Research

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Benefit Effects Of Abexol (Beeswax Alcohols) In Healthy Subjects With Gastrointestinal Discomfort And Symptoms

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1. Abstract

1.1. Background: Gastrointestinal symptoms such as heartburn, indigestion/dyspepsia, bloating and constipation are quite common in general population and affect the quality of life of the subjects who suffer from them. Abexol, a mixture containing primary aliphatic alcohols purified from beeswax (Apis mellifera), is a nutritional supplement that produces gastroprotective, anti-inflammatory and antioxidant effects in experimental models and in clinical studies being safe and very well tolerated.

1.2. Objectives: To investigate the effects of Abexol for six weeks in subjects with gastrointestinal discomfort and symptoms.

1.3. Methods: This is a monocentric, double-blinded, randomized, placebo controlled study with two parallel groups receiving Abexol (50 mg) or placebo twice a day for six weeks. The change on GSRS (Gastrointestinal Symptom Rating Scale) total score was considered as the primary efficacy variable and treatment was considered effective if the value obtained at the end of the study was significantly lower compared to baseline and placebo. The intensity of the symptoms and health perception evaluation were considered as secondary efficacy variables. Statistical analysis was performed according to the intention to treat-method.

1.4. Results: Both groups were statistically similar at baseline. No significant changes occurred in placebo group. Abexol reduced significantly the overall GSRS score as compared to baseline and placebo, and the rate of Abexol-treated subjects who reported improved health perception was significantly greater than in placebo. No subject in the Abexol-treated group required antacid use, whereas all subjects in the placebo-treated group required it ($p<0.0001$) between Abexol-treated and placebo-treated groups). Abexol was safe and well tolerated. Only three placebo-treated subjects reported moderate adverse experiences during the trial.

1.5. Conclusion: Abexol administered for six weeks, improved the symptoms in subjects with transitory symptoms of gastrointestinal discomfort, decreased the consumption of antacids, improved the general perception of health and was safe and well tolerated.

2. Keywords:
Abexol, beeswax alcohols, gastrointestinal symptoms, GSRS, health perception

3. Introduction

Gastrointestinal (GI) symptoms are common in otherwise healthy adults and very often require specialized care before a specific diagnosis can be made. Prior to receiving any diagnoses from healthcare providers, individuals first experience symptoms, which may then prompt care seeking. Only in the United States, using weighted national data, in 2014 there were more than 40.7 million ambulatory visits for GI symptoms and 54.4 million ambulatory visits with a primary diagnosis code for a GI disease. The symptom of abdominal pain was responsible for more than 21.8 million total visits, followed by vomiting (4.7 million visits) and diarrhea (3.4 million visits). Abdominal pain was also the most frequent diagnosis with 16.5 million annual visits. There were more than 5.6 million visits for gastroesophageal reflux disease and reflux esophagitis. Constipation and hemorrhoids each accounted for 2.5 million visits. [1]

In line with this, the Nationally Representative Survey made in 2015 in a total number of 71,812 community-dwelling adults in the United States, showed that around the 63% had at least one of eight specific GI symptoms over the prior week. The top three reported symptoms were heartburn/reflux (31%), abdominal pain (25%), and bloat/gas (21%). [2]
Taking into account the side effects of common over-the-counter medications to reduce gastrointestinal symptoms, dietary supplements have been considered as alternatives and complements. It is estimated that 57 to 80% of adults in the United States, for example, consume dietary supplements, ranging from category-leading multivitamins to benefit-specific products to help support immunity and digestive health.[3,4]
Abexol (D-002), a mixture that contains higher primary aliphatic

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alcohols obtained from beeswax (Apis mellifera), [5] has antioxidant, gastroprotective and anti-inflammatory effects, demonstrated in experimental models [6-29] and in clinical studies,[30-35] as well as its safe and very well tolerated.[30-35] The aim of this study was to investigate the effects of Abexol in healthy subjects with gastrointestinal symptoms.

4. Subjects And Methods

4.1. Study Design

This study was conducted in the Surgical Medical Research Centre (Havana City, Cuba), wherein the study protocol, which complied with the principles of the Helsinki Declaration and the Cuban Guidelines of Good Clinical Practices,36 was approved by the institutional ethic and scientific boards. All subjects gave their written informed consent at enrolment (Visit 1) and were interviewed about their symptoms. They were required to be in generally good health apart from gastrointestinal symptoms. A physical examination and medical history were obtained at this visit.

Eligible subjects were randomized (Visit 2), under double-blind conditions, to receive placebo or Abexol (50 mg bid) for 6 weeks and attended to follow-up visits at 3 and 6 weeks on treatment (Visits 3 and 4). Subjects were advising to continue their usual dietary habits during the trial. Following the initial screening, physical examination was performed at each visit, and gastrointestinal symptoms, treatment compliance, health perception, and request of adverse experiences (AE) were controlled in visits 3 and 4. Laboratory analyses were performed at baseline and after 6 weeks on treatment.

4.2. Subjects

The study enrolled healthy men and women (40-80 years old) who experienced temporary GI symptoms with a Gastrointestinal Symptom Rating < 1.0 in mean score,37 but were not defined as having "functional gastrointestinal (GI) disorders" by the Rome IV classification,38, who were eligible for randomization if they were otherwise in good health according to their medical history, physical examination and laboratory results. The participants had no evidence of organic disease such as peptic ulcer disease, H. pylori-associated gastritis diagnosed by the presence of anti-H. pylori antibodies in the blood, gastric cancer, or gastritis, based on their answers to a physician's questions, The enrolled participants met the following inclusion criteria: (1) healthy men and women aged from 40 to 80 yr. old, (2) with an GSRS mean score of 0.1~1.5 and (3) who understood the details of the study and provided written informed consent. Exclusion criteria were (1) H. pylori infection; (2) regular use of gastrointestinal drugs or supplements: (3) functional dyspepsia (Rome IV classification); (4) refusal to stop taking healthy foods that might affect gastrointestinal symptoms; (5) food allergy; (6) severe complications or diseases requiring urgent treatment; (7) a medical history of diseases or operations affecting digestion, absorption, or defecation; (8) those deemed unsuitable for the study based on blood results of the screening test; (9) those who were pregnant or lactating or planning to become pregnant during the study; (10) those receiving treatment for or with a history of drug addiction or alcoholism; (11) those planning to participate or already participating in other clinical studies; and (12) those deemed unsuitable for the study by the investigator for other reasons.

Causes of premature discontinuations were to experience any adverse effect (AE) justifying such a decision, included those motivated by doctor or subject decision. Withdrawals not related with AE included those due to protocol violations (inadequate conditions of laboratory testing, consumption of forbidden treatments, failure in taking study treatments for 5 days) and to other causes (unwillingness to follow-up and/or address changes that make impossible attend to visits).

4.3. Treatment

Subjects consumed two daily tablets of Abexol (50 mg) or placebo, identical in appearance and package, for six weeks. Consumption of medications and/or supplements with recognized gastroprotective (proton pump inhibitors –PPI-, histamine 2 receptor antagonists -H2RA-, mucoprotective agents) or antioxidant effects was not allowed during the entire trial and to be eligible for the trial should be stopped consumption for at least 3 weeks before the inclusion. Consumption of antacids for symptoms relief, however, was allowed and carefully recorded.
Treatment compliance was controlled by counting the remainder tablets and making interviews to subjects. At trial completion, non-used tablets were recovered. Compliance was good if the subjects taken at least 85 % of the tablets scheduled from the previous visit.

4.4. Primary Efficacy Endpoints

The primary efficacy variable was to obtain a significant reduction (≥ 20 %) of the overall score of the Gastrointestinal Symptom Rating Scale (GSRS) as compared to placebo. This is a validated questionnaire,37 to discriminate digestive symptoms, which consists of 15 items combined into five symptom clusters. GSRS has a point graded scale (from 1 to 3) where higher scores represent more troublesome symptoms. The overall score ranges from 0-45 points, the lower the better the subject´s status in terms of gastrointestinal symptoms.37

4.5. Secondary Efficacy Endpoints

Improvement of the gastrointestinal-related health perception, assessed through a three scores system: 1 (improved), 2 (unchanged) and 3 (worsened), and the daily consumption of antacids were secondary efficacy variables.

4.6. Safety and Tolerability

Data from physical examination, laboratory indicators and interview for AE, were considered for safety and tolerability analysis. All undesirable events occurred to a subject during the trial, disregarding the cause, should be considered as AE, whenever they newly appeared during the trial.39

4.7. Laboratory Analyses

For laboratory analysis, venous blood samples were obtained under fasting conditions. The hematological variables (hemoglobin, hematocrit, red

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blood cell count, white blood cell count, and platelet count) were determined automatically in a Hematological Complex. Blood biochemistry variables (AST, ALT, glucose, creatinine) were determine by enzymatic methods using reagent kits (Roche, Switzerland). The determinations were made in automatized equipment located in the Clinical Laboratory of the Surgical Medical Research Centre (Havana, Cuba). A systematic quality control of the precision (within-day and between-day variations) and accuracy (evaluated versus standard references) was performed.

4.8. Statistical Analysis

A sample size of 20 subjects/treatment group was expected to provide 80% power to detect a 20.0% between-group difference in the mean percent change from baseline. Data analyses were performed on an intention to treat (ITT) basis, including all randomized subjects, regardless of study treatment compliance. Assuming a 10% of premature withdrawals, 40 subjects should be enrolled. Comparisons of continuous variables were performed using the Wilcoxon test for paired samples (within group comparison) and the Mann Whitney U Test (between group comparisons). Comparisons of categorical variables were done with the two tailed Fisher's Exact Test. A value of =0.05 was assumed for statistical significance. Comparisons were done with the Statistics software for Windows (USA).

5. Results

Thirty-seven (37) of 40 enrolled were eligible for randomization. Three subjects were not included due to lower values (< 11 g/L) of hemoglobin (1), uncontrolled diabetes (1) and high values of hepatic enzymes (> 55 U/L) (1). The main baseline characteristics of both groups were well balance (Table 1), therefore, they were homogeneous at randomization.

The most frequently reported symptoms (> 90%) were heartburn, regurgitation, belching, flatulence, and the sensation of incomplete evacuation. All the subjects reported more than one symptom at baseline. Table 2 shows the results on overall GSRS score. Both groups were well balance at baseline. No significant changes occurred in placebo.

Table 1. Main baseline characteristics of study population

	Abexol (n = 18)		**Placebo (n = 19)**		**Total (n = 37)**	
Age (years) (X ± SD)	66 ± 6		66 ± 7		66 ± 7	
Body mass index (kg/m²) (X ± SD)	27.0 ± 3.8		27.6 ± 3.6		27.3 ± 3.7	
	n	%	n	%	n	%
Sex: Women	15	83.3	16	84.2	31	83.8
Men	3	16.7	3	15.8	6	16.2
Distribution of symptoms at baseline	n	%	n	%	n	%
Abdominal pain	8	44.4	6	31.6	14	37.8
Acidity / heartburn	18	100.0	18	94.7	36	97.3
Regurgitation	18	100.0	19	100.0	37	100.0
Stomach emptiness	14	77.8	16	84.2	30	81.1
Nauseas and vomits	7	38.9	6	31.6	13	35.1
Abdominal murmurs	17	94.4	14	73.7	31	83.8
Bloating	14	77.8	16	84.2	30	81.1
Eructation	17	94.4	17	89.4	34	91.9
Flatulence	17	94.4	19	100.0	36	97.3
Slow intestinal transit	0	0.0	1	5.2	1	2.7
Accelerated intestinal transit	0	0.0	3	15.8	3	8.1
Soft feces	9	50.0	6	31.6	15	40.5
Hard feces	5	27.8	7	36.8	12	32.4
Urgent defecation	15	83.3	17	89.4	32	86.5
Incomplete evacuation feeling	16	88.9	19	100.0	35	94.6
Overall GSRS score	11.2	-	11.1	-	11.15	-
Mean GSRS score	0.7	-	0.7	-	0.7	-
Subjects with more >1 symptom	18	100.0	19	100.0	37	100.0
Mean GSRS value ≥ 1	0	-	0	-	0	-
Rome IV criteria/ classification	0	-	0	-	0	-

All comparisons were not significant (Mann Whitney U Test, Fisher´s Exact Probability Test)

Table 2. Effects on the Gastrointestinal Symptom Rating Scale (GSRS) score

Treatment	**Baseline**	**Week 3**	**Week 6**	**Changes (%)**
	Abdominal pain			
Placebo	0.5 ± 0.7	0.5 ± 0.5	0.3 ± 0.5	-40
Abexol	0.4 ± 0.5	0.1 ± 0.4*	0.0 ± 0.0*+	100

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	Acidity/heartburn			
Placebo	1.3 ± 0.5	1.2 ± 0.5	1.2 ± 0.5	-7.7
Abexol	1.3 ± 0.6	0.2 ± 0.5^{***+++}	0.0 ± 0.0^{***+++}	100
	Regurgitation			
Placebo	1.5 ± 0.6	1.2 ± 0.6	1.3 ± 0.5	-13.3
Abexol	1.2 ± 0.4	0.2 ± 0.5^{**+}	0.0 ± 0.0^{***+++}	100
	Stomach emptiness			
Placebo	1.2 ± 0.6	0.9 ± 0.6	0.9 ± 0.6	-25
Abexol	0.9 ± 0.8	0.4 ± 0.5^{*+}	0.0 ± 0.0^{**+++}	100
	Nauseas and vomits			
Placebo	0.4 ± 0.6	0.4 ± 0.5	0.4 ± 0.5	0
Abexol	0.5 ± 0.6	0.2 ± 0.4*	0.0 ± 0.0^{*+}	100
	Abdominal murmurs			
Placebo	0.9 ± 0.4	0.8 ± 0.4	0.9 ± 0.4	0
Abexol	1.0 ± 0.4	0.1 ± 0.3^{**+++}	0.0 ± 0.0^{**+++}	100
	Bloating			
Placebo	1.0 ± 0.6	1.0 ± 0.6	1.0 ± 0.5	0
Abexol	0.8 ± 0.5	0.2 ± 0.5^{**+++}	0.0 ± 0.0$^{***++++}$	100
	Eructation			
Placebo	1.0 ± 0.5	1.0 ± 0.5	1.0 ± 0.5	0
Abexol	1.1 ± 0.5	0.7 ± 0.5*	0.1 ± 0.4^{**+++}	-90.9
	Flatulence			
Placebo	1.3 ± 0.5	1.2 ± 0.5	1.2 ± 0.4	-7.7
Abexol	1.2 ± 0.5	0.5 ± 0.5^{**+}	0.1 ± 0.4^{**+++}	-91.7
	Slow intestinal transit			
Placebo	0.1 ± 0.5	0.0 ± 0.2	0.0 ± 0.2	100
Abexol	0.0 ± 0.7	0.0 ± 0.2	0.0 ± 0.0	0
	Accelerated intestinal transit			
Placebo	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.2	0
Abexol	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0
	Soft feces			
Placebo	0.4 ± 0.5	0.4 ± 0.5	0.4 ± 0.5	0
Abexol	0.6 ± 0.6	0.3 ± 0.5	0.3 ± 0.5*	-50
	Hard feces			
Placebo	0.6 ± 0.6	0.6 ± 0.6	0.7 ± 0.6	16.7
Abexol	0.4 ± 0.6	0.2 ± 0.4*	0.1 ± 0.4*	-75
	Urgent defecation			
Placebo	1.0 ± 0.4	0.9 ± 0.4	0.9 ± 0.3	-10
Abexol	0.8 ± 0.4	0.8 ± 0.4	0.6 ± 0.5	-25
	Incomplete evacuation feeling			
Placebo	1.1 ± 0.5	1.0 ± 0.4	1.1 ± 0.3	0
Abexol	0.9 ± 0.6	0.7 ± 0.5*	0.5 ± 0.5^{*+}	-44.4

Mean ± standard deviation. $^{*}p < 0.01$, $^{**}p < 0.001$, $^{****}p < 0.0001$. Comparison vs baseline (Wilcoxon Test)

$^{+}p < 0.01$, $^{++}p < 0.001$, $^{+++}p < 0.0001$. Comparison vs placebo (Mann Whitney U Test)

After 3 weeks on treatment, Abexol reduced significantly the GSRS overall score as compared to baseline and placebo ($p<0.0001$ for both comparisons) (Table 3). This treatment effect did not wear off, but improved throughout the time, so that at study completion the overall GSRS score reduction versus baseline was 84.7% and vs placebo was 81.1% (net reduction). Also, from the third week to the trial completion, Abexol treatment decreased significantly several GSRS sub-scores (abdominal pain, acidity/heartburn, regurgitation, stomach emptiness, nauseas and vomits, abdominal murmurs, bloating, eructation, flatulence and incomplete evacuation feeling) as compared to placebo. Abexol also reduced the symptoms hard/soft feces vs baseline but not vs placebo. The urgent defecation symptom was not significantly modified with the treatment (Table 3).

Table 3. Overall GSRS Total Score

Treatment	Baseline	Week 3	Week 6	Changes (%)
Placebo	11.2 ± 2.9	11.0 ± 2.8	10.8 ± 2.7	-3.6
Abexol	11.1 ± 2.6	4.5 ± 2.1^{***+++}	1.7 ± 1.0^{***+++}	-84.7

Mean ± standard deviation. $^{*}p < 0.01$, $^{**}p < 0.001$, $^{****}p < 0.0001$. Comparison vs baseline (Wilcoxon Test)

$^{+}p < 0.01$, $^{++}p < 0.001$, $^{+++}p < 0.0001$. Comparison vs placebo (Mann Whitney U Test)

At trial completion, the rate of Abexol-treated subjects who reported improved health perception (18/18, 100 %) was significantly greater than in placebo (0/19, 0 %) (Table 4), where 2 subjects got worse and the rest did not report any change on symptoms.

Table 4. Effects on health perception (reported by subjects)

Treatment	Week 3		Week 6	
	n	%	n	%
Improved				

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Placebo	0	0.0	0	0.0
Abexol	15	83.3^{+}	18	100^{+}
Unchanged				
Placebo	18	94.7	17	89.5
Abexol	3	16.7^{+}	0	0.0^{+}
Worsened				
Placebo	1	5.3	2	10.5
Abexol	0	0.0	0	0.0

$^{+}p < 0.0001$ Comparison with placebo (Fisher's Exact Probability Test)

No Abexol treated subjects (0/18, 0 %), but 19/19 (100 %) placebo subjects consumed antacids ($p < 0.0001$ between Abexol-treated and placebo-treated groups). Abexol was safe and well tolerated. Consumption did not affect physical or laboratory safety indicators (Table 5 and 6) and the individual values of all those variables remained within normal range.
No subject withdrew from the study, and only two placebo-treated subjects experienced moderate AE during the trial (diarrheas, dizziness).

Table 5. Effects on physical safety indicators (X ± SD)

Treatment	**Baseline**	**Week 3**	**Week 6**
	Body weight (kg)		
Placebo	68.3 ± 8.8	68.0 ± 8.5	68.2 ± 8.3
Abexol	70.5 ± 8.5	71.0 ± 8.8	70.4 ± 8.5
	Pulse (beats/min)		
Placebo	71.2 ± 3.5	70.6 ± 2.6	71.4 ± 1.9
Abexol	70.2 ± 3.2	70.4 ± 2.4	70.7 ± 1.7
	Diastolic blood pressure (mm Hg)		
Placebo	78.4 ± 3.5	78.4 ± 3.5	78.4 ± 3.7
Abexol	78.3 ± 3.6	78.3 ± 3.7	78.3 ± 3.5
	Systolic blood pressure (mm Hg)		
Placebo	123.9 ± 9.8	123.9 ± 9.6	124.0 ± 7.2
Abexol	125.6 ± 8.9	125.6 ± 7.6	124.2 ± 7.9

X mean, SD standard deviation
All comparisons were not significant (Wilcoxon Test, Mann Whitney U est)

Table 6. Effects on blood safety indicators (X ± SD)

Treatment	**Baseline**	**Week 6**
	Haemoglobin (g/L)	
Placebo	12.8 ± 0.9	12.9 ± 0.8
Abexol	12.8 ± 0.8	12.8 ± 0.8
	Hematocryte (%)	
Placebo	38.1 ± 3.2	38.2 ± 2.4
Abexol	39.1 ± 2.3	39.2 ± 1.8
	Red blood cells (cells x 10^3)	
Placebo	4.2 ± 0.4	4.2 ± 0.4
Abexol	4.3 ± 0.3	4.3 ± 0.3
	White blood cells (cells x 10^3)	
Placebo	6.1 ± 1.5	6.1 ± 1.5
Abexol	6.3 ± 1.4	6.1 ± 1.4
	Platelets (cells x 10^3)	
Placebo	225.2 ± 54.2	232.5 ± 58.1
Abexol	237.9 ± 41.8	244.6 ± 37.2
	ALT (U/L)	
Placebo	19.3 ± 5.1	19.8 ± 4.2
Abexol	18.3 ± 3.5	19.6 ± 4.6
	AST (U/L)	
Placebo	25.3 ± 7.8	25.1 ± 6.1
Abexol	23.8 ± 6.5	23.3 ± 5.8
	Glucose (mmol/L)	
Placebo	5.23 ± 0.60	5.17 ± 0.58
Abexol	4.97 ± 0.69	5.01 ± 0.65
	Creatinine (mmol/L)	
Placebo	85.4 ± 18.2	89.2 ± 16.3
Abexol	84.7 ± 19.7	86.8 ± 14.8

X mean, SD standard deviation
All comparisons were not significant (Wilcoxon Test, Mann Whitney U Test)

6. Discussion

This study confirmed that oral treatment with Abexol for six weeks improves temporary gastrointestinal symptoms in subjects otherwise healthy. The study included subjects aged from 40 to 80 years, most of them older than 60 years old, thirty-one women (83.8 %) and seven man (17.2 %), who referred to experience gastrointestinal symptoms according to the GSRS. The frequency of symptoms reported were similar in both groups at baseline, which supports that the effects here found were treatment-related.

Abexol reached the efficacy criterion since the third week on treatment, a result that did not wear off but increase after 6 weeks on treatment, with a net difference of the overall GSRS score in the treated group versus placebo above 20 % (81.1%). Abexol was effective in improving almost all the symptoms included in the scale, with the exception of symptoms

related to intestinal transit, which were not reported by any subject in this treatment group and only by 1 subject in the placebo group. In general, the symptoms related to gastrointestinal transit were the least frequent in this population (< 10%).

These results and the significant reduction of various individual GSRS items as compared to placebo, are consistent with previous data of the gastroprotective effects of Abexol on similar populations. [32-34] The GSRS scale, originally developed for being used in patients with peptic ulcer and irritable bowel syndrome, has demonstrated good psychometric characteristics when is used in subjects with a wide variety of gastric diseases and for evaluating the efficacy of several treatments on gastrointestinal symptoms. Keeping in mind these facts, this study confirms the gastroprotective efficacy of Abexol.

Abexol improvement of symptom assessed with the GSRS is consistent with previous clinical results. [32-34] The gastroprotective effects of Abexol have been associated, at least in part, to the increased secretion and improved composition of the gastric soluble mucus, [18,19] a crucial defensive factor of the gastric mucosa, [40,41] to the reduction of the lipid peroxidation in the stomach,[14] and to the reduction of the concentration of TxA2, a vasoconstrictor substance, in the gastric mucosa.[18] These results are in correspondence with those reported in short and medium term studies [31-34] using Abexol and with those obtained in an open-label follow-up study in which a significant improvement of different gastrointestinal symptoms was observed in subjects taking Abexol. [35] The treatments were safe and well tolerated, as they did not affect the safety indicators investigated and no adverse experiences associated with their use were reported.

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