

Crave Crush™ lozenges containing gymnemic acids reduce consumption of high sugar foods

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ABSTRACT

Reduction in sugar intake can have a positive effect on body weight and increased intake a negative impact. Gymnemic acids (GA) are antagonists at tongue glucose receptors thus blunting sweet taste. In a previous study GA were formulated in a lozenge, and administered to healthy subjects. Results showed that Crave Crush™, containing GA, significantly reduced endpoints of intake and pleasantness for high sugar foods (HSF), but desire for HSF was not significantly reduced. The present trial re-examined the lack of significance in desire in the previous study, with greater number of subjects, additional inclusion criteria and used a cross over design to assess carryover effects. Percent of subjects who choose to eat the first candy offering subsequent to Crave Crush™ dosing, total candy consumption, pleasantness and desire ratings were assessed. Desire rating for a second candy offering immediately after Crave Crush™, but before tasting a second candy, was significantly reduced by comparison to placebo. Additionally, study design improvements broaden the demographic applicability of this lozenge GA approach. No order effects were observed during the crossover. Subjects given Crave Crush™ lozenges also ate less candy, less often and their perceived pleasantness for their preferred candy was reduced. Crave Crush™ lozenges significantly reduced desire for and consumption of HSF relative to a placebo. This study provides further support regarding the role of GA in carbohydrate intake reduction, and broadens their potential applications as aids in supporting a healthy weight.

Keywords: Gymnemic acids, high sugar foods, Crave Crush™, food desire, food pleasantness.

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INTRODUCTION

Reduction in sugar intake can have a positive effect on body weight and conversely, its increase a negative impact (Te Morenga et al., 2013). Thus, ways to limit High Sugar Foods (HSF) intake can help in maintaining a healthy body weight.

Gymnemic acids (GA), found in *Gymnema sylvestre* (Zarrelli et al., 2013a; Di Fabio et al., 2013; Zarrelli et al., 2013b), a long standing Ayurvedic medicinal plant (Ulbricht et al., 2011; Di Fabio et al., 2014) are antagonists at tongue glucose receptors (Sanematsu et al., 2014; Di Fabio et al., 2015) thus blunting sweet taste. In a previous study (Stice et al., in press) GA were formulated in a lozenge named Crave Crush™ to mask its bitterness and administered to healthy subjects.

Results of that study showed that the Crave Crush™ lozenge significantly reduced the intake and pleasantness for HSF, but not the desire for them.

The present double blind placebo controlled randomized trial was carried out to re-examine the lack of significance in the desire endpoint in the previous study. In addition, this study had greater number of subjects, additional inclusion criteria, including assessment of desire for HSF, broader demographics and used a cross over design to assess carryover effects. We evaluated whether it reduces desire for an HSF and reduces consumption of HSF, before any HSF is tasted, post GA dosing. Percent of subjects who choose to eat the first candy offering subsequent to Crave Crush™ dosing, total

candy consumption, pleasantness and desire ratings were assessed. Safety and tolerability were assessed via vitals determination and adverse event monitoring.

METHODOLOGY

Eligibility criteria

A total of 44 male and female subjects in good general health, between the ages of 18 and 65 with a BMI of 18 to 32 kg/m² were recruited into the study. All subjects were expected to be able to read, understand, accept and sign the informed consent document. Recruitment and study were performed by Global Clinicals, Inc. in Los Angeles, California. Subjects were also expected to score at least 40 on a Visual Analogue Scale (VAS) of 0 to 100 units regarding their overall desire for HSF. They also agreed to have a small meal at the site and a good night's sleep before the day of testing.

Subjects were excluded from the study if they met any of the following criteria: Prior history of adverse reactions to any of the ingredients in the study preparations. Concomitant medication deemed by the clinical investigator to potentially interfere with or confound the study results included: any metabolic disorder including known electrolyte abnormalities that were not treated and stable; heart disease, arrhythmias, diabetes, thyroid disease, a history of hypertension, hepatorenal, autoimmune, neurologic disease or history of malignancies that were not treated and stable; current or history of chronic alcohol and/or drug abuse; uncontrolled psychiatric disorder; participation in another clinical study within the past 30 days; simultaneous participation in another clinical trial; any condition, which in the opinion of the investigator made the subject unsuitable for inclusion. All female subjects underwent a urine pregnancy test before enrolling in the study, unless they were postmenopausal or surgically sterilized. If positive they were excluded from the study.

Participant flow and trial design

Consenting eligible male and female subjects, meeting the inclusion/exclusion criteria were required to visit the study site two times. The 44 subjects enrolled were randomly assigned to two groups for visit 1, using a SAS-based computer-generated randomization scheme developed by the study data management provider, and crossed over from Crave Crush™ or placebo on visit 2. There was a one week washout period between visits 1 and 2.

The study protocol and consent form were IRB approved. During screening on visit 1 to the study site, Informed Consent and Bill of Rights forms were signed by subjects after a thorough review with the PI or CRC. Subjects completed a screening health questionnaire and underwent a brief physical examination by the PI. Subjects selected to participate in the study were provided with instructions on completing the various forms related to the study endpoints and study procedures, and were instructed to check with the Investigators or Clinical Research Coordinator (CRC) if they had any questions. Study treatments were administered as indicated below under "Study Interventions".

Study endpoints

The efficacy outcome measures were: Percent of Subjects who choose to eat the first candy offering, Total Candy Consumption, Desire VAS ratings and Pleasantness VAS ratings. Safety measurements were: Subject subjective adverse event monitoring form, Heart Rate and Blood Pressure, Physical Exam and Medical

History.

Study interventions

The composition of active product Crave Crush™ lozenges (400 mg total weight) was: Sorbitol, zinc gluconate, gymnemic acids, natural flavors, and spirulina blue powder. The composition of placebo product lozenges (400 mg total weight) was: Sorbitol and spirulina blue powder.

The gymnemic acid mixture used in the active lozenges contained GA-I, GA-II, GA-III, GA-IV and GA-B with a fingerprint of 12.6, 23.8, 22.1, 8.0 and 5.5 area % respectively, based on Ultra Performance Liquid Chromatography with Charged Aerosol Detection (UPLC-CAD) analysis. It was manufactured and released by FOUR LLC, New York, NY.

Testing procedure

Subjects were given a small meal at the study site 45 min prior to start of testing. At the start of testing subjects were assessed for their level of hunger using a VAS rating. Participants were then given a choice of and asked to select a candy treat among six brands. The candy each subject chose was used for that subject's candy offerings during the entire study, on both visit 1 and visit 2. There was a maximum of six candy offerings, one prior to active/placebo and five possible after that. Subjects could choose to stop earlier by refusing another candy.

Participants then ate a small serving of their selected candy and rated its pleasantness as well as their desire level for a second serving immediately after finishing it. Next, participants randomly received a Crave Crush™ or a placebo lozenge. Immediately following complete dissolution of the lozenge subjects were asked to rate their desire for another candy serving. Next, participants were offered up to five additional servings, one serving at a time. If an offering was accepted it was consumed and immediately followed by ratings for pleasantness of that offering, as well as desire for another portion. However, if an offering was declined, testing and data collection for that participant ended.

Statistical analysis

A randomized treatment list was generated for assigning each subject to one of two treatment order groups (treatment order A/B or treatment order B/A). For continuous variables, means and standard deviations are reported. Independent samples t-tests were used to compare means between treatment order groups. Chi-Square tests were used for categorical variables. Paired t-tests were used to test for within group treatment differences for continuous measures, and McNemar's tests were used for paired proportions. Linear mixed effects models with a random effect to account for repeated measures were used to test for treatment group differences. SAS 9.4 software (SAS Inst, Cary NC) was used for all analyses and the accepted level of significance was $\alpha = 0.05$.

RESULTS

Demographics and drop outs

Demographics and vitals were compared with independent t-tests for means and Chi-square test for proportions. No differences were found between the two groups ($p > 0.05$). These data are shown in Table 1. There

Table 1. Demographics and vitals by randomization sequence.

Variable	Sequence AB (n = 22)	Sequence BA (n = 22)	p-value ²
Age yrs., mean (SD)	40.6 (13.9)	37.4 (16.4)	0.49
Range	20 to 64	18 to 64	
Gender, n (%)			0.55
Females	10 (45%)	12 (55%)	
Males	12 (55%)	10 (45%)	
Body mass index, mean (SD)	26.8 (4.6)	26.7 (4.6)	0.97
Weight lbs., mean (SD)	170.7 (34.8)	169.7 (35.8)	0.93
Blood pressure mmHg, mean (SD) Period 1:			
Systolic BP	116.0 (12.1)	112.5 (16.0)	0.42
Diastolic BP	75.6 (9.2)	72.1 (12.3)	0.29
Change in systolic BP ¹	3.5 (10.3)	3.7 (9.9)	0.95
Change in diastolic BP ¹	-0.8 (7.2)	1.1 (8.9)	0.44
Blood pressure mmHg, mean(SD) Period 2:			
Systolic BP	115.4 (11.9)	113.9 (19.2)	0.76
Diastolic BP	72.8 (10.2)	71.5 (10.8)	0.68
Change in systolic BP ¹	1.8 (9.4)	1.9 (8.5)	0.96
Change in diastolic BP ¹	0.2 (9.9)	-0.3 (8.3)	0.84

1 Change = end of study - pre-treatment

2 T-test used to compare means; Chi-square test for proportions.

Table 2. Study endpoints.

Endpoints	Active (n = 44)	Placebo (n = 43)	Difference, mean (SE)	P-value
Proportion of subjects who ate candy2 ¹ , n (%)	22 (51%)	32 (74%)		0.008 ⁴
Total candy consumption ² , mean (SD)	2.1 (1.6)	2.9 (1.7)	0.7 (0.3)	0.007 ⁵
Desire VAS rating post-treatment ³ , mean (SD)	36.6 (29.1)	51.3 (30.0)	14.1 (5.2)	0.009 ⁵
Pleasantness VAS rating, Candy2 ¹ , mean (SD)	47.4 (32.3) (n = 22)	71.6 (23.6) (n = 32)	22.2 (6.8)	0.003 ⁶

1 - Candy2 = first optional candy offering

2 - Total includes candy1; possible range is 1 to 6

3 - Post-treatment and before second candy

4 - McNemar's test for paired samples

5 - Paired t-test

6 - Linear mixed model with random effect to account for repeated measures, controlled for randomization sequence and visit.

was one drop out from the control group.

Hunger, desire and pleasantness ratings

Hunger, desire and pleasantness ratings (all pre-treatment) were compared between randomization sequence groups using independent t-tests. No differences were found between groups.

Table 2 and Figure 1 show the results for the study endpoints. In summary, these results revealed significant

decreases for the active group vs. placebo, in the proportion of subjects who ate candy number 2, in total candy consumption and VAS ratings for desire and pleasantness.

Statistical detail is described below:

The proportion of subjects who ate candy 2 after GA dosing was 22 of 43 (51%), compared to 32 of 43 (74%) after placebo. McNemar's test indicated that this difference was statistically significant ($p = 0.008$).

Total candy consumption was 2.1 average servings after GA dosing and 2.9 after placebo. Paired t-test

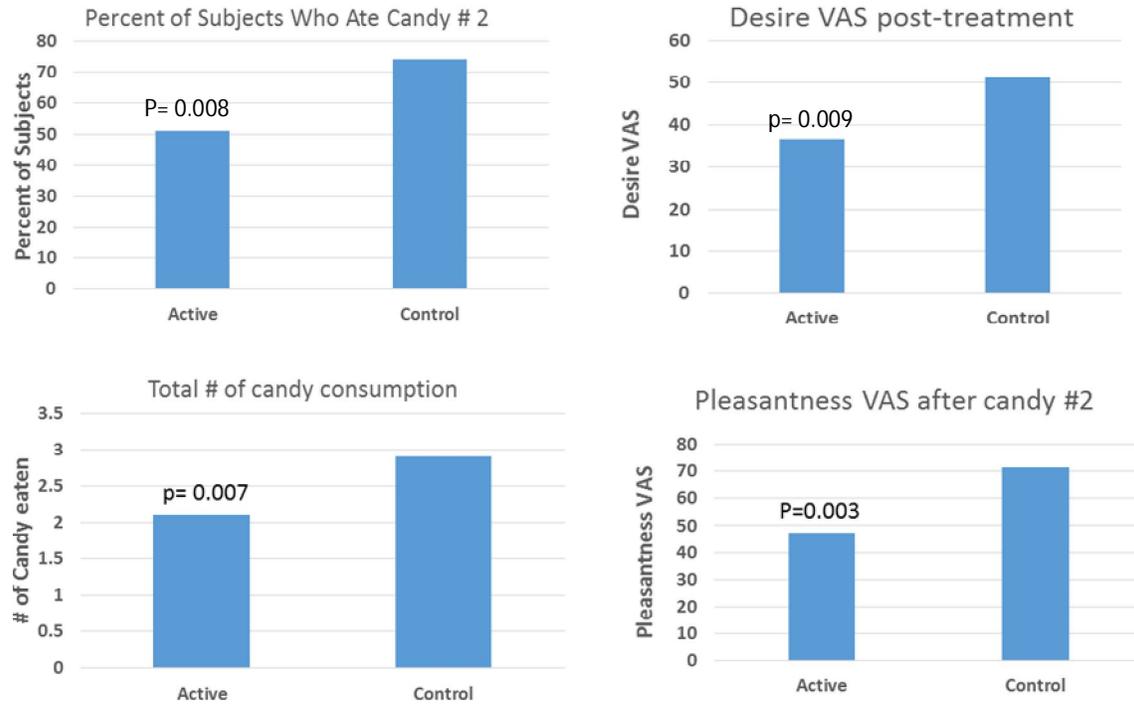


Figure 1. Study endpoints.

indicated a statistically significant within subject mean difference (SE) of 0.7 (0.3), $p = 0.007$. A generalized linear mixed effect model (with random effect for correlated subjects) was used to test for treatment differences while controlling for randomization sequence and visit effects. Total candy consumption did not differ by sequence or visit.

Mean (SD) for desire VAS rating was 36.6 (29.1) after GA dosing and 51.3 (30.0) after placebo. Mean (SE) within subject difference of 14.1 (5.2) was statistically significant (paired t-test, $p = 0.009$). Linear mixed model with random effect for repeated measures did not reveal sequence or visit differences in desire rating.

Among subjects who ate candy 2, pleasantness VAS ratings were compared by treatment. Due to unbalanced sample size (not all subjects who ate candy 2 had ratings at both visits), a linear mixed model was used. The random effect accounted for repeated measures, and the model was controlled for sequence and visit. Pleasantness rating was lower after GA dosing compared to placebo, with a statistically significant mean (SE) difference of 22.2 (6.8), $p = 0.003$. Pleasantness rating did not differ by sequence or visit.

Subject reported side effects

The study preparation was very well tolerated. Two subjects in the active group experienced a mild transient gastrointestinal stomach upset.

DISCUSSION

The results of this placebo controlled double blind, randomized cross over study showed convincingly that the desire rating for a second candy offering immediately after Crave Crush™, but before tasting the second candy, was significantly reduced by comparison to placebo.

There was also a significantly lower percentage of subjects in the active group who choose to eat the first candy offering immediately after Crave Crush™, and a reduction in total candy consumption. Pleasantness rating of the second candy, for those who chose to have it, was also significantly reduced in the active group.

In an earlier study (Stice et al., in press) desire for a second candy was not significantly reduced. A significant reduction in desire immediately following GA administration is critical to the hypothesis proposed by the authors, namely that the GA lozenge causes a reduction in the desire to consume HSF, separately from the result of reduced pleasurable taste of HSF by GA. Mechanistically, this is an important distinction that will guide future research. Therefore establishing that a statistically significant reduction in desire exists is critical.

By using a cross over design we were able to determine that there were no sequence effects for the study endpoints. Subjects in the present study were unable to tell the difference, or were not affected by any differences between active and placebo lozenges, ruling out GA bitterness or lozenge relative sweetness as a factor. Thus, cross over designs using the Crave Crush™

lozenge and related placebo can be employed in future studies, when they are appropriate.

These findings are important with respect to the utility of the GA Crave Crush™ lozenge in terms of future mechanistic studies that can lead to better carbohydrate reduction interventions, but also in its own right as an aid in supporting a healthy weight, both through short and long term use.

Conclusion

The results of this placebo controlled double blind, randomized cross over study showed convincingly that the desire rating for a second candy offering immediately after Crave Crush™, but before tasting the second candy, was significantly reduced by comparison to placebo.

Additionally, study design improvements broadened the demographic applicability of this lozenge GA approach. Also, we observed no order effects during the crossover. Subjects given Crave Crush™ lozenges ate less candy, less often and their perceived pleasantness for their preferred candy was reduced. GA lozenges, marketed under the name Crave Crush™ and SweetDefeat™, significantly reduced desire for and consumption of high sugar foods relative to a placebo. This study provides further support regarding the role of GA in carbohydrate intake reduction, and broadens their potential applications as aids in supporting a healthy weight.

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Ethical issues

The study protocol and consent form were approved by an IRB committee.

Competing interests

FOUR LLC, New York, NY, the company that created the GA lozenges, contracted with Global Clinicals, Inc., (www.globalclinical.com) in Los Angeles, CA, to perform this study.

Authors' contributions

All authors contributed to the design and execution of this study.

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