LETTER TO THE EDITOR

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# Unsupported conclusions in the article "Synephrine-containing dietary supplement precipitating apical ballooning syndrome in a young female"

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**Comments on Article by Chung et al. Korean J Intern Med 2013;28:356-360**

*To the Editor,*

The article entitled "Synephrine-containing dietary supplement precipitating apical ballooning syndrome in a young female" by Chung et al. [1] contains scientifically unsupported assumptions and unsubstantiated conclusions regarding *p*-synephrine, the primary protoalkaloid present in *Citrus aurantium* (bitter orange). No evidence is provided that there is a causal relationship between *p*-synephrine and the observed syndrome. Furthermore, the authors failed to review current scientific literature regarding *p*-synephrine and extracts of *C. aurantium*. No serious adverse events have ever been directly attributable to *C. aurantium* extract and *p*-synephrine [2-4].

The authors purport that apical ballooning syndrome was caused by a product that contained synephrine and caffeine, stating that the subject had been taking dietary supplements containing these ingredients. The authors have provided no evidence or information substantiating their claim. The authors do not indicate how many different dietary supplements were being taken, the names of the products, the actual compositions of the products, the amounts of the various ingredients in the products, how much of the products were being taken by the subject, and the conditions under which the supplements were being taken. There is no evidence directly linking supplement use with the observed syndrome. As a consequence, it is not possible to establish a cause and effect relationship.

Case reports are frequently and inappropriately cited as unequivocal evidence that dangerous adverse effects or herb-drug interactions have occurred. It should be clearly noted that "case reports are incomplete, uncontrolled, retrospective, lack operational criteria for identifying when an adverse event actually occurred, and resemble nothing so much as hearsay evidence, a type of evidence that is prohibited in all courts in all of industrialized societies" [5].

The authors [1] state that the toxicity of synephrine is largely unknown, especially in combination with caffeine. The authors did not cite recent

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reviews that have been published with respect to the safety of *p*-synephrine and *C. aurantium* extracts in animals and humans and their efficacy in humans [3,4,6,7]. Over 20 human published and unpublished human clinical studies have been conducted which demonstrate that bitter orange extract and *p*-synephrine alone and in combination with other ingredients support modest weight loss in conjunction with diet and exercise without significant adverse effects being observed [4]. The majority of the subjects in these studies were overweight/obese, and a large percent of the subjects consumed caffeine (up to 528 mg/day) in combination with *p*-synephrine (up to 80 mg/day) [4].

Intertek-Cantox, a global leader in toxicology and regulatory services. It is known for its conservative approach to dietary supplements, its reports are widely used as a basis for making recommendations regarding the use and safety of supplements. Intertek-Cantox conducted a detailed scientific literature review and issued a report on *C. aurantium* extract and *p*-synephrine consumption in combination with caffeine [6]. The Report states that "*p*-synephrine is unlikely to have significant effects on inotropy, vasoconstriction, or blood pressure." The report further states that the following dosages are "not likely to cause adverse effects": up to 70 mg *p*-synephrine alone or 40 mg in combination with 320 mg of caffeine; and If taken as divided doses spaced out over the course of the day, 100 mg of p-synephrine alone or 70 mg *p*-synephrine in combination with 400 mg caffeine [6].

The Natural Health Products Directorate of Health Canada has conducted an extensive review of *C. aurantium* and *p*-synephrine, and in May 2011 released a 49 page health risk assessment report on *p*-synephrine and caffeine and defined its current guidelines for the use of these natural ingredients [7]. Health Canada approved the use of up to 50 mg per day of *p*-synephrine alone in healthy adults, and 40 mg per day or less of *p*-synephrine when combined with 320 mg per day or less of caffeine. Health Canada is the equivalent of the U.S. Food and Drug Administration (FDA).

The authors [1] assume that because *p*-synephrine has structural similarities to various amines as epinephrine, amphetamine and ephedrine that it will *de facto* exert similar effects. The structural (stereochemical) differences between *p*-synephrine relative to other biogenic amines as epinephrine, ephedrine and *m*-synephrine result in markedly different adrenergic receptor binding and pharmacokinetic characteristics, and therefore significantly different pharmacological properties [8]. The properties of other phenethylamines and phenpropylamines cannot be extrapolated to *p*-synephrine based on some structural similarities.

Contrary to the general statements of the authors [1] regarding sympathomimetic actions and cardiovascular effects, *p*-synephrine exhibits little or no binding to α-, and β-1 and β-2 adrenergic receptors which is essential to producing cardiovascular effects [8]. This lack of adrenergic receptor binding readily explains the observed lack of cardiovascular effects of *p*-synephrine.

The authors did not include any dosing information [1], and therefore it is not possible to make meaningful comparisons with published studies. In a recently completed double-blind, placebo-controlled study, 46 healthy human subjects were given bitter orange extract (49 mg *p*-synephrine) twice a day (total of 98 mg/day of *p*-synephrine) for 60 days, while 23 subjects received the placebo [9]. No cardiovascular effects were observed nor were there any adverse effects with respect to blood chemistries or blood cell counts with differentials, indicating a high degree of safety of these ingredients.

The safety of *C. aurantium* and *p*-synephrine was examined in a human placebo-controlled, double blind, cross-over study where subjects were given 49 mg *p*-synephrine daily for 15 days [10]. *p*-Synephrine did not exert any significant effects on heart rate, blood pressure, electrocardiograms, blood cell counts, or blood chemistries or enzymes over the 15 days of the study.

Finally, the authors appear to be unaware that various orange juices have been shown to contain up to 20 to 25 mg *p*-synephrine per quarter liter [11,12], concentrations that exceed the amounts of *p*-synephrine in many dietary supplements. *p*-Synephrine is consumed on a daily basis in the form of juices and orange-related food products as marmalades alone and in combination with caffeine from beverages as coffee and tea without adverse events.

In summary, the authors have omitted critical details of the case, made unsupported extrapolations, failed to appropriately review the scientific literature,

and arrived at conclusions that lack scientific support or merit. Contrary to their assertions, there is little that is similar between *p*-synephrine and ephedrine with respect to pharmacokinetic properties, adrenergic receptor binding, and pharmacological and toxicological effects.

**Keywords:** *p*-Synephrine; Bitter orange; Citrus aurantium

### Conflict of interest

The author has served as a consultant for Nutratech Inc. (West Caldwell, NJ, USA).

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*Author Reply*

# Potential hazard of indiscriminate abuse of synephrine-containing dietary supplement should not be overlooked

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The U.S. Food and Drug Administration (FDA) recently declared obesity as a disease entity because it is a major public health concern that has been linked to many health problems, including cardiovascular disease. Moreover, the robustness of obesity treatment and management is an emerging issue, especially in industrialized countries. In this regard, we should not overlook the indiscriminative abuse of dietary supple-


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ments under the guise of obesity treatment.

Since the FDA determined that ephedra and ephedrine-containing dietary supplements are unsafe for unregulated use and forbade their sale in 2004, *p*-synephrine has been widely used as an alternative to ephedra in dietary supplements. *p*-Synephrine is a sympathomimetic amine derived from the plant *Citrus aurantium*. *p*-Synephrine is structurally similar to various amines such as epinephrine, amphetamine, and ephedrine, although its receptor-binding affinity is considered to be much lower than that of other sympathomimetic amines [1]. Although *p*-synephrine is generally considered to be safer than ephedra, controversy surrounds its toxic effects, especially in combination with caffeine, which is known to potentiate the cardiovascular effect of *p*-synephrine. Previous animal studies revealed that *p*-synephrine can promote vasoconstriction [2]. Although vasoconstriction is less likely to occur in association with *p*-synephrine than with sympathomimetic amines in humans, the possibility of vasoconstriction precipitated by *p*-synephrine cannot be completely eliminated because some individuals are very susceptible to *p*-synephrine, similar to the individual susceptibility to caffeine. *P*-synephrine is also known to act by stimulating norepinephrine release, which is a much more potent sympathomimetic amine, prone to vasoconstriction, than is *p*-synephrine *per se* [3].

In May 2011, the Natural Health Products Directorate (NHPD) of Health Canada conducted an extensive review of *C. aurantium* and *p*-synephrine. The NHPD released a 49-page health risk assessment report on *p*-synephrine and caffeine and defined its current guidelines for the use of these natural ingredients [1]. This report approved the use of ≤ 50 mg/day of *p*-synephrine alone in healthy adults and ≤ 40 mg/day of *p*-synephrine when combined with ≤ 320 mg/day of caffeine. On the other hand, this report enumerated fatal adverse cardiovascular case reports from the literature in detail: acute myocardial infarction, coronary vasospasm, stroke (cerebral artery vasospasm), and ventricular fibrillation. Interestingly, many of the patients in the case reports took the recommended dosage of *p*-synephrine-containing dietary supplements. Of course, this report annexed a *proviso* that case reports do not demonstrate causation or association. However, at the same time, this report stated that repeated co-occurrences can be considered signals that can be used to generate hypotheses and, potentially, to raise safety concerns.

We recognize that our previous publication entitled "Synephrine-containing dietary supplement precipitating apical ballooning syndrome in a young female" was the first report to demonstrate the adverse cardiovascular effects of *p*-synephrine-containing dietary supplements precipitating apical ballooning syndrome (ABS) [4]. As mentioned above, many case reports addressing adverse cardiovascular effects such as coronary vasospasm and acute myocardial infarction have already been published in the literature. Notably, coronary vasospasm is thought to be one of the possible mechanisms for the development of ABS. Therefore, we consider the possibility that this syndrome is precipitated after the administration of *p*-synephrine-containing dietary supplements.

A recent study suggested that there are no adverse cardiovascular effects of *p*-synephrine in healthy obese/overweight individuals [5]. This study has value in terms of a longer follow-up (60 days), higher dosage of *p*-synephrine administration (98 mg), and enrollment of an obese/overweight study cohort (body mass index of 30.8) compared with previous studies. However, there are several issues to be raised before establishing hasty conclusions regarding the safety of *p*-synephrine-containing dietary supplements. First, this study did not evaluate the safety of *p*-synephrine in combination with caffeine, which is widely used in dietary supplements. According to the extensive review by NHPD of Health Canada, the overwhelming majority of adverse effects occurred in individuals with *p*-synephrine combined with caffeine, not *p*-synephrine alone. Second, although this study involved a longer follow-up period, the results may not be used to justify long-term safety in that most of the dietary supplements are likely be taken for a more prolonged period. Third, the study comprised "healthy" obese/overweight individuals, so the results may not necessarily be applied to all obese/overweight individuals, as these people are subject to various comorbidities. Fourth, this study involved a small patient sample (75 individuals). Indeed, this study did not justify the sample size or power. The authors did not perform a

power calculation for the estimation of an adequate sample size to validate their results. Moreover, the drop-out rate was > 10% (8/75) despite the fact that the follow-up period was not very long. As a consequence, the study involved only the remaining 68 patients, which was an even smaller sample size.

Dietary supplements can currently be purchased easily, not only from pharmacies and health food stores but also from supermarkets and online markets. However, both health care workers and the general public lack perception with regard to the potential hazards associated with the indiscriminate abuse of these dietary supplements. To the best of our knowledge, there are no detailed regulations from the Korea Food and Drug Administration (KFDA) regarding the safe dosage of *p*-synephrine combined with caffeine or of *p*-synephrine alone. Therefore, we believe that the KFDA should take a stronger position regarding the regulation of these dietary supplements and warn health care workers and the general public to be cautious of the potential hazards of indiscriminate abuse of these dietary supplements.

**Keywords**: Synephrine; Dietary supplements; Adverse effects

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## Conflict of interest

No potential conflict o f interest relevant to this article was reported.

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