

Arrhythmogenicity of weight-loss supplements marketed on the Internet

Alireza Nazeri, MD, Ali Massumi, MD, James M. Wilson, MD, Christopher M. Frank, MD, Michael Bensler, MD, Jie Cheng, MD, PhD, Mohammad Saeed, MD, Abdi Rasekh, MD, Mehdi Razavi, MD

From the Center for Cardiac Arrhythmias and Electrophysiology, Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, Texas.

BACKGROUND We examined nonprescription weight-loss supplements marketed on the Internet for ingredients with potential arrhythmogenic and life-threatening cardiac adverse effects.

OBJECTIVE We aimed to define the risks of life-threatening cardiac adverse effects that are associated with weight-loss supplements marketed on the Internet.

METHODS We entered the key words "weight-loss supplements" and "diet pills" into three popular Internet search engines. The top four nonoverlapping hits from each search engine were purchased. After receipt, the products and their ingredient lists were inspected, and Medline and the Natural Medicines Comprehensive Database were searched for reports of significant associations between each ingredient and various key words for life-threatening cardiac adverse effects.

RESULTS All supplements had the list of ingredients on the label. We identified 60 different ingredients (7.25 ± 4.66 per supplement; range 1–21). Eleven ingredients representing eight different substances (because multiple names were used for some

substances) were each associated with two or more reports of life-threatening cardiac complications or death. Eight of the 12 products contained one or more such ingredients, but none of these eight products had warnings about life-threatening cardiac adverse effects on the Web pages, on the labels, or in the package inserts. One product contained *ma huang* (Chinese ephedra), even though the marketing of ephedra-containing products is banned in the United States.

CONCLUSIONS The Internet provides easy access to weight-loss supplements, several of which contain ingredients with potentially life-threatening adverse effects. There is a need for increased public education and awareness regarding such weight-loss products.

KEYWORDS Weight loss; Tachyarrhythmias; Cardiac side effects; Supplements; Obesity; Death

(Heart Rhythm 2009;6:658–662) © 2009 Heart Rhythm Society. All rights reserved.

Introduction

Obesity is rapidly becoming a health problem of epidemic proportions. Since the mid-1970s, the prevalence of overweight and obesity has increased sharply in both adults and children. Data from two National Health and Nutrition Examination Surveys show that among adults aged 20–74 the prevalence of obesity increased from 15% in 1976–1980 to 33% in 2003–2004.¹

Use of over-the-counter weight-loss supplements has become more common in the United States.^{2,3} Retail sales of weight-loss supplements were estimated to be more than \$1.3 billion in 2001. Possible reasons for the popularity of these supplements include the social stigma of obesity, desire for a "magic bullet" for weight loss, the supplements' rapid availability without prescription or consultation with a health care professional, the perception that "natural equals safe," and inflated advertising claims.⁴

The Internet is a growing resource for finding health information and purchasing health products, including weight-loss supplements.⁵ To our knowledge, the U.S. Food and Drug Administration (FDA) does not strictly regulate the sale and marketing of these supplements on the Internet; unlike prescription drugs, dietary supplements are not required to pass safety studies before being sold to consumers, and the companies that make these supplements are not required to obtain FDA approval to sell them. Furthermore, as Jordan et al⁶ have shown, Internet Web sites selling weight-loss supplements do not accurately describe (or do not describe at all) the potential health hazards these products may pose.

The cardiovascular adverse effects of various herbal supplements have been reported previously. With this background, we aimed to define the risks of arrhythmogenic and life-threatening cardiac adverse effects that are associated with weight-loss supplements readily found and purchased on the Internet.

Methods

During the winter of 2007, we used three search engines—www.yahoo.com (Yahoo), www.google.com (Google), and

This paper was presented as an oral abstract at Heart Rhythm 2008, San Francisco, California. **Address reprint requests and correspondence:** Mehdi Razavi, M.D., 6624 Fannin, Suite 2480, Houston, Texas 77030. E-mail address: mehdirazavi1@gmail.com.

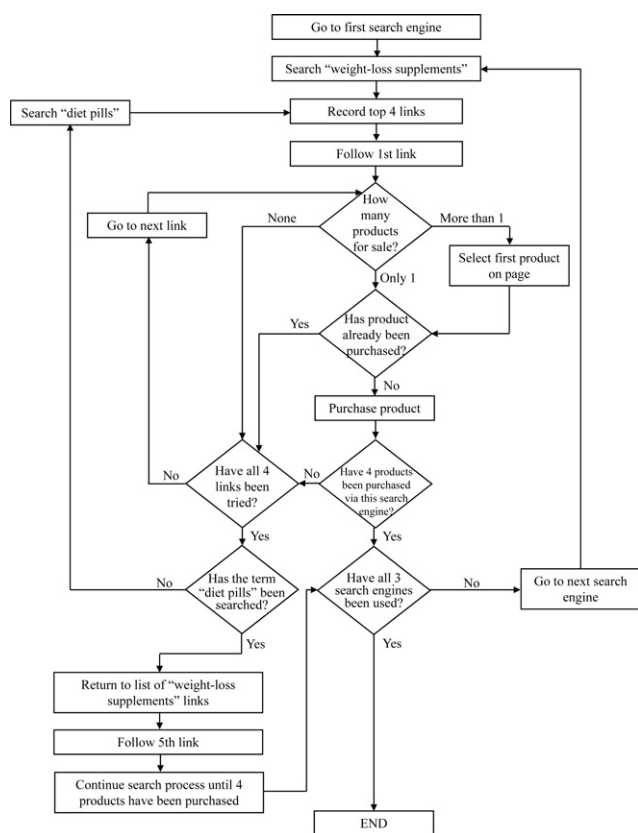


Figure 1 Search method used to identify supplements for purchase.

www.msn.com (MSN)—with the goal of purchasing four nonoverlapping products from each search engine for a total of 12 products. Our search procedure (see Figure 1) was as follows: We first searched the term “weight-loss supplements” on each search engine—Yahoo first, then Google, then MSN. If any search produced overlapping results (i.e., if one or more of the top four hits from a given search engine matched a hit from a previously used search engine), we then searched for the term “diet pills.” If there was still overlap, we returned to the list of hits from the “weight-loss supplements” search, starting with the fifth hit and continuing down the list until four products were purchased via that search engine.

The Web pages and all packages and inserts were inspected for warnings about cardiovascular adverse effects. We identified the ingredients exactly as they were listed on the package labels, and we performed a comprehensive search of Medline and of the Natural Medicines Comprehensive Database for any reported association between each ingredient and cardiac arrhythmias or other life-threatening cardiac adverse effects. The key words “cardiac arrhythmias,” “ventricular tachycardia,” “ventricular fibrillation,” “myocardial infarction,” “cardiac arrest,” and “death” were used in each database search.

Results

Each of the 12 products was purchased online and delivered to us at a designated U.S. address without any restrictions.

All products had a list of ingredients on the label. From these lists, we identified 60 different ingredients (7.25 ± 4.66 per supplement; range 1–21) exactly as they were listed on the labels. Of these ingredients, 42 were herbal extracts, five were synthetic compounds, four were minerals, and nine were vitamins or other organic substances. Eleven of the listed ingredients—which corresponded to eight different substances, because some ingredients were listed by various names—were associated with at least one report of life-threatening cardiac events or death; in fact, all eight ingredients were associated with two or more such reports. Eight of the 12 products included at least one of these ingredients. Warnings about potential adverse effects did not appear on any of the Web pages from which we purchased these eight products or on the labels and other materials shipped with these products. One product’s list of ingredients included *ma huang* (Chinese ephedra), even though the marketing of ephedra-containing products is banned in the United States.

The other potentially hazardous ingredients were bitter orange (also listed as *Citrus aurantium* and synephrine HCl), green tea (also listed as *Camellia sinensis*), buckwheat, guarana, ginseng (listed as Korean ginseng), licorice root, caffeine anhydrous, and *ma huang* root. Eight of the 12 products contained one or more of these ingredients (see Table 1).

Discussion

In this study, we examined 12 weight-loss supplements and identified eight ingredients with reported life-threatening cardiac adverse effects. We briefly review these ingredients and discuss the risks that they may pose to consumers.

Ma huang, or Chinese ephedra, is also known as ephedra, *Ephedra distachya*, and *Ephedra vulgaris*. Its principal alkaloid constituents are ephedrine and pseudoephedrine, both of which are nonselective α - and β -receptor agonists. Ephedra is taken orally for weight loss and to enhance athletic performance.⁷ In 2001, ephedra accounted for less

Table 1 The distribution of ingredients with reported serious cardiac adverse effects among the 12 weight-loss products

Product	Ingredient(s)
1	Bitter orange ^a
2	None
3	Bitter orange, ^b buckwheat
4	Bitter orange, ^a ginseng
5	Bitter orange, green tea, guarana
6	None
7	Caffeine anhydrous, green tea ^c
8	Green tea
9	None
10	None
11	Bitter orange, ^b caffeine anhydrous, green tea, licorice root
12	<i>Ma huang</i> root (ephedra)

^aLabeled “synephrine HCl.”

^bLabeled “*Citrus aurantium*.”

^cLabeled “*Camellia sinensis*.”

than 1% of herbal product sales but caused 64% of herbal adverse reactions reported to poison control centers.⁸ Ephedra is associated with life-threatening cardiac adverse effects, including cardiomyopathy, hypersensitivity myocarditis, chest tightness, myocardial infarction, cardiac arrest, cardiac arrhythmias, and sudden cardiac death.^{9–12} In healthy volunteers, ephedra causes electrocardiographic changes; prolonged QT interval and premature atrial contractions can both occur after ingestion of ephedra.¹³ The FDA banned the sale and marketing of ephedra-containing products in the United States in 2004.¹⁴

Bitter orange is also known as green orange, *Citrus aurantium*, aurantium, synephrine HCl, and synephrine. Bitter orange fruit and peel, which are taken orally for weight loss,⁷ contain the adrenergic agonists synephrine and octopamine. Structurally, synephrine is similar to epinephrine, and octopamine is similar to norepinephrine. Several case reports have associated bitter orange with significant adverse cardiovascular effects. Between 1998 and 2004, Health Canada received 16 reports of serious adverse cardiovascular reactions to bitter orange.¹⁵ The reported cardiac side effects we identified included tachycardia, tachyarrhythmias, QT prolongation, variant angina, myocardial infarction, cardiac arrest, ventricular fibrillation, syncope, and death.^{15–20} Most of these side effects occurred when bitter orange was taken with caffeine or ephedrine. Because bitter orange can inhibit the metabolism of drugs by cytochrome P450 3A4 (CYP3A4), taking bitter orange with CYP3A4-metabolized drugs can increase blood levels of those drugs and thus increase the risk of adverse effects. The extent of this interaction effect is not yet known.⁷

Green tea is also known as *Camellia sinensis* and *Camellia thea*. It is taken orally and can be used for weight loss.⁷ Green tea contains polyphenols, catechins, and 2%–4% caffeine (10–80 mg caffeine per cup).^{21,22} Very large doses of caffeine can cause catecholamine release, resulting in hypokalemia, chest pain, sinus tachycardia, premature contractions, and arrhythmias.⁷ Thus, consuming green tea—mainly in very large doses or in combination with bitter orange or caffeine-containing herbs like guarana—can increase the risk of serious cardiovascular adverse effects.^{7,9} The caffeine in green tea can also have harmful interactions with a variety of drugs, including, but not limited to, adenosine, quinolone antibiotics, dipyridamole, verapamil, and cimetidine.⁷

Ginseng is also known as *Panax ginseng* and Korean ginseng. Orally, ginseng is used as a so-called adaptogen for increasing resistance to environmental stress. It may improve abstract thinking, mental arithmetic skills, and reaction times in healthy middle-aged people.²³ There are no reports on its efficacy for weight loss.⁷ Ginseng has several constituents, including ginsenosides, various flavonoids, B vitamins, and pectin. Using ginseng concomitantly with bitter orange may prolong the QT interval, because these two substances have synergistic sympathomimetic effects.⁷ Similarly, ginseng has been reported to have an additive

effect with ephedra, increasing the risk of life-threatening ventricular arrhythmias.^{7,24,25} Ginseng can increase the QT interval in healthy adults on the first day of use.²⁶ Ginseng's effects have not been studied in individuals with cardiovascular disease. Ginseng can diminish the effects of warfarin.⁷

Licorice is also known as *Glycyrrhiza glabra*, Gan Cao, glycyrrhizic acid, and isoflavone. The applicable part of licorice is the root. There is conflicting information about the effectiveness of licorice for weight loss.^{7,27} Licorice has antispasmodic, anti-inflammatory, laxative, and soothing properties.⁷ The mineralocorticoid effects of licorice can induce fluid retention and worsen congestive heart failure. Licorice can also cause severe hypokalemia, increasing the risk of arrhythmias. There are multiple case reports of patients with life-threatening ventricular tachyarrhythmias and torsades de pointes due to licorice-induced hypokalemia, presumably caused by a mineralocorticoid excess syndrome associated with licorice consumption.^{28–30} Overusing licorice or combining it with cardiac glycoside therapy may increase the risk of cardiac toxicity due to potassium loss. Patients with heart disease should avoid licorice. In addition, licorice can reduce the effects of antihypertensive drugs, and it may have adverse interactions with other drugs, including (but not limited to) warfarin, digoxin, and furosemide.⁷

Caffeine anhydrous, scientifically known as 1,3,7-trimethylxanthine, is commonly called caffeine. Its uses include weight loss and treating type 2 diabetes.⁷ Caffeine is a methylxanthine compound and is structurally related to theophylline, theobromine, and uric acid. It is 100% bioavailable after oral administration. Its possible mechanisms of action include adenosine receptor blockade and phosphodiesterase inhibition. Caffeine is thought to act on adenosine receptors to increase the release of dopamine and other neurotransmitters. In large doses, caffeine can stimulate massive catecholamine release, causing sinus tachycardia, metabolic acidosis, hyperglycemia, and ketosis.³¹ In rare cases, caffeine overdose can result in death from ventricular fibrillation.³² Using caffeine in combination with bitter orange or caffeine-containing herbs, such as green tea, black tea, oolong tea, guarana, mate, kola nut, and ephedra, increases the risk of serious life-threatening or debilitating adverse effects such as hypertension, myocardial infarction, stroke, seizure, and death.^{7,9} It must be emphasized that caffeine's deleterious effects occur almost exclusively when caffeine is combined with other stimulants or taken in massive doses.

Guarana is also known as *Paullinia cupana* and Brazilian cocoa. Taken orally, guarana is used for weight loss and enhancing athletic performance.⁷ Oral guarana may promote weight loss when used in combination with mate and damiana.³³ Guarana contains 3.6%–5.8% caffeine (compared with 1%–2% in coffee),³⁴ which is responsible for guarana's pharmacologic effects.⁸ When taken in combination with other caffeine-containing herbs or with bitter orange, guarana can increase blood pressure and heart rate in

otherwise healthy, normotensive adults, potentially increasing their risk of serious cardiovascular adverse effects.^{9,35} Some reports have associated the use of a product containing both ephedra and guarana with jitteriness, hypertension, seizures, temporary loss of consciousness, and hospitalization requiring life support. Also, like other caffeine-containing supplements, guarana may have adverse interactions with a variety of drugs.⁷

Buckwheat is also known as buchweizen, grano turco, and sarrasin. The active constituents of buckwheat include tocopherols, phenolic acids, and flavonoids. Buckwheat is taken orally to treat diabetes, improve vascular tone, and prevent hardening of the arteries.⁷ In both adults and children, allergic reactions to ingested buckwheat can include skin sensitization, allergic rhinitis, asthma, and anaphylaxis.^{36–38} Noma et al³⁹ reported a case in which buckwheat had caused fatal food-dependent exercise-induced anaphylaxis and cardiopulmonary arrest; additionally, the authors found specific IgE bands that were associated with the patient's reaction to buckwheat. Kashima et al⁴⁰ reported a case of sudden death in a patient who had eaten *nyan-mien*, or Korean buckwheat noodles.

The use of weight-loss supplements is common. In a study performed by Blanck et al² to assess the prevalence of nonprescription weight-loss supplement use in the United States, an estimated 15.2% of adults (20.6% of women and 9.7% of men) had used a weight-loss supplement. The greatest use was among women aged 18–34 years (16.7%), and 73.8% of the supplements used by these women contained one or more stimulants, including ephedra, caffeine, and bitter orange. Of 3500 U.S. adults surveyed at random by Pillitteri et al³ in 2005, 41.2% had made serious weight-loss attempts during their lifetimes, and 33.9% of this group reported using a weight-loss supplement during at least one attempt. The survey also found that many users and nonusers of dietary supplements had misconceptions about these products: many believed that the FDA assured the safety and efficacy of the supplements and that dietary supplements were categorically safer than over-the-counter or prescription medications.

The Internet is a popular medium for the marketing and purchase of health care products, including weight-loss supplements. According to data reported in 2003, 80% of adult Internet users in the US (about 93 million Americans) have searched at least one major health topic online; 44% of these users looked for dietary supplements, vitamins, or nutritional supplements.⁵

In our study, we purchased 12 weight-loss products marketed on the Internet. These were the most highly ranked products on the most popular Internet search engines. This was done to mimic real consumer behavior. None of the products came with any warnings about life-threatening adverse effects. Additionally, some potentially dangerous ingredients were listed under different names for different products. For example, bitter orange was variously listed as bitter orange, synephrine HCl, and *Citrus aurantium* in five

different products. The lack of standardized nomenclature can mislead consumers, even if they are aware of a given substance's adverse effects under another name. This problem can also increase the risk of uninformed consumption, and it may impair health care providers' ability to counsel individual patients.

The total number of weight-loss supplements available to consumers is unknown, as is the proportion of these products that contain potentially hazardous ingredients. In our small sample of 12 products, we identified eight that contained one or more ingredients with potentially life-threatening cardiac adverse effects. One of these products contained ephedra, even though it is banned in the United States. In our experience, this ban has not prevented the sale of ephedra-containing products to U.S. consumers via the Internet.

Limitations

Most of the published evidence of adverse effects was found in case reports. Also, most of the reported effects were induced by substances taken in large doses or in combination with other substances. There is a lack of strong evidence from clinical trials on the safety of weight-loss supplements.

Conclusion

The Internet provides easy access to weight-loss supplements, including those with potentially life-threatening effects. Consumers are vulnerable to them because there is inadequate information or no information on the marketing Web sites about the life-threatening cardiac adverse effects of these products. The general public, health care professionals, and especially weight-loss consultants need to be educated about these products. We recommend more strict regulation of the sale and marketing of weight-loss supplements on the Internet.

Acknowledgments

Drs. Razavi and Nazeri had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Stephen N. Palmer, Ph.D., E.L.S., contributed to the editing of this manuscript.

References

1. Overweight and obesity. <http://www.cdc.gov/nccdphp/dnpa/obesity/>. Accessed February 2008.
2. Blanck HM, Serdula MK, Gillespie C, et al. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* 2007;107:441–447.
3. Pillitteri JL, Shiffman S, Rohay JM, et al. Use of dietary supplements for weight loss in the United States: results of a national survey. *Obesity (Silver Spring)* 2008;16:790–796.
4. Saper RB, Eisenberg DM, Phillips RS. Common dietary supplements for weight loss. *Am Fam Physician* 2004;70:1731–1738.
5. Fox S, Fallows D. Internet Health Resources. Pew Internet and American Life Project. <http://www.pewinternet.org>. Accessed January 2008.
6. Jordan MA, Haywood T. Evaluation of internet websites marketing herbal weight-loss supplements to consumers. *J Altern Complement Med* 2007;13:1035–1043.
7. Natural Medicines Comprehensive Database. <http://www.naturaldatabase.com>. Accessed January 2008.

8. Bent S, Tiedt TN, Odden MC, et al. The relative safety of ephedra compared with other herbal products. *Ann Intern Med* 2003;138:468–471.
9. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000;343:1833–1838.
10. Okada S, Rohan PJ, Miller FW. Myopathies following ingestion of special nutritional products. *Arthr Rheum* 1996;39:S49.
11. Theoharides TC. Sudden death of a healthy college student related to ephedrine toxicity from a ma huang–containing drink. *J Clin Psychopharmacol* 1997;17:437–439.
12. Zaacks SM, Klein L, Tan CD, et al. Hypersensitivity myocarditis associated with ephedra use. *J Toxicol Clin Toxicol* 1999;37:485–489.
13. Gardner SF, Franks AM, Gurley BJ, et al. Effect of a multicomponent, ephedra-containing dietary supplement (Metabolife 356) on Holter monitoring and hemostatic parameters in healthy volunteers. *Am J Cardiol* 2003;91:1510–1513, A1519.
14. Jordan S, Murty M, Pilon K. Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions. *Can Adverse Reaction News* 2004;14.
15. Jordan S, Murty M, Pilon K. Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions. *CMAJ* 2004;171:993–994.
16. Firenzuoli F, Gori L, Galapai C. Adverse reaction to an adrenergic herbal extract (Citrus aurantium). *Phytomedicine* 2005;12:247–248.
17. Food and Drug Administration. <http://www.fda.gov/oc/initiatives/ephedra/february2004/>. Accessed February 2008.
18. Nykamp DL, Fackih MN, Compton AL. Possible association of acute lateral-wall myocardial infarction and bitter orange supplement. *Ann Pharmacother* 2004;38:812–816.
19. Nasir JM, Durning SJ, Ferguson M, et al. Exercise-induced syncope associated with QT prolongation and ephedra-free Xenadrine. *Mayo Clin Proc* 2004;79:1059–1062.
20. Gange CA, Madias C, Felix-Getzik EM, et al. Variant angina associated with bitter orange in a dietary supplement. *Mayo Clin Proc* 2006;81:545–548.
21. Foster S, Duke JA. *Eastern/Central Medicinal Plants*. New York: Houghton Mifflin Co, 1990.
22. Kaegi E. Unconventional therapies for cancer: 2. Green tea. The Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative. *CMAJ* 1998;158:1033–1035.
23. Sørensen H, Sonne J. A double-masked study of the effects of ginseng on cognitive functions. *Curr Ther Res Clin Exp* 1996;57:959–968.
24. Caron MF, Hotsko AL, Robertson S, et al. Electrocardiographic and hemodynamic effects of Panax ginseng. *Ann Pharmacother* 2002;36:758–763.
25. McBride BF, Karapanos AK, Krudysz A, et al. Electrocardiographic and hemodynamic effects of a multicomponent dietary supplement containing ephedra and caffeine: a randomized controlled trial. *JAMA* 2004;291:216–221.
26. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. *Diabetes Care* 1995;18:1373–1375.
27. Armanini D, De Palo CB, Mattarello MJ, et al. Effect of licorice on the reduction of body fat mass in healthy subjects. *J Endocrinol Invest* 2003;26:646–650.
28. Böcker D, Breithardt G. [Induction of arrhythmia by licorice abuse]. *Z Kardiol* 1991;80:389–391.
29. Bryer-Ash M, Zehnder J, Angelchik P, et al. Torsades de pointes precipitated by a Chinese herbal remedy. *Am J Cardiol* 1987;60:1186–1187.
30. Eriksson JW, Carlberg B, Hillorn V. Life-threatening ventricular tachycardia due to liquorice-induced hypokalaemia. *J Intern Med* 1999;245:307–310.
31. Benowitz NL, Osterloh J, Goldschlager N, et al. Massive catecholamine release from caffeine poisoning. *JAMA* 1982;248:1097–1098.
32. Holmgren P, Norden-Pettersson L, Ahlner J. Caffeine fatalities—four case reports. *Forensic Sci Int* 2004;139:71–73.
33. Andersen T, Fogh J. Weight loss and delayed gastric emptying following a South American herbal preparation in overweight patients. *J Hum Nutr Diet* 2001;14:243–250.
34. Cannon ME, Cooke CT, McCarthy JS. Caffeine-induced cardiac arrhythmia: an unrecognized danger of healthfood products. *Med J Aust* 2001;174:520–521.
35. Schulz V, Hänsel R, Tyler VE. *Rational Phytotherapy: A Physician's Guide to Herbal Medicine*. 3d ed. Berlin: Springer, 1998.
36. Schiffrer R, Przybilla B, Burgdorff T, et al. Anaphylaxis to buckwheat. *Allergy* 2001;56:1020–1021.
37. Lee SY, Lee KS, Hong CH, et al. Three cases of childhood nocturnal asthma due to buckwheat allergy. *Allergy* 2001;56:763–766.
38. Heffler E, Guida G, Badiu I, et al. Anaphylaxis after eating Italian pizza containing buckwheat as the hidden food allergen. *J Investig Allergol Clin Immunol* 2007;17:261–263.
39. Noma T, Yoshizawa I, Ogawa N, et al. Fatal buckwheat dependent exercised-induced anaphylaxis. *Asian Pac J Allergy Immunol* 2001;19:283–286.
40. Kashima T, Fukui M, Masuda Y, et al. [A case of acute death taking “nyanmien,” Korean buckwheat noodle]. *Nihon Hoigaku Zasshi* 1961;15:391–394.