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REVIEW

The Safety of *Citrus aurantium* (Bitter Orange) and its Primary Protoalkaloid *p*-Synephrine

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***Citrus aurantium* (bitter orange) extract and its principal protoalkaloidal constituent *p*-synephrine are widely used in weight loss and weight management as well as in sports performance products. However, questions are raised frequently regarding the safety of these ingredients. The potential inherent dangers associated with the use of products containing *C. aurantium* extract are frequently touted, while conversely, millions of doses of dietary supplements have been consumed by possibly millions of individuals in recent years. Furthermore, millions of people consume on a daily basis various juices and food products from *Citrus* species that contain *p*-synephrine. This review summarizes current information regarding the safety of *C. aurantium* (bitter orange) extract and *p*-synephrine based on human, animal and *in vitro* assessments as well as receptor binding and mechanistic studies. The data indicate that based on current knowledge, the use of bitter orange extract and *p*-synephrine appears to be exceedingly safe with no serious adverse effects being directly attributable to these ingredients. Copyright © 2011 John Wiley & Sons, Ltd.**

Keywords: Citrus aurantium; bitter orange; *p*-synephrine; clinical studies; animal studies; receptor binding.

INTRODUCTION

The extract of the immature fruit or peel of *Citrus aurantium* (bitter orange) and its principal protoalkaloidal constituent, *p*-synephrine, are used widely in weight management and weight loss as well as in sports performance products. Historically, bitter orange had been used in traditional Chinese medicine for a variety of clinical applications, including indigestion, diarrhea and dysentery, constipation and as an expectorant (Blumenthal, 2004; Stohs and Shara, 2007). Bitter orange has also been used in South American folk medicine to treat insomnia, anxiety and epilepsy (Stohs and Shara, 2007).

However, *C. aurantium* (bitter orange) has been listed by *Consumer Reports* (Anon, 2010) as being possibly unsafe and a dietary supplement 'to avoid'. The assumption is generally made that, because of structural similarities with sympathomimetic agents as ephedrine and nor-epinephrine, *p*-synephrine can be expected to exert central nervous system (CNS) stimulatory activity and hemodynamic effects as an increase in blood pressure and heart rate. As will be discussed below, these effects have not been supported by the vast majority of scientific data as well as widespread use, largely due to the structural differences which are reflected in the structure–activity relationships, marked differences in receptor binding, and the resultant physiological and pharmacological properties.

Various articles cite the potential cardiovascular hazards that may be associated with the use of products containing these ingredients (Bent *et al.*, 2004; Penzak *et al.*, 2001; Fugh-Berman and Myers, 2004; Haaz *et al.*, 2006, 2010; Rossato *et al.*, 2011; Inchiosa, 2011), with reference being made to clinical case reports that involve multi-herbal and poly-alkaloidal and poly-protoalkaloidal products (Stohs, 2010; McGuffin, 2006). Current confusion regarding the safety and efficacy of bitter orange extract and *p*-synephrine is clouded by multiple issues, including the use of complex mixtures of ingredients in products that include bitter orange extract, the release of misleading information by governmental agencies, and misunderstandings regarding the isomeric forms of synephrine and their differing pharmacological properties. In addition, the projected warnings regarding cardiovascular risks are extrapolated from studies involving *m*-synephrine and ephedrine which are not components of bitter orange extract, and from studies involving the intravenous administration of *p*-synephrine at concentrations that are not attained by oral ingestion in foods or supplements. The following information summarizes current research and knowledge regarding bitter orange extract and *p*-synephrine, its primary protoalkaloid.

CHEMISTRY

The primary pharmacologically active protoalkaloid in bitter orange peel and its extracts is *p*-synephrine (Pellati *et al.*, 2002, 2004, 2005; Avula *et al.*, 2005; Nutratech, Inc, 2005; Mattoli *et al.*, 2005; Nelson *et al.*,

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2007; Tsujita and Takaku, 2007; Arbo *et al.*, 2008; Roman *et al.*, 2008; Mercolini *et al.*, 2010; Rossato *et al.*, 2010b; Percy *et al.*, 2010; Uckoo *et al.*, 2010) which comprises greater than 85% of the total protoalkaloids (Nelson *et al.*, 2007). Other minor protoalkaloidal constituents include octopamine, hordenine, tyramine and *N*-methyltyramine (Pellati *et al.*, 2002, 2004; Nelson *et al.*, 2007; Roman *et al.*, 2008; Mercolini *et al.*, 2010), and octopamine is present in trace amounts or absent in bitter orange extracts. *p*-Synephrine is a phenylethanolamine derivative with the hydroxy group in the *para* position on the benzene ring of the molecule (Fig. 1). *p*-Synephrine is the form found in bitter orange products (e.g. the patented bitter orange extract, Advantra Z® (Nutratech, Inc, 2005). Much confusion exists in both the scientific and lay literature because there is also *m*-synephrine, which is also known as phenylephrine (hydroxyl group in the *meta*-position on the benzene ring; Fig. 2). *m*-Synephrine is a Food and Drug Administration (FDA)-approved over-the-counter (OTC) drug ingredient used in nasal decongestants and sprays.

m-Synephrine does not occur naturally in *C. aurantium* extract (Pellati *et al.*, 2002, 2004, 2005; Avula *et al.*, 2005; Mattoli *et al.*, 2005; Tsujita and Takaku, 2007; Nelson *et al.*, 2007; Arbo *et al.*, 2008; Roman *et al.*, 2008; Rossato *et al.*, 2010b; Mercolini *et al.*, 2010), contrary to some commentaries and discussions in various articles and reviews (Penzak *et al.*, 2001; Bent *et al.*, 2004; Smedema and Muller, 2008; Stephensen and Sarlay, 2009; Clauson *et al.*, 2008; Rossato *et al.*, 2010b; Haaz *et al.*, 2010), and does not occur in widely sold bitter orange extracts (Nutratech, Inc, 2005). No evidence has ever been presented that it occurs in natural products. Furthermore, *m*-synephrine is not a constituent of or has it been identified in standardized bitter orange reference materials prepared by the National Institute of Standards and Technology (Sander *et al.*, 2008; Evans *et al.*, 2008). Pellati and Benvenuti (2007) reviewed 19 chromatographic and electrophoretic analytical methods for phenylethanolamine protoalkaloids in *Citrus aurantium*, and in no case was *m*-synephrine detected. When *m*-synephrine has been reported in weight loss products (Allison *et al.*, 2005), it is believed to be due to the addition of this synthetic isomer (Rossato *et al.*, 2010b). However, to further complicate the issue, *m*-synephrine (phenylephrine) has been assessed as a potential ingredient in a weight loss product (Greenway *et al.*, 2006). In addition, although the origin is not known, trace amounts of *m*-synephrine have been reported in human plasma (Andrew *et al.*, 1993).

Chemically, *p*-synephrine is structurally related to ephedrine (Fig. 3). However, ephedrine is a phenylpropanolamine derivative and does not contain a *para*-substituted hydroxy group, whereas *p*-synephrine is a phenylethanolamine derivative. These two chemical differences greatly change the stereochemistry and alter the pharmacokinetic properties, including the ability of *p*-synephrine to cross the blood–brain barrier. The addition of the *para* hydroxy group on the *p*-synephrine molecule, as well as the lack of the additional methyl group on the side-chain, greatly decrease the lipid solubility of *p*-synephrine compared with ephedrine, resulting in little transport into the CNS compared with ephedrine (Colker *et al.*, 1999; Arch, 2002; Jones, 2004). As a consequence, *p*-synephrine exhibits little or no CNS and cardiovascular stimulation. However, *p*-synephrine may act locally on the cardiovascular system.

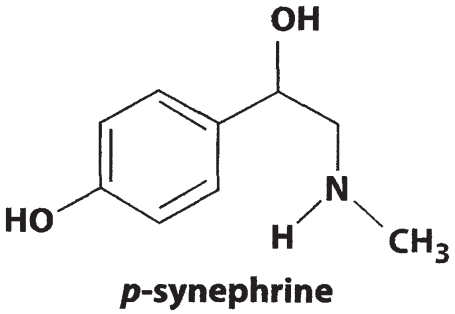

Figure 1. Structure of *p*-synephrine.

HUMAN CARDIOVASCULAR AND HEMODYNAMIC STUDIES

The preponderance of human clinical studies have reported that bitter orange extract (*p*-synephrine) either alone or in combination with caffeine and other ingredients has no effect on blood pressure (Penzak *et al.*, 2001; Haaz *et al.*, 2006; Colker *et al.*, 1999; Min *et al.*, 2005; Sale *et al.*, 2006; Gougeon *et al.*, 2005; Haller *et al.*, 2005, 2008; Zenk *et al.*, 2005; Hoffman *et al.*, 2006; Seifert *et al.*, 2011; Stohs *et al.*, 2011; Stohs and Shara, 2011) or heart rate (Penzak *et al.*, 2001; Colker *et al.*, 1999; Min *et al.*, 2005; Sale *et al.*, 2006; Gougeon *et al.*, 2005; Zenk *et al.*, 2005; Hoffman *et al.*, 2006; Seifert *et al.*, 2011; Stohs *et al.*, 2011, Stohs and Shara, 2011). Several studies involving products that contained *p*-synephrine in addition to other constituents including caffeine have reported increases in blood pressure (Bui *et al.*, 2006) and heart rate (Bui *et al.*, 2006; Haller *et al.*, 2005, 2008). One study has reported a significant decrease in systolic and diastolic blood pressure following ingestion of a product containing a *Citrus* extract (Oben *et al.*, 2008). Several of these studies will be discussed in more detail below.

Haller *et al.* (2005) examined the cardiovascular effects associated with a single dose of a multi-component dietary supplement (Xenadrine®) containing 5.5 mg *p*-synephrine, 239 mg caffeine, 5.7 mg octopamine and undisclosed amounts of other ingredients including catechin polyphenols. The hemodynamic effects of a single dose of a *C. aurantium* extract (Advantra Z®) that contained 46.9 mg *p*-synephrine were also examined. The multi-component dietary supplement but not the *p*-synephrine-containing *C. aurantium* extract increased both systolic and diastolic blood pressures at 2 h post treatment relative to the control group. No significant effects of either treatment on heart rate were noted over the first 3 h after ingestion of the products. However, a significant increase in heart rate over control was noted at only the 6 h time point by both treatments.

This study (Haller *et al.*, 2005) is complicated by the fact that all subjects consumed a meal 3 h after treatment ingestion. After eating, an increase in heart rate occurred in the two treatment groups as well as in the control group. The increase in heart rate does not coincide with the pharmacokinetics including blood levels and half-life of *p*-synephrine (Haller *et al.*, 2005, 2008) but does coincide with the thermic effect of food (Gougeon *et al.*, 2005). Given that the heart rates of the control group responded similarly to the two treatment groups after the meal at the 4 and 8 h measurements (1 and 5 h after the

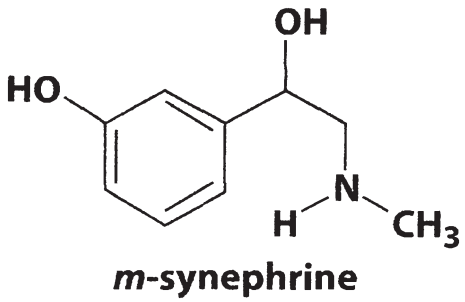

Figure 2. Structure of *m*-synephrine.

meal), the apparently significant difference seen at only the 6 h time point (3 h after the meal) does not appear to be attributable to product use.

Gougeon *et al.* (2005) assessed the thermic effects of food, and reported that the thermic effect of food increased by 29% in 17 females after they ingested 26 mg *p*-synephrine. The thermic effect of *p*-synephrine was greater in males than females in the absence of a meal, and no significant changes occurred in pulse rate or blood pressure when compared with baseline values.

Haller *et al.* (2008) have also examined the effects under resting and exercise conditions of a dietary supplement designed to enhance athletic performance. The product (Ripped Fuel Extreme Cut™) contained 21 mg *p*-synephrine, 304 mg caffeine, as well as extracts of green tea, ginger root, cocoa seed, willow bark and wasabi. The placebo or product was taken 1 h before 30 min of moderately intense exercise. There were no treatment-related differences in post-exercise heart rate, systolic blood pressure or body temperature. A significant product-related increase in diastolic blood pressure (8.7 mmHg) was reported, apparently counteracting the vasodilatory effects of exercise. Due to the poly-herbal and poly-alkaloidal nature of this product, the ingredient or ingredients responsible for the observed effect cannot be determined, although the authors implicated the bitter orange extract.

Bui *et al.* (2006) conducted a randomized, placebo-controlled, double blind crossover study on subjects given a single oral dose of 900 mg bitter orange extract (Nature's Way) that contained 6% *p*-synephrine (54 mg *p*-synephrine) or the placebo. Small but significant increases were observed in heart rate, and systolic and diastolic blood pressures for up to 5 h. Of interest is the fact that Min *et al.* (2005) used this same product in a similarly designed study randomized, placebo controlled cross-over study, and saw no effect on systolic or diastolic blood pressure, or on the rate-corrected QT (QTc) interval.

Oben *et al.* (2008) conducted an 8 week, placebo-controlled double blind study in which participants were given a placebo or product twice daily consisting of a combination of *Citrus sinensis* peel and *Phellodendron amurense* bark. After 8 weeks, the participants receiving the product lost a significant amount of weight, with a small but significant decrease in systolic and diastolic blood pressures as well as decreases in fasting glucose levels, triglycerides and cholesterol. The amount of *p*-synephrine in the product was unfortunately not noted. *Phellodendron* is not known to exert cardiovascular effects.

Stohs *et al.* (2011) assessed the effects of 50 mg *p*-synephrine (Advantra Z®) alone or in combination with several bioflavonoids in human subjects on blood pressure, heart rate, resting metabolic rate, and a self-reported 10 item rating scale at baseline and after 75 min. The study was double blinded, randomized and placebo-controlled with 10 subjects per treatment group. None of the treatment groups exhibited changes in blood pressure or heart rate, although all treatment groups demonstrated increases in resting metabolic rates.

Stohs and Shara (2011) conducted a randomized, placebo-controlled, double blind crossover study involving 16 healthy subjects who consumed a capsule containing 50 mg *p*-synephrine (Advantra Z®) or the placebo daily for 14 days. ECGs, blood pressures and heart rates were determined over the course of the study. At this daily dosage of *p*-synephrine, no significant effects were observed on blood pressure or heart rate, and no cardiovascular abnormalities were observed.

The above results suggest the cardiovascular effects that have been observed with complex dietary supplements may be due to caffeine, ingredients other than *p*-synephrine or possibly a combination of ingredients in the products. Caffeine is well known to produce cardiovascular effects (Riksen *et al.*, 2011) particularly in caffeine-sensitive individuals (Yang *et al.*, 2010), and many dietary supplements that contain bitter orange extract contain high amounts of caffeine.

ANIMAL STUDIES

Relatively few studies have been conducted concerning the safety as well as efficacy of bitter orange extracts and *p*-synephrine in animals. One of the most widely cited studies is the work of Huang *et al.* (1995) who investigated the effects of a bitter orange extract and *p*-synephrine on portal hypertensive rats after infusion into the femoral vein. A dose-dependent decrease in portal venous pressure and heart rate with a dose-dependent increase in mean arterial pressure was observed.

In another study, Huang *et al.* (2001) investigated the hemodynamic effects of administering *p*-synephrine by gavage twice a day for 8 days to portal hypertensive rats. Portal hypertension was induced either by bile duct ligation or partial portal vein ligation. Similar results were obtained when 1 mg/kg or 10 mg/kg *p*-synephrine was given. *p*-Synephrine significantly ameliorated the hyperdynamic state in both hypertensive models, and the authors concluded that oral *p*-synephrine exhibited beneficial hemodynamic effects. However, it is not clear how relevant these portal hypertension models are to

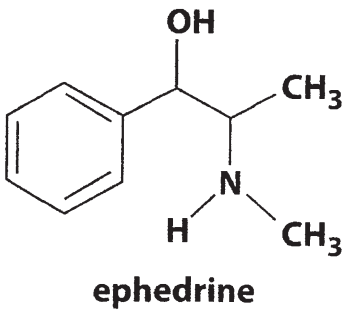

Figure 3. Structure of ephedrine.

the human oral consumption of dietary supplements containing *p*-synephrine at doses that are a fraction of those used in these animal studies.

Calapai *et al.* (1999) examined the effects of repeatedly administering orally 2.5–20 mg/kg of two *C. aurantium* fruit extracts that had been standardized to 4% and 6% *p*-synephrine. Animals were treated for 7 consecutive days and the various measurements were recorded for 15 consecutive days. Significant dose-dependent decreases in food intake as well as body weight were observed. No significant changes were observed in blood pressure, while ECG alterations were significant after 10 days of treatment. Unfortunately, the chemical composition of the bitter orange extract was not reported other than the *p*-synephrine content.

Parra *et al.* (2001) determined the LD_{50} of various plant extracts including *C. aurantium* in mice. Their calculated LD_{50} for a bitter orange extract was approximately 477 mg/kg in mice. The concentration of *p*-synephrine or other protoalkaloids was not reported. In another study, a single dose oral toxicity of a 6% *p*-synephrine-containing bitter orange extract (Advantra Z®) was evaluated in both male and female Sprague-Dawley rats (Nutratech, Inc, 1997). The animals received a single oral dose of 10000 mg/kg body weight of the extract. Gross necropsies were performed at the end of 14 days. No animals died and no gross pathological findings were observed. The acute oral LD_{50} of the bitter orange extract was estimated to be greater than 10000 mg/kg in these rats. This equates to a LD_{50} of greater than 600 mg *p*-synephrine/kg body weight in these animals. The reason for the vast differences in LD_{50} may be related to the animal species or method of extraction. Other constituents other than *p*-synephrine may have been responsible for the toxicity in the mouse studies (Parra *et al.*, 2001).

Titta *et al.* (2010) have conducted an interesting study on the inhibition of fat accumulation in mice given juice from either a blood orange (which contains high levels of anthocyanins) or a blond orange. Dietary supplementation with juice from the blood orange but not the blond orange significantly reduced body weight gain and fat accumulation. The antiobesity effect of the blood orange juice could not be explained solely on the basis of the anthocyanin content, and the authors surmised that the anthocyanins may synergize with *p*-synephrine to produce the observed effect. Unfortunately, this hypothesis was not specifically tested.

Arbo *et al.* (2009) treated mice daily with bitter orange extract (7.5% *p*-synephrine) at doses of 400, 2,000 or 4000 mg/kg (corresponding to 30, 150 and 300 mg *p*-synephrine/kg) or 30 or 300 mg *p*-synephrine/kg. These doses are very high relative to doses of *p*-synephrine consumed by humans in dietary supplements. A reduction in body weight gain was observed at all doses relative to controls. No effects were observed on organ weights, biochemical parameters, blood pressure or heart rate in the treated mice. However, both doses of *p*-synephrine and the high dose of the bitter orange extract resulted in increases in hepatic reduced glutathione, while bitter orange extract decreased malondialdehyde content (an indicator of lipid peroxidation and lipid damage), and *p*-synephrine increased catalase activity by as much as 6-fold. High doses of both products produced modest deceases in glutathione peroxidase activity. The results suggest a beneficial effect with respect to weight loss without adverse effects while also providing an antioxidant and tissue protective effect based on the increased glutathione levels and increased catalase activity with no increase in lipid peroxidation.

Several other studies using *Citrus* peel extracts have demonstrated antioxidant and chemoprotective effects. Tounsi *et al.* (2010) have shown an extract of *C. aurantium* exhibits higher antioxidant activity than several other *Citrus* species. Kang *et al.* (2011) demonstrated that a methanol extract of *C. aurantium* exhibited antiinflammatory properties in a mouse macrophage cell line by modulating the expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines as tumor necrosis factor-α (TNF-α) and interkeukin-6 (IL-6) via the NF-κB pathway. Since inflammation and oxidative tissue damage are associated with obesity, these studies suggest another mechanism for potential beneficial effects of *p*-synephrine and bitter orange extract in weight management and strenuous physical activity.

In a study involving a model of myocardial ischemia in rats, Ou *et al.* (2009) observed that an extract of *Citrus* peel provided cardio-protection as demonstrated by a significant decrease in ST segment elongation and the extension of myocardial infarction. There were also significant decreases in serum lactate dehydrogenase, creatine kinase and malondialdehyde, as well as increases in the antioxidant enzymes superoxide dismutase and glutathione peroxidase. The authors postulated that protection was related to an antioxidant effect with inhibited lipid peroxidation.

Rossato *et al.* (2010a) examined the uptake of *p*-synephrine and *m*-synephrine by rat cardiomyocytes and the effect of these two isomers on intracellular glutathione content. Although both isomers were taken up by the cells, only the *m*-synephrine resulted in a depletion of both total and reduced glutathione. The effect was independent of α-1 adrenoreceptor stimulation. The authors incubated the cardiomyocytes with 1 mM concentrations of the two isomers, a concentration that is over 80000-fold higher than the 2 ng/mL observed at peak blood levels following oral ingestion of 46.9 mg *p*-synephrine (Haller *et al.*, 2005). Thus, the clinical relevance of the results is questionable. However, the study does demonstrate that the cardiomyocytes differentiate between the two isomers, and only the *meta*-isomer produced a potentially toxic effect.

In summary, in most animal studies, oral administration of bitter orange extract or *p*-synephrine results in weight loss or a decrease in weight gain without adverse cardiovascular or histopathological effects. Adverse effects have been reported when the extract is administered intravenously at high doses.

MECHANISM AND RECEPTOR BINDING

It is well known that, in general, binding to α-adrenergic receptors results in vasoconstriction, cardiovascular contractility and increased heart rate in response to β-1 adrenergic receptor binding, while bronchodilation occurs in response to β-2 adrenergic receptor binding (Inchiosa, 2011). As previously noted, it is widely assumed that *p*-synephrine will exhibit adrenoreceptor binding similar to that observed for nor-epinephrine,

ephedrine and *m*-synephrine due to some structural similarities (Penzak *et al.*, 2001; Bent *et al.*, 2004; Smedema and Muller, 2008; Clauson *et al.*, 2008; Stephensen and Sarlay, 2009). However, based on receptor binding studies discussed below, *p*-synephrine exhibits little binding affinity for β-1 and β-2 as well as α- adrenoreceptors. Several studies have shown that *p*-synephrine may act primarily as a β-3 adrenergic receptor agonist, resulting in increased thermogenesis and lipolysis (Tsujita and Takaku, 2007; Arch, 2002; Jones, 2004; Carpene *et al.*, 1999; Dulloo, 1993). Activation of β-3 adrenoreceptors has been shown to reduce food intake and weight gain in rats as well as enhance lipolysis in adipose tissue, while improving insulin resistance, glycemic control and lipid profiles (Alemzadeh *et al.*, 2008). β-3-Adrenoreceptors endogenously exist in adipose tissues and activation increases lipolysis and lipid metabolism (Oana *et al.*, 2005; Hamilton and Doods, 2008).

Based on receptor binding studies using human and animal cells, *m*-synephrine exerts its effects on α-, β-1 and β-2 adrenergic receptors (Jordan *et al.*, 1987; Ma *et al.*, 2010; Brown *et al.*, 1988; Hwa and Perez, 1996) resulting in increased blood pressure and heart rate effects. *m*-Synephrine is 100-fold and *p*-synephrine 40000-fold less potent than nor-epinephrine with respect to binding to β-1 and β-2 adrenoreceptors in guinea-pig atria and trachea (Jordan *et al.*, 1987). In addition, *p*-synephrine is approximately 50-fold less potent than *m*-synephrine in activating human α-1a adrenoreceptors, and does not act as an agonist with respect to human α-2a and α-2c adrenoreceptors (Ma *et al.*, 2010). Ma *et al.* (2010) also concluded that *p*-synephrine may act as an antagonist of pre-synaptic α-2a and α-2c adrenoreceptors present in nerve terminals.

Brown *et al.* (1988) compared the binding activities of the *meta* and *para* isomers of synephrine as well as octopamine to rat aorta and α-1 and α-2 adrenoreceptors. The binding of *m*-synephrine to α-1 and α-2 adrenoreceptors was 6-fold and 150-fold less, respectively, than nor-epinephrine. Furthermore, *p*-synephrine was 1000-fold less active than nor-epinephrine in binding to these two receptors. Based on these receptor binding studies, *p*-synephrine would be expected to exert little or no effect on blood pressure or heart rate relative to *m*-synephrine or nor-epinephrine.

Hwa and Perez (1996) examined the structural features necessary for binding and activation of the α-1a adrenoreceptor. They concluded that it is the *meta*-hydroxy of endogenous agonists that hydrogen bonds to a serine moiety at the receptor site, and not the *para*-hydroxy that allows receptor activation. Thus, *m*-synephrine (phenylephrine) will bind to and activate the receptor resulting in vasoconstriction and an increase in blood pressure, while *p*-synephrine does not.

Hibino *et al.* (2009) assessed the ability of *p*-synephrine to constrict isolated rat aorta at concentrations of 1×10^{-7} to 3×10^{-5} mol/L. Using selected receptor antagonists, the authors concluded that the constrictor effects were exerted via α-1adrenoreceptors and serotonergic (5-HT_{1D} and 5-HT_{2A}) receptors. The concentrations of *p*-synephrine used to produce aortic constriction were as high as 2500 times the peak blood levels (2 ng/mL) observed when 46.9 mg *p*-synephrine was given to human subjects that did not produce an increase in either systolic or diastolic blood pressures (Haller *et al.*, 2005). These results suggest that *p*-synephrine may produce vasoconstriction but only at concentrations many times above the blood levels achieved under normal conditions of oral usage for weight management and sports enhancement.

Tsujita and Takaku (2007) have shown that a segment wall extract rich in *p*-synephrine from mandarin oranges induced lipolysis in rat fat cells in a concentration dependent manner. A juice sac extract from this same source failed to induce lipolysis. The non-selective β-antagonist propranolol completely inhibited lipolysis, whereas the α-antagonist phenoxybenzamine had no effect, providing additional mechanistic insight into the thermogenic and potential weight management effects of *p*-synephrine containing products. The authors suggest that a useful functional food that acts as a fat reduction material may be derived from the segment wall of mandarin oranges.

Of interest is the fact that β-3 adrenoreceptors have been identified in cardiovascular tissues (Rozec and Gauther, 2006), and evidence suggests that their activation modulates sympathetic overstimulation through regulation of nitric oxide (Moens *et al.*, 2010). Thus, one can postulate that *p*-synephrine stimulation of β-3 adrenoreceptors in the cardiovascular system does not result in an increase in blood pressure or heart rate but may exhibit a cardio-protective effect. This cardiovascular receptor response may explain why an increase in heart rate or blood pressure is generally not seen when *p*-synephrine is used alone or when caffeine is combined with *p*-synephrine or bitter orange extract (see Human Cardiovascular and Hemodynamic Effects) in dietary supplements, in spite of the fact that caffeine alone is well known to produce an increase in these parameters.

These binding studies provide extensive evidence that the *meta* and *para* isomers of synephrine do not have similar receptor binding, and provide further mechanistic understanding for the vastly different physiological and pharmacological effects of the two isomers. The assumption that the two forms of synephrine have similar if not identical effects has led to mis-information, and the inappropriate attribution of potentially adverse effects produced by *m*-synephrine to *p*-synephrine, with only the latter occurring naturally in plant materials including in bitter orange.

SAFETY CONSIDERATIONS

A series of review articles regarding the safety and efficacy of bitter orange has been published (Preuss *et al.*, 2002; Penzak *et al.*, 2001; Bent *et al.*, 2004; Stohs and Shara, 2007, 2011; Haaz *et al.*, 2006, 2010). None of these reviews has reported any serious or significant adverse events that are directly attributable to bitter orange extract or *p*-synephrine. However, most of these reviews did not include a discussion of receptor binding or structure–activity relationships, and over the past 5 years a large number of additional studies involving bitter orange extract and *p*-synephrine have been published and are included in this review. As described above, the preponderance of the research literature does not support the development of adverse cardiovascular or neurological events in

humans or animals. Several recent reviews on bitter orange and synephrine have purported that the existence of *m*-synephrine in bitter orange is unclear and controversial, and that in essence all 'synephrine alkaloids' exert similar cardiovascular effects (Haaz *et al.*, 2010; Rossato *et al.*, 2011), contrary to the extensive literature cited above.

During the past several years, a number of case studies have been reported for products containing *C. aurantium* that involved adverse cardiovascular or other events where the authors suggested that the causative agent was synephrine or bitter orange extract (Stohs, 2010). The adverse events associated with the published clinical case studies included acute lateral-wall myocardial infarction (Nykamp *et al.*, 2004), exercise induced syncope associated with QT prolongation (Nasir *et al.*, 2004), ischemic stroke (Bouchard *et al.*, 2005), variant angina (Gange *et al.*, 2006), ischemic colitis (Sultan *et al.*, 2006), coronary spasm and thrombosis (Smedema and Muller, 2008), vasospasm and stroke (Holmes and Tavee, 2008), ST segment-elevation myocardial infarction (Thomas *et al.*, 2009), ventricular fibrillation (Stephensen and Sarlay, 2009) and exercise-induced rhabdomyolysis (Burke *et al.*, 2007). Another case report has suggested that the *C. aurantium* extract in a multi-component product may have masked bradycardia and hypotension in an anorexic individual (Gray and Woolf, 2005), although no evidence was reported that an adverse event had occurred. In each of the cases, the product in question contained multiple herbal constituents including bitter orange extract with a total of 5 to12 alkaloidal and protoalkaloidal ingredients, and it is not possible or plausible to ascribe the effects specifically to one of these constituents.

A number of the cases involved body builders or serious athletes (Smedema and Muller, 2008; Stephensen and Sarlay, 2009; Thomas *et al.*, 2009; Burke *et al.*, 2007) and dehydration was involved in at least two of the cases (Smedema and Muller, 2008; Nasir *et al.*, 2004). Furthermore, in each case, various other reported and unreported factors may have been responsible for the observed effects, and detailed histories were lacking in some cases. For example, had the person involved been using steroids, anabolic agents or other ergogenic or thermogenic agents, or various prescription and non-prescription drugs? The product may not have been used as directed (Stephensen and Sarlay, 2009). Other confounding factors and pre-existing conditions existed such as a history of substance abuse (Thomas *et al.*, 2009), undetected heart disease (Nykamp *et al.*, 2004), sickle cell trait (Burke *et al.*, 2007), hypertriglyceridemia (Gange *et al.*, 2006), history of tobacco smoking (Stephensen and Sarlay, 2009; Nykamp *et al.*, 2004; Bouchard *et al.*, 2005) and the consumption of large quantities of caffeine daily (Nykamp *et al.*, 2004; Thomas *et al.*, 2009). In addition, there is a high probability that the events were concurrent but random and unrelated, based on the fact that cardiovascular events occur in millions of people annually.

The historical use of extracts of bitter orange in traditional Chinese medicine for hundreds of years as well as the fact that millions of doses of products containing bitter orange extract (containing *p*-synephrine) may have been consumed in the United States in recent years without the report of serious incidents aid in putting the safety issue into context. Two percent of respondents in a survey reported taking a dietary supplement containing bitter orange (Klonz *et al.*, 2006), which if extrapolated nationwide would include at least several million individuals. As previously noted, no serious adverse events have been directly attributable to bitter orange or *p*-synephrine (Preuss *et al.*, 2002; Bent *et al.*, 2004; Fugh-Berman and Myers, 2004; Haaz *et al.*, 2006, 2010; Stohs and Shara, 2007, 2011).

A final consideration regarding the safety of *p*-synephrine is the exposure of millions of people who daily consume, without ill effect, various juices and food products as marmalade from *Citrus* species as Seville orange, grapefruit, mandarin and other orange-related species that contain *p*-synephrine (Pellati *et al.*, 2002, 2004, 2005; Blumenthal, 2004; Avula *et al.*, 2005; Mattoli *et al.*, 2005; Dragull *et al.*, 2008; Arbo *et al.*, 2008; Roman *et al.*, 2008). A typical sweet orange contains about 6 mg *p*-synephrine (Mattoli *et al.*, 2005). A wide variety of *Citrus* juices contain approximately 5 mg *p*-synephrine per 8 ounce glass (Blumenthal, 2004; Pellati *et al.*, 2002, 2004, 2005). A U.S. Department of Agriculture study of the *p*-synephrine content of mandarin orange juice from 10 different groves in California found that the *p*-synephrine content ranged from 73 to 158 mg/L, with an overall mean of 93 mg/L (Dragull *et al.*, 2008). Another study has shown the juice from Clementines, a variety of mandarin oranges, contained on average of 114 mg p-synephrine/L while Marrs sweet oranges yielded 85 mg/L (Uckoo *et al.*, 2010). Therefore, consuming an 8 ounce glass of mandarin orange juice may deliver as much as 40 mg *p*-synephrine, similar to the amount of *p*-synephrine in the typical dietary supplement.

No deaths have ever been directly attributed to bitter orange or *p*-synephrine, and the U.S. Poison Control Centers again reported no deaths due to vitamins/minerals and dietary supplements in 2009 (Bronstein *et al.*, 2010). The margin of safety for *p*-synephrine appears to greatly exceed that of aspirin and acetaminophen (Lee, 2004) as well as many prescription and OTC drugs.

A contributor to the concerns regarding the safety of bitter orange and *p*-synephrine has been the U.S. Federal government. In 2004, the FDA supplied information to a major newspaper indicating that 85 adverse reactions and seven deaths had been associated with bitter orange-containing dietary supplements. Subsequently, the purported number of adverse events increased to 169. A dissection of the FDA information by McGuffin (2006) obtained through the Freedom of Information Act and on which the reports were based, clearly indicated that no credible adverse events could be attributed to bitter orange. A recent review of 22 FDA adverse event reports and 10 published clinical case reports over the past 5 years has again concluded that no serious adverse events can be directly attributed to bitter orange extract or *p*-synephrine (Stohs, 2010). The FDA has noted some 'misstatements' about bitter orange in *The Tan Sheet* (Anon, 2006).

SUMMARY

In summary, based on current research as well as the extensive ingestion of bitter orange and *p*-synephrine in the form of supplements as well as fruits, juices and

other *Citrus* food products, the data indicate that bitter orange extract and *p*-synephrine are exceedingly safe. No credible adverse events have been directly attributed to bitter orange, or its primary protoalkaloid *p*-synephrine.

Conflict of Interest

SJS and HGP have served as consultants for Nutratech, Inc., a company that markets bitter orange extracts.

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