Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update

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Received 15 November 2004; revised 24 January 2005; accepted 26 January 2005

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Summary

Obesity is a major health problem facing the developed and developing world. Efforts by individuals, health professionals, educators, and policy makers to combat the escalating trend of growing obesity prevalence have been multifaceted and mixed in outcome. Various dietary supplements have been marketed to reduce obesity. These products have been suggested to accomplish this by decreasing energy intake and energy absorption, and/or increasing metabolic rate. Ephedra, one such supplement, was banned from sale in the US market because of concerns about adverse events. Another substance, Citrus aurantium, which contains several compounds including synephrine alkaloids, has been suggested as a safe alternative. This review examines the evidence for safety and efficacy of C. aurantium and synephrine alkaloids as examined in animal studies, clinical weight loss trials, acute physiologic studies and case reports. Although at least three reviews of C. aurantium have been published, our review expands upon these by: (i) distinguishing and evaluating the efficacy of C. aurantium and related compounds; (ii) including results from previously unreviewed research; (iii) incorporating recent case reports that serve to highlight, in an anecdotal way, potential adverse events related to the use of C. aurantium and related compounds; and (iv) offering recommendations to guide the design of future trials to evaluate the safety and efficacy of C. aurantium. While some evidence is promising, we conclude that larger and more rigorous clinical trials are necessary to draw adequate conclusions regarding the safety and efficacy of C. aurantium and synephrine alkaloids for promoting weight loss.

Keywords: bitter orange, Citrus aurantium, herbal supplements, synephrine.

Introduction

Recent estimates indicate that over 30% of adults in the USA are obese (body mass index: BMI greater than 30 kg m⁻²) and about six out of 10 US adults are overweight (BMI 25–29.9) (1,2). The USA is certainly not alone in the world in its struggles with high obesity prevalence. In the mid-1990s, nations around the world reported levels of obesity of 20–75% (3). A growing public health concern is that the prevalence of obesity among children aged 6–19 is up to 16.5% in the USA (2) and has also increased in Europe, Asia, Africa and South American countries (3). Despite increased attention given to overweight and obesity by virtually every major body concerned with public health, including the National Institutes of Health (NIH) (4), the Centers for Disease Control (5), the United States Department of Agriculture (6) and the World Health Organization (7), primary and secondary prevention efforts have generally been disappointing. Obesity impacts many facets of society. For example, it is economically costly to society (8), increases mortality rate (9), reduces quality of life (10) and increases the risk of various morbidities (11). Extreme
obesity has been estimated to truncate the lifespan of young adults by 5–20 years (12).

Unfortunately, with the exception of surgery (a procedure appropriate for only a minority of obese individuals), available treatments for obesity are, at best, of modest efficacy. With regard to nonsurgical treatments for obesity, Ayyad and Andersen (13), in a quantitative synthesis of the literature, found that even in the best of conditions, the median percentage of patients who achieved and maintained clinically meaningful weight loss for at least 3–5 years was only about 20%, whereas others have reported that of those who lose weight, 90–95% eventually regain it (14,15).

Considering the above, enjoinders to healthier eating and increased physical activity appear insufficient to produce sustained weight loss in the majority of obese adults. As such, the pharmaceutical and nutritional/dietary supplement industries seek to develop weight loss products that are efficacious and that have no common serious adverse effects to health and well-being. Beta-3 agonists appear to be a viable class of medications for weight loss as they have been shown to affect both body weight and fat mass in rodents (16), and though promising, results in humans are still preliminary (17). Ephedra was perhaps the most popular dietary supplement for weight loss. It promotes weight and fat loss through its ability to increase thermogenesis (18) and reduce appetite (19). However, intense media attention concerning serious events, such as high blood pressure, heart ailments and stroke (20), among people consuming ephedra led to its withdrawal from the marketplace (21). As consumer groups advocate more strongly for medical reimbursement of obesity-related treatment, it may be of even greater interest to test currently available products (22).

**Citrus aurantium**

*C. aurantium* (C. aurantium) is the Latin name for a plant commonly named bitter orange, sour orange or Seville orange. Components of the fruit are sometimes used as a food, but the plant is more widely used as a medicinal or dietary supplement. Similar to ephedra, it contains alkaloids that are adrenergic agonists and is often incorporated into supplements designed to aid in weight loss (23,24). These alkaloids are believed to primarily be a-adrenergic agonists, but also have some b-adrenergic agonist properties. It is important to distinguish between three related but distinct substances: *C. aurantium*, para-synephrine (p-synephrine; p-s) and meta-synephrine (m-synephrine; m-s).

The bitter orange fruit (*C. aurantium*) contains a number of phytochemicals of interest, including p-Octopamine and synephrine alkaloids (SAs) (25). These molecules are adrenergic agonists and are usually cited as its ‘active ingredients’. Some authors (26) stated that *C. aurantium* contains m-s, whereas others (27) stated that it contains only p-s. Dr Ikhlas A. Khan (personal communication, 14 January 2005) indicated that research he has conducted shows that *C. aurantium* naturally contains p-s and does not contain m-s. Ibrahim et al. (28) also showed that some citrus fruits contained p-s and not m-s, but *C. aurantium* was not one of the fruits tested. We have recently discovered that at least one over-the-counter (OTC) product purportedly containing SAs from *C. aurantium* contains both p-s and m-s, perhaps confirming that it is not necessarily possible to rely on ingredient labels of such products (29). There is also an ortho isomer of synephrine (o-synephrine) and p-s, m-s, and o-synephrine can each come in d or l forms. We have no knowledge of the o-synephrine content or lack thereof in *C. aurantium*. Therefore, further evidence is needed regarding the composition of synephrine in naturally occurring *C. aurantium*, its extracts and products purportedly containing SAs from *C. aurantium*. Currently, the United States National Institute on Standards and Technology (NIST) is conducting such evaluations.

*P*-synephrine, often referred to as simply synephrine (30), is an a-adrenergic agonist (31) that also has some b-adrenergic properties (32). *P*-s occurs naturally in the human body in small quantities and may act as a neurotransmitter (33). Since 1927, usually under the name oxedrine, it has been used as a pharmaceutical (34), commonly in the form of eye drops. Oxedrine is thought to be the primary ingredient in *C. aurantium* that produces weight loss, but neither this nor whether *C. aurantium* produces weight loss in humans is firmly established.

*M*-synephrine, often referred to as phenylephrine, is an isomer of *p*-s. It is also an a-adrenergic agonist that also has some b-adrenergic agonist properties. It has been studied far more extensively than *p*-s and is one of the two most widely used OTC decongestants today (30).

Because of the similar properties of these components and the overlap of their inclusion in supplements for research and commercial preparations, we will refer to them collectively as SAs. Forms of SAs are used clinically as decongestants (30), during surgical procedures as a vasopressor (35), for acute treatment of priapism (36) and in ophthalmological exams for pupil dilation (37).

Although at least three reviews of *C. aurantium* have been published (23,27,30), our review expands upon these by: (i) distinguishing and evaluating the efficacy of *C. aurantium* and related compounds; (ii), including results from previously unreviewed research; (iii), incorporating recent case reports that serve to highlight, in an anecdotal way, potential adverse events related to the use of *C. aurantium* and related compounds; and (iv) offering recommendations to guide the design of future trials to evaluate the safety and efficacy of *C. aurantium*.
Use volume

With the US Food and Drug Administration’s (FDA) ban of ephedrine-containing dietary supplements, the sale of dietary supplements containing SAs is believed to have increased dramatically (38). According to the FDA (39), some products previously containing ephedrine have been reformulated to include C. aurantium, which contains synephrine. Some of these reformulated products have even higher sales than the original formulation (40), which is put into perspective by the sales estimate of greater than three billion servings of ephedrine-containing products during their peak year (41).

According to Richard Cleland, Senior Attorney and Assistant Director for the Federal Trade Commission’s Division of Advertising Practices, SAs currently are among the top five ingredients in OTC weight-loss products sold (R. Cleland, personal communication, 1 June 2004). He also notes that the estimated annual retail weight-loss product sales for dietary supplements are about $1.2 billion and bitter orange is included in about one-third of the products (R. Cleland, personal communication, 1 June 2004).

Potential mechanisms of action

As a sympathomimetic agent with both α- and β-adrenergic receptor agonist, SAs would be expected to potentially increase energy expenditure and decrease food intake (18). In addition, there is some evidence that adrenergic agonists, including SAs, decrease gastric motility (42). By analogy to compounds such as cholecystokinin (CCK) and other gut peptides that both decrease gastric motility and food intake (43), one might conjecture that SAs may also decrease food intake via reducing gut motility.

Because of its wide scale availability and use, the safety and efficacy of C. aurantium-containing products (CAPs) and/or SAs deserve rigorous examination, due both to their potential utility in promoting weight loss, and to their similarity to the controversial substance ephedrine. Although our emphasis in this paper will be on human studies, we will briefly review the most relevant animal studies, specifically studies of rodents that address the efficacy, physiological effects and safety of SAs. Though SAs have several other clinical uses, this review is limited to their safety and efficacy for weight loss in particular.

Animal studies

Synephrine alkaloids are well documented to reduce food intake in rodents (44), and several studies indicate that SAs can reduce body weight in rodents (30,44,45). SAs have been shown to promote lipolysis in adipocytes through beta-adrenergic stimulation (46). These data suggest the ability to selectively reduce body fat without compromising lean tissue. Similarly, SAs were noted to increase lipoprotein lipase activity in the parametrial fat pad of female hamsters (47). On the other hand, among monosodium glutamate-treated obese mice, SAs induced weight gain but had no effect on percentage body fat (48). Thus, the effect of SAs on adiposity per se remains conjectural.

Preliminary data suggest m-s may prolong life in rodents. A 2-year study by the National Toxicology Program (30) evaluated the effects of m-s on spontaneous food intake of male and female rats and mice. At 2 years, there were no significant differences in survival among the mice or female rats. However, for male rats, there was a significant reduction in mortality rate. It is noteworthy that there was some increased mortality in the early phase of the study at the highest dose. In contrast, mortality rate was reduced for the study overall, resulting in longer life. Similar results have been reported for ephedrine, another sympathomimetic amine (49). This was only a 2-year study however, and too few deaths occurred during this time to provide the degree of precision and power desired in a longevity study (50).

A more recent study (45) of male Sprague–Dawley rats reported what the authors believed was evidence of cardiotoxicity when C. aurantium fruit extracts standardized to 4% and 6% SAs were administered. Calapai et al. (45) also observed increased mortality in their CAPs-treated rats. In a particular strain of mice, increased mortality has been seen as well, though such mice were selected to be uniquely susceptible to ill-effects as a result of adrenergic stimulation (51).

Human studies

Few clinical trials have examined the effects of CAPs alone or in combination with other ingredients on body weight and/or body composition. It should be kept in mind that these trials are of short duration and sample sizes are frequently inadequate. Nonetheless, in these short-term studies, body weight and/or fat loss appears to be enhanced by CAPs or SAs. This may be partially attributed to a suppressing effect of appetite and/or a moderate increase in resting energy expenditure.

Weight loss trials (see Table 1)

Armstrong and colleagues (55) administered a combined exercise programme and herbal preparation containing ma huang, bitter orange (5 mg SAs) and guarana supplement over 6 weeks in a randomized, controlled trial. Significant reductions were observed in fat mass, with a nearly significant reduction in BMI and fat percentage. No significant changes were noted in resting energy expenditure (REE), blood chemistries or dietary intake in the placebo or experimental groups.

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Table 1 Summary of clinical weight loss trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Design</th>
<th>Sample size</th>
<th>Duration</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>975 mg <em>Citrus aurantium</em>, +528 mg caffeine and 900 mg St John’s Wort; placebo (with pill) and control (no pill)</td>
<td>Blinded parallel groups RCT</td>
<td>Supplement, n = 9; Placebo, n = 7; control group (no pills), n = 4</td>
<td>6 weeks</td>
<td>Supplement group lost more fat (3.1 kg; <em>P</em> &lt; 0.05) than other groups and increased resting metabolic rate (2-3%)</td>
<td><em>C. aurantium</em> may assist individuals in losing body fat, attributed to increased energy and reduced energy intake expenditure. No adverse events were reported</td>
</tr>
<tr>
<td>53</td>
<td>1 week low-energy diet followed by 1 week administration of 325 mg <em>C. aurantium</em> +125 mg <em>Paullinia cupana</em> + 5 mg <em>Grinkgo biloba</em> (27-68 mg of alkaloids). Product contained 5 mg synephrine</td>
<td>Open-labelled</td>
<td>9 overweight/obese women</td>
<td>2 weeks</td>
<td>Week 1: 0.94 kg weight loss; Week 2 with supplement = 2.4 kg weight loss (<em>P</em> &lt; 0.05)</td>
<td><em>C. aurantium</em> may assist individuals in losing bodyweight</td>
</tr>
<tr>
<td>54</td>
<td>Ephedrine and synephrine alkaloids (5 mg twice daily)-based product vs. placebo with exercise and diet</td>
<td>Prospective, randomized double blind</td>
<td>30 overweight subjects; BMI &gt; 27</td>
<td>8 weeks</td>
<td>3.4 kg weight loss in experimental group vs. 2.05 kg in placebo (<em>P</em> &lt; 0.05)</td>
<td>No adverse events; findings indicate apparent short-term safety and efficacy of ephedrine and synephrine-based compound.</td>
</tr>
<tr>
<td>55</td>
<td>Exercise programme with assignment to drug (Ma Huang, bitter orange and guarana) or placebo. Bitter orange standardized for 5 mg synephrine</td>
<td>Randomized trial – unclear if study is blinded</td>
<td>5 overweight men/14 women</td>
<td>44 days</td>
<td>Supplement increased fat loss (2.5 kg; <em>P</em> = 0.033) more than placebo (0.5 kg)</td>
<td>Low statistical power, no marked side effects</td>
</tr>
</tbody>
</table>

RCT, randomized clinical trial.
In a double-blind, placebo controlled, randomized trial, Colker et al. found that subjects receiving *C. aurantium*, caffeine and St. John’s Wort, in combination with strict diet and exercise, lost a statistically significant amount of body weight. Analysis comparing changes in this group to those in placebo or control groups on the same diet and exercise regimen did not show significant differences, though loss of fat mass was significantly greater in the test group (52). The group reported that blood pressure, heart rate, electrocardiographic, blood and urine analysis did not show significant changes for any groups.

An open-labelled uncontrolled study of nine women showed a greater mean weight loss during the second week, when *C. aurantium* (along with *Paullinia cupana*, which contains caffeine, *Ginkgo biloba* and *Panax ginseng*) was administered, compared to the first week when it was not (53). It should be noted that the participants ranged in BMI from 23.1 (normal) to 33.4 (moderately obese). Caloric restriction was included in both phases of the trial.

Another randomized clinical trial (54) of 30 overweight individuals measured the effects of supplementation on body composition, in conjunction with diet and exercise. Supplementation included ephedrine, SAs, caffeine and calcin, along with a cross-training exercise regimen and dietary education programme. Greater weight loss and fat loss occurred for the supplemented group compared to the placebo group, which underwent behavioural changes alone.

Overall, studies that examined weight loss reported a loss of 2.4–3.4 kg among participants using SAs, while placebo groups lost 0.94–2.05 kg. There is a suggestion of some benefit to weight loss from SA supplementation, beyond that of behavioural intervention alone, but results from these few small studies cannot be considered conclusive at this point because they do not separate the effects of *C. aurantium* or SAs from those of other ingredients, particularly ephedrine.

**Acute physiologic studies**

Several investigators examined the effects of acute administration of SAs on cardiovascular indicators. These trials, however, vary in sophistication and sample sizes and frequently lack the statistical power to make robust conclusions for anything but the most common potential side effects. Nonetheless, several of these studies provide interesting insight into the potential effects of SAs in the context of obesity-related studies. Both isolated *p*-s and *C. aurantium* extract have been shown to increase blood pressure in animal studies (45). Thus, one may speculate that CAPs may be harmful to individuals with cardiovascular conditions.

Kalman et al. (56) tested a commercial product containing 335 mg Ma Huang standardized for 20 mg ephedrine alkaloids, 910 mg guarana standardized for 200 mg caffeine and 85 mg bitter orange standardized for 5 mg SAs per two capsules. Twenty-seven overweight adults were randomized to treatment or placebo for 14 days. Several cardiovascular indices were evaluated before and after treatment [blood pressure, heart rate, electrocardiogram (EKG) and Doppler echocardiograms]. The investigators found ingestion of this commercial weight-loss supplement did not produce any noticeable cardiovascular side effects.

Penzak et al. (26) examined cardiovascular outcomes in normotensive individuals. They administered 8 oz of Seville orange juice and water in a crossover fashion, followed by a repeat ingestion 8 h later. The juice product contained 13–14 mg SAs, which is a comparable dose to *m*-s contained in decongestant-containing cold preparations. These investigators found no changes in cardiovascular indices (blood pressure, maximal arterial pressure and heart rate) in 12 healthy subjects.

Thomas et al. (57) evaluated the cardiovascular effects of 10 mg oral SAs in healthy volunteers over a 4-h period on impedance cardiography and forearm phethysmography. They found an elevation in total peripheral resistance in healthy subjects 30–60 min after dosing, although other haemodynamic indexes were not affected.

Two other studies examined the acute effects of *C. aurantium* alone or in combination with a meal in obese (58) and normal weight volunteers (59). In obese participants, increases in resting metabolic rate (RMR) were observed with *C. aurantium*, both alone and with food, beyond the thermic effect of food (TEF) alone. In the normal weight group, there was also an increase in RMR when the extract was taken with a meal. No adverse changes in pulse rate or blood pressure were reported in either study.

A recent abstract from *Medicine and Science in Sports and Exercise* described a study to examine the effects of two dietary supplement formulas on RMR and other body indicators (60). When compared to placebo, Formula A (ephedra, guarana, green tea, yohimbe, quercetin) and Formula B (*C. aurantium*, jing jie, fang feng, guarana, green tea, yohimbe, quercetin) resulted in increased total RMR, decreased respiratory exchange ratio (RER) towards fat burning and increased body core temperature (BCT). Heart rate increased and RMR increased at each 15-minute interval with Formula A only. Blood pressure increased for both, but to a greater extent with Formula A.

**Case reports**

Case reports do not demonstrate causation or association, but repeated co-occurrences can generate hypotheses and, in some cases, raise concerns. Several case reports regarding events following or in conjunction with ingestion of SAs are worth noting, if only to raise awareness and promote further investigation.
Nykamp et al. (61) describe a case of acute lateral-wall myocardial infarction co-occurring with consumption of CAPs in a 55-year-old woman with undetected coronary vascular disease. She had reported taking a multicomponent dietary supplement for weight loss containing 300 mg of bitter orange for the past year.

A Consumer Reports article (62) highlighted a 21-year-old woman who took ephedra-free Xenadrine EFX (which contains C. aurantium). After using the supplement for 3 weeks, she suffered a seizure. Her neurologist is reported to believe that the bitter orange in the supplement was the most likely the cause, though the basis for this conclusion is unknown.

Another case involved the use of m-s as a daily nasal spray (TID) (63). A 57-year-old man suffered a stroke within 3 h of inhalation. He had been using the product over a 4-month period and had a prior history of systemic hypertension.

A recent case report (64) described exercise-induced syncope in a healthy 22-year-old woman that occurred 1 h after a second dose of Xenadrine EFX, a weight-loss supplement including ephedrine and synephrine. The electrocardiography revealed prolongation of the QT interval, which resolved in 24 h. This product contains several compounds whose effects are unknown.

Health Canada (65) reported that from 1 January 1998 to 28 February 2004 it received ‘16 reports in which products containing bitter orange or synephrine were suspected of being associated with cardiovascular ARs, including tachycardia, cardiac arrest, ventricular fibrillation, transient collapse and blackout. All cases were considered serious’.

The safety of C. aurantium-containing products

Case reports and media attention aside, some experts have hailed the potential therapeutic value of CAPs (23), while others have warned about possible safety concerns (45,66). Reservations mainly surround potentially adverse cardiovascular and cerebrovascular effects. Safety-related information regarding CAPs primarily comes from the four sources described above: animal studies, clinical trials, acute physiologic studies in humans and case reports. To our knowledge, no large epidemiologic (case–control or cohort) studies of the safety of CAPs exist.

As the FDA noted in its final rule on ephedrine alkaloids, one cannot confidently extrapolate from short-term studies of substances used for one indication in one population (e.g. several days for relief of nasal congestion among the general population) to long-term use for another indication in another population (e.g. several months or years for weight loss among obese individuals). Although substantial safety-related data exist for CAPs in general (30,67,68), there is no published human trial of CAPs for weight loss with more than 20 people or for more than 7 weeks, limiting current conclusions.

Many studies addressing the safety of CAPs are performed using normotensive subjects. Because hypertension is more common in overweight and obese subjects than normal-weight individuals, more studies are warranted looking at the effects of CAPs in a hypertensive population. Additionally, there are no case–control or epidemiologic cohort studies of CAPs with respect to hard safety endpoints such as myocardial infarction or stroke.

While C. aurantium extracts have been used in a variety of cultures for thousands of years, they have not been traditionally utilized for long periods of time, or specifically for weight loss (23). Some clinical studies have also suggested that CAPs may change drug metabolism (26,69,70). Currently, there is little if any basis for making definitive statements about safety or risk of CAPs used for weight loss (Table 2).

Quality control

Because herbal and dietary supplements are not regulated by the FDA with anywhere near the degree of control as are pharmaceuticals, there is a great degree of variability in the contents and relative quantities of substances contained within them. Currently, manufacturers are not required to report quantities of a given substance on labels, allowing for variability between identical packages (71). For example, in a sample of 20 supplements containing ephedra alkaloids, half were found to exhibit discrepancies between the label claim and actual contents (72).

<table>
<thead>
<tr>
<th>Physiological effects</th>
<th>Effects on weight</th>
<th>Effects on body composition</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable changes in blood pressure in animals; generally stable blood pressure, heart rate, pulse, blood and urine measures in humans; inconsistent changes to resting metabolic rate</td>
<td>Weight loss documented in rodents; weakly supported in humans, as studies used multiple supplements or did not find significant difference from controls</td>
<td>Limited support for loss of fat mass in human studies, noting a trend towards using multiple supplements, for animals, some increased lipase activity</td>
<td>Inconsistent mortality data in rodents; no consistent side effects in human studies, but several case reports of serious adverse events</td>
</tr>
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</table>

Table 2 | Summary of effects, safety and efficacy of Citrus aurantium

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The composition of products also varies between manufacturers and postmarketing surveillance studies by manufacturers are the exception (73). Within C. aurantium products, the difference between reported and actual concentrations of SAs have been found to range from 0.3% to 0.99% (25). A study testing herbal products for prohibited anabolic androgenic steroids, or prohormones, found that 15% contained prohormones that not declared on the label, most of which were manufactured in the USA, but also sold in many European countries (74). If regulations are not put in place to ensure consistency of product and accuracy of labelling, it will be difficult to ensure the safety and efficacy of commercially available herbal supplements such as C. aurantium and other synephrine-containing products.

**Dose considerations**

There is no definitive knowledge as to the dose of C. aurantium, p-s, or m-s that would be optimal for weight loss. Table 3 highlights dosage information from previous studies and contexts as a means of providing perspective. Although we realize that generalizing across species and substances is difficult and can only provide a basis for conjecture, we note the following comparisons with ephedrine. Data were analysed from reference 47 in which ephedrine or m-s were given to mice. We regressed weight and food intake on dose of ephedrine or m-s. We found that the slopes were (in absolute value) approximately four to six times greater for ephedrine than for m-s. That is, if we allowed ourselves to make linear projections, it takes four to six times the dose of m-s (in these mice) to achieve equivalent reduction of intake and body weight as for ephedrine. In human studies of ephedrine, doses of about 60 mg per day begin to be effective (77). Although obviously an extrapolation, this might suggest a useful clinical dose as high as 240–360 mg per day. From a safety point of view, we also note that m-s on a mg per mg basis has much less potential than does ephedrine to raise blood pressure. In fact, from human studies, it seems that 15- to 30-fold of the dose of m-s is required to elevate blood pressure to the same degree as ephedrine (78–80). This suggests that even such high doses might be well-tolerated, but clearly more data are needed.

With respect to administration, according to reference 76 m-s is readily absorbed after oral administration. About 80% of oral doses are excreted in the urine within 24 h. After single oral doses, peak plasma concentrations are typically reached in 1–2 h. Plasma half-life is ~2–3 h. Sympathomimetic drugs for weight loss are typically given TID before breakfast, lunch and dinner (81) with the opportunity to reduce the evening dose if sleep problems arise.

**Recommendations for future clinical trials design**

For progress to be made in clinical trials, several aspects are critical. First, dose finding or flexible dose strategies are needed to better determine appropriate doses. Second, if we are to understand the effects of CAPs or SAs per se, then studies will need to test these components without combining them with other ingredients postulated to have anti-obesity effects. Dietary supplement manufacturers are often unmotivated to do so because they prefer to test proprietary blends. Therefore, it may be incumbent upon academic investigators to seek non-industry funding to

<table>
<thead>
<tr>
<th>Dose</th>
<th>Information</th>
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<tbody>
<tr>
<td>5–14 mg day⁻¹</td>
<td>Citrus aurantium extract with SAs has been used (51–54), and no serious adverse events were reported. These doses purportedly showed efficacy, but products tested included substances beyond Citrus aurantium, notably ephedrine, which we know to be effective for weight loss. We believe that these doses of SAs are very unlikely to be effective when used without ephedrine.</td>
</tr>
<tr>
<td>32 mg day⁻¹</td>
<td>Jones (52) provides suggestive evidence of effective weight loss at this dose of SAs.</td>
</tr>
<tr>
<td>80 mg day⁻¹</td>
<td>The nasal decongestant Endal (see <a href="http://www.pediamedpharma.com/pdfs/EndalTablets_PI(9_20).pdf">http://www.pediamedpharma.com/pdfs/EndalTablets_PI(9_20).pdf</a>) contains 20 mg of m-s per tablet and two tablets per dose twice per day are recommended.</td>
</tr>
<tr>
<td>100 mg day⁻¹</td>
<td>Jones (52) advocates SA doses on the order of 1 mg kg⁻¹ day⁻¹ as a potentially safe and efficacious dose of synephrine. Thus, for a 100-kg individual (approximately the average weight of an individual entering university-based weight loss RCTs), doses of 100 mg day⁻¹ would be reasonable.</td>
</tr>
<tr>
<td>120 mg day⁻¹</td>
<td>Via Citrus aurantium extract, SAs are marketed in over-the-counter products for weight loss. In products, such as Nutres Lipo 6 (Body Building.com) the directions suggest that for ‘extreme fat loss’ a recommended dosage is two capsules three times per day. The SA content per capsule is 20 mg; this provided a maximal recommended dose of 120 mg day⁻¹.</td>
</tr>
<tr>
<td>300 mg day⁻¹</td>
<td>According to Clarke’s Analysis of Drugs and Poisons (75), oxedrine (p-synephrine) is used clinically at ~300 mg day⁻¹.</td>
</tr>
<tr>
<td>1000 mg day⁻¹</td>
<td>Minimum adult lethal dose of m-synephrine according to reference 76.</td>
</tr>
</tbody>
</table>

Table 3 Dosage Information on Citrus aurantium or synephrine alkaloids (SAs)

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Conduct such tests. Third, given concerns about product integrity and quality control (25), it is critical to use ‘certified’ material from a highly trusted source such as the NIST, to regularly test batches of product to determine actual contents, or to use purified components from a pharmaceutical or chemical supplier. Fourth, sample sizes used to date have been quite minimal for determining efficacy and so small as to only be capable of detecting extremely common side effects. Clearly, larger studies and also longer studies are needed to address both safety and efficacy. Finally, multiple populations merit study. Although it might be wise to first study whether CAPs or SAs appear to be safe and effective in non-elderly, nonhypertensive obese adults, subsequently it will be important to evaluate children, the elderly, and those with hypertension – critical groups that may be exposed and may be differentially susceptible to any beneficial or harmful effects that may exits.

**Conclusion**

Given the broad exposure and the unknown safety and efficacy, the question of the effects of CAPs is of enormous public health significance. Nevertheless, as our review suggests, the available data are markedly limited, making it difficult to formulate CAPs-related public health recommendations with confidence.

Several clinical trials used compounds containing multiple substances with potentially thermogenic and/or anorexic effects. *C. aurantium* contains components other than SAs (such as octopamine, hordenine, *m*-methyltyramine and tyramine) that may also have effects on body weight or fat mass (23). Caffeine, commonly combined with *C. aurantium* or ephedra (82), has also been found to increase RMR and alter thermogenesis in formerly obese and control subjects (83–85). Other compounds utilized, such as *Panax ginseng* and *Ginkgo biloba*, may have effects on physiology and mental state that impact weight loss and/or weight loss-related behaviour (65,77). As stated above, variability of contents for products with identical labels can also add complications to comparison between and within studies.

**Future directions**

Clinicians, public health officials, regulatory bodies and consumers require stronger evidence on which to make decisions about SAs than that currently exists. More randomized clinical trials with rigorous design, large sample sizes, reliable well-established outcomes, and active surveillance of side effects and adverse effects are required if we are to adequately evaluate the safety and utility of SAs for weight loss. Future trials may examine differences between types of synephrine-containing compounds from a variety of sources, measured for consistency and potency. While SAs show some potential for reducing weight, this possibility requires more well-powered studies to be conclusive. It is also essential that the safety of these products are firmly established, with minimal risks and side effects (comparable to regulated and approved substances) before they can be promoted for use as a weight-loss supplement by health clinicians, scientists and other professionals.

**Acknowledgement**

Supported in part by NIH grant No. P30DK056336 and AR49720-01A1.

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