



Recent Studies Regarding the Safety and Efficacy of Bitter Orange Extract (P-Synephrine)



Sidney J Stohs^{1*}, Sidhartha D Ray² and Howard Miller³

¹Creighton University Medical Center, USA

²Manchester University College of Pharmacy, USA

³Proformance Ingredients, USA

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*Corresponding author: Dr. Sid Stohs, Creighton University Medical Center, USA 7068 Maumee Valley Court, Frisco, TX 75034, USA, Tel: 214-215-6655; Email: sid.stohs9@gmail.com

Abstract

Citrus aurantium (bitter orange) extract and its primary protoalkaloidal constituent p-synephrine have been widely used for weight management, appetite suppression, sports performance, energy and focus. Although questions have been raised regarding the safety of p-synephrine, over 30 research studies involving over 700 human subjects as well as animal studies have demonstrated its safety and efficacy. No significant adverse effects were reported in any of these studies. In addition, in vitro studies have provided extensive data regarding the multiple mechanisms of action of bitter orange extract and p-synephrine which acts as a metabolic enhancer and thermogenic agent without cardiovascular stimulant properties.

Keyword: Bitter orange; *Citrus aurantium*; P-synephrine; Safety; Efficacy; Human studies; Safety studies

Introduction

Bitter orange (*Citrus aurantium* L) extract and its primary active constituent p-synephrine are widely used for weight management, sports performance, appetite suppression, energy and focus. Because of some structural similarity of p-synephrine to ephedrine, questions have been raised about the safety of bitter orange and p-synephrine [1], in spite of the extensive literature that is available that demonstrates otherwise. The majority of research on bitter orange has been conducted in recent years and published in peer reviewed journals. Over 30 research studies involving over 700 human subjects as well as animal and in vitro studies have provided extensive data regarding the safety, efficacy and mechanism(s) of action of bitter orange extract and p-synephrine. Contrary to common belief and classification [1], the data indicate that p-synephrine is not a cardiovascular or central nervous system stimulant when given orally but acts as a metabolic enhancer. As a result of human, animal and in vitro safety studies, bitter orange extracts standardized to p-synephrine (Advantra Z®) have received self-affirmed GRAS (generally recognized as safe) status [2].

Discussion

A number of studies in recent years have specifically addressed cardiovascular safety. In a randomized double-

blinded study, human subjects were given bitter orange extract (49mg p-synephrine) twice daily (total of 98mg/day) (Advantra Z®) for 60 days. At the end of the study, no adverse effects were noted with respect to blood pressures, heart rate, blood chemistries, or blood cell counts with differentials [3].

In double-blinded, placebo-controlled cross-over studies in which human subjects were given bitter orange extract (49mg p-synephrine) (Advantra Z®) as a single dose [4] or daily for 15 days [5], no significant changes occurred in heart rates, systolic pressures, electrocardiograms, blood chemistries or blood cell counts in either the control or p-synephrine treated groups. Small decreases in diastolic blood pressure were observed in response to the p-synephrine.

In a randomized, placebo-controlled crossover designed study, subjects were given two chocolate-flavored chew daily for three days containing 100mg of p-synephrine in the form of standardized bitter orange extract (Advantra Z®), 100mg of p-synephrine with 100mg of caffeine or placebo [6,7]. A controlled resistance exercise protocol was performed by all subjects. Each supplement treatment was separated by a one-week washout period. p-Synephrine in the presence or absence of caffeine resulted in no adverse effects being observed or reported. p-Synephrine increased lipolysis, fat oxidation,

energy expenditure, oxygen consumption, and carbohydrate metabolism [7]. p-Synephrine consumption increased total repetitions performed and volume load by approximately 10% while having no effect on blood lactate or ratings of perceived exertion. When caffeine was consumed in addition to p-synephrine, an increased mean power and velocity of squat performance was observed without increasing total repetitions and volume load [6].

Questions have been raised about the safety of p-synephrine in combination with caffeine. A double-blinded, randomized cross-over study was conducted whereby subjects received single dose of placebo, p-synephrine as standardized bitter orange extract (Advantra Z®), caffeine or a combination of p-synephrine and caffeine [8,9]. p-Synephrine consumption alone (103mg) did not significantly affect systolic blood pressure, heart rate or ECG at any time point [8], nor alter acute blood parameters [9]. A small decrease in diastolic blood pressure was observed which has been observed in several other studies [4,5]. In contrast, only high caffeine doses (325mg and 337mg) significantly elevated systolic blood pressures. p-Synephrine added to caffeine had no effect beyond the effects of caffeine alone. Similar responses were observed in both habitual caffeine consumers and those who were not regular consumers of caffeine. Thus, the addition of p-synephrine to caffeine does not enhance the cardiovascular effects of caffeine nor does p-synephrine exhibit cardiovascular effects on its own at commonly used oral doses [1,10].

Several human studies have been published in recent years using synthetic p-synephrine HCl [11-13]. In two randomized, cross-over, double-blind studies, human subjects were given orally either a placebo or p-synephrine HCl (3mg/kg body weight), and energy expenditure and fat oxidation were assessed during a cycle ergometer ramp exercise [11,12]. p-Synephrine HCl ingestion at rest did not affect heart rate or blood pressure, nor did it have any effect on energy expenditure or substrate oxidation. However, with low to moderate intensity exercise, p-synephrine HCl resulted in an increase in the rate of fat oxidation while concurrently reducing the rate of carbohydrate oxidation. Both p-synephrine HCl and 3mg/kg of caffeine alone increased fat oxidation. Furthermore, the combination of p-synephrine HCl and caffeine did not produce an additive effect [12]. In a dose response study involving p-synephrine HCl demonstrated that maximum fat oxidation during exercise occurred at doses of 2 and 3mg/kg [13].

With respect to these studies involving p-synephrine HCl, several factors must be taken into consideration [11-13]. It is important to note that p-synephrine which occurs naturally in plants as *Citrus aurantium* exists in the l- or [R-(-)] enantiomeric form. Synthetic p-synephrine HCl is a racemic mixture (equal parts) of the l- and d- enantiomeric forms and possesses less than half of the pharmacological activity of the naturally occurring p-synephrine due to the fact that the

d-enantiomer of p-synephrine exhibits about one-hundredth the adrenergic receptor binding activity of the l-enantiomer [14]. Furthermore, the synthetic p-synephrine is used as the HCl salt which adds weight. In a 70kg individual, a dose of 3mg of synthetic p-synephrine HCl per kg is 210mg. Therefore, 210mg of p-synephrine HCl will be physiologically equivalent to approximately 86mg of the naturally occurring l- form of p-synephrine present in bitter orange extracts when these two factors are taken into consideration.

There is also another issue with respect to synthetic p-synephrine HCl regarding its use in dietary supplements. In 2016, the United States Food and Drug Administration (USFDA) published "Dietary Supplements: New Dietary Ingredients Notifications and Related Issues: Guidance for Industry, Draft Guidance" [15]. According to this draft guidance document, synthetic forms of substances that occur naturally cannot be used in dietary supplements in the United States, and as a consequence, synthetic p-synephrine HCl is not a permitted ingredient in dietary supplements.

In a placebo-controlled, double-blinded 30-day study which assessed efficacy, overweight subjects were given a chocolate-flavored chew twice daily that contained 51.5mg p-synephrine (Advantra Z®) per chew (103mg p-synephrine per day) [16]. No adverse effects were reported or observed, while a statistically significant increase in eating/food intake control and energy levels were reported by the subjects who consumed the p-synephrine containing chews as compared to the subjects who consumed the placebo.

In order to obtain GRAS status, detailed animal studies are required. As a consequence, a number of recent animal studies have been conducted and the results published. In an LD50 (lethal dose for 50 % of the animals) study, a dose of 5,000mg/kg of a 50% p-synephrine containing extract (Advantra Z®) produced no deaths in rats. Therefore, the LD50 of this extract was greater than 5,000mg/kg [17]. As a point of comparison, the LD50 of common table salt, sodium chloride, is about 3,000mg/kg.

In order to assess long term effects of p-synephrine, a 90-day subchronic toxicity study with a bitter orange extract standardized to 50 % p-synephrine (Advantra Z®) was performed in male and female rats. Daily doses of 0, 100mg/kg, 300mg/kg and 1000mg/kg of the extract were given to the animals by gavage [18]. Throughout the 90days of the study, no adverse effects were observed in male or female rats with respect to clinical signs, body weights, food consumption, functional observations of sensory reactivity, grip strength and motor activity, ophthalmology, hematology, and urinalysis. In addition, no significant changes or adverse effects were observed at termination with respect to organ weights, or gross and microscopic pathology at any dose including 1000mg/kg/day.

The no-observed-effect level (NOEL) in both sexes of rats for the bitter orange extract standardized to 50 % p-synephrine was 300mg/kg/day. The no-adverse-effect-level (NOAEL) in male and female rats was 1000mg/kg/day [17,18]. The question regarding mutagenicity of p-synephrine and bitter orange extract was addressed by use of the Salmonella typhimurium reverse mutation (Ames Test) assay which was performed on 5 tester strains in the presence and absence of metabolic activation (S9). The results of the Ames Test showed that the bitter orange extract containing 50% p-synephrine (Advantra Z®) was non-mutagenic and did not induce cytotoxic effects [17].

A large number of in vitro mechanistic studies involving p-synephrine have been conducted which appear to be largely ignored in the popular press, social media and various web sites [1]. Cardiovascular effects are associated with the binding of ligands to adrenergic receptors. The lack of cardiovascular effects associated with p-synephrine is observed because it binds from 1000-10,000 times less to α -1, α -2, β -1 and β -2 adrenergic receptors than nor-epinephrine and epinephrine [1,14,19-21]. On the other hand, p-synephrine does exhibit binding to β -3 adrenergic receptors which does not result in cardiovascular stimulation but is associated with lipid metabolism [1,22-23] thus explaining its ability to enhance fat oxidation.

Conclusions

p-Synephrine cannot be equated with ephedrine based on available evidence from multiple studies. No adverse cardiovascular effects were reported in association with over 30 human studies. The effects of ephedrine and other adrenergic agonists cannot be extrapolated to p-synephrine due to structural differences which markedly alter receptor binding characteristics, pharmacokinetic properties and the effects produced. These observations are contrary to various publications which did not adequately review and interpret the current scientific literature but reiterated unsubstantiated dogma. At commonly used oral dosage levels, p-synephrine in the form of bitter orange extract is unlikely to produce cardiovascular or other adverse events while exhibiting a variety of beneficial effects.

Disclosures

SJS and HM have served as consultants for Novel Ingredients which markets standardized bitter orange extracts (Advantra Z®). Brazil.

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