MINIREVIEW

Citrus aurantium, an Ingredient of Dietary Supplements Marketed for Weight Loss: Current Status of Clinical and Basic Research

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Seville orange (*Citrus aurantium*) extracts are being marketed as a safe alternative to ephedra in herbal weight-loss products, but *C. aurantium* may also have the potential to cause adverse health effects. *C. aurantium* contains synephrine (oxedrine), which is structurally similar to epinephrine. Although no adverse events have been associated with ingestion of *C. aurantium* products thus far, synephrine increases blood pressure in humans and other species, and has the potential to increase cardiovascular events. Additionally, *C. aurantium* contains 6′,7′-dihydroxybergamottin and bergapten, both of which inhibit cytochrome P450-3A, and would be expected to increase serum levels of many drugs. There is little evidence that products containing *C. aurantium* are an effective aid to weight loss. Synephrine has lipolytic effects in human fat cells only at high doses, and octopamine does not have lipolytic effects in human adipocytes. Exp Biol Med 229:698–704, 2004.

Key words: *Citrus aurantium;* Seville orange; herbal medicine; weight-loss products; synephrine; octopamine; bergapten; dihydroxybergapten

The popularity and largely unregulated sale of herbal preparations in the United States in recent decades have created concern about their potential adverse health effects. Scientific research into the physiological and pathological effects of herbs has been relatively sparse. The recent banning of ephedra (*Ephedra sinica*) by the Food and Drug Administration, long after its clinical association with strokes, heart attacks, hypertension, and psychiatric problems (1) illustrates not only the need for reevaluation of the regulatory environment for herbal medicines, but also the need for more basic and clinical research in this area.

Ephedra-free herbal weight-loss preparations have rapidly replaced ephedra products on drugstore shelves. Many of these new products contain *Citrus aurantium,* which until recently, was a rather obscure medicinal herb. Like ephedra, compounds contained in *C. aurantium* have adrenergic effects that theoretically might result in appetite suppression and lipolysis, but also might carry the same health risks as ephedra. This paper will address the safety, efficacy, and pharmacology of *C. aurantium* extracts for weight loss and body composition.

C. aurantium (also called Seville orange, or sour orange) is a small citrus tree, about five meters tall, with scented white flowers. *C. aurantium* is too sour to be popular for eating, but the ripe fruit is eaten in Iran (2), and in Mexico the fresh fruits are sometimes eaten with salt and chili paste (3). Immature fruits are sometimes pickled and used as a condiment. The peel of *C. aurantium* is often used in marmalade, and dried peel is used in bouquet garni and for flavoring a Belgian beer called Orange Muscat (4). Essential oil from the dried peel of unripe fruit flavors Curaçao, Cointreau, and Triple Sec. The flowers are used in tea, whereas the essential oil from the flowers, called neroli, is used in perfumes, liqueurs, and orange-flower water, which is used to flavor sweets (4).

The most common use of *C. aurantium* is medicinal rather than culinary. The dried, entire unripe fruit is used in Asian herbal medicine primarily to treat digestive problems. It is called Zhi shi in Chinese, Kijitsu in Japanese, and Chisil in Korean. Dried peel of the unripe or ripe fruit is also used in Western herbal medicine to stimulate appetite and gastric

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secretion (in contrast to the recent marketing of *C. aurantium*–containing products as weight-loss aids). It is a common ingredient in "Swedish bitters" and other gastrointestinal remedies (5). The flowers are occasionally used in folk medicine as a mild sedative.

There is thus a history of benign human consumption of *C. aurantium* fruit, but the culinary or medicinal use of the herb is limited and would not be likely to result in significant daily intake. The use of the herb as a weight-loss aid could result in very different levels of intake and perhaps a different safety profile. Several components of *C. aurantium* are cause for concern.

Active Components and Pharmacology

The most active components in *C. aurantium* fruit are synephrine (also called p-synephrine or oxedrine) and octopamine. *C. aurantium* peel also contains flavonoids, including limonene, hesperidin, neohesperidin, naringin, and tangaretin. Furanocoumarins are also present (5).

Structurally, the active components in *C. aurantium* are closely related to endogenous neurotransmitters and ephedrine (Fig. 1). Synephrine is structurally similar to epinephrine, and octopamine is similar in structure to norepinephrine (they differ only in the number of hydroxyl groups on the aromatic ring; Ref. 6). Closely related to synephrine is l-m-synephrine (phenylephrine, neosynephrine). Phenylephrine is an alpha adrenoreceptor agonist used in conventional medicine as a nasal decongestant and as a midriatic agent (7). It will not be discussed here because it is not present in *C. aurantium.*

Both synephrine and octopamine are trace endogenous bioamines widely distributed among plants, bacteria, invertebrates, and vertebrates, including humans. Octopamine is found in sympathetic nerves, in the same regions as norepinephrine, whereas synephrine and m-synephrine are found only in the adrenal glands (8). A recent study in healthy men and women detected octopamine in the plasma of all 16 subjects, synephrine in 15 subjects, and tyramine, a precursor of octopamine and synephrine, in 6 subjects (9). Octopamine and synephrine, but not tyramine, were detectable in the platelets of most subjects. In rats, p-octopamine has been identified in adrenals, heart, spleen, vas deferens, brain, liver, kidney, large intestine, bladder, and lung (8).

Dopamine beta-hydroxylase converts tyramine into octopamine; this biosynthesis is enhanced by monoamine oxidase inhibition (10). Phenylethanolamine N-methyl transferase catabolizes octopamine into synephrine (9). Synephrine has alpha-adrenergic effects and activates β-3 (but not β-1 or β-2) adrenoreceptors (9). Octopamine appears to be a selective β-3 adrenoreceptor agonist (10). Both synephrine and octopamine appear to inhibit cAMP production (6).

The functions of endogenous synephrine and octopamine have not been well delineated. Once termed "false neurotransmitters," synephrine, octopamine, and tyramine may in fact be true neurotransmitters (9). These amines may affect platelet-mediated signaling events, and may contribute to the pathophysiology of migraine and other types of headaches (11).

The compound d,l-m-octopamine has an antidipsogenic effect on angiotensin II-induced water intake in rats. The effect is apparently mediated by α-2-adrenoreceptors, because it is blocked by yohimbine (12). Synephrine had antidepressant-like effects in a mouse model utilizing immobility tests, but the effect was not dose-related. No effect was noted at the lowest (0.3 mg/kg) or highest (30 mg/kg) dose, and the effects of 3 mg/kg and 10 mg/kg were similar (13). Alpha-1 adrenoreceptors appear to be involved, because the effects of synephrine were reversed by administration of the α-1 antagonist prazosin. In a later study by the same group, S-(+)-p-synephrine was more effective than R-(−)-p-synephrine in reducing immobility in the tail suspension test (14).

Synephrine Content in *C. aurantium* Products

Synephrine has been identified in a variety of *C. aurantium* products, with the lowest concentrations occurring in fresh fruit. Synephrine concentration is apparently higher in smaller fruits, compared with larger fruits (15). One study compared synephrine and octopamine levels in different *C. aurantium* products. A reverse phase–high-performance liquid chromatography analysis found that fresh fruits contained 0.02% d,l-synephrine, whereas dried fruits contained 0.35% d,l-synephrine. Dried extracts contained 3% d,l-synephrine, and concentrations in three unidentified herbal products ranged from 0.3% to 0.99% (16). Synephrine enantiomers were stable to heat at temperatures used for extraction. Octopamine levels were very low, ranging from below the limit of quantification to <0.03% in all but one herbal product, which contained 0.15% octopamine. In another study, the mean synephrine concentration of freshly squeezed *C. aurantium* juice was 56.9 μg/ml. Octopamine was not present in the juice (17).

It appears from the limited data available that dried fruits, extracts, and commercial *C. aurantium* products contain significant amounts of synephrine, but octopamine may not be present in sufficient amounts to be of concern.

Hemodynamic Effects

Alpha and beta-adrenergic drugs have well-documented effects on the cardiovascular system, and *C. aurantium* would be predicted to have similar hemodynamic effects, with potential implications for adverse effects. Although *C. aurantium* extract has not been tested in clinical studies, synephrine clearly raises blood pressure in humans and other species.

Few studies have been performed. In 12 healthy men, synephrine (4mg/min continuous iv infusion) significantly increased systolic and mean arterial pressures, whereas

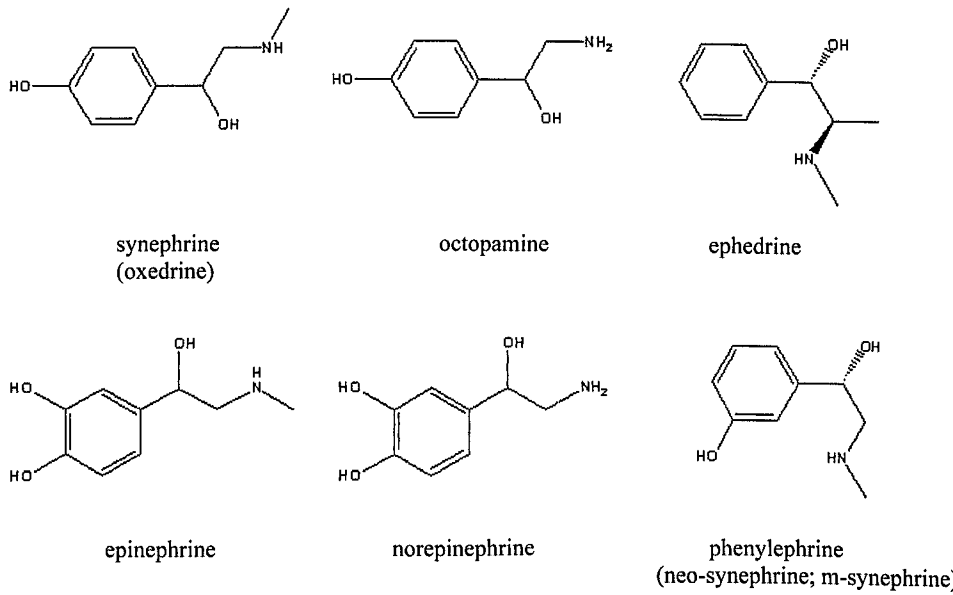

Figure 1. Chemical structure of synephrine, octopamine, and related compounds. Alternate nomenclature appears in parentheses.

diastolic pressure and heart rate were unchanged (18). Systolic blood pressure increased from a mean of 123 mm Hg to 150 mm Hg ($P < 0.005$), and mean arterial pressure increased from 91 mm Hg to 100 mm Hg ($P < 0.005$). Cardiac index increased significantly from 3.6 to 4.6 L/min/m^2 ($P < 0.001$), whereas left ventricular contractility parameters, assessed echocardiographically, also increased significantly. The authors also reported a drop in total peripheral resistance (although one would expect the opposite action for an alpha agonist).

A weight-loss study of a combination product containing 975 mg *C. aurantium* extract (6% synephrine alkaloids) found no effect on blood pressure at 6 weeks (19). A crossover, open-label study in 12 normotensive adults tested the cardiovascular effects of *C. aurantium* juice (17). Eight ounces of juice was administered orally in two doses, 8 hours apart, and the test was repeated with water a week later. It was estimated that subjects consumed approximately 13–14 mg of synephrine, approximately comparable to a dose of phenylephrine in an over-the-counter cold preparation. Blood pressure was taken every hour for 5 hours after the second dose of juice. Systolic and diastolic blood pressures, mean arterial pressure, and heart rate were not significantly altered. Oddly, hemodynamic indices were not measured after the initial dose of *C. aurantium* juice. The omission of blood pressure measurements after the initial dose of juice considerably limits the interpretation of this study.

A Chinese study reported that 50 children with infective shock were treated with a combination of synephrine and N-methyltyrosamine (in a 1:1 ratio; doses ranged from 1.66 to 24.0 mg/kg; Ref. 20). The inexplicable claim that "curative effects were seen in 48 cases" is contradicted by the next sentence, which states that 10 patients died. This does not appear to be a reliable study. In the same report, a beneficial effect of a *C. aurantium* extract or a synthetic combination of synephrine and N-methyltyrosamine (each 4 mg/kg/hr iv) was claimed on an endotoxin-induced shock model in dogs (20). Another study of a combination product containing synephrine and N-methyltyramine extracted from *C. aurantium* as well as saponins from ginseng (*Panax* spp) found similar effects on blood pressure and contractility in both normal dogs and dogs in endotoxic shock (21).

Effects of *C. aurantium* have also been studied in a rat model in which the hepatic portal vein was partially ligated to produce portal hypertension. Infusion of either a preparation made from a crude aqueous extract of *C. aurantium* (containing 12.5 mg synephrine/g extract), infused at 1.25, 2.5, or 5.0 mg/kg, or pure synephrine (infused at 0.095, 0.19, or 0.38 mg/kg/min) reduced portal pressure both in rats with surgically induced portal hypertension and sham-treated rats. The *C. aurantium* extract had a significantly greater effect in the portal hypertension model (22). In this model, the efficacy of vasoconstrictors to reduce portal pressure can probably be attributed to their constrictive actions in the splanchnic arterial circulation, and to the greater efficacy of *C. aurantium* extract in the portal hypertensives compared with sham-operated rats, and is consistent with a predominantly arterial, as opposed to venous, constrictive action of the extract.

Systemically, both the *C. aurantium* extract and synephrine elevated arterial blood pressure, as expected. In vitro, *C. aurantium* extract induced greater contraction of the aorta and mesenteric artery than the portal vein, whereas synephrine caused contraction of the aorta but was largely ineffective in the portal vein and mesenteric artery. Thus, *C. aurantium* extract appears to constrict arterial vessels and would therefore reduce splanchnic blood flow into the portal circulation. In addition, the effects of *C. aurantium* and synephrine differ to some degree, suggesting that the hemodynamic effects of *C. aurantium* are not entirely due to synephrine (22).

An 8-day study in two models of portal hypertensive rats (portal vein ligation and bile duct ligation) found that, compared with vehicle control, synephrine (1 mg/kg/12 hours by gavage) significantly reduced portal venous pressure and, in general, improved many of the hemodynamic alterations associated with the portal hypertension and systemic and splanchnic hyperemic states that characterize these models (23). The effects of synephrine in ameliorating portal hypertension were moderate, and less than those of propranolol (30 mg/kg/day) or octreotide (100 μg/kg/12 hrs).

In summary, synephrine appears to increase blood pressure in humans, rats, and dogs, but *C. aurantium* preparations may have hemodynamic effects that differ from those of synephrine. A pharmacokinetic study suggests no acute hemodynamic effect of *C. aurantium* juice in humans at the doses tested, and a combination product containing *C. aurantium* extract did not affect blood pressure at 6 weeks. In portal hypertensive rats, *C. aurantium* extract increased systemic blood pressure and affected portal hypertension in a manner consistent with arterial constriction. Available data are sparse and not entirely consistent. There are insufficient data to draw definitive conclusions about the hemodynamic effects of *C. aurantium* as compared with synephrine, and more studies are needed in this area.

Effects on Weight Loss and Lipolysis

Little evidence supports the use of *C. aurantium* for weight loss, despite its inclusion in over-the-counter weight-loss products. The only clinical trial of *C. aurantium* for weight loss tested a combination product. A double-blind, randomized, placebo-controlled, three-armed study of 23 subjects with body mass index >25 kg/m^2 compared treatment, placebo, and no treatment as an adjunct to a 1800 kcal American Heart Association Step I diet and a weight circuit training exercise program 3 days a week under the direction of an exercise physiologist (19). The tested combination contained 975 mg *C. aurantium* extract (6% synephrine alkaloids), 528 mg caffeine, and 900 mg St. John's wort (3% hypericum [sic]), taken daily for 6 weeks. Outcome measures included weight, fat loss, and mood. Twenty subjects completed the study. The study reports that treated subjects lost a significant amount of weight (1.4 kg) compared with the placebo group (which lost 0.9 kg) and the control group (which lost 0.04 kg). However, the table in the publication appears to indicate that the differences are significant only compared with baseline but not in comparison with the other groups at the end of the trial.

The treatment group lost 2.9% of fat, whereas there was no significant change in the placebo or control groups. No significant changes were seen in any group in a Profile of Mood States Questionnaire, blood lipids, blood pressure, heart rate, electrocardiogram, serum chemistries, or urinalyses. The treated group experienced a significant increase in basal metabolic rate, whereas the placebo group experienced a significant decrease in basal metabolic rate. There was no change in the untreated control group. No side effects were reported.

Assuming that the 3% hypericum actually means 0.3% hypericin, the dose of St. John's wort (*Hypericum perforatum*) in this particular product would be a therapeutic antidepressant dose. There is no clinical evidence that St. John's wort helps weight loss, but depression can certainly predispose to overeating.

This product contains a generous amount of caffeine, the equivalent of about 4 cups of coffee or 10 cups of tea. Caffeine has a thermogenic effect, and this effect is synergistic with other sympathomimetic agents. Even 100 mg caffeine has a thermogenic effect lasting 1–2 hrs, and dosages >600 mg/day increase 24-hr energy expenditure under respiratory chamber conditions (24).

Beta-3 adrenoreceptor agonists do have lipolytic effects in the fat cells of rats, hamsters, and dogs, but they are much less active in human fat cells. Octopamine was more potent than synephrine (but far less potent than norepinephrine) for stimulating lipolysis in adipocytes from rats, hamsters, or dogs; however, the effect was not significant in fat cells from guinea pigs or humans (10). Octopamine was fully lipolytic in adipocytes from the garden dormouse and Siberian hamster (25).

In rat cells, activation of lipolysis by octopamine was found to be a specific β-3 adrenergic effect, and was reversible by administration of a β-3 adrenoreceptor antagonist (β-1 and β-2 receptors did not appear to be activated; Ref. 10). Human fat cells respond only to activation of β-1 or β-2 receptors (although low levels of β-3 adrenergic receptors are also expressed). Only high concentrations of synephrine (0.1–1 mM) significantly stimulated lipolysis in the fat cells of humans, hamsters, and guinea pigs, and the effect was not significant in rats (10).

In summary, the only published trial of a *C. aurantium*–containing weight-loss product found that the product was not superior to placebo for weight loss. There is no evidence that synephrine and octopamine in levels that would be found in weight-loss products would have any lipolytic effect on human adipocytes.

Adverse Effects and Drug Interactions

C. aurantium would be expected to have sympathomimetic effects, but *C. aurantium* extracts have not been associated with adverse effects to date. A thinly described case report linked a large myocardial infarction in a 28-year-old male to the abuse of synephrine tablets (26).

C. aurantium, grapefruit (*C. paradisi*), and pomelo (*C. maximi*) contain several flavonoids that affect drug metabolism, including 6′,7′-dihydroxybergamottin, which is used to selectively block intestinal cytochrome P450 isoenzyme CYP3A4 in bioavailability studies. *C. aurantium,* but not grapefruit, also contains a furocoumarin, bergapten, that also inhibits CYP3A4 in cultured intestinal epithelial cells, but the effect is weaker than that of 6′,7′-dihydroxybergamottin (27).

CYP3A4 metabolizes more than a quarter of pharmaceuticals, and grapefruit juice increases blood levels of many drugs (28). *C. aurantium,* predictably, also increases drug levels, and because it contains bergapten as well as 6′,7′-dihydroxybergamottin, may have an even stronger effect than grapefruit juice.

A recent clinical pharmacokinetics study found that *C. aurantium* juice, but not grapefruit juice, significantly increased plasma levels of concurrently administered indinavir (29). Another clinical study found that *C. aurantium* juice affected felodipine pharmacokinetics similarly to grapefruit juice, increasing maximum concentration and AUC (area under the concentration-time curve) without affecting terminal elimination half-life (27). And a third pharmacokinetics study found that both *C. aurantium* juice and grapefruit juice increased the bioavailability of dextromethorphan (30).

The only clinical study that found no effect of *C. aurantium* compared the effects of grapefruit juice and *C. aurantium* juice on the pharmacokinetics of cyclosporine. Although *C. aurantium* reduced enterocyte concentration of CYP3A4 by 40%, only grapefruit juice affected cyclosporine disposition (31). This can be explained by the fact that bioavailability of cyclosporine is affected by P-glycoprotein (a membrane-localized drug transporter) as well as CYP3A4, and grapefruit, but not *C. aurantium,* is known to affect P-glycoprotein. Also, species differences may affect results. In swine, coadministration of a *C. aurantium* decoction doubled the AUC and significantly increased the C_{max} of cyclosporine, and several animals manifested signs of cyclosporine toxicity (32).

Discussion

There is little evidence that *C. aurantium*–containing products would be effective for weight loss, but a dearth of clinical trials is no deterrent to consumers eager to lose weight. No clinical trials have been performed with *C. aurantium* alone. The one clinical trial (of a high-caffeine combination product) did not appear to affect weight loss more than placebo. Although change in fat mass was higher in the treated group, this effect cannot be attributed to *C. aurantium* alone.

Potential health risks exist. The documented effects of synephrine on blood pressure would be expected to increase the risk of cardiovascular events, especially in those with preexisting cardiovascular disease. The single clinical study of *C. aurantium* juice that showed no effect on hemodynamics should not be reassuring for several reasons. First, herbal products contain not only fruit, but also rind, which is much higher in synephrine than the fruit. Second, the effect of initial dosing with the juice was inexplicably not determined, and the lack of effect of the second dose may reflect tolerance. Finally, the study was conducted in normotensive adults, who may react differently to vasopressors than hypertensive adults. Hypertension is common among overweight individuals, the population targeted for promotion of weight-loss products.

C. aurantium juice is a potent inhibitor of CYP3A4 and would be expected to increase the blood level of many drugs. This could potentially increase the toxicity of drugs, including warfarin, that have a narrow therapeutic window.

Some herbal weight-loss products combine *C. aurantium* and St. John's wort (*H. perforatum*). While *C. aurantium* inhibits CYP3A4, St. John's wort induces CYP3A4 as well as the drug transporter P-glycoprotein. St. John's wort reduces levels of many drugs, including digoxin, tricyclic antidepressants, phenprocoumon (a warfarin-type anticoagulant not used therapeutically in the United States), and cyclosporine (33). A product containing both *C. aurantium* and St. John's wort would be expected to have unpredictable interactions with drugs.

An argument may be made that *C. aurantium* has been used for thousands of years in traditional Chinese medicine and that such use should be an indirect marker of safety. The same argument has been used for ephedra. Ephedra has been used for asthma and other respiratory problems, and *C. aurantium* has been used as an expectorant or for digestive problems. However, neither ephedra nor *C. aurantium* has been used traditionally for weight loss.

What we do know about ephedra should warn us about *C. aurantium.* The traditional use of ephedra for specific indications and for short periods of time does not appear to be dangerous. Virtually all adverse effects associated with ephedra have been observed with ephedra-containing products promoted for weight loss, exercise enhancement, energy enhancement, or recreational use. None of these uses are traditional indications, and all utilize doses meant to speed metabolism.

C. aurantium, as well, is traditionally used in crude form, for short periods of time, and for specific indications. Weight loss is not a traditional indication. Additionally, the use of concentrated extracts, perhaps combined with other sympathomimetic herbs or drugs, over extended periods of time, has no precedent in traditional use. Given what we know about the cardiovascular effects of synephrine, modern usage in weight-loss products should not be presumed to be safe.

There is some evidence that *C. aurantium* extracts have different effects than pure synephrine, but these differences must be explored in appropriately designed studies. It is not unusual for crude herb extracts to have very different effects than isolated constituents. However, data available to date are insufficient to support safety claims of *C. aurantium* extracts.

Consumers may find it difficult to determine whether or not a product contains *C. aurantium,* because the botanical name may not appear on the label. Citrus oils are considered by the Food and Drug Administration to be Generally Recognized as Safe (GRAS) and are commonly used as food flavorings and additives. Manufacturers are not required to state the amount present nor the botanical name of citrus oils, and the only clue on some labels that essential oils are present may be the term "natural flavoring." Products containing synephrine or octopamine should at least be labeled with the amount. This could help determine whether manufacturers are "spiking" products with higher levels of synephrine or octopamine than would normally be found in *C. aurantium.*

Unless and until the short- and long-term safety and efficacy of *C. aurantium* extracts are established, consumers should be advised to avoid *C. aurantium*–containing weight-loss products, which may have adverse effects on hemodynamics and may interact with many drugs. While the limited literature available provides a basis for concern, basic testing on safety and efficacy has not been performed, and both basic and clinical research into the physiological and pathological effects of *C. aurantium* and its active components should be encouraged.

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