Scientific Research Publishing

Food and Nutrition Sciences, 2022, 13, 424-438
https://www.scirp.org/journal/fns
ISSN Online: 2157-9458
ISSN Print: 2157-944X

The Effect of Gum Acacia on Post-Prandial Glucose and Insulin Levels in Healthy Subjects

Udo Bongartz, Constantin Erlenbeck, Irene Wohlfahrt*

analyze & realize GmbH, Berlin, Germany
Email: *iwohlfahrt@a-r.com

How to cite this paper: Bongartz, U., Erlenbeck, C. and Wohlfahrt, I. (2022) The Effect of Gum Acacia on Post-Prandial Glucose and Insulin Levels in Healthy Subjects. *Food and Nutrition Sciences*, **13**, 424-438.
https://doi.org/10.4236/fns.2022.134031

Received: March 21, 2022
Accepted: April 23, 2022
Published: April 26, 2022

Abstract

This double-blind, controlled, randomized, three-way cross-over study evaluates the effect of 40 g (D1 group) and 20 g (D2 group) of acacia gum (AG) versus no treatment (NT group) on post-prandial glucose (PPG) levels in normal-weight and overweight subjects. Additionally, post-prandial insulin (PPI) levels as well as the safety and tolerability of gum acacia were assessed. 35 healthy subjects aged 25 - 60 years, body mass index 18.5 kg/m^2 - 29.9 kg/m^2, received one treatment of 20 g, 40 g, or 0 g of AG each. Glucose and insulin values were determined at −15 min and prior to the intake (time "0") as well as 15, 30, 45, 60, 90 120, and 180 min after the "0 min" blood draw. The mean PPG levels were lower (34% in D1 group, p = 0.003; 35% in D2 group, p = 0.005) than in the NT group. PPI concentration was statistically significantly lower at all time points except baseline in both treatment groups compared to NT groups. Global benefit and tolerability were rated as "very good" or "good" by 100% of subjects in the treatment groups. This study provides robust evidence of the significant benefits of AG consumption on PPG and PPI levels in healthy subjects. Moreover, very good tolerability was demonstrated.

Keywords

Acacia Gum, Post-Prandial Glucose, Post-Prandial Insulin, Glycemic Response Control

1. Introduction

Complex carbohydrates (fibers) are not degraded by enzymes in the stomach and small intestines and enter the colon undigested [1]. In the colon, they can be fermented by the gut flora leading to the production of short-chain fatty acids [2]. Fibers are known for their effect on lowering the glycemic response [3] and

are considered to have potentially satiety-enhancing properties [4] [5].

The consumption of dietary fibers is widely accepted as an important strategy for maintaining digestive and general health. Epidemiological studies have suggested an inverse relationship between dietary fibre consumption and metabolic syndrome [6].

Accordingly, non-digestible carbohydrates are well recognized for their beneficial effect on post-prandial glucose. They are authorized in the EU to carry the claim "consumption of foods/drinks containing < name of all used non-digestible carbohydrates > instead of sugars induces a lower blood glucose rise after their consumption compared to sugar-containing foods/drinks" (Annex [7]).

Recently, FDA [8] published a final rule amending the Nutrition and Supplement Facts label regulations defining dietary fiber "as non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health". According to FDA [9], several beneficial physiological effects are associated with the consumption of non-digestible carbohydrates, such as attenuation of blood glucose, insulin, and cholesterol concentrations.

Acacia gum (AG), also known as gum arabic, is a heteropolysaccharide (molecular weight 350 - 850 kDa) harvested from stems and branches of *Acacia seyal* or *Acacia senegal*. It is highly soluble and broadly used in numerous solid and liquid food matrices. AG powder is odorless, colorless and flavorless, and instantly soluble in water at room temperature. It is widely used in the food industry (e.g. in ice creams, jellies, candies, soft drinks, beverages, syrups, chewing gums, etc.) and has a generally recognized as safe (GRAS) status in the USA.

AG is considered to be a prebiotic due to its inaccessibility to the digestive enzymes in the small intestine which results in the stimulation of growth or activity of health-promoting bacteria [1] [10]. Dietary intake of AG has been linked to a number of beneficial effects such as lowering plasma glucose levels [11] and inducing satiety [12].

In order to be able to extrapolate the results to the general population, the aim of the present trial was to expand the clinical evidence with respect to the beneficial effects of AG on post-prandial blood glucose and post-prandial insulin levels in generally healthy, *i.e.* normoglycemic, normal-weight and overweight subjects.

2. Methods

The main objective of this double-blind, controlled, randomized, three-way cross-over study was to evaluate the effect of AG versus no treatment on post-prandial glucose (PPG) levels in normal-weight and overweight subjects. Additionally, post-prandial insulin (PPI) levels as well as the safety and tolerability of AG were assessed.

36 generally healthy men and women between 25 and 60 years old with a body

mass index (BMI) of 18.5 kg/m^2 - 29.9 kg/m^2 and normal fasting blood glucose levels (3.9 to <5.6 mmol/L (70 to <100 mg/dL) were enrolled in the study at one investigational site in Germany in the period time from June to September 2019. Participation was based upon written informed consent by the participant, following written and oral information by the investigator regarding the nature, purpose, consequences, and possible risks of the clinical study. Among the exclusion criteria were self-reported disorders, eating disorders, or dietary habits that might interfere with the study conduct or evaluation. The main inclusion and exclusion criteria are listed in Supplementary Table S1.

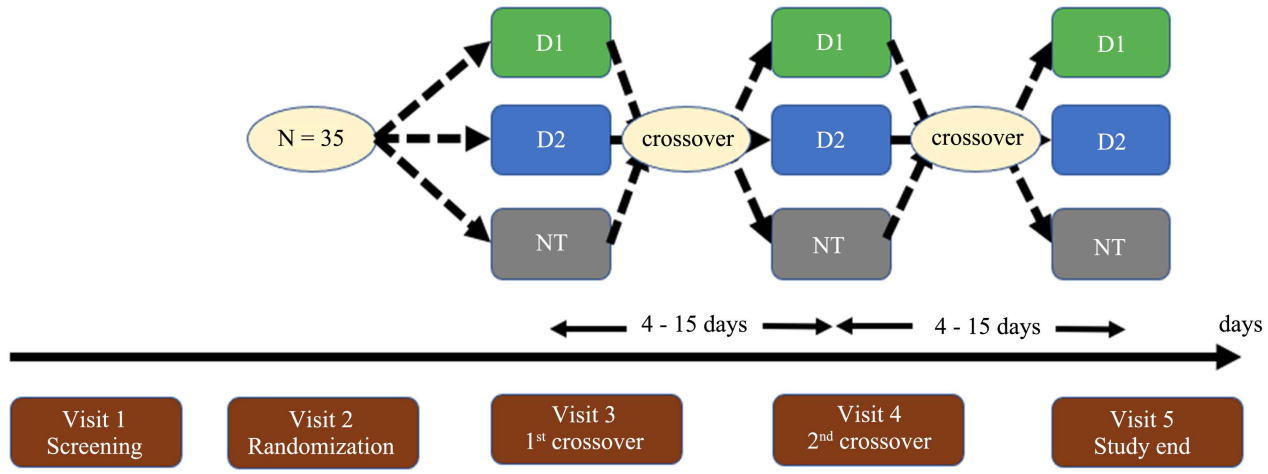
All subjects of the full analysis set (FAS) population were Caucasian. Two subjects were affected by amnestic findings at V1 (lactose intolerance and arterial hypertension, respectively).

All subjects voluntarily gave their written informed consent. The clinical investigation was approved by the Ethics Committee of Charité University Berlin and was performed according to the principles of the World Health Organization (Declaration of Helsinki), and EU recommendations for Good Clinical Practice (CPMP/ICH/135/95), ICH E6 (R2).

The investigational study product AG powder (Fibregum^{TM}) was obtained from Nexira (Rouen, France).

There were three treatment types in the study: 40 g AG powder (D1), 20 g AG powder (D2), and 0 g AG powder (no treatment, NT). Each treatment type was applied once with the standardized breakfast (with the study product mixed into the orange juice served) on the test days visit 2 (V2), visit 3 (V3), and visit 4 (V4).

Study subjects were randomized into each of the three treatment groups (40 g, 20 g, and 0 g AG) in a cross-over setting according to the scheme detailed in Figure 1. Visits were conducted according to the visit schedule in Table 1. The study period between each test visit (V2, V3, and V4) was defined as 4 - 15 days.



D1 = 40 g acacia gum; D2 = 20 g acacia gum; NT = 0 g acacia gum (no treatment)

Figure 1. Study design.

Table 1. Visit schedule.

Procedure	Visit 1 Screening	Visit 2 Randomization	Visit 3 1st cross-over	Visit 4 2nd cross-over	Visit 5 End of study
Oral and written information about the nature, purpose, possible risks and benefits of the study provided to the subjects by the investigator	X				
Written consent of the subject to participate; the subject understands the requirements of the clinical investigation and is willing to comply	X				
Questioning and documentation of the anamnestic data (including medical history, concurrent diseases), concurrent treatment and supplementation, demographic and anthropometric data, and physical examination by the investigator	X				
Confirmation that all inclusion criteria are met and that there are no violations of any exclusion criteria	X				
Assessment of body weight & height, BMI	X				
Blood sampling for screening laboratory parameters (including HbA1c, fasting blood glucose and thyroid-stimulating hormone)	X				
Dipstick urinalysis for the assessment of glucose and proteins	X				
Pregnancy test in urine (women with childbearing potential)	X				
Measurement of blood pressure and pulse rate	X	X	X	X	
Documentation of possible occurrence of adverse events (AEs)	X	X	X	X	X
Questioning on menstrual cycle	X	X	X	X	
Issue of information on restrictions prior to test days	X				
Handing out standardized meal for the dinner on the day before next visit	X	X	X		
Questioning and documentation of new or changed concurrent treatment and supplementation/possible occurrence of AEs		X	X	X	X
Questioning on adherence to restrictions prior to test days		X	X	X	
Questioning with respect to any changes in dietary/sleep habits and level of physical activity		X	X	X	
Randomization and use of 1st IP		X			
Assessment of body weight		X	X	X	
Standardized breakfast		X	X	X	
Blood sampling for glucose and insulin −15 to 180 min		X	X	X	

Continued

Gastrointestinal tolerability assessment by subject 0 to 240 min	X	X	X	
Handing out subject diary and instructions for use	X	X	X	
Global evaluation of benefit and tolerability of the treatment type by the subjects and by the investigators	X	X	X	
First cross-over and use of 2nd IP		X		
Collection and control of subject diary		X	X	X
Second cross-over and use of 3rd IP			X	

BMI, Body Mass Index; IP, investigational product.

The defined restrictions prior to the test days comprised the following: 2 days prior to visits, subjects had to abstain from drinking alcohol and from any medium or heavy physical activities, keep a low-fiber diet (in accordance with the provided list of foods to be avoided), consume no other food or calorie-containing beverages than the provided standardized dinner in the evening of the day prior to visit (including chewing gum, sweets, etc.), and observe an overnight fast of 12 h (except water) before the visit and ensure sufficient sleep in the two nights preceding the visit. On test days, they were required to use the least strenuous option of transport to the site possible (e.g. by car, or public transportation) and to only consume food and beverages provided at the site during the visits.

The standardized isocaloric (±3 kcal) breakfast meal had the same content of digestible carbohydrates (±0.4 g) and included 300 ml orange juice (with either 40 g, 20 g, or 0 g AG powder added), two English muffins topped with cream cheese and peanut butter as well as a cup of 150 ml water. The standardized breakfast had to be completely consumed at an individual pace yet within a maximum of 15 minutes.

Venous blood samples were drawn for the determination of glucose and insulin values, with sampling times at −15 min and immediately prior to the intake of the standardized breakfast (time "0") as well as 15, 30, 45, 60, 90 120, and 180 min after the "0 min" blood draw. In accordance with the Oral Glucose Tolerance Test and orientation to similar studies (e.g. [11]), the measuring time for the primary endpoint was limited to 120 minutes.

Global evaluations of benefit and tolerability were evaluated in a global scaled evaluation with "very good", "good", "moderate", or "poor" by subjects and investigators.

GI tolerability was assessed as described by Boler *et al.* [13], assessing the items burping, cramping, distension, flatulence, nausea, and vomiting, scored by means of a 4-point scale: 1 = none, 2 = mild, 3 = moderate, 4 = severe, on test days only, at 0 min (before the standardized breakfast) and 1, 2, 3, 4, 6, 12 and 24 hours after intake of standardized breakfast in a subject diary.

Any adverse event (AE) that occurred during the clinical study had to be rec-

orded in the CRF. At each visit, the investigator had to question the subject of any unfavorable event occurred and record the respective AE.

Sitting blood pressure and pulse rate were measured using standard procedures.

The subjects and investigators had to evaluate the tolerability of the treatment type (global scaled evaluation with "very good", "good", "moderate", or "poor").

Bodyweight (kg) was measured in subjects in fasting condition wearing only underwear and barefoot, after emptying the bladder and bowels as needed, using standardized weighing scales (Tanita BC-420MA).

The subjects were questioned with respect to any changes in their dietary habits (e.g. lower or higher calorie intake), their sleep habits (e.g. less or more sleep) and their level of physical activity (e.g. lower or higher activity level).

The null hypothesis for the primary endpoint $H0_1$ was that there were no statistical differences between the AG dosage D1 vs. NT group with respect to post-prandial glucose $iAUC_{(0\text{-}120)}$ and was tested against the alternative hypothesis HA_1 (two-sided), suggesting a statistical difference between the compared groups. The null hypothesis for the main secondary endpoint $H0_2$ was that there were no statistical differences between the AG dosage D2 vs. NT group with respect to post-prandial glucose iAUC 0 - 120 min and was tested against the alternative hypothesis HA_2 (two-sided), suggesting a statistical difference between the compared groups. The non-parametric Wilcoxon test was used, supposing an error of the 1st kind a = 5% (two-sided). The confirmative testing of the defined hypotheses for the primary and the main secondary endpoint was performed by considering ordered hypotheses. At first, the primary endpoint was tested. Once the corresponding null hypothesis $H0_1$ had been rejected at level $\alpha = 5\%$ (two-sided), then the main secondary endpoint, connected with the null hypothesis $H0_2$, was tested at the same (full) level α.

All endpoints and the concurrent variables were analyzed using non-parametric statistical tests; Fisher's exact test for qualitative data, Mann-Whitney-U test for two independent groups for quantitative data, and Wilcoxon-test for paired observations. The main benefit endpoints were analyzed additionally by using a nonparametric covariance analysis (Wald-Chi-Square) with the baseline values as covariates. Possible carry-over effects and interactions between treatment and period were also examined. All tests were performed with a significance level (type I error) of 5% (two-tailed). 95% confidence intervals were calculated. Multiple tests were performed without correction of significance level in explorative analysis.

In order to ensure a data set with regard to the primary endpoint, the sample size sufficient to detect differences between both verum groups and no treatment had to be estimated (at a significance level of 5% (two-sided) and a power of 80%) for the three-way cross-over design. Sharma [11] had shown an effect size of more than 1.0 for the dosage of 20 g AG. In a comparable study with another product [14], a similar effect size had been observed. For the sample size estimation in the present study, an effect size of 1.0 was postulated, resulting in a total

of 30 subjects in the three-way cross-over. Accounting for the drop-out rate of 15% and the randomization block size, a total of 36 subjects had to be included.

3. Results

35 of the 36 included subjects finished the study according to protocol. One subject terminated the study after visit V2 because a blood draw was not possible, leading to exclusion of that subject from FAS.

The baseline characteristics of the FAS population are shown in Table 2. There were no statistically significant differences between the groups for any of the parameters.

Postprandial blood glucose (PPG) levels

Subjects in the treatment groups overall showed smaller rises in PPG levels over time compared to the NT group (Figure 2). The reduction of post-prandial glucose was most pronounced 30 minutes post-meal. The mean PPG level in the D1 group, measured via $iAUC_{(0\text{-}120)}$, was 87.2 ± 57.7 mmol*min/L, which is 45.9 ± 84.8 mmol*min/L (=34%) lower than in the NT group (133.1 ± 109.5 mmol*min/L, p = 0.003, Table 4, primary endpoint), with 74% of subjects with an $iAUC_{(0\text{-}120)}$ in the D1 group less than NT and 25.7% of subjects greater than NT (Table 3).

Also, PPG levels in the D2 group, measured via the $iAUC_{(0\text{-}120)}$, were lower for 60.0% of subjects than the NT group (Table 3). The mean PPG level in D2 was 79.4 ± 51.6 mmol*min/L, which is 53.7 ± 106.8 mmol*min/L (=35%) lower than in NT group (p = 0.005, Table 4).

Both endpoints were also statistically significant when considering the baseline value as covariate (D1 vs NT: $p_{group} = 0.034$; D2 vs NT: $p_{group} = 0.008$).

Maximal PPG concentration was also statistically significantly lower for both groups ($p_t < 0.001$ for both D1 vs. NT and D2 vs. NT, Table 4). Differences in PPG levels, calculated as iAUC, were statistically significant for both groups at all time points compared to the NT groups (Table 4).

Table 2. Subject demographic and other baseline characteristics.

Parameters	FAS (n = 35)	D1 (n = 11)	D2 (n = 12)	NT (n = 12)
Gender				
Male	30	10	11	9
Female	5	1	1	3
Age (mean (SD))	42.5 (10.3)	45.4 (7.9)	37.2 (11.3)	45.2 (9.9)
Body height [cm] (mean (SD))	178.5 (9.2)	178.0 (11.0)	178.1 (7.1)	179.3 (10.0)
Body weight [kg] (mean (SD))	79.03 (10.29)	76.57 (8.57)	81.23 (9.71)	79.07 (12.43)
Glucose [mmol/l] (mean (SD))	5.078 (0.319)	5.133 (0.330)	4.945 (0.281)	5.161 (0.328)
HbA1c [%] (mean (SD))	5.28 (0.24)	5.29 (0.30)	5.22 (0.22)	5.32 (0.19)

FAS, full analysis set; D1, 40 g acacia powder; D2, 20 g acacia powder; NT, no treatment.

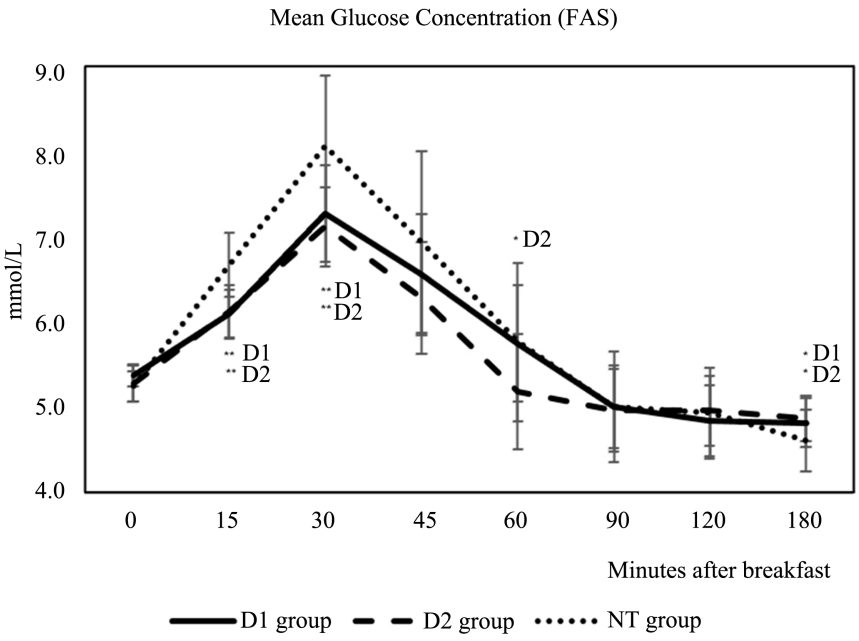


Figure 2. Overview glucose concentration (FAS). FAS, Full Analysis Set; D1, 40 g acacia gum; D2, 20 g acacia gum; NT, 0 g acacia gum (no treatment). Error bars are SD. *, statistically significantly different to NT ($p > 0.05$); **, statistically highly significantly different to NT ($p > 0.001$).

Table 3. Comparisons of incremental $AUC_{(0\text{-}120)}$.

Glucose	Total (N = 35)		
	number	percentage	p-value
D1 less than NT	26	74.3	
D1 equal to NT	0	0.0	0.003
D1 greater than NT	9	25.7	
D2 less than NT	21	60.0	
D2 equal to NT	0	0.0	0.016
D2 greater than NT	14	40.0	

D1, 40 g acacia gum; D2, 20 g acacia gum; NT, 0 g acacia gum (no treatment).

There were no statistically significant differences in PPG levels between the two treatment groups (not shown).

Post-prandial insulin (PPI)

PPI concentration was statistically significantly lower in both the D1 groups and the D2 groups compared to NT groups for all time points except baseline (Figure 3). Insulin reduction was most pronounced 45 minutes post-meal.

Maximal insulin concentration was 47.0 ± 23.0 mU/L in the D1 group and 51.3 ± 26.3 mU/L in the D2 group versus 69.3 ± 33.1 mU/L in the NT group, also with a statistically significant difference ($p_t < 0.001$ for both D1 vs. NT and D2 vs. NT, Table 5).

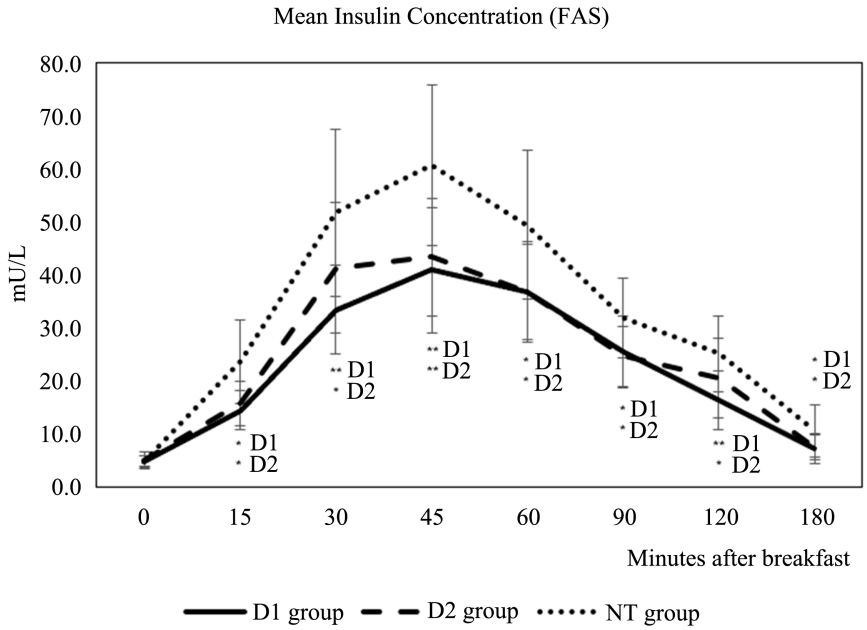


Figure 3. Overview of insulin concentration (FAS). FAS, Full Analysis Set; D1, 40 g acacia gum; D2, 20 g acacia gum; NT, 0 g acacia gum (no treatment). Error bars are SD. *, statistically significantly different to NT ($p > 0.05$); **, statistically highly significantly different to NT ($p > 0.001$).

Table 4. Comparison of the PPG levels for the treatment groups (FAS) at various time points.

Treatment group	NT	D1			D2		
N = 35	Mean (SD)	Mean (SD)	Difference vs NT	p-value	Mean (SD)	Difference vs NT	p-value
$iAUC^{a}_{(0\text{-}15)}$	10.9 (5.7)	5.6 (3.9)	−5.3 (5.3)	<0.001	6.6 (3.5)	−4.3 (6.1)	<0.001
$iAUC_{(0\text{-}30)}$	45.0 (20.1)	28.2 (12.6)	−16.8 (16.6)	<0.001	29.3 (10.6)	−15.6 (18.4)	<0.001
$iAUC_{(0\text{-}45)}$	80.7 (43.1)	53.0 (24.3)	−27.7 (28.8)	<0.001	52.0 (21.0)	−28.7 (36.6)	<0.001
$iAUC_{(0\text{-}60)}$	102.6 (65.9)	68.7 (36.6)	−33.9 (44.7)	<0.001	64.3 (31.1)	−38.3 (57.9)	<0.001
$iAUC_{(0\text{-}90)}$	123.1 (94.5)	82.2 (50.8)	−40.9 (69.9)	0.001	73.9 (43.7)	−49.2 (89.4)	0.003
$iAUC_{(0\text{-}120)}$	133.1 (109.5)	87.2 (57.7)	−45.9 (84.8)	0.003	79.4 (51.8)	−53.7 (106.8)	0.005
$iAUC_{(0\text{-}180)}$	141.8 (123.2)	90.7 (63.7)	−51.1 (122.3)	0.005	85.3 (60.2)	−56.4 (122.3)	0.010
Maximal concentration[b]	8.35 (1.6)	7.5 (1.0)	−0.9 (1.0)	<0.001	7.4 (0.8)	−1.0 (1.2)	<0.001

D1, 40 g acacia gum; D2, 20 g acacia gum; NT, 0 g acacia gum (no treatment); iAUC, incremental area under the curve; a = mmol*min/L; b = mmol/L.

Table 5. Comparison of insulin levels for the treatment groups (FAS) at various time points.

Treatment group	NT	D1			D2		
N = 35	Mean (SD)	Mean (SD)	Difference vs NT	p-value	Mean (SD)	Difference vs NT	p-value
$iAUC^{a}_{(0\text{-}15)}$	142.1 (105.1)	71.8 (48.5)	−70.3 (110.5)	0.001	80.6 (49.0)	−61.6 (109.8)	0.002
$iAUC_{(0\text{-}30)}$	635.8 (403.5)	357.2 (177.5)	−278.5 (337.7)	<0.001	432.9 (248.6)	−202.9 (300.1)	<0.001
$iAUC_{(0\text{-}45)}$	1407.4 (784.6)	841.1 (397.4)	−566.2 (558.2)	<0.001	992.1 (519.7)	−415.2 (484.7)	<0.001
$iAUC_{(0\text{-}60)}$	2162 (1112)	1350 (628.0)	−812.2 (750.9)	<0.001	1518 (727.5)	−644.2 (868.6)	<0.001
$iAUC_{(0\text{-}90)}$	3239 (1586)	2136 (964.6)	−1103 (1079)	<0.001	2289 (1034)	−950.5 (1092)	<0.001
$iAUC_{(0\text{-}120)}$	3951 (1876)	2619 (1210)	−1332 (1272)	<0.001	2815 (1274)	−1136 (1343)	<0.001
$iAUC_{(0\text{-}180)}$	4738 (2303)	3037 (1495)	−1701 (1503)	<0.001	3368 (1655)	−1370 (1601)	<0.001
Maximal concentration	69.3 (33.1)	47.0 (23.0)	−22.3 (22.9)	<0.001	51.3 (26.3)	−18.0 (17.3)	<0.001

D1, 40 g acacia gum; D2, 20 g acacia gum; NT, 0 g acacia gum (no treatment); iAUC, incremental area under the curve; a = mU*min/L; b = mU/L.

Differences in PPI concentration as calculated via iAUC also were statistically significant in both treatment groups versus the NT group for all time points (Table 5).

There were no statistically significant differences in PPI levels between the two treatment groups (not shown).

Global evaluation of efficacy

The benefit was rated as "very good" or "good" by 100.0% of subjects in the D1 group and by 82.9% of subjects in the D2 group compared to 45.7% of subjects in the NT group ($p_U < 0.001$ for both D1 vs. NT and D2 vs. NT) and by the investigators for 100.0% of subjects in the D1 group and 82.8% of subjects in the D2 group compared to 45.7% of subjects in the NT group ($p_U < 0.001$ for both D1 vs. NT and D2 vs. NT).

Safety and tolerability evaluation

There were no relevant differences between either verum dose and placebo in the occurrence of AEs, vital signs, or gastrointestinal tolerability (though distention and flatulence appeared somewhat more frequent in D1) during the study. None of the AEs were related to the use of IP. Both the subjects and the investigators rated tolerability as "very good" or "good" in 100% of cases in each verum group.

Other results

There were no relevant differences in body weight between each verum dose vs NT at any of the time points analyzed. Also, there were no relevant differences in appetite, satiety, or physical well-being reported between study groups or vs NT. All subjects kept their dietary habits, their sleep habits, and their level of physical activity during the study.

4. Discussion

In this double-blind, placebo-controlled, clinical study in healthy subjects, it was demonstrated that a single intake of AG (Fibregum™) has beneficial effects on glycemic control. The glucose AUC at 120 minutes after meal consumption was 34% lower with consumption of 40 g Fibregum™ compared to no consumption, and 35% lower with consumption of 20 g Fibregum™ (**Table 4**). The magnitude of effects was widely comparable between both AG doses, indicating that most probably the plateau of the effect was achieved at D2 (20 g) (**Figure 2**), beyond which no dose-effect can be observed.

These results confirm previous research showing that AG has glycemic attenuation effects. Sharma [11] found that 20 g AG added to a 100 g load of glucose resulted in a 16.1% reduction of plasma glucose and an 11.2% reduction of serum insulin at 90 minutes. In a cross-over design study by Akeo *et al.* [15], 12 healthy subjects consumed a sucrose solution with 0 g (control), 5 g, or 10 g of AG. The PPG peak was statistically significantly lower upon consumption of AG (either dose) compared to the control. This observation has been confirmed in the present study as well, with statistically significantly lower PPG peaks for both doses, in comparison with no treatment.

Further results obtained for the secondary endpoints in the present study provide additional evidence of the beneficial effect of Fibregum™ on glycemic control parameters. Incremental PPG AUC levels were lower for both AG doses in comparison to no treatment, with differences statistically significant at all measured time points (from 0 - 15 to 0 - 120 min). Lower total PPG AUC levels were observed at most measured time points: the differences were statistically significant for D1 at 15, 30, 45, and 60 min and D2 at 15, 30, 45, 60, 90, and 120 min; there was a strong statistical trend (pt = 0.054) for D1 at 90 min (**Table 4**).

Maximal PPG concentration was statistically significantly lower for both AG doses in comparison to no treatment.

Confirming the glycemic response attenuation exerted by AG, insulin response in the treatment groups was also lower than in the NT group (**Figure 3**). Differences in the insulin AUC between both treatment groups versus NT were statistically significant for all time points except baseline, and at most time points even highly significant (**Table 5**), showing a consistently and clearly reduced insulin response compared to the NT group. Again, and in keeping with the observed changes in glucose levels, there was no statistically significant difference in insulin levels between treatment groups, which indicates that an in-

take amount of 20 g AG is sufficient to obtain the effect both for post-prandial glucose and for post-prandial insulin reduction. This result indicates that less insulin may be secreted in response to a reduced postprandial glucose peak, and/or that hepatic insulin clearance may be improved. In either case, the effect might be beneficial for individuals with insulin resistance.

During the study, all subjects kept their body weight, dietary habits, sleep habits as well as a level of physical activity. The number of digestible carbohydrates and other nutrients in the standardized breakfast ingested before the assessment of PPG/PPI was the same on all test days. By means of the standardized dinner before all test days, the bias was further minimized. Overall, it may be considered that the observed beneficial effects were not due to an impact of any of these potential confounding factors that were controlled for in the present study.

In contrast to the majority of clinical trials investigating the benefits of dietary fibers on glycemic response attenuation, the population of the present study was normoglycemic, as shown by the values for fasting blood glucose and HbA1c within the reference ranges at the study start. Further, the subjects had no relevant concurrent ailments. Accordingly, the effects shown in the study population may be regarded as relevant for the general healthy population. Moreover, the similarity of the applied test meal to nutritional habits in the United States implies that the results are not only relevant for German or EU populations, but would also apply to the U.S. population.

The global benefit was rated as "very good" or "good" by 100.0% of subjects in the D1 group and by 82.9% of subjects in the D2 group compared to 45.7% of subjects in the NT group. Investigators gave the same rating to 100.0% of subjects in the D1 group and 82.8% of subjects in the D2 group compared to 45.7% of subjects in the NT group. The differences in ratings between each dose and NT were statistically significant.

The documented AEs and the gastrointestinal tolerability evaluation showed a very good tolerability profile for AG. The overall assessment of tolerability demonstrated comparability of AG to no treatment: both doses were rated as "very good" or "good" by 100% of the subjects as well as by investigators for all subjects.

5. Conclusion

The present study provides robust evidence of significant beneficial physiological effects with regards to glycemic response to the consumption of AG (Fibregum^{TM}) together with a meal, specifically on PPG and PPI levels in healthy subjects, shown in the present appropriately designed, double-blind, randomized controlled trial. Moreover, the very good tolerability of the product was demonstrated.

Acknowledgements

The authors thank Bernd Bitterlich for the statistical analysis.

Compliance with Ethical Standards

The study protocol and amendment, the informed consent (IC), and other relevant information were reviewed by the responsible Ethics Committee (Ethics Committee Charité, Berlin, Germany) in accordance with the applicable regulations. The procedures set out in this study were designed to ensure that the sponsor and investigators abide by the principles of the Good Clinical Practice guidelines of the ICH, and the Declaration of Helsinki. Furthermore, the study was performed in accordance with the applicable legal requirements.

Subject Information and Informed Consent

It was the responsibility of the investigator to inform the subject prior to inclusion in the clinical study about the nature, purpose, possible risk, and importance of the study. The subject had to be comprehensively and adequately informed both verbally and in writing prior to consent for study participation. In doing so, care had to be taken to avoid any pressure or undue influence on the subject's participation and to respect the legal rights of the subject. Moreover, the subject had to be notified that he/she was free to discontinue the study at any time without giving any reason and without prejudice for him-/herself.

The subject information contained detailed information about the clinical study, e.g. regarding the study aim, the possible benefit and anticipated risks, data protection as well as the financial expense allowance. The subject had to be given sufficient time to read the subject information and consent form and to reflect on participation. If the subject consented to all conditions of the clinical study, he/she signed and dated the consent form, which was to be separately stored after completion and signature. The investigator had to countersign this form. The subject had to receive a copy of the signed and dated informed consent form and subject information. If the subject did not agree with the transfer of his/her pseudonymized data (only information about the subject number, age, and sex) as stated in the consent form, he/she could not be included in the clinical study.

Personal subject data were restricted to those necessary to evaluate the efficacy and safety of the investigational product and had to be collected and processed in compliance with applicable data privacy protection laws and regulations.

Conflicts of Interest

The authors declare no conflict of interest. The sponsor had no input in the writing of the manuscript.

Authors' Contributions

U.B. led the clinical phase of the investigation. C.E. was the project leader. I.W. did the medical writing.

Funding Information

This study was sponsored by Nexira, Rouen, France.

References

[1] Gibson, G.R. and Roberfroid, M.B. (1995) Dietary Modulation of the Human Colonic Microbiota: Introducing the Concept of Prebiotics. *The Journal of Nutrition*, **125**, 1401-1412. https://doi.org/10.1093/jn/125.6.1401

[2] Scholz-Ahrens, K.E., Schaafsma, G., Van den Heuvel, E.G. and Schrezenmeir, J. (2001) Effects of Prebiotics on Mineral Metabolism. *The American Journal of Clinical Nutrition*, **73**, 459s-464s. https://doi.org/10.1093/ajcn/73.2.459s

[3] Henry, C.J., Lightowler, H.J. and Strik, C.M. (2007) Effects of Long-Term Intervention with Low- and High-Glycaemic-Index Breakfasts on Food Intake in Children Aged 8-11 Years. *British Journal of Nutrition*, **98**, 636-640. https://doi.org/10.1017/S0007114507727459

[4] Bortolotti, M., Levorato, M., Lugli, A. and Mazzero, G. (2008) Effect of a Balanced Mixture of Dietary Fibers on Gastric Emptying, Intestinal Transit and Body Weight. *Annals of Nutrition and Metabolism*, **52**, 221-226. https://doi.org/10.1159/000138127

[5] Burton-Freeman, B. (2000) Dietary Fiber and Energy Regulation. *The Journal of Nutrition*, **130**, 272S-275S. https://doi.org/10.1093/jn/130.2.272S

[6] Papathanasopoulos, A. and Camilleri, M. (2010) Dietary Fiber Supplements: Effects in Obesity and Metabolic Syndrome and Relationship to Gastrointestinal Functions. *Reviews in Basic and Clinical Gastroenterology*, **138**, 65-72. E2. https://doi.org/10.1053/j.gastro.2009.11.045

[7] Regulation (EC) (2006) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on Nutrition and Health Claims Made on Foods.

[8] FDA (2016) Federal Register of May 27 (81 FR 33742).

[9] FDA (2018) Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30): Guidance for Industry.

[10] Roberfroid, M. (2007) Prebiotics: The Concept Revisited. *The Journal of Nutrition*, **137**, 830S-837S. https://doi.org/10.1093/jn/137.3.830S

[11] Sharma, R.D. (1985) Hypoglycemic Effect of Gum Acacia in Healthy Human Subjects. *Nutrition Research*, **5**, 1437-1441. https://doi.org/10.1016/S0271-5317(85)80054-3

[12] Calame, W., Thomassen, F., Hull, S., Viebke, C. and Siemensma, A.D. (2011) Evaluation of Satiety Enhancement, including Compensation, by Blends of Gum Arabic. A Methodological Approach. *Appetite*, **57**, 358-364. https://doi.org/10.1016/j.appet.2011.06.005

[13] Boler, B.M., Serao, M.C., Bauer, L.L., Staeger, M.A., Boileau, T.W., Swanson, K.S., *et al.* (2011) Digestive Physiological Outcomes Related to Polydextrose and Soluble Maize Fibre Consumption by Healthy Adult Men. *British Journal of Nutrition*, **106**, 1864-1871. https://doi.org/10.1017/S0007114511002388

[14] Buckley, J.D., Thorp, A.A., Murphy, K.J. and Howe, P.R. (2006) Dose-Dependent Inhibition of the Post-Prandial Glycaemic Response to a Standard Carbohydrate meal following Incorporation of Alpha-Cyclodextrin. *Annals of Nutrition and Metabolism*, **50**, 108-114. https://doi.org/10.1159/000090498

[15] Akeo, K., Kojima, M. and Uzuhashi, Y. (2002) Physiological Functions of Gum Arabic. Food Chemicals Monthly.

Abbreviations

AG: Acacia Gum
AUC: Area Under the Curve
BMI: Body Mass Index
D1: Dose 1, 40 g AG powder
D2: Dose 2, 20 g AG powder
FAS: Full Analysis Set
FDA: U.S. Food and Drug Administration
iAUC: incremental Area Under the Curve
IC: Informed Consent
NT: No Treatment, 0 g AG powder
PPG: Post-Prandial Glucose
PPI: Post-Prandial Insulin
RMD: Resistant Maltodextrin
V1 - V4: Visit 1 - Visit 4

Supplementary

Table S1. Main inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Body mass index (BMI) of 18.5 kg/m^2 - 29.9 kg/m^2	Known allergy or hypersensitivity to the components of the investigational product or study meals
Normal fasting blood glucose (FBG) 3.9 to <5.6 mmol/L (70 to <100 mg/dL)	A history and/or presence of clinically significant self-reported disorders as per investigator's judgement
HbA1c of 4% to <5.7%	Difficult vein access or sensitivity to blood draws
A habit of regularly consuming 3 main meals/day, with breakfast and lunch as dominant meals	A habit of nighttime eating or snacking (after 10 pm)
	A habit of excessive consumption of artificial sweeteners (e.g. in beverages)
	A history and/or presence of eating disorders like bulimia, anorexia nervosa, binge-eating as per investigator's judgement
Familiarity with components of the study meals	
No disliking and/or extreme preferences for any of the items	Use of treatment or supplementation in the last 2 months prior to V1 and during the study, as per investigator's judgment, that could influence gastrointestinal functions, body weight, blood glucose levels or otherwise interfere with study conduct or evaluation
Readiness to comply with study procedures (adhering to the defined restrictions prior to and procedures on the test days, maintaining the habitual level of physical activity and sleep habits during the study, and filling out the study diary)	Deviation of safety laboratory parameter(s) at V1, unless the deviation is justified by a previously known but not clinically relevant condition (e.g. Gilbert's syndrome)
	Diets or weight loss programs within the last 3 months prior to V1 and during the study
Stable body weight in the last 3 months prior to visit 1 (V1) (≤3% self-reported change)	Recent blood donation within the last 1 month prior to study
Stable concomitant medications (if any) for at least last 3 months prior to V1	A habit of smoking within the last 6 months prior to V1 and during the study
	A vegetarian, vegan or other restrictive diet
Commitment to use contraception methods and a negative pregnancy testing (beta human chorionic gonadotropin test in urine) at V1 (women of childbearing potential)	Night shift work
	A history or current abuse of alcohol, drug and/or medication
	Pregnant or nursing women of childbearing potential
	Inability to comply with study procedures
No participation in another clinical study during this study	Participation in another study during the last 30 days prior to V1
	Any other reason deemed suitable for exclusion, per investigator's judgment.