseline and final assessment (week 8).

Assessment of QOL

QOL was assessed with the self-administered Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire for each patient, which consists of 28 subcategorized items on 4 scales (physical discomfort, social discomfort, worries, and satisfaction). The response option is a Likert scale from 0 to 4, the higher the score obtained, the lower the quality. This intervention was performed at baseline before fiber consumption and at 8 weeks at the end of the study.

Usual Diet

During the study, the diet of the patients was not modified, however, control of fiber consumption was carried out from the beginning of the treatment. Food intake was evaluated using the Food Processor software to assess fiber intake and check that the study patients did not consume > 20 g of dietary fiber.

Organoleptic Characteristics of the Prebiotic Fibers

All patients were given a shaker cup, where they placed 250 mL of water and were instructed to dissolve the fiber powder, then they closed the container and shake it vigorously for 30 seconds; after that, the solution was drunk. Taste and ease of preparation and solubility of the powder

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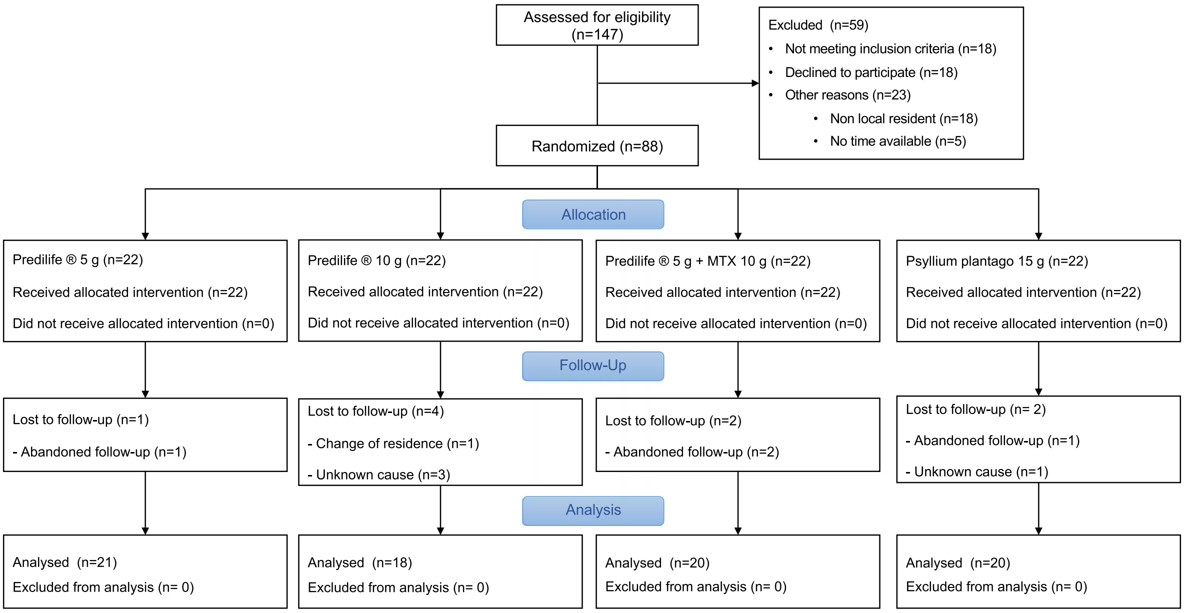

FIGURE 1. Recruitment diagram (consort). MTX indicates maltodextrin.

were rated by patients on a scale of 0 to 10. These characteristics were compared between groups to assess which was rated best to define this aspect of patient acceptance.

Adverse Events

They were evaluated through a diary of possible symptoms in which the patients reported if there was an unexpected appearance of symptoms throughout the study after fiber consumption.

Statistical Analysis

For continuous variables, the results were presented as medians and percentiles and as frequencies and percentages when they were categorical. For the comparison of intragroup quantitative variables before and after the intervention, the Wilcoxon test was used in the case of the comparison of categorical variables, χ^2 was used. The Kruskal-Wallis was used for comparison between groups. The data obtained will be analyzed with the statistical program SPSS, version 24.

The sample size was calculated to test what treatment arm was more effective for improving the symptoms of constipation.

A precision of 95% was used (probability of 0.05 of committing a type I error or α) and a force or power of 80% (probability of 0.20 of committing a type II error or β). Considering 20% of patient follow-up loss, each group needed 18 allocated participants per group.

RESULTS

Baseline Demographic and Evacuation Characteristics

A total of 79 patients were included in the study [women 62 (78.4%), median age: 35 (30.5 to 45)]. After randomization, the groups were distributed as follows: AF 5 g, 21 patients (Predilife); group 2: AF 10 g, 18 patients (Predilife); group 3: AF 5 g patients (Predilife)+10 g MTDx, 20 and group 4: PP 5 g MTDx 10 g, 20 patients with a similar distribution of women in all groups. Figure 1 shows the flowchart for study recruitment. Table 1 summarizes the baseline demographic parameters of the study population.

There were 43 patients with at least 1 mild comorbidity, 31 with overweight, 6 with obesity, and 7 with well controlled diabetes mellitus. There were no significant differences in terms of distribution between groups ($P=0.69$).

Response to Intervention (Primary Endpoint)

For the primary endpoint, it was observed that the percentage of responders (≥1 CSBM from baseline) in the

TABLE 1. Demographic Characteristics of the Study Population (Study Inclusion)

Variables	AF 5 g (N = 21)	AF 10 g (N = 18)	AF 5 g+MTDx 10 g (N = 20)	Psyllium platango 5 g+MTDx 10 g (N = 20)	*P*
Demographics					
Age (y)	35.00 (31.00-46.75)	33.50 (26.00-49.75)	39.50 (27.50-44.00)	30.00 (26.00-41.75)	0.56
Gender (women) [n (%)]	18 (90.00)	14 (77.80)	15 (75)	19 (95.00)	0.41
Antropometric					
Weight (kg)	66.80 (54.10-74.90)	65.85 (60.40-71.10)	62.70 (58.00-67.50)	64.20 (60.10-71.30)	0.72
BMI (kg/m^2)	25.23 (23.22-27.95)	25.77 (23.87-26.28)	24.80 (22.34-28.17)	25.76 (23.93-29.00)	0.28

AF indicates agave fructans; BMI, body mass index; MTDx, maltodextrin.

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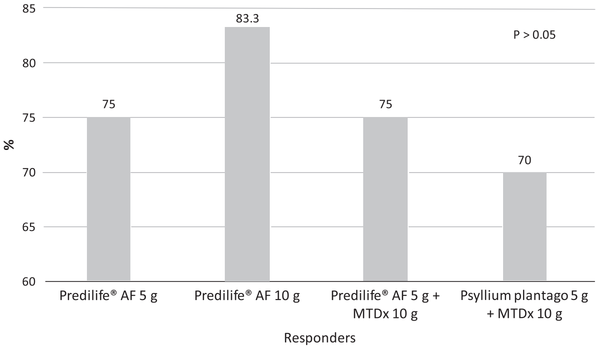

FIGURE 2. Percentage of sustained response at 8 weeks after the intervention in the different groups. AF indicates agave fructans; MTDx, maltodextrin.

study was similar in all the intervention groups, without finding significant differences ($P > 0.05$). However, the percentage of responders was slightly higher with AF 10 g (Fig. 2).

Secondary Endpoints

For secondary parameters, significant differences were observed after 8 weeks of intervention in all groups in relation to the increase in weekly CSBM and SBM when comparing the baseline with the end of the intervention (Table 2). When comparing the groups, a higher number of total bowel movements per week was observed in the AF 5 g+MTDx 10 g group ($P = 0.025$) but there were no differences in the frequency of CSBM ($P = 0.32$) between the groups (Table 2).

Regarding stool consistency evaluated with the Bristol scale, after 8 weeks of intervention, the percentage of patients with Bristol scale type 3 and 4 were: 12 (80%) for AF 5 g, 11 (78.6%) AF 10 g, 12 (70.6%) AF 5 g+MTDx 10 g, and 9 (64.3%) for PP 5+MTDx 10 g, without significant difference between groups ($P = 0.79$).

Similarly, no significant differences were found in the decrease of symptoms of pain during defecation, excessive straining, sense of incomplete evacuation, <3 bowel movements per week, and bloating (Fig. 3).

QOL

Uniformly, a similar increase in QOL was found in all groups in relation to the QOL in general as well as similar decrease in all subscales of the PAC-QOL questionnaire ($P > 0.05$) (Table 3).

Usual Diet

The consumption of energy (kcal) and dietary fiber was similar between the groups and there was no difference when comparing baseline consumption to the end of the intervention ($P > 0.05$). Similarly, the calculation of protein intake, carbohydrates, and lipids was similar without significant differences between groups ($P > 0.05$) (Table 4).

Solubility and Acceptance

No differences were found in the acceptance due to the taste of the fibers. A better acceptance was found concerning the ease of drinking fiber ($P = 0.01$) and its solubility ($P = 0.007$) for fibers with AF when compared with PP.

Adverse Events

Adverse events were similarly reported during the intervention with no significant difference ($P > 0.05$),

TABLE 2. Change in Bowel Movements From Baseline to End of Follow-up (Week 8)

	AF 5 g (N = 21)			AF 10 g (N = 18)			AF 5 g+MTDx 10 g (N = 20)			Psyllium platango 5 g+MTDx 10 g (N = 20)			
Variables	Basal	Final	*P	Basal	Final	P*	Basal	Final	P*	Basal	Final	P*	P†
CSBM	2.00 (0.00-3.00)	7.00 (6.00-12.00)	0.001	1 (0.00-400)	6.00 (3.00-9.00)	0.002	2.00 (2.00-4.00)	8.00 (4.00-11.00)	0.008	2.00 (1.00-2.00)	6.00 (2.00-7.00)	0.003	0.32
SBM	6.00 (3.25-7.00)	9.00 (8.00-12.25)	< 0.001	4.50 (3.00-7.25)	8.00 (7.75-10.75)	0.001	7.00 (5.00-9.75)	11 (10.00-14.00)	0.002	3.50 (3.00-7.00)	8.00 (7.00-10.25)	0.001	0.025

*Wilcoxon test to assess within-group.
†Kruskal-Wallis test to assess between-group, Mann-Whitney U test with Bonferroni adjustment, $P = 0.0125$.
AF indicates agave fructans; CSBM, complete spontaneous bowel movement; MTDx, maltodextrin; SBM, spontaneous bowel movement.

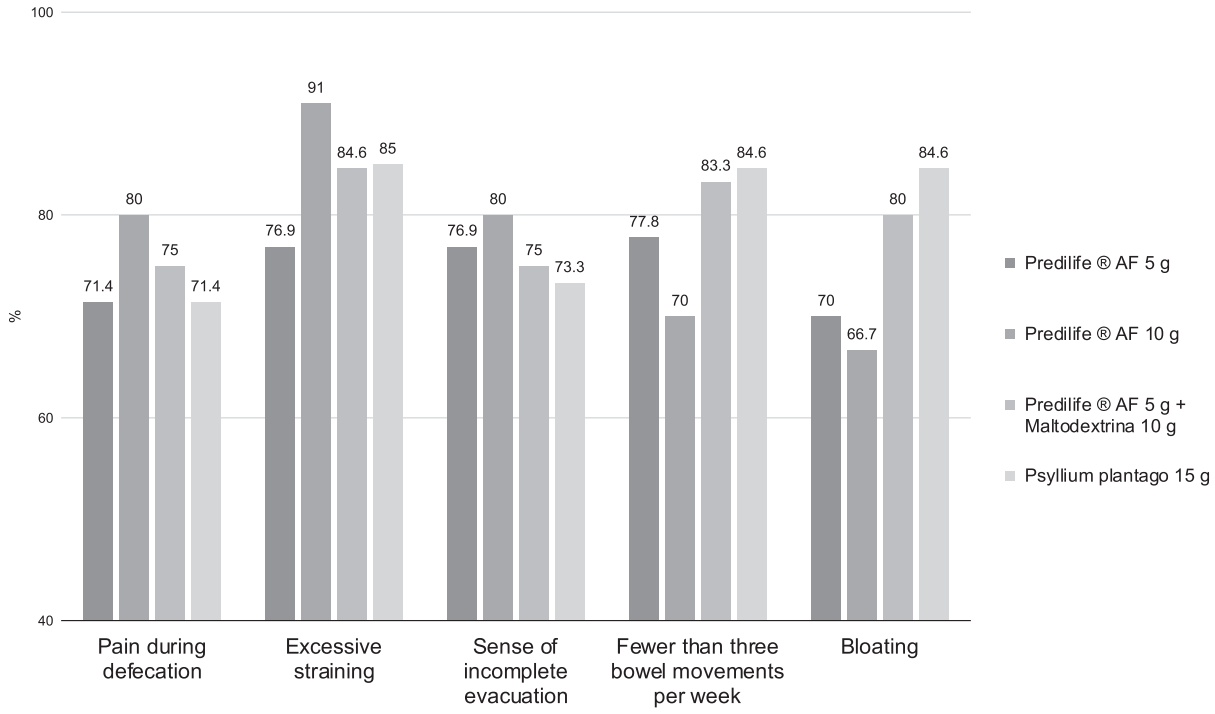

FIGURE 3. Percentage of patients with a decrease of their symptoms in at least 1 point at week 8 from baseline. AF indicates agave fructans.

flatulence in 1 patient with AF 5 g, 3 with AF 10 g, 1 with AF 5 g+MTDx 10 g, and 3 with PP and bloating. Abdominal pain occurred in 1, 2, 1, and 3 patients, respectively. Diarrhea occurred in 1 case in each group except for the AF 5 g group. These mild and transient adverse effects did not lead to discontinuation or loss of follow-up (Table 5).

Rescue Therapy

Rescue therapy was required in 2 patients in the AF 5 g group, 6 in the AF 10 g group, 3 in the AF 5 g+MTDx 10 g group, and in 7 with PP ($P > 0.05$). Most of the patients who used this rescue therapy were at the beginning of the intervention, was not maintained and this did not cause a loss of follow-up in the study.

DISCUSSION

The cornerstone in the treatment of constipation is the supplementation of fiber.[5] Different types of fiber have been explored with good results. In our study, we were able to corroborate that the administration of fructans derived from agave alone or in combination with MTDx was as effective in increasing the number of CSBM when compared with PP. The combined administration of AF 5 g+MTDx 10 g, produced a higher frequency of SBM.

Other studies have explored the administration of fibers for the treatment of FC. In one study, the administration of prunes (6 g) was compared with PP (6 g of fiber) for 3 weeks. In this study, prunes showed a higher response rate (increase in CSBM) compared with PP, but without differences in the global scale of symptoms of constipation or pushing effort.[13] A randomized clinical trial showed that the supplementation of a mixed fiber (5 g) (derived from fruits and plums) is equally effective as the supplementation of PP (5 g) with a percentage of responders of 75% in both groups.[7] Other clinical trials showed that the administration of kiwi, plums, and PP presented very good tolerability and efficacy in patients with FC. Studies seem to indicate that fiber supplementation offers favorable effects, regardless of the type of fiber used.[17]

A meta-analysis with systematic review showed that fibers, regardless of their origin, fermentable or non-fermentable, induce moderate improvement in constipation symptoms, however, the authors of the meta-analysis stated that most of the studies are not completely comparable due to the heterogeneity of the fibers as well as their dosage and mode of administration.[18] In this same meta-analysis, it is mentioned that although there are symptoms due to the administration of fibers, these are not serious, they tend to decrease over time and the risk-benefit of their administration must be assessed individually.

In other diseases, such as IBS, adverse effects derived from gas have been described that even lead to stopping fiber supplementation. However, results of a meta-analysis that evaluated fiber consumption in IBS, showed that although there are symptoms associated with gas derived from the administration of these components, it is also shown that it exists for a single adaptation period of a few days and subsequently shows its sustained beneficial effect.[19]

In our study, the administration of AF in any presentation, as well as PP, showed a profile of similar symptoms, which appeared in the first weeks, did not lead to discontinuation of treatment, and even more, patients showed improvement of these symptoms at the end of intervention period when making the comparison with the baseline scores. That is, the administration of AF was well tolerated and the incidence of adverse effects did not differ significantly from that of PP.

The exact mechanisms by which fiber supplementation leads to a favorable effect are not exactly known. It has been

TABLE 3. PAC-QOL Domains Comparison From Baseline to Week 8

	AF 5 g (N = 21)			AF 10 g (N = 18)			AF 5 g+MTDx 10 g (N = 20)			Psyllium platango 5 g+MTDx 10 g (N = 20)			
Variables	**Basal**	**Final**	***P***	**Basal**	**Final**	***P***	**Basal**	**Final**	***P***	**Basal**	**Final**	***P***	***P****
Physical discomfort	2.25 (1.30-2.50)	1.00 (0.56-1.50)	0.005	2.00 (1.40-2.50)	0.75 (0.68-1.50)	0.001	1.75 (1.20-2.25)	0.75 (0.50-1.25)	0.002	1.80 (1.50-2.50)	0.75 (0.75-1.00)	< 0.001	0.68
Social discomfort	1.06 (0.56-1.68)	0.43 (0.15-1.06)	0.009	1.00 (0.46-1.90)	0.37 (0.12-0.87)	0.02	0.87 (0.62-1.75)	0.37 (0.12-0.87)	0.002	0.87 (0.56-1.18)	0.37 (0.21-0.50)	0.002	0.49
Worries	1.81 (1.18-2.43)	0.77 (0.45-1.80)	0.001	1.30 (0.88-2.25)	0.45 (0.36-1.09)	0.008	1.63 (1.09-2.18)	0.45 (0.36-1.09)	< 0.001	1.50 (1.06-2.09)	0.45 (0.42-0.54)	< 0.001	0.10
Satisfaction	0.80 (0.60-1.40)	1.60 (1.00-2.30)	0.020	1.00 (0.60-1.40)	1.80 (1.60-2.40)	0.003	1.40 (1.00-2.20)	1.80 (1.60-2.40)	0.160	1.00 (0.60-2.60)	1.60 (1.50-1.90)	0.160	0.46

*Kruskal-Wallis test to assess between-group, Mann-Whitney *U* test with Bonferroni adjustment, $P = 0.0125$.
AF indicates agave fructans; MTDx, maltodextrin; PAC-QOL, Patient Assessment of Constipation Quality of Life.

TABLE 4. Assessment of Dietary Consumption at Both, Baseline and End of follow-up (Week 8)

	AF 5 g (N = 21)			AF 10 g (N = 18)			AF 5 g+MTDx 10 g (N = 20)			Psyllium platango 5 g+MTDx 10 g (N = 20)			
Variables	**Basal**	**Final**	***P***	**Basal**	**Final**	***P***	**Basal**	**Final**	***P***	**Basal**	**Final**	***P***	***P****
Energy (kcal)	1752.31 (1440.94-2126.50)	1768.54 (1561.99-2047.46)	0.19	1868.20 (1798.11-2317.63)	1896.31 (1646.83-2116.45)	0.49	1802.82 (1737.76-2007.56)	1755.23 (1416.57-1875.75)	0.73	1533.60 (1271.32-1637)	1735.70 (1690.57-1922.37)	0.24	0.30
Proteins (g)	96.19 (76.18-103.96)	80.06 (57.26-102.04)	0.27	90.88 (75.97-102.85)	75.58 (62.37-89.49)	0.28	80.31 (78.70-86.23)	62.94 (42.76-81.80)	0.04	62.74 (40.52-76.64)	64.40 (59.35-73.92)	0.55	0.32
Carbohydrates (g)	253.41 (169.69-268.17)	249.30 (190.98-283.80)	0.64	201.46 (171.85-266.73)	201.03 (158.79-325.19)	0.38	234.78 (104.54-278.58)	222.15 (173.64-279.37)	0.43	207.42 (158.13-256.32)	221.01 (204.57-264.04)	0.51	0.82
Lipids (g)	62.82 (46.67-85.37)	54.46 (27.37-82.50)	0.19	79.84 (55.36-95.80)	69.69 (55.37-89.81)	0.68	66.43 (62.41-68.25)	64.14 (51.32-83.90)	0.97	47.55 (35.14-60.38)	65.34 (57.76-71.80)	0.07	0.14
Total dietary fiber (g)	11.10 (9.88-12.56)	9.34 (7.68-12.41)	0.11	15.71 (12.50-21.01)	10.05 (8.3-19.51)	0.28	13.50 (8.9-20.49)	9.90 (7.70-16.47)	0.33	10.19 (7.33-10.77)	6.90 (6.03-11.59)	0.36	0.10
Sugars (g)	70.84 (60.05-90.53)	85.22 (66.30-167.52)	0.50	72.33 (65.17-85.39)	47.15 (36.41-72.12)	0.50	94.42 (94.03-98.63)	59.98 (38.75-146.54)	0.73	94.80 (68.34-122.93)	47.59 (14.02-68.52)	0.03	0.07
Liquids (mL)	551.70 (494.46-720.48)	513.05 (293.23-673.08)	0.23	494.58 (443.59-635.65)	232.35 (230.5-600.80)	0.55	880.00 (654.27-984.01)	262.79 (232.35-927.01)	0.006	441.00 (381.16-656.43)	538.08 (379.97-892.74)	0.47	0.79

*Kruskal-Wallis test to assess between-group, Mann-Whitney *U* test with Bonferroni adjustment, $P = 0.0125$.
AF indicates agave fructans; MTDx, maltodextrin.

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TABLE 5. Adverse Events After 8 Weeks of Intervention in the Study Groups

	n (%)				
Variables	AF 5 g (N = 21)	AF 10 g (N = 18)	AF 5 g+MTDx 10 g (N = 20)	Psyllium platango 5 g+MTDx 10 g (N = 20)	*P*
Gas	1 (4.7)	3 (16.6)	1 (5)	3 (16.6)	0.53
Distension	1 (4.7)	2 (11.1)	1 (5)	3 (16.6)	0.62
Diarrhea	0 (0)	1 (5.5)	1 (5)	1 (5)	0.70

AF indicates agave fructans; MTDx, maltodextrin.

proposed that they are bolus-forming agents that increase fluid retention and acceleration of intestinal transit.[9] However, the mechanisms of each fiber could be different, some are highly fermentable, and require less quantity to have the desired effect, while others require more input to be effective. Initial studies with bolus-forming agents such as PP and Bran, which are highly nondigestible fibers, showed persistency in a greater percentage into the colon and increased fecal mass. Other more digestible and fermentable fibers, such as fructans or inulins, have a greater osmotic effect and less bolus effect.[20]

In addition, there are regulatory mechanisms of the intestinal microbiota, production of short-chain fatty acids, and functions of the intestinal immune interaction that are being studied and lead to a differentiated effect according to the type of fiber.

Thus, the mechanisms of action vary but the clinical effect is similar. According to the results of our study, where a highly fermentable fiber is provided, such as AF and, on the other hand, PP, with moderate fermentability and greater bolus effect, it does not seem to differ in its effectiveness and percentage of clinical response in patients with FC.

Another study that evaluated the use of inulins derived from Chicory (*Cichorium intybus*) demonstrated an acceleration of colonic transit, softening of stools, and improvement in satisfaction, when compared with placebo with adequate tolerance derived from symptoms associated with gas.[21] A meta-analysis evaluated the consumption of inulins in the treatment of FC; the result of this evaluation indicated that inulins improve stool consistency, improve colonic transit, and the frequency of bowel movements.[22]

Our study is not without limitations. The sample size is the main one, with few patients in each intervention group this study would offer the possibility to have an underpowered result. However, patients were carefully followed up and selected based on appropriate criteria (ROME III) and the vast majority completed the study. Other studies published in patients with constipation have included a similar number of patients with outcomes similar to ours,[7,13] so we consider that the results are consistent with those previously published. The absence of a control group could be considered a limitation; however, our objective was to compare the therapeutic efficacy of AF against a well-established comparator such as PP, which has shown benefits in the treatment of chronic constipation[23] and IBS.[24] Therefore, we do not consider that the absence of a control group significantly affects the results obtained. Also, despite our efforts to prevent dropout rates, a subset of patients in our study experienced missing follow-up outcomes, resulting in an incomplete dataset for the analysis due to the study design (2 visits only). We acknowledge that the lack of an intention-to-treat analysis due to missing follow-up outcomes is a limitation of our study. However, we believe our decision to analyze as per protocol data, provides a valid representation of the treatment effect.

Our study has strengths. Patients with well-defined criteria (ROME III) were included, with no differences in baseline characteristics. All patients had a similar diet during the study without variation in dietary fiber consumption, which makes it more feasible to evaluate the effect of fiber supplementation. Another advantage of our study was that it was carried out for 8 weeks, observing a response during this time. Other studies have shown data for interventions ranging from 2 to 4 weeks. The longer duration of our study generates data that promote the use of this intervention in the mid-long term.

Also, we evaluated the solubility and flavor of the fibers, showing a similar and comparative effect in relation to the acceptance of all the types of fibers administered. This is important because consistence and flavor are causes of treatment discontinuation. In this context, the easier the solubility the better the adherence. Agave-derived fructans were shown to be more dissolvable than PP.

There were no significant differences in the discontinuation of our groups, therefore we consider that this comparator behaves similarly regardless of the fiber intake.

The intake of AF (Predilife) during 8 weeks of intervention in patients with FC relieves constipation symptoms and improves the QOL with a similar response compared with PP, showing good tolerance and an excellent safety profile with nonserious and mostly transient adverse events. With these results, we conclude that AF supplementation in any dose used in this study, offer a similar effect than PP and can be considered as a treatment option for FC. Additional studies are required to evaluate the effect of AF on the improvement of metabolic biomarkers and the intestinal microbiota due to its effect as a functional food and prebiotic.

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