International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 11 (7): 719-725, 2015
ISSN 1811-7775

RESEARCH ARTICLE OPEN ACCESS

DOI: 10.3923/ijp.2015.719.725

Effectiveness of *Hizikia fusiformis* Extract on Erosive Gastritis: A 4-week, Randomized, Double-blind and Placebo-controlled Trial

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ARTICLE INFO

Article History:
Received: May 07, 2015
Accepted: July 10, 2015

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ABSTRACT

In our previous study, *Hizikia fusiformis* extract (HFE) has gastroprotective effects in animal model for gastric ulcer. The purpose of this study was to investigate whether HFE had similar gastro-protective effects in human subjects. A randomized, double-blind, placebo-controlled trial was conducted. To fulfill this purpose, a group of subjects with erosive gastritis were orally supplemented with the HFE or placebo for 4 weeks and efficacy and safety were measured. Primary outcome (number of erosions, endoscopic score and estimated cure rates of erosions) and the secondary outcomes (estimated improvement rates of erosions, subjects' symptom questionnaires and blood profiles) before and after the 4-week intervention period were compared. The HFE supplementation showed a significant reduction in number of erosions compared with placebo group. In subjects whose endoscopic score were 4 points (erosions more than 6) at baseline, HFE supplementation resulted in a significant decrease of number of erosions compared with placebo group. High sensitive-C reactive protein (hs-CRP) levels showed a tendency to decrease in HFE-supplemented group. Finally, blood parameters and clinical findings for organ toxicity remained within the normal range. These results suggest that HFE may have therapeutic potential in subjects with erosive gastritis.

Key words: *Hizikia fusiformis*, erosive gastritis, erosions, clinical trial, RTC

INTRODUCTION

Gastritis is an inflammatory condition that occurs in the mucosal lining of the stomach. It has heterogeneous and broad-spectrum etiologic factors. It is a very common disease in eastern Asian countries and patients suffer from nausea, indigestion, abdominal bloating, anorexia, pain and gastric hemorrhage. Its main causes include excessive

alcohol consumption, expanded use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and *Helicobacter pylori* infection (Malfertheiner *et al.*, 2009; Valle, 2011). In general, gastritis can be classified into acute or chronic based on Sydney System. Chronic gastritis is divided into nonatrophic (*H. pylori* related), atrophic and special types (Dixon *et al.*, 1996). Like peptic ulcer, gastritis is likely to result from imbalance between mucosal offensive and defensive factors, such as gastric acidity and mucus barrier (Laine *et al*., 2008). Therefore, the suppression of gastric acid and pepsin secretion by using H2 receptor antagonists or proton-pump inhibitors is a main therapeutic strategy (Yuan *et al.*, 2006). However, current prescribed antacids usually achieve a partial relief of symptoms and are often associated with high incidence of relapse and various side effects such as nausea, diarrhea, constipation, rebound gastric hypersecretion, drug interaction or renal failure (Katelaris, 2004; Savarino *et al.*, 2009). These negative outcomes provide the rationale for the development of nontoxic and efficient antiulcer preparation. In this regard, plant extracts have a lot of attention because they are relatively safe and possess good tolerability even at higher doses. Indeed, quite a number of plant extracts have been shown to produce promising results in the treatment of gastrointestinal disorders including erosive gastritis (Seol *et al*., 2004; Schmeda-Hirschmann and Yesilada, 2005).

Hizikia fusiformis, commonly known as hijiki, is a brown alga growing wild on rocky coastlines around Korea, Japan and China. Ethanol extract of *Hizikia fusiformis* extract (HFE) has been claimed to have immunomodulating (Liu *et al.*, 1997; Shan *et al.*, 1999), hepatoprotective (Hwang *et al.*, 2008) and free radical scavenging (Kim *et al.*, 2009) activities. Of many types of major components isolated from the ethanol extract, polysaccharide Hf-PS-1 has shown to have gastroprotective activity. By oral administration, Hf-PS-1 protected rat against ethanol-induced gastric injury (Kim *et al.*, 2009; Choi *et al.*, 2010). However, there have been no studies of HFE in subjects with gastrointestinal disease. The present study, was carried out to evaluate the efficacy and safety of HFE compared with placebo in subjects with erosive gastritis.

MATERIALS AND METHODS

Subjects and ethics approval: The study Participants were recruited from the Clinical Trial Center for Functional Foods (CTCF2) in Chonbuk National University Hospital (Jeonju, Republic of Korea) between August, 2011 and April, 2012 via a local newspaper advertisement. A total of 79 subjects agreed to participate in the current study. We divided stomach into four topographical areas (cardia, corpus, angle and antrum) and counted the number of erosive mucosal injuries including acute or chronic gastritis. Inclusion criteria for the study included the following: (1) Age between 19 and 70 years, (2) Diagnosis of erosive gastritis by endoscopy at screening visit and (3) Subjects giving written informed consent. Exclusion criteria included the following: (1) A diagnosis of gastrointestinal disease, such as ulcer and cancer within 1 month, (2) Allergic or hypersensitive response to any of the ingredients in the test products, (3) A history of disease that could interfere with the test products or impede their absorption, such as gastrointestinal disease or gastrointestinal surgery, (4) A past history of taking antibiotics and stomach medicines, such as steroid, bismuth compound and proton pump inhibitor within 1 month, (5) A diagnosis of disease of pyloric region, such as obstruction within 1 month, (6) Participation in any other clinical trials within past 2 months, (7) Laboratory test, medical or psychological conditions that might interfere with successful participation in the study based on the judgment of the investigators, or (8) Pregnancy or breast feeding. The study, which was conducted according to the declaration of Helsinki, was approved by the Functional Foods Institutional Review Board (FFIRB) of Chonbuk National University Hospital (FFIRB number: 2011-02-002).

Test supplement: Capsules containing HFE and placebo were provided by Pukyong National University (Busan, Republic of Korea). HFE was prepared as previously described (Kim *et al.*, 2009). Briefly, an aqueous extract of *H. fusiformis* was precipitated with three volumes of ethanol and filtered. The HFE was standardized to 3.6 mg polysaccharide Hf-PS-1 per 1.0 g powder. The arsenic content in the HFE was 14.8 $\mu g\ g^{-1}$. The daily dose was calculated from the results of our previous animal study (unpublished results). Placebo was made with the same taste, smell and appearance but without the principal ingredient that was present in the HFE. The placebo supplements were composed primarily of flour and caramel color.

Study design: The current study was conducted under the 4-week, randomized, double-blind, placebo-controlled trial, preformed according to a computer-generated randomization schedule designed to assign subjects to the HFE or placebo groups. Neither the investigators nor the subjects knew the randomization code or the result was complete. Subjects attended a screening visit (within three weeks), at which inclusion and exclusion criteria were assessed. The enrolled subjects were scheduled for their first visit and subjects were randomly assigned to one of two groups, either the HFE (n = 27) or placebo group (n = 27). Subjects received either the HFE or placebo capsules every 2 weeks and all subjects were instructed to take either four HFE capsules or four placebo capsules per day (1.3 g day^{-1}) for four weeks. Subjects were asked to visit the research center every two weeks for a total four visits, which included the screening visit (screening, 0, 2 and 4 weeks). At each visit, current medication use, smoking status and alcohol intake were investigated and subjective symptoms for gastrointestinal Adverse Events (AEs) was also investigated. During a 4-week intervention period, subjects

were asked to continue their usual diets and activity and were asked not to take any other functional foods or dietary supplements. Endoscopic parameters and subjects' symptoms, biochemical parameters, anthropometric and vital signs were measured before and after the intervention period for both groups. Every fourth week the subjects were asked to report for assessment of any adverse events or any changes in training, lifestyle or eating patterns and to assess capsule compliance. Compliance was assessed by the number of returned capsules. Subjects whose compliance with the HFE or placebo is ≤70% of the total dose were considered to have dropped-out.

Study outcomes: The primary outcomes were number of erosions, endoscopic score and estimated cure rates of erosions. The secondary outcomes included its effect on estimated improvement rates of erosions, subjects' symptom questionnaires and blood profiles. Endoscopic parameters (number of erosions, endoscopic score, estimated cure rates and estimated improvement rates of erosions) were measured before and after the intervention. Endoscopic score was evaluated according to the following grades: Score 1, no erosions, Score 2 (mild), erosion number between 1 and 2, Score 3 (moderate), erosion number between 3 and 5, Score 4 (severe), erosion number more than 6, for the evaluation of cure rate and improvement rate. Estimated cure rate of erosions was determined when standard erosion score of 2, 3, or 4 was reduced to Score 1. Estimated improvement rate of erosions was determined when there was more than two points between estimated cure rates and erosion score. Subjects' symptom questionnaires (heart burn, abdominal distension, nausea, vomiting, epigastric pain, lower abdominal pain, diarrhea and symptoms of digestive organs and the frequency of defecation) were performed at every visit. Blood samples were collected after a minimum of 12 h of fasting before and after the 4-week intervention period for measuring the high sensitive-C reactive protein (hs-CRP), gastrin, pepsinogen I, pepsinogen II and pepsinogen I/II ratio.

Safety measures: Safety assessments included anthropometric, electrocardiogram and laboratory tests (WBCs, RBCs, hemoglobin, hematocrit, platelets, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], glucose, gamma-glutamyl transferase [GGT], total bilirubin, total protein, albumin, Blood Urea Nitrogen (BUN), creatinine, total cholesterol, triglycerides, High-Density Lipoprotein-Cholesterol (HDL-C) and Low-Density Lipoprotein-Cholesterol [LDL-C]) before and after the 4-week intervention period and blood pressure and pulse at every visit.

Statistical analysis: For sample size calculation, there was no previous clinical trial to compare the HFE with placebo, therefore, this study was designed as a trial to calculate the appropriate sample size for future rigorous randomized clinical trials. We assumed that the primary outcome was estimated cure rates of erosions, whereby 36% was expected a clinically relevant difference between the two groups, with alpha set on 5% and power on 80%. This resulted in a required number of 21 subjects in each group. With an estimated 20% dropout rate, we set the total sample size at 54.

Statistical analysis was performed using SAS version 9.2 for Windows (SAS Institute, Cary, NC). Data were shown as mean values and Standard Deviation (SD). General characteristics between HFE and placebo group were analyzed by the independent t-test or Chi-square test. The significance of the differences within or between groups was tested by a linear mixed-effect model and a paired t-test of the mean. The Chi-square test was performed to determine differences in frequencies of categorized variables between the groups. Sub-group analyses of number of erosions and endoscopic score were performed according to baseline endoscopic score. A value of $p<0.05$ was considered statistically significant.

RESULTS

General characteristics of the subjects: The sampling and trial profiles are summarized in Fig. 1 with the number of subjects who completed the study. A total of 79 subjects were screened. In addition, 25 subjects were excluded from the current analysis because they did not meet all the inclusion criteria either by endoscopy and/or laboratory tests. The remaining 54 subjects were divided equally and randomly into the HFE or placebo group. Five subjects from the HFE group and six subjects from the placebo group failed to complete the study. Four subjects were not eligible for study participation because of inadequate intake of the prescribed supplements or not participating in other aspects of the study and four subjects voluntarily withdrew a written informed consent for personal reasons. Two subjects were discontinued treatment, because of protocol violation. As a result, 43 subjects (HFE = 22 and Placebo = 21) remained. At each visit, symptom or AEs information was recorded, but no serious AEs reported, during the 4-week study period. The results of the safety assessments were in the normal range, so no subjects withdrew because of AEs (data not shown).

General characteristics of the subjects are shown in Table 1. There were no significant differences in baseline characteristics such as age, sex, height, weight, body mass index, alcohol intake and smoking status between the HFE and placebo groups.

Endoscopic parameters: Endoscopic parameters are summarized in Table 2. After 4 weeks of supplementation, subjects in the HFE group showed a significant reduction in number of erosions ($p = 0.049$), compared with placebo group. Endoscopic score showed a tendency to decrease in the HFE

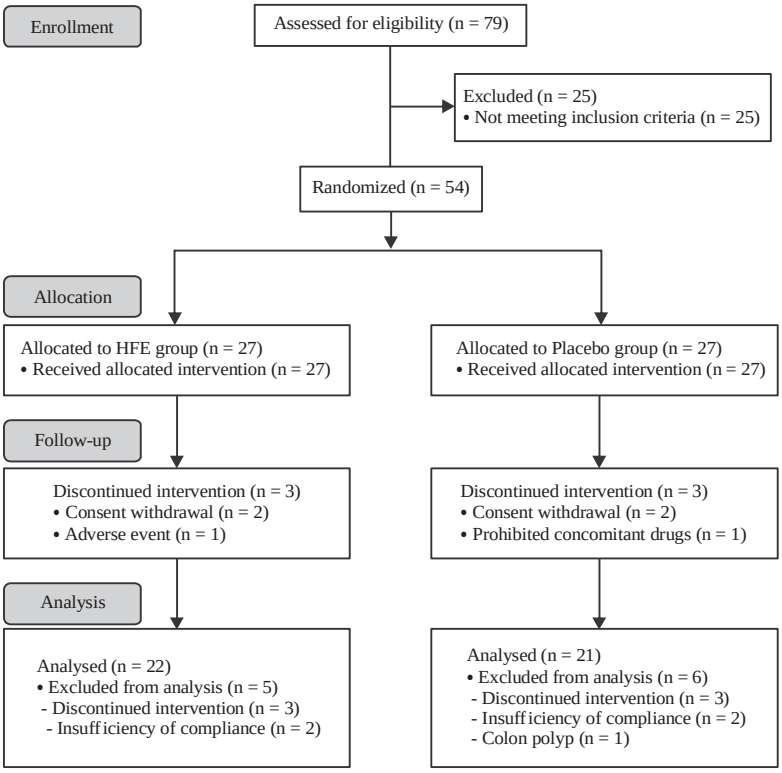

Fig. 1: Flow chart for the study subjects. Number of study participants enrolled, allocated, followed and analyzed

Table 1: Demographic characteristics of study subjects

Demographic characteristics	Placebo group (n = 27)	HFE group (n = 27)	Total (n = 54)	p-value[1)]
Age (years)	38.74±10.02	39.11±11.92	38.93±10.91	0.902
Sex (M/F)	5/22	9/18	14/40	0.214[2)]
Height (cm)	162.44±7.54	162.56±9.67	162.50±8.659	0.959
Weight (kg)	60.07±11.16	62.09±14.50	61.08±12.85	0.570
BMI (kg m^{-2})	22.73±3.55	23.29±3.73	23.01±3.62	0.573
Alcohol drinker (Yes/No)	15/12	16/11	31/23	0.783[2)]
Unit/week	16.9±15.1	10.5±13.6	13.6±14.5	0.225
Smoker (Yes/No)	8/19	8/19	16/38	1.000[2)]
A piece/day	13.1±7.0	11.3±4.8	12.2±5.9	0.558

Data is presented as Mean±SD. M: Male, F: Female, BMI: Body mass index, [1)]Analyzed by independent t-tests and the p-value represents the comparison to the placebo group, [2)]Analyzed by Chi-square tests and the p-value represents the comparison to the placebo group

Table 2: Number of erosions and endoscopic score

	Placebo group (n = 21)			HFE group (n = 22)			
Parameters	Baseline	4 week	p-value[1)]	Baseline	4 week	p-value[1)]	p-value[2)]
Gastric corpus	2.48±2.29	1.62±2.20	0.025	3.27±2.03	1.91±1.63	0.001	0.325
Gastric angular	0.00±0.00	0.19±0.51	0.104	0.18±0.39	0.14±0.35	0.576	0.091
Gastric antrum	0.71±1.42	0.38±1.07	0.049	0.82±1.71	0.27±0.94	0.124	0.581
Gastric cardia	0.19±0.51	0.24±0.70	0.803	0.09±0.29	0.00±0.00	0.162	0.482
Number of erosions	3.38±2.89	2.43±3.28	<0.001	4.36±2.48	2.32±2.10	<0.001	0.049
Endoscopic score	2.71±0.78	2.05±1.12	<0.001	3.00±0.76	2.23±0.92	<0.001	0.626

Data is presented as the Mean±SD, Endoscopic score: 1 point (no erosion; none), 2 point (1~2 erosions; mild), 3 point (3~5 erosions; moderate), 4 point (6 more erosions; severe), [1)]Analyzed by paired t-test between baseline and 4 weeks in each group, [2)]Analyzed by linear mixed-effect model and the p-value represents the comparison to the placebo group

group, but there were no significant differences between the HFE and placebo groups. In case of subjects who were an endoscopic score of 4 point (severe group; the number of erosions more than 6 in baseline), HFE supplementation resulted in a significant decreases of number of erosions compared with placebo group (p = 0.026, Table 3).

Table 3: Number of erosions and endoscopic score in severe group

	Placebo group (n = 4)			HFE group (n = 6)			
Parameters	Baseline	4 week	p-value[1)]	Baseline	4 week	p-value[1)]	p-value[2)]
No. of erosions	8.25±3.30	8.50±1.91	0.846	7.83±1.17	3.83±2.64	0.0103	0.026
Endoscopic score	4.00±0.00	4.00±0.00	-	4.00±0.00	3.00±0.89	0.041	0.060

Data is presented as the Mean±SD, Endoscopic score: 1 point (no erosion; none), 2 point (1~2 erosions; mild), 3 point (3~5 erosions; moderate), 4 point (6 more erosions; severe), [1)]Analyzed by paired t-test between baseline and 4 weeks in each group, [2)]Analyzed by linear mixed-effect model and the p-value represents the comparison to the placebo group

Table 4: Estimated cure rates and estimated improvement rates of erosions

Parameters	Placebo group (n = 21)	HFE group (n = 22)	p-value[1)]
Estimated cure rates of erosions (Yes/No)	38.10 (8/13)	22.73 (5/17)	0.273
Estimated improvement rates of erosions (Yes/No)	38.10 (8/13)	31.82 (7/15)	0.666

Data is presented as the % (Yes/No), Estimated cure rates of erosions and estimated improvement rates of erosions were determined as described in the methods, [1)]Analyzed by Chi-square test and the p-value represents the comparison to the placebo group

Table 5: Subjects' symptom questionnaire

	Placebo group (n = 21)				HFE group (n = 22)				
Symptoms	Baseline	2 week	4 week	p-value[1)]	Baseline	2 week	4 week	p-value[1)]	p-value[1)]
Heart burn	0.90±0.83	0.86±0.85	0.67±0.66	0.442	0.59±0.59	0.73±0.63	0.68±0.72	0.569	0.370
Abdominal distension	0.81±0.81	0.52±0.60	0.52±0.75	0.135	0.64±0.58	0.59±0.59	0.55±0.51	0.697	0.414
Nausea	0.38±0.59	0.33±0.66	0.24±0.44	0.319	0.36±0.66	0.41±0.50	0.36±0.73	0.917	0.660
Vomiting	0.43±0.60	0.43±0.60	0.29±0.46	0.283	0.23±0.43	0.27±0.46	0.23±0.43	0.787	0.515
Epigastric pain	0.48±0.68	0.29±0.56	0.29±0.56	0.037	0.32±0.48	0.32±0.48	0.32±0.48	1.000	0.247
Lower abdomen pain	0.38±0.67	0.19±0.40	0.29±0.56	0.088	0.27±0.46	0.27±0.46	0.27±0.46	1.000	0.286
Diarrhea	0.38±0.59	0.48±0.75	0.29±0.56	0.182	0.18±0.50	0.36±0.58	0.27±0.55	0.344	0.510
In addition digestive organs symptom	0.14±0.65	0.00±0.00	0.00±0.00	0.377	0.18±0.66	0.18±0.50	0.09±0.29	0.524	0.620
Defecation number	1.02±0.52	1.15±0.56	1.05±0.56	0.158	1.12±0.62	1.06±0.43	1.02±0.47	0.303	0.114
Total	3.90±4.15	3.10±3.43	2.57±3.37	0.035	2.77±2.56	3.14±2.53	2.77±3.18	0.646	0.099

Data is presented as the Mean±SD, [1)]Analyzed by linear mixed-effect model and the p-value represents the comparison to the placebo group

Table 6: Blood profiles

	Placebo group (n = 21)			HFE group (n = 22)			
Parameters	Baseline	4 week	p-value[1)]	Baseline	4 week	p-value[1)]	p-value[2)]
hs-CRP (mg L^{-1})	0.16±0.19	0.75±2.01	0.184	0.63±1.24	0.23±0.40	0.106	0.052
Gastrin (pg mL^{-1})	36.44±16.88	27.61±10.86	0.012	37.36±16.43	32.05±15.27	0.127	0.453
Pepsinogen I (ng mL^{-1})	54.72±16.24	57.96±19.42	0.112	50.15±14.78	55.28±19.08	0.008	0.471
Pepsinogen II (ng mL^{-1})	12.65±7.46	13.66±8.09	0.067	13.40±8.38	15.39±10.16	0.0101	0.271
Pepsinogen I/II ratio	5.17±1.83	5.07±1.73	0.424	4.66±1.86	4.56±1.84	0.509	1.000

Data is presented as the Mean±SD, [1)]Analyzed by paired t-test between baseline and 4 weeks in each group, [2)]Analyzed by linear mixed-effect model and the p-value represents the comparison to the placebo group

However, after HFE supplementation, no significant changes were observed in estimated cure rates and estimated improvement rates of erosions (Table 4). In addition, no significant changes or differences were observed in subjective symptoms between the two groups (Table 5).

Blood profiles: Changes in blood profiles before and after the 4-week intervention period are shown in Table 6. After the intervention of 4 weeks, hs-CRP levels showed a tendency to decrease in HFE group ($p = 0.052$), whereas the placebo group showed an increasing trend. No significant changes were observed in blood gastrin, pepsinogen I, pepsinogen II and pepsinogen I/II ratio in either the HFE or placebo group.

DISCUSSION

In traditional medicine, several plants and herbs have been used to treat gastrointestinal disorders, including gastric ulcers (Gadekar *et al.*, 2010). Usually, anti-ulcerogenic compounds obtained from plants and herbs exert their effects by stimulating the secretion of mucus and bicarbonate or by inhibiting acid secretion (Borrelli and Izzo, 2000). In the present study, we orally administered ethanol extract of HFE to patients with erosive gastritis and found that HFE possesses ulcer-healing activity as evidenced by a significant reduction in number of erosions.

HEF might include the active constituents to stimulate the secretion of gastroprotective factor. Among them, Hf-PS-1, a polysaccharide, appears to be one of the major bioactive components that offer antiulcer effects. In our previous study, Hf-PS-1 was effective in protecting rats against ethanol-induced gastric damage (Kim *et al.*, 2009). Ethanol is a well-known necrotizing agent that destroys the mucus barrier, increases vascular permeability and decreases the anti-oxidant factor such as glutathione (GSH), which leads to hemorrhagic gastric erosion (Kwiecien *et al.*, 2002;

Repetto and Llesuy, 2002). The Hf-PS-1 restores anti-oxidant activity by inhibiting c-Jun N-terminal kinase (JNK) pathway and prevents the formation of acute hemorrhagic erosion caused by oral ethanol administration. Apart from anti-oxidant activity, Hf-PS-1 can also prevent caspase activation which is indicative of apoptotic cell death in gastric mucosa. Given that gastroduodenal ulceration is due to apoptotic cell death of the gastric mucosa (Szabo and Tarnawski, 2000; Gong *et al*., 2010), it is thus possible that HFE has anti-ulcerogenic activity by blocking apoptotic cell death in addition to its antioxidant activity.

Studies have shown that hijiki contains potentially toxic quantities of inorganic arsenic (Rose *et al*., 2007; Ichikawa *et al*., 2010) and food safety agencies of several countries except Japan have advised against its consumption. In support of this advice, Nakamura *et al*. (2008), reported that the cancer risk posed to Japanese people through hijiki consumption exceeds the acceptable range. Yokoi *et al*. (2012), fed the rats with 3% hijiki diet that contained 30 g commercial hijiki powder/kg diet and found an elevated body temperature, arsenic accumulation in blood and tissues and various abnormal blood chemistries. In contrast to these negative reports, the Japanese Ministry announced that the health risk of hijiki consumption was minimal because arsenic intake through hijiki consumption was estimated not to exceed the Provisional Tolerable Weekly Intake (PTWI) of 15 μg kg^{-1} $week^{-1}$, proposed by the World Health Organization (WHO., 1989). Ministry of Food and Drug Safety (MFDS) also established the "Items for Establishment of Detrimental Substance Specifications" for arsenic of <150 μg day^{-1} for an adult with a body weight of 60 kg. Arithmetically, WHO and MFDS allow an adult to eat roughly 1 mg $week^{-1}$. In this study, HFE was supplemented at a dose of 1.3 g day^{-1}, which contains 19 μg of arsenic. Therefore, subjects were supplemented with HFE far below the allowed dose suggested by both guidelines. In addition, blood parameters and physical findings suggested that it had no significant adverse effects at the doses used.

A possible weakness of this study is that the diets and activity levels were not controlled and therefore future studies should include a diet and exercise component. Moreover, because this study is placebo-controlled trial, the psychological effects of placebo and the effects of placebo components were not considered. Moreover, small sample size in this study limits the generalization of our results to other populations with erosive gastritis. Another limitation is that we assessed erosive gastritis only by measuring endoscopy and questionnaires and did not perform *H. pylori* status. Nevertheless, we could observe a significant reduction in number of erosions and a tendency to decrease in endoscopic score in HFE group. Of note, HFE supplementation was not effective in reducing number of erosion, however in severe group, it decreased both the number of erosions and endoscopic score with significance, suggesting HFE might have therapeutic efficacy in subjects with severe erosive gastritis rather than milder group. Further large scale clinical study including subjects with chronic erosive gastritis might strengthen the therapeutic efficacy of HFE.

CONCLUSION

The present study demonstrates for the first time that HFE supplementation has anti-ulcer effects without any noticeable AEs. At present, it remains uncertain how the HFE shows protective effects for the erosive gastritis, but this study might open up more elaborate and extensive study to establish HFE as a functional food to control erosive gastritis.

ACKNOWLEDGMENTS

This research was supported by a grant from Marine Bioprocess Research Center of the Marine Biotechnology Program funded by the Ministry of Land, Transport and Maritime, Republic of Korea (M2010-04). This study was conducted at the Clinical Trial Center for Functional Foods in Chonbuk National University Hospital.

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