ORIGINAL RESEARCH

Safety and Tolerability of Dr Ohhira's OM-X Capsules in Healthy Volunteers

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Abstract

Context: Digestive discomfort, abdominal pain, indigestion, reflux, nausea, bloating, constipation, diarrhea, and other gastrointestinal (GI) symptoms occur very frequently among otherwise healthy individuals. Some researchers believe probiotics improve symptoms in a number of gastrointestinal conditions. Several clinical trials of probiotic supplements have occurred that support safety and efficacy.

Objectives: The research team designed the study to evaluate the safety of Dr Ohhira's OM-X capsules over a 1-mo period.

Design: This study was a phase I, double-blind, controlled trial with an experimental (active) group and a placebo group.

Setting: The study took place at a clinical research center, MedVadis Research Corporation, in Boston, MA, USA.

Participants: Fifty-one healthy men and women were recruited and 50 were enrolled from the community through the research center.

Intervention(s): The participants were given one of Dr Ohhira's OM-X capsules 2×/d for 30 d.

Outcome Measure(s): Laboratory evaluation was done at baseline and after participants had taken the study's product for 30 d. Adverse events were monitored at 2 wks and at the end of the study.

Results: Forty-six participants completed all of the laboratory and other assessments. No laboratory abnormalities were identified during the trial. The adverse events were transient in most participants, and no participant dropped out because of adverse events. Eleven participants in each group reported adverse events, including abdominal pain, diarrhea, constipation, flatus, bloating, nausea, fatigue, and dry mouth.

Conclusions: No significant laboratory abnormalities occurred in the group of participants treated with Dr Ohhira's OM-X capsules, and the treatment was well-tolerated.

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Digestive discomfort, abdominal pain, indigestion, reflux, nausea, bloating, constipation, diarrhea, and other gastrointestinal (GI) symptoms occur very frequently among otherwise healthy individuals.[1,2,3] Similar symptoms also occur as a part of specific GI disease. For individuals who do not have a disease of the gastrointestinal system and are healthy, the GI symptoms can be minor, self-limited, and intermittent, but others experience persistent GI symptoms that recur often, are more severe, and reduce quality of life.[4] For such individuals, physicians and nutritionists recommend dietary and lifestyle changes that are sometimes successful in ameliorating bothersome GI symptoms in otherwise healthy patients. Some patients can improve their symptoms by increasing fiber intake, avoiding foods that contribute to acid indigestion, drinking at least eight glasses of water per day, and exercising regularly.

The digestive tract contains billions of symbiotic bacteria from more than 400 different species, which promote a healthy digestive system by stimulating immune responses and controlling pathogenic bacteria.[5] For example, probiotic bacteria, such as lactobacterial strains and *Enterococcus faecalis*, are not pathological but act as mediators in the control of the bowel flora and function. The beneficial effects of specific bowel bacteria have been studied and defined for many years. Evidence exists that the endogenous bacteria can provide antibacterial, antifungal, and other activity within the intestine.

Probiotics are beneficial bacteria found in fermented foods, yogurt, and miso as well as in food supplements. Probiotics that enhance intestinal function may relieve GI symptoms.[6] Data have accumulated that support the use of probiotics to prevent or treat symptoms of intestinal disorders.[7,8] Probiotics and the specific strains that they contain have been found to improve diarrhea and treat pneumonia in infants. They also have been shown to hasten relief of symptoms in dengue fever and to reduce urinary tract infection in children with urinary tract abnormalities.[9,10] Most probiotics come from food sources, especially cultured milk products. Probiotic supplements can be consumed as capsules, tablets, beverages, or powders.

GI diseases such as Crohn's disease or ulcerative colitis require specific medical intervention in addition to symptomatic treatment. Probiotics, however, are believed to improve symptoms in several gastrointestinal conditions including inflammatory bowel disease, antibiotic-related diarrhea, colitis, infectious diarrhea, hepatic encephalopathy, irritable bowel syndrome, and allergies.[11,12] However, only certain types of bacteria have been shown to work in the human digestive tract.[13] For this reason, mixed probiotic supplements of multiple strains may provide the most benefit.[14]

Several clinical trials of probiotic supplements have occurred that support safety and efficacy.[15,16,17,18] This article reports the results of a double-blind, parallel, placebo-controlled clinical trial that documents the safety and tolerability for Dr Ohhira's OM-X capsules.

Methods

Participants

Fifty-one healthy men and women were recruited and enrolled from the community through a clinical research center, MedVadis Research Corporation, to participate in a parallel, double-blind, placebo-controlled trial of Dr Ohhira's OM-X capsules. Subjects were recruited through the research center's network of volunteers and with advertisements.

The investigator and research staff interviewed each participant and explained the study at the screening visit. The participants were informed of the requirements of the trial and gave informed consent. The trial was approved by the New England Institutional Review Board (NEIRB). Participants were paid to participate.

The study included individuals who (1) had given signed, informed consent, (2) were 18 to 60 years old, (3) had not previously used Dr Ohhira's OM-X capsules, and (4) had no history of significant illness, such as renal failure requiring dialysis, cirrhosis with liver failure, unstable coronary artery disease, amyotrophic lateral sclerosis, multiple sclerosis (MS), cancer being treated with chemotherapy, or other diseases that would interfere with assessments of the product.

The study excluded individuals who (1) were using prescribed medication currently or had used it in the prior 30 days, except oral contraceptives; (2) were planning to use any other supplements during the trial; (3) had any diagnosed medical condition that might confound the evaluation of safety; (4) had a history of depression, anxiety, or other psychiatric condition that had caused hospitalization within the prior 6 months or was uncontrolled on medication; (5) had a history of allergic reactions to latex, drugs, bee stings, or other common antigens; (6) were pregnant—females were given a pregnancy test—or were breastfeeding; (7) had tested at more than two times the normal range on any screening lab test done for the study or had a lab test less than two times the normal range that the investigator decided was significantly abnormal; (8) had had a cold, flu, or any upper respiratory condition in the prior month; (9) had had a gastrointestinal condition—colic, diarrhea, viral, or other—in the prior month; (10) had chronic fatigue, fibromyalgia, arthralgias, or other pain symptoms; (11) had chronic low back pain; or (12) had other unexplained and untreated symptoms that were recurrent.

Measurements

Those participants who met the inclusion criteria and did not meet the exclusion criteria had the screening laboratory evaluation, a brief physical exam, an EKG, and a measurement of vital signs. The following laboratory tests were obtained at the screening and final visits: (1) a complete blood count (CBC); (2) liver function tests (LFT); and (3) tests for thyroid stimulating hormone (TSH), blood urea nitrogen (BUN), creatinine, calcium, magnesium, glucose, electrolytes (Na, K, C_l, CO_2), prothrombin time (PT), partial thromboplastin time (PTT), urine analysis (including microscopic), and a 12-lead EKG.

The 51 participants were recruited, signed the consent, and had the screening evaluation. One subject failed to meet the laboratory inclusion criteria and was dropped. Fifty participants were randomized.

Participants who had normal lab values at screening were enrolled in the trial at the baseline visit. At baseline, each blinded participant received either Dr Ohhira's OM-X capsules or the placebo for the first 2-week period of treatment. After 2 weeks, the participant returned for a compliance assessment, measurement of blood pressure (BP) and pulse, and an inquiry about adverse events. Each participant was then given another 2-week supply of the blinded study supplement consistent with the previous supply. They returned after another 2 weeks for the same assessments and also a repeat of the laboratory tests. Participants were on either the active capsules or the placebo for at least 30 days.

A nondirected assessment of symptoms or adverse effects was administered at the interim and final visits. The severity of each adverse event reported by the participant was characterized into one of three categories:

Mild. The adverse event did not interfere in a significant manner with the patient's normal function; it was an annoyance.

Moderate. The adverse event produced some impairment of function but was not hazardous to health; it was uncomfortable.

Severe. The adverse event produced significant impairment of function or incapacitation; it was a hazard to the patient's health.

An adverse event was considered not related to the study if any of the following circumstances existed: (1) an unreasonable temporal relationship between the study and the onset of the adverse event; (2) a causal relationship between the study and the adverse event was biologically implausible; or (3) a more likely alternative explanation for the adverse event was present.

Intervention

Dr Ohhira's OM-X capsules have been available for several decades as a food or dietary supplement and are currently available in health food stores and from health care professionals in the United States and all over the world. The capsules are fermented using 12 strains of bacterium in a proprietary blend of lactic acid bacteria. The product contains the following probiotic species: *Bifidobacterium breve* subsp *breve*, *Bifidobacterium infantis* subsp *infantis*, *Bifidobacterium longum*, *Enterococcus faecalis* TH10, *Lactobacillus acidophilus*, *Lactobacillus brevis*, *Lactobacillus bulgaricus*, *Lactobacillus casei* subsp *casei*, *Lactobacillus fermentum*, *Lactobacillus helveticus* yogurt, and *Lactobacillus plantarum*. The probiotic bacteria strains in the capsules are fermented for 3 years in a process that combines them with fruits, mushrooms, vegetables, and seaweed. At that point, the fermented blend contains probiotics, prebiotics, enzymes, bacteriocins, organic acids, and trace amounts of vitamins, minerals, and amino acids. The supplement is produced in compliance with the standards of Japanese Good Manufacturing Practice. All bacterium strains used during fermentation may not persist into the final product, which is encapsulated for oral administration.

Dr Ohhira's Probiotics is the actual product used in the current trial. It sells in Japan as Ohhira's Probiotics OM-X and by other trade names in other nations. An unpublished, open-label safety trial sponsored by Essential Formulas, Inc, was conducted in 2010 using these capsules with 25 healthy male and female participants, between the ages of 18 and 60 years. There were no serious adverse effects in those subjects. The compound was tolerated and none of the subjects withdrew because of adverse effects.

For the current study, the dose was one capsule administered twice per day for 30 days. The participants' supplies were randomly packed in blocks of four. The randomized selection of the placebo and active groups was done by the sponsor, and the blinded investigator dispensed the capsules serially by numbers in blocks of four participants. The placebo was identical in appearance to the active product but contained only the excipient without the active probiotic.

Data Analysis

The research team compared the safety data, including adverse events as described above, and the laboratory evaluations and vital sign assessments at baseline and at the final visit at the end of 30 days, evaluating the differences between the two points for each parameter.

Adverse events were described at each visit for each cohort. EKG and urine analysis results were described as normal or abnormal. Compliance was determined by pill counts and by a diary kept by each participant. The number of pills taken divided by the number of pills prescribed was used as a percentage of the required total dose.

The variance of the change in laboratory parameters between the active and placebo cohorts was analyzed using a two-tailed *t* test to detect a significant difference between the baseline and the 30-day visit. All participants had normal data at the onset of the trial.

Results

Out of the 51 recruited participants, 46 completed all of the laboratory and other assessments, 24 in the active group and 22 in the placebo group. Compliance, judged by pill counts, was over 90% for all participants (mean percentage = 97% in both groups). One participant in the active group used 65% of the prescribed dose. The noncompliant participant was on the active product, had no change in the assessments and no adverse effects, and was included in the safety analysis. Four participants dropped out of the trial.

One participant in the active group withdrew from the trial at the interim visit because of twitching of the orbicularis oris muscle. The principal investigator judged that the complaint was not caused by the product. Three participants taking the placebo dropped out. Two of those participants completed the trial, but the lab lost the final lab data, and, therefore, their data were incomplete. The other participant was not enrolled because the baseline lab values were not within the normal range.

The analysis was done on 46 participants; 25 were male and 21 were female, with 25 being white, 13 black and three Asian. Five participants were not categorized by ethnicity. The 24 participants in the active group and the 22 participants in the placebo group were similar in age. Mean age in the active group was 37 years; in the placebo group, the mean age was 41 years.

Adverse Events

Participants in the active group, who received one capsule two times per day for 30 days, showed no significant adverse effects. The capsules were well-tolerated, and laboratory tests—CBC, LFT, general chemistry, and renal—showed no abnormalities. Some participants reported dizziness, while other participants reported GI complaints, including mild distention, abdominal pain, satiety, belching, loss of appetite, indigestion, nausea and vomiting, increased bowel sounds, urgent defecation,

diarrhea, and constipation. The adverse events were mild and did not cause the participants to drop out of the trial.

Among the 24 active participants who completed the study, 13 reported no adverse effects during the trial (54%), four had adverse effects at the interim visit only (17%), and five had adverse effects at the final visit only (20%). One participant (4%) had adverse events at both visits (ie, an upper respiratory infection and elevated blood pressure), which the research team judged to be unrelated to the study's intervention. The adverse effects were considered mild in all cases, and none of the participants stopped using the product.

Among the participants on active product, the adverse events reported were (1) nausea, (2) increased appetite, (3) bloating, and (4) flatus. The symptoms were not reported at both interim and final visits in any participant. Anemia, increased alanine aminotransferase (ALT), and elevated blood pressure were recorded in three different participants at the final visit. These abnormalities were not clinically significant and were not considered related to the active product.

Among the participants on placebo the adverse events noted were (1) nausea, (2) diarrhea, (3) abdominal pain, (4) flatus, and (5) constipation. Three participants had symptoms at both visits; the others had symptoms at only the interim visit. The investigator judged them to be unrelated to the study capsules, and they were not clinically significant.

Among the 22 participants in the placebo group who completed the study, 11 participants were without adverse effects during the trial (50%). Five had adverse events at the interim visit only (23%), three at the final visit only (14%), and three at both visits (14%). All of the adverse events were judged mild, and no participant dropped out.

Laboratory Data

Laboratory data were collected at the initial screening and the final visits. The evidence for safety is that there was no difference between the screening and the final visit, either in the placebo or the active group. No clinically significant abnormalities in the laboratory values occurred between visits for any participant. The changes between baseline and final visits for each laboratory parameter were not different between the two groups, except for TSH, C_l, and CO_2, each of which were in the normal range at both test points.

Discussion

This randomized, double-blind, placebo-controlled trial was designed to the same standards that are used in drug trials. The endpoints were established, adverse events were carefully monitored, and the subjects were carefully chosen to reduce variability. The trial conforms to a phase I safety trial and the results are similar to those obtained in a previous unpublished trial of the OM-X product.[19]

Table 1. Two-tailed *t* Test Analysis of the Change Between Baseline and Final Lab Values for the Active and Placebo Groups

	Mean Change in Each Group		2-tailed *t* Test
	Active	**Placebo**	***P* Value**
Glucose	-8.71	-3.09	.4092
Na	-0.14	0.18	.8473
K	-0.10	0.05	.1873
C_l	4.32	-0.55	**.0011**[a]
CO_2	-0.14	0.23	**.0004**[a]
BUN	0.27	-0.27	.8531
Creatinine	-0.01	-0.01	.9141
Ca	0.06	-0.05	.2968
Mg	0.07	0.06	.9908
TPROT	0.14	-0.12	.1424
T Bilirubin	-0.05	-0.04	.2425
Alk Phos	1.36	0.02	.1180
AST	-9.36	-1.36	.1216
ALT	-5.68	2.73	.1509
TSH	0.31	1.36	**.0218**[a]
PTT	-0.50	0.32	.2128
WBC	0.12	-0.16	.6092
Hb	-0.03	-1.33	.1350
HCT	0.06	0.28	.8812
Platelets	11.18	1.95	.4834
Prothrombin Time	-0.03	-0.07	.3186
Systolic BP	-4.64	-0.82	.3320
Diastolic BP	-2.05	0.32	.4035
Pulse	-3.45	-2.00	.9432

Abbreviations: TPROT = total protein; BUN = blood urea nitrogen; T Bilirubin = total bilirubin; ALK Phos = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; TSH = thyroid stimulating hormone; PTT = partial thromboplastin time; WBC = white blood cell; Hb = hemoglobin; HCT = hematocrit; BP = blood pressure.

[a]Statistically significant values.

There was normal variation between the screening and the final visit in the laboratory data for each participant in both groups. In order to capture any difference in the two groups, the mean change in the laboratory data was used for each parameter to compare the active and the placebo groups for toxicity. There were no significant abnormal results. There was a significant difference, however, between the two groups for the mean change in TSH, C_l, and CO_2. The reason for the effect is not clear and, although there was a statistically significant difference, the values remained in the normal range. Thus, there was no evidence of toxicity but a significant variation within the normal range.

Adverse events were self-reported, which allowed the participant to freely report any symptom during the trial. The self-reported adverse effects were mild and transient in most cases. They did not interfere with the activities of the participants. The compliance in this trial was strong and the participants were able to complete the study using the prescribed dose of the study products. The participant who dropped out for facial twitching had no adverse events similar to the others in the trial.

The number of subjects in each group was small so the evidence for safety is limited. The subjects were all healthy, and therefore the safety in patients with gastrointestinal illness or other illness remains unknown. This trial did not measure efficacy and the participants had no overt GI symptoms before enrolling. Other trials are needed to establish efficacy for the product.

Doctors, regulators, and consumers are increasingly concerned with the safety of supplements, and manufacturers are now motivated to demonstrate safety with valid clinical trials. Supplements are no longer assumed to be safe just because they are "natural."[20] Although the safety regulations for food supplements are not the same as for pharmaceuticals, the trials that establish safety must conform to the same standards.

Conclusion

Dr Ohhira's OM-X capsules were tolerated by the participants in the study's active group, 23 normal adults, without any significant laboratory changes during a 30-day trial of 2 capsules per day. The adverse effects (1) were mild, (2) did not cause withdrawal from the trial, and (3) were similar in the active and the placebo groups, with the active group not having more adverse effects than the placebo group. Diarrhea, bloating, and constipation occurred in both groups but were intermittent between the two visits in most cases. Symptoms caused by the changes in the GI flora or by successful treatment of bacterial infections (Jarisch-Herxheimer reaction) sometimes appear transiently in patients using supplements and may explain some of the transient symptoms reported by the participants. The trial included no instrument used to evaluate improvement in daily bowel or other GI function. However, four participants in the active group and three in the placebo group spontaneously reported better bowel function. Dr Ohhira's OM-X capsules were well-tolerated and did not have any adverse effects on liver, renal, hematologic, or other laboratory markers for the participants in this trial.

Author Disclosure Statement

This trial was sponsored by Essential Formulas Incorporated (Irving, TX, USA) and BIOBANK Co, Ltd, Kita-ku, Okayama-shi Okayama Prefecture, Japan. Dr Spierings, the principal investigator for the trial, has no relationship with the sponsor and the research was done under contract through MedVadis. Dr Walshe has no relationship with the sponsor and he was contracted to design the research protocol and to monitor the trial. Dr Pescatore is a consultant to the sponsor.

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