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# Effects of Cactus Fiber on the Excretion of Dietary Fat in Healthy Subjects: A Double Blind, Randomized, Placebo-Controlled, Crossover Clinical Investigation



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## ARTICLE INFO

## Article history:

Accepted 7 February 2014

## Key Words:

dietary fat

fat binding

fat excretion

obesity

*Opuntia ficus-indica*

weight management

## ABSTRACT

**Background:** Cactus (*Opuntia ficus-indica*) fiber was shown to promote weight loss in a 3-month clinical investigation. As demonstrated by in vitro studies, cactus fiber binds to dietary fat and its use results in reduced absorption, which in turn leads to reduced energy absorption and ultimately the reduction of body weight.

**Objective:** The objective of our study was to elucidate the dietary fat binding capacity of cactus fiber through determination of fecal fat excretion in healthy volunteers.

**Subjects and Methods:** This clinical investigation was performed as a double-blind, randomized, placebo-controlled, crossover study in healthy subjects for a period of approximately 45 days. Twenty healthy volunteer subjects were randomized to receive cactus fiber or placebo, 2 tablets thrice daily with main meals. All subjects were provided with meals during the study period (except washout) according to a standardized meal plan, with 35% of daily energy need coming from fat. Two 24-hour feces samples were collected during both the baseline and treatment periods for analysis of the fat content.

**Results:** Cactus fiber showed an increased fecal fat excretion compared with placebo (mean [SD] = 15.79% [5.79%] vs 4.56% [3.09%];  $P < 0.001$ ). No adverse events were reported throughout the study period.

**Conclusions:** Cactus fiber has been shown to significantly promote fecal fat excretion in healthy adults. The results of our study support the hypothesis that cactus fiber helps in reducing body weight by binding to dietary fat and increasing its excretion, thus reducing dietary fat available for absorption. ClinicalTrials.gov identifier: NCT01590667.

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## Introduction

The prevalence of overweight and obesity has been recognized as a global epidemic, affecting not only developed but also developing countries.<sup>1</sup> World Health Organization estimates showed that in 2008, more than 1.4 billion adults worldwide were overweight and that > 500 million were obese.<sup>2</sup> Notably, 68.8% of adults aged 20 years and older were overweight or obese in the United States during 2009 to 2010.<sup>3</sup> Data from Eurostat<sup>4</sup> suggest that the predominance of obesity is as alarming in Europe—more than 50% of the European Union population is overweight or obese.

Accumulating evidence indicates a strong association between obesity and elevated health risks, including insulin resistance,

hypertriglyceridemia, decrease in HDL level, and increase in LDL level, leading to life-threatening diseases such as type 2 diabetes mellitus, hypertension, cardiovascular disease, stroke, and certain cancers.<sup>1,5–7</sup> It is also of no surprise that obesity tends to negatively affect quality of life.<sup>1,6,8</sup>

The increasing proportion of dietary fat is believed to be 1 of the major contributors to the prevalence of obesity worldwide. Studies have suggested that energy derived from fat plays a more significant role in promoting obesity than energy derived from carbohydrates and proteins.<sup>9–11</sup> It is therefore reasonable to hypothesize that weight loss can be achieved by reducing the consumption of fat, or the absorption of dietary fat.

The drastic increase of obesity worldwide has spurred research into more effective weight management solutions. Modern therapeutic strategies usually focus on the manipulation of enzymes and biomolecules involved in fat metabolism. Lipase inhibitors, agents that act on the inhibition of enzymes responsible for the

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digestion of long-chain triglycerides, are generally regarded as a safer choice of treatment for weight management.<sup>12,13</sup> However, these antiobesity agents are not without downsides. Apparent gastrointestinal side effects, such as increased defecation, soft stools, fatty oils evacuation, and oily spotting have been reported.<sup>13</sup> Also, the question of possible liver damage associated with the use of lipase inhibitors remains unanswered.<sup>14</sup>

Due to concerns over drug toxicity and side effects, there is increasing interest to seek alternative nonpharmacologic approaches from natural sources for weight management. *Opuntia ficus-indica* (also known as nopal) is a species of cactus found abundantly in Mexico and over a large area of Latin America, South Africa, and the Mediterranean.<sup>15</sup> The fruit (prickly pear or cactus pear) and the pad (cladode) of the cactus are common ingredients in Mexican cuisine. Besides culinary use, prickly pear fruit has been traditionally used in the management of ulcer, dyspnea, glaucoma, liver conditions, wounds, and fatigue.<sup>16</sup> The *Opuntia* genus is also widely used by Pima Indians for treatment of diabetes and hyperlipidemia. Previous findings suggested that daily consumption of prickly pear fruit could be beneficial to cardiovascular health through a reduction of total cholesterol and LDL-C,<sup>17</sup> whereas the intake of cactus pad could potentially lower fasting blood glucose levels.<sup>18</sup> Aqueous extracts from prickly pear have been shown to exhibit high total antioxidant capacity. The sources of the antioxidant properties were mainly vitamin C, with small fractions of carotenoids and vitamin E.<sup>15</sup>

On the other hand, the cladode of *Opuntia ficus-indica* is a rich source of dietary fiber,<sup>19</sup> and its dehydrated powder has been shown to bind to dietary fat in laboratory settings. It is postulated that dietary fat bound by the fiber complex is not available for digestion and is eventually eliminated unabsorbed, thus helping to reduce energy intake and promote weight loss.<sup>20</sup> A cactus fiber preparation (IQP-G-002AS), supplied by InQpharm Group (Hertfordshire, United Kingdom) used in our study is derived from the dehydrated cladode of *Opuntia ficus-indica* and fortified with soluble fiber from *Acacia* spp. The cactus fiber preparation is composed of soluble and insoluble dietary fibers, including cellulose and hemicellulose, and is standardized in its fat binding capacity (1 g compound binds to 10 g fat). The in vivo efficacy of the standardized cactus fiber on weight loss was previously established during a 14-week study on 123 obese or overweight subjects. The double-blind, randomized, placebo-controlled, parallel group study showed that subjects who consumed cactus fiber experienced significant weight loss compared with the placebo group.<sup>21</sup>

Postulation of weight loss due to fat binding and reduction in fat absorption would lack credibility unless such an effect could be demonstrated under the controlled conditions of a human clinical trial.<sup>22</sup> The quantification of fat excreted in fecal matter should be used as the primary assessment to examine the reduction of dietary fat absorption and establish that a product has fat-binding properties.<sup>22,23</sup> A pilot study (unpublished) had previously been conducted to evaluate the efficacy of cactus fiber on fecal fat excretion, in comparison to placebo. Cactus fiber was shown to significantly increase fecal fat excretion. However, several design limitations of the pilot trial hindered drawing a firm conclusion. Our study aimed to elucidate the dietary fat binding capacity of cactus fiber through determination of fecal fat excretion in healthy white subjects.

## Patients and Methods

Our double-blind, randomized, placebo-controlled, crossover single-center study was conducted from May to July 2012 in Berlin, Germany, and was approved by the ethics committee of the Charité Universitätsmedizin before initiation. This clinical investigation was performed according to the principles of the World Medical

Association (Declaration of Helsinki), as well as the European Union recommendations for Good Clinical Practice (CPMP/ICH/135/95), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH E6 (R1)<sup>24</sup> and ICH E3.<sup>25</sup> Subjects were randomized using randomization scheme of BiAS version 9.2 (2009) (Goethe-Universität Frankfurt/M., epsilon-Verlag Hochheim Darmstadt, Germany) in blocks of 4. Both the investigator and the subjects were kept blind to the allocation. The study was registered on ClinicalTrials.gov (identifier: NCT01590667). All subjects provided written informed consent before any study-related procedures were carried out.

## Subjects

Subjects who met the inclusion criteria were aged between 18 and 60 years, had body mass index between 20 and 30, reported regular bowel movements (self-reported 1–2 bowel movements per day), and used appropriate birth control methods (for female subjects).

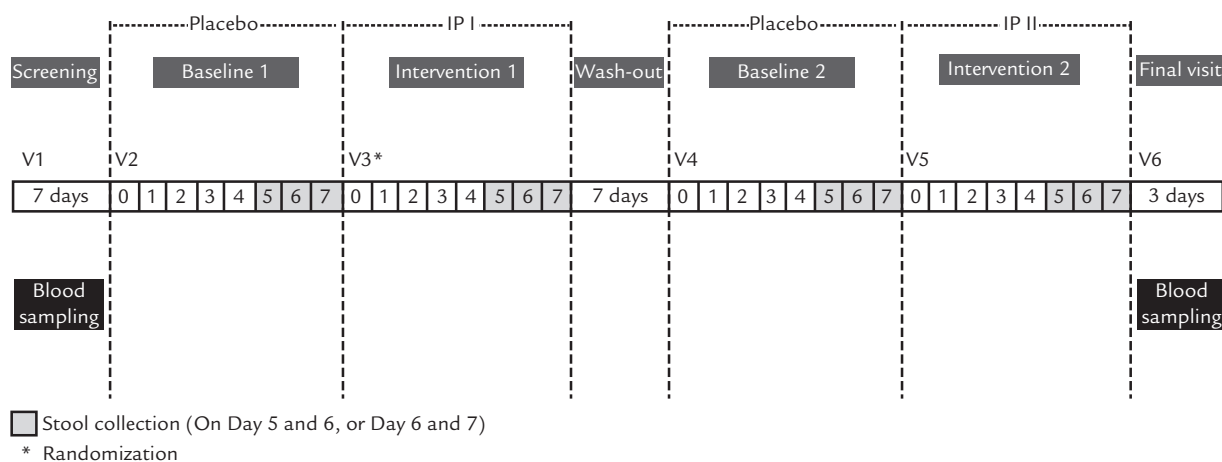
The exclusion criteria were known hypersensitivity to the ingredients of the investigational product, history of or concurrent endocrine disorders, use of other weight management products, use of antidepressants, uncontrolled hypertension, history of or concurrent gastrointestinal diseases, bariatric surgery, history of eating disorder, use of medications/products that could affect gastrointestinal function, pregnant or nursing, or excursions of safety parameters.

## Study intervention

The study period was approximately 45 days, as described in Figure 1. Subjects fulfilling all inclusion criteria entered a 7-day baseline period (Baseline 1 [B1]), during which they were provided with a standardized diet containing 35% of fat in total energy required. Daily energy needs were estimated for each subject depending on sex, age, and physical activity.<sup>26</sup> Subjects were given a diary at B1 and were instructed to record their daily food intake and to adhere strictly to the meal plan based on the food provided. Inspection of food diary was carried out at every subsequent clinic visit to ensure compliance. All subjects were instructed to take placebo tablets during B1. Subjects compliant with the meal plan and investigational product (IP) regimen during B1 entered a 7-day intervention phase (Intervention 1) and were randomized to either receive cactus fiber tablets or matching placebo, 2 tablets TID after each main meal. Each cactus fiber tablet contains 500 mg standardized cactus fiber, as well as common tableting excipients. Identical placebo tablets were manufactured based on the same formulation, but the active ingredient was replaced by a mixture of microcrystalline cellulose (316.5 mg) and calcium hydrogen phosphate dihydrate (183.5 mg).

A 7-day washout period followed by a second baseline measurement period (Baseline 2) took place before subjects were crossed over to the second treatment arm (Intervention 2). Subjects continued to consume the standardized diet provided throughout the study, except during the washout period.

All subjects needed to collect 2 24-hour stool samples during each baseline and intervention week. All bowel movements within a 24-hour period (beginning from 12:00 AM to 11:59 PM of each day) were collected on Day 5 and Day 6, or on Day 6 and Day 7. Samples were collected in tightly closed containers (Fecontainer, AT Medical BV, the Netherlands), labeled with the subject number and collection date, and refrigerated (at  $\leq 4^{\circ}\text{C}$ ) until stool collection was completed and transferred to a freezer ( $\leq -20^{\circ}\text{C}$ ). The stool samples were collected and delivered under controlled condition in a cooler box with thermal packs to the laboratory for analysis.



**Figure 1.** Clinical trial study schedule comparing and analyzing the fecal fat extraction effect of cactus fiber. There were 6 clinical visits (V1–V6) throughout the study period. V1 = screening + blood sampling; V2 = Baseline 1 (subjects were given a standardized meal, with placebo); V3 = subjects compliant to the meal plan and investigational product regimen were randomized to receive cactus fiber or placebo and a 7-day washout period followed; V4 = baseline 2 (similar to Baseline 1); V5 = subjects compliant to the meal plan and investigational product regimen were crossed over to the second treatment arm; V6 = blood sampling. Stool was collected on both Day 5 and Day 6, or Day 6 and Day 7 of baseline and intervention period. IP = investigational product.

### Efficacy end point

The end point of note was difference in the amount of fat excreted in the feces (relative to fat intake) with administration of cactus fiber compared with the placebo.

### Efficacy parameter

The stool samples from each container of 24-hour collection were homogenized and the fat content in the feces was quantified by the near-infrared reflectance analysis<sup>27</sup> at 700 to 2500 nm, using FENIR 8820-Infrared Analyzer (Stimotron, Wendelstein, Germany). The mean values from the 2 24-hour samples were used as the measurement results. Absolute fat mass excreted in the feces was then determined from the stool weight.

### Safety parameters

Venous blood samples were obtained at screening and the final visit of the study. Full blood count and clinical chemistry, including liver function parameters (ie, alanine transaminase, aspartate aminotransferase,  $\gamma$ -glutamyltransferase, alkaline phosphatase, and bilirubin), renal function parameters (ie, creatinine, urea), protein metabolism parameter (ie, uric acid), and lipid metabolism parameters (ie, total cholesterol, HDL-C, LDL-C, and triglycerides) were analyzed in a central laboratory. Adverse events were recorded at every visit.

### Sample size determination

The sample size was determined based on the results of a previous pilot trial conducted on standardized cactus fiber (unpublished). The effect size was estimated at between 1.16 and 1.27. At a significance level of 5%, power of 80%, and drop out rate estimated at 10%, a sample size of 20 was recommended by the study statistician.

### Statistical analyses

Statistical analysis was performed with SPSS Statistics software, version 19 (IBM-SPSS Inc, Armonk, NY).

All efficacy and safety end points received an explorative examination and were descriptively assessed. The variables were described by number, mean (SD), and median (number, mean [SD],

and median). For ordinal data, (discrete data) the frequency distribution was performed.

The testing of the primary efficacy end point data was performed with the nonparametric Mann-Whitney *U* test by analyzing the rank sums and supplemented by covariance analysis. The a priori hypothesis that no residual effects occur within this crossover study design was tested, as was the occurrence of a period effect.

All secondary outcomes and the concurrent variables were also evaluated primarily using nonparametric procedures. Due to the small samples size, Fisher exact test was used. Changes in clinical parameters over time (repeated measurements) were analyzed using analysis of variance with respect to differences in groups and systematic changes over time within each group, respectively.

## Results

### Demographics

Twenty-one subjects were screened, of whom 20 were included in B1 and randomized (Figure 2). All 20 subjects were included in the intent-to-treat population. There were 7 men (35.0%) out of the 20 subjects in the trial. The gender distribution was not significantly different between the cactus fiber group and the placebo group ( $P = 1.000$ ). The baseline characteristics, including age, body weight, body mass index, and energy requirements of the cactus fiber group and placebo group were similar (Table I).

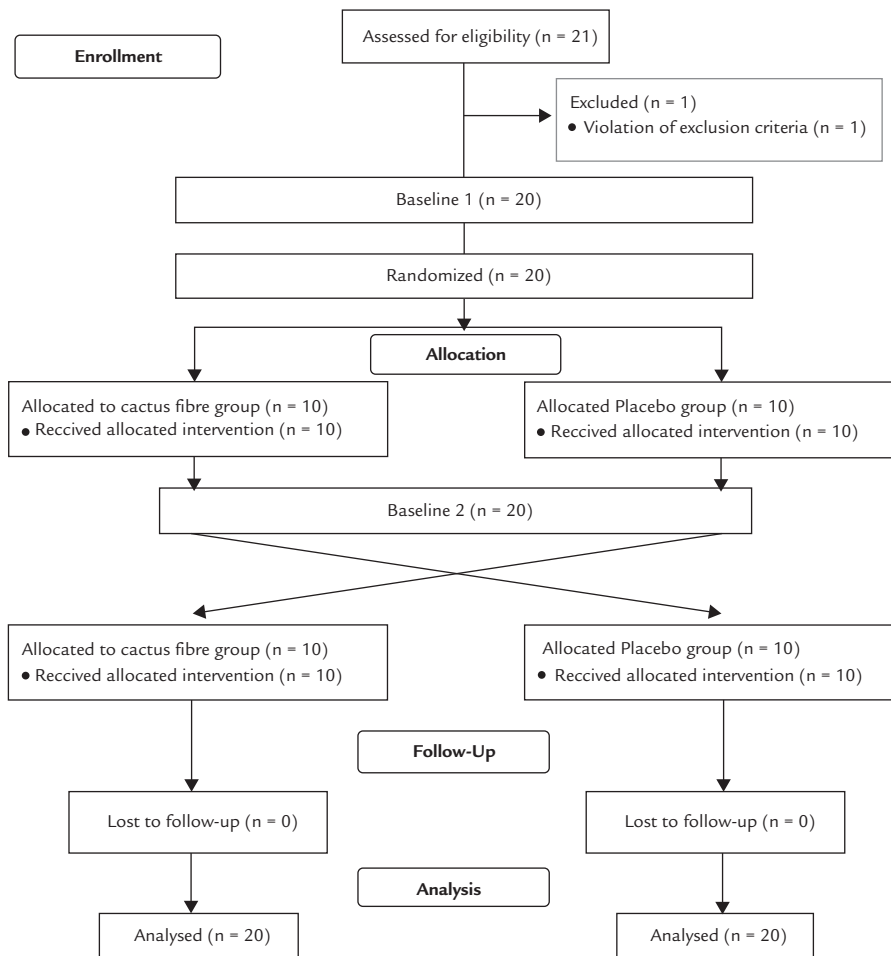
### Energy intake and compliance

Based on the calculated energy requirements, subjects were categorized into 3 groups that received a standardized meal plan providing 3 different energy levels: 2200 kcal/d (85 g fat), 2600 kcal/d (101 g fat), or 3000 kcal/d (115 g fat) (Table II). There was no statistically significant difference in energy requirement between the cactus fiber group and the placebo group at the beginning of the study.

All subjects complied with the IP administration instructions.

### Daily stool weight

Mean (SD) daily stool mass across the entire study period was 153.0 (73.7) g, with a range of 34.9 g to 481.4 g. There was no significant difference in the stool mass collected between the cactus



**Figure 2.** Subject flow diagram. Twenty-one subjects were screened and 20 subjects were randomized. All 20 subjects were included in the analysis.

fiber group and the placebo group from baseline to the end of the intervention ( $P \geq 0.05$  for all stool collections). Stool mass for both groups during the intervention periods are detailed in [Table III](#).

#### Fecal fat excretion

During both intervention periods, the absolute fat mass excreted was significantly more pronounced in the cactus fiber group compared with the placebo group. Based on subjects' assigned dietary plans and energy levels, the percentage of fat excreted relative to daily fat intake (equivalent to 100%) was calculated. At the end of both intervention periods, there was a significant difference in the percentage of dietary fat excreted between the 2 groups ([Table III](#) and [Figure 3](#)).

#### Safety and tolerability

There were no adverse events reported throughout the study period. There were also no clinically significant abnormalities in the laboratory parameters reported.

**Table I**  
Subject characteristics at baseline.

Parameter	Cactus fiber (n = 10) Placebo (n = 10)		P
	Mean (SD)		
Age (y)	39.8 (10.0)	46.9 (10.9)	0.147
Body weight (kg)	74.8 (7.7)	73.8 (10.2)	0.927
Body mass index	24.9 (2.3)	25.3 (3.0)	0.579
Energy requirements (kcal/d)	2320.2 (344.5)	2340.9 (388.3)	0.971

## Discussion

#### Fat excretion and weight loss

A previous study on standardized cactus fiber clearly demonstrated its effect in promoting weight loss in obese or overweight patients.<sup>21</sup> Nevertheless the proposed fat-binding property as a mechanism of action of cactus fiber remains to be clearly established.

The results of our study show that consumption of cactus fiber over a short period (5–6 days) increases the amount of fat excreted in the feces, with a mean (SD) of 15.11 (6.35) g fat excreted daily in comparison to 4.33 (2.91) g in the placebo group. In relation to the amount of daily fat intake, cactus fiber facilitates excretion of 15.79% (5.79%) of the dietary fat in comparison to 4.56% (3.09%) in

**Table II**  
Sample meal plan (2200 kcal/d).

Meal	Food	Approximate weight (g)	Fat content (g)
Breakfast	2 slices bread	100	1
	1 Tbsp butter	10	8
	2 slices ham	60	3
	1 slice cheese	20	9
	milk	400	6
Lunch	2 slices toasted bread	250	2
	2 Tbsp butter	20	16
	2 slices cheese	40	12
	1 c cream cheese	125	4
Dinner	Prepackaged ready meal	480	24.5

**Table III**

Stool mass, absolute fat excretion, and percentage of dietary fat excreted (in relation to total fat intake) at both intervention periods.

Parameter	Cactus fiber (n = 20)			Placebo (n = 20)			p
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	
Stool mass (g)	162.3 (59.5)	155.9	42.8–300.1	133.5 (64.3)	138.6	44.9–284.7	0.148
Absolute fat excretion (g)	15.11 (6.35)	14.06	4.31–28.77	4.33 (2.91)	3.77	1.28–11.92	< 0.001
Dietary fat excreted (%)	15.79 (5.79)	15.06	5.07–28.39	4.56 (3.09)	3.76	1.51–14.02	< 0.001

subjects consuming placebo. The results of our study further strengthen the mode of action of cactus fiber in binding and reducing fat absorption. In comparison, a retrospective analysis of the dose–response relationship of orlistat suggests that mean fecal fat excretion plateaus at approximately 35% of daily fat intake at daily doses of  $\geq 400$  mg/d.<sup>28,29</sup> At the recommended dose of orlistat 120 mg TID and 60 mg TID, the inhibition of dietary fat absorption is estimated to be at 30% and 25%, respectively.<sup>29</sup> Flaxseed, another food ingredient with high dietary fiber content, which has previously been suggested to be able to reduce fat digestion, was found to result in higher fecal fat excretion of 4.96 (0.31) g per day, compared with 3.20 (0.33) g per day in control when given as drink at a dosage of 3 g fiber per day for 7 days.<sup>30</sup> Even though there are differences in the study design, our study showed that cactus fiber may possess higher fat excretion capacity in comparison to flaxseed-extracted fiber; the difference may be due to differences in the compositions of flaxseed fiber and cactus fiber in the studies. Although the flaxseed-extracted fiber comprises arabinoxylans, galactose, fructose residues, and some pectin,<sup>30</sup> the cladode of *Opuntia ficus-indica* is reported to contain 40% to 50% dry weight of dietary fibers, which consist of mucilage, gum, pectin, and hemicellulose.<sup>31–33</sup> Bendtsen et al<sup>34</sup> showed that an increase in calcium intake can lead to fecal fat loss, with a mean (SD) excretion of 11.5 (1.4) g fecal fat per day from a high calcium diet ( $\sim 2300$  mg/d) as opposed to 5.4 (0.5) g per day fecal fat from a low calcium diet ( $\sim 700$  mg/d). It should be noted that the levels of calcium included in the diets of this study are much higher than the levels used in the active and placebo tablets of our study (81 mg and 337 mg calcium per day, respectively) and the fecal fat excretion observed is unlikely a result of calcium found in the IPs.

Approximate weight loss effect from the absolute amount of fat excreted from cactus fiber consumption can be extrapolated from a model proposed by Hall et al,<sup>35</sup> which takes into account the compensatory effects of the body toward energy expenditure during weight loss. Given that 1 g fat equals 9 kcal energy, 15.11 g fat excreted per day would correspond to 136 kcal of reduced energy intake per day. Assuming—according to the model of Hall et al<sup>35</sup>—that a permanent 10 kcal energy deficit would result in a weight loss of 0.45 kg, and that 1 year is needed to achieve 50%,

and 3 years to achieve 95% of this weight loss, the 136 kcal energy deficit per day would lead to a loss of approximately 3 kg body mass after 1 year, and 5.8 kg after 3 years. As quoted above, the reported fecal fat excretion of orlistat at 180 mg/d is 25%, yet in a study of 16 weeks' duration, orlistat at 60 mg TID has been shown to only result in a 3.50 kg weight loss compared with 1.90 kg in the placebo group, with a net weight loss of 1.6 kg.<sup>36</sup> In comparison, 2.4 kg mean net body weight loss was observed over a 3-month period during a previous study of cactus fiber,<sup>21</sup> suggesting a more pronounced weight loss effect size than explained by the reduced energy intake due to fat excretion alone. The additional weight loss effect may be attributed to other functional properties of fibers contained in cactus fiber; for example, the effects of fibers on promoting satiety<sup>37,38</sup> and delaying absorption of nutrients during digestion,<sup>32,33,39</sup> which have been frequently reported in literature. Despite being a nonpharmacologic ingredient, cactus fiber demonstrated substantial efficacy in weight management.<sup>21</sup>

#### Study design and limitations

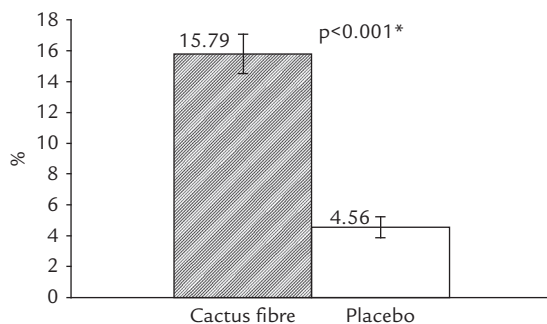
Our study design incorporated considerably long baseline periods of 7 days, to adhere subjects to the standardized diet plan and also to ensure compliance of subjects to the study protocol, in both stool collection and investigational product intake. There is variation in terms of daily stool weight, ranging from 34.9 g to 481.4 g, with a mean (SD) of 153.0 (73.7) g. This figure is nevertheless in line with the findings of Cummings et al,<sup>40</sup> who reported stool weight with a range of 72 to 470 g/d in the different populations of the world. Our investigation decided against a longer study period with additional stool collection, considering that the task of stool collection may be unpleasant or stressful for subjects and that the use of standardized diet in a longer study may reduce compliance with the diet plan and stool collection. Additionally, a second baseline measurement was incorporated after the washout period to further rule out any possible carryover effect. These measures were perceived to be beneficial in ensuring the consistency and reliability of results.

A limitation of our study is that it does not provide indication if the increase in fecal fat excretion can be sustained and if tolerance/adaptation effects may develop as a result of longer-term consumption of cactus fiber. Nonetheless, a sustained positive effect of cactus fiber on weight management has been clearly established in a previous clinical investigation.<sup>21</sup>

A subgroup analysis carried out among subjects assigned to a diet of different daily energy requirement levels showed a possible positive relationship between the amount of fat intake and percentage of fat excreted (data not shown). However, due to the small sample size at each energy level, the correlation needs further confirmation in a study with a larger population.

#### Safety

Cactus fiber demonstrated a good tolerability profile as a product derived from natural sources. No adverse events were reported throughout the study.



**Figure 3.** Percentage of dietary fat excreted (in relation to total fat intake). Error bar represents 1 standard error of mean. With cactus fiber, mean (SD) 15.79% (5.79%) of fat was excreted, in comparison with placebo, which contributed 4.56% (3.09%) of fat excretion ( $P < 0.001$ ). \*Significant difference.

## Conclusions

In our study, the administration of cactus fiber resulted in significant increases of dietary fat excretion in the feces. This finding confirmed the in vivo fat-binding capability of cactus fiber; furthermore, it supports the hypothesis that its weight loss effect is achieved by reducing dietary fat absorption, which leads to lower energy intake and promotes weight loss. Because cactus fiber promotes dietary fat excretion, and previous research has indicated that cactus fiber exerts a noticeable hypolipidemic effect,<sup>17</sup> future investigations on the effects on cactus fiber on blood lipid levels may add value to the research of its use beyond weight management.

## Acknowledgments

The authors thank Dr. N. Bitterlich for providing valuable assistance. InQpharm Europe Ltd, sponsor of this study, was involved in study design, interpretation of data, writing of manuscript, and submitted the manuscript for publication. The authors of this study, Prof. Ralf Uebelhack contributed in the critical review of study design and manuscript writing, Pee-Win Chong and Zhi-Ming Beah provided oversight to the clinical trial and wrote the manuscript. Felix Alt was the project manager. Regina Busch was the investigator of this trial.

## Conflicts of Interest

This study was funded by InQpharm Europe Ltd. P.-W. Chong and Z.-M. Beah are employees of InQpharm Europe Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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