



American Botanical Council

Bitter Orange Peel and Synephrine

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Bitter Orange Peel and Synephrine: Part 1

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By Mark Blumenthal

The announcement in late December by the U.S. Food and Drug Administration (FDA) that it intends to issue regulations banning the sale of dietary supplements containing the controversial herb ephedra (*Ephedra sinica*) has stimulated a flurry of media articles about the sale, potential safety risks, and need for additional regulation of so-called “ephedra-free” dietary supplements and alternatives to ephedra supplements.*

Articles on this subject have appeared in *The New York Times*, *USA Today*, the *Los Angeles Times*, *Time* magazine, and many other publications and electronic news outlets (e.g., CNN, major television networks and local newscasts) about these alternative products. I have been interviewed by many of the above in the two weeks subsequent to the FDA’s announcement of the proposed ban, as well as during the past year. One of the most frequently mentioned ingredients in all of these stories is bitter orange peel and its primary alkaloid, synephrine.

During this post-ephedra ban announcement period, bitter orange has become increasingly controversial. On January 20, FDA Commissioner Mark McClellan M.D., Ph.D. announced that FDA would be taking a stronger look at bitter orange to determine its safety (and presumably, its efficacy) as an ingredient in dietary supplements being marketed as “ephedra-free” products for weight loss (Weise 2004).

Over the past few years, especially since the highly publicized death of Baltimore Orioles pitcher Steve Bechler in February 2003—a case that has been linked to Bechler’s consumption of an ephedra supplement—many manufacturers have shifted to the so-called “ephedra-free” products for various reasons, most notably their desire to avoid the increasing adverse publicity associated with ephedra, and the other, because of the rising costs of product liability insurance coverage for ephedra.

The “ephedra-free” products contain a variety of herbs, some containing caffeine (*e.g.*, green tea extract [*Camelia sinensis*], guarana [*Paullinia cupana*], cola nut [*Cola acuminata*, *C. nitida*], mate’ aka yerba mate’ [*Ilex paraquariensis*]), and cocoa extract [*Theobroma cacao*]), as well as the fruits of *Garcinia cambogia* and other ingredients. But it’s the bitter orange peel extract and its synephrine content that are getting most of the media’s, and recently, the FDA’s attention.

Botany and Distribution

Bitter orange also called Seville orange, is known botanically as *Citrus x aurantium*, L. of the family Rutaceae, and sometimes by its taxonomic synonyms, *C. aurantium* L. subsp. *aurantium* and *C. aurantium* subsp. *amara* (L.) Engler. Bitter orange is known by many local common names in countries around the world where it is used for food, fragrance and medicinal purposes. The peel of the immature fruit is known as *Chi shi* or *zhi shi* in Traditional Chinese Medicine (TCM). According to one authoritative source, *zhi shi* is sometimes derived from the immature fruit of *C. sinensis* Osbeck collected from May to June (Tang and Eisenbrand 1992). The peel of the mature fruit, also used in TCM, is called *zhi qiao*, although some sources confuse these two materials.

Bitter orange most likely originated in Southeast Asia and was initially propagated in India and Persia. In the 10th and 11th centuries Arab traders spread it around the Mediterranean countries: Syria, Palestine, North Africa, Sicily, Sardinia, the south coast of France, (*i.e.*, Provence), and Spain. After the discovery of the New World it was introduced into the Caribbean (Peyron 2002). It is presently commercially cultivated in southern Europe and other subtropical areas, particularly Spain, Portugal, Israel, and the various islands of the Caribbean (Bisset and Wichtl 1994).

Modern Food, Fragrance Uses

The bitter orange tree is the source of numerous commercial products used in the fragrance and food industries. Neroli oil is steam distilled from the flowers. Petitgrain oil is made by steam distillation from the buds and leaves of bitter orange; the term *petitgrain* was first used for oil made from the small green fruits (oranges) (Peyron 2002).

In the fragrance industry, the products from the bitter orange tree include neroli oil, bitter orange flower absolute (an absolute is a concentrated flower oil used in the fragrance industry), bitter orange flower water absolute, bitter orange petitgrain oil (bitter orange leaf oil), bitter orange leaf water absolute, bitter orange petitgrain absolute and other petitgrain oils (Bucelato 2002).

In the food industry, bitter orange oil, which is usually expressed from the fresh peels, is widely used as a flavoring agent. Bitter orange oil is used as flavorings for beverages, particularly liqueurs and to intensify the orange character of soft drinks (Colombo *et al.* 2002).

Bitter orange fruits, peels, and the oil from peel are all used to make orange marmalade. Most orange marmalades produced in the United States are made with the fruits and peels of the sweet orange (*C. sinensis*), while most of the original-style, more bitter-tasting marmalades made with true bitter orange (Seville orange) are made in the United Kingdom. Thus, as I have repeatedly told the media, bitter orange is not an exotic ingredient. According to an FDA guidance document, “There is no formal standard of identity for marmalades. However, to avoid misbranding, a product labeled sweet orange marmalade should be prepared by mixing at least 30 pounds of fruit (peel and juice) to each 70 pounds sweetening ingredients. Sour or bitter (Seville) orange marmalade, lemon marmalade, and lime marmalade should be prepared by mixing at least 25 pounds of fruit (peel and juice) to each 75 pounds of sweetening ingredient. *The amount of peel should not be in excess of the amounts normally associated with fruit.* [emphasis added] The product should be concentrated to not less than 65% soluble solids.” (FDA guidance 2004). A study published in 1995 showed that a sample of orange marmalade made from *C. unshiu* contained a total of 12.46 mg synephrine (0.36 d-synephrine + 12.1 mg l-synephrine,) based on mg/100 grams of marmalade, according to high-performance liquid chromatography (HPLC) (Kusu *et al.* 1995). These calculations suggest synephrine at 0.01% in the marmalade, or about 12 mg in 3.5 ounces, an extremely low level of synephrine.

Bitter orange materials are not as plentiful in the market as sweet orange. In contrast to the production of sweet orange oil, the production of bitter orange is “barely sufficient to satisfy commercial demands.” (McHale 2002). Because its production is more limited, the bitter orange oil is more expensive than sweet orange oil and is thus subject to potential adulteration with cheaper materials (McHale 2002).

The peels of both bitter orange and sweet orange are used in the formulation of herbal teas due to the peels’ flavor profiles, their digestive and carminative effects, and for the production of stomachic, carminative, and laxative products (Leung, Foster 1996).

Use of bitter orange Peel in TCM

The two Chinese traditional medicines, *zhi qiao* and *zhi shi*, are obtained from the bitter orange fruit, the former from the more matured orange peel, collected in July (though still green) and the latter from the immature orange (collected May through June, not fully developed). They both are used to treat what westerners term indigestion, though they are more generally used to treat what is referred to in TCM as “*qi* stagnation” (Dharmananda S. Personal communication to M. Blumenthal, Jan. 31, 2004).

In TCM, *zhi shi* is used for the following indications, as described within the language of TCM: “To break *qi* [*chi*, *i.e.*, life force energy] and reduce food accumulation; to resolve phlegm and eliminate distention and fullness.” (Dharmananda 2003). The indications for which it is used

include “food retention, constipation with abdominal pain, diarrhea and dysentery with tenesmus [the urgent feeling to urinate or defecate, without success]; distention and full sensation in the chest and epigastrium [the upper middle abdominal area] caused by phlegm-turbidity blocking the circulation of qi.” (Dharmananda 2003). The dosage ranges 3-10 grams of the dried fruit in decoctions per day. TCM precautions include using caution when using in patients with spleen and stomach deficiency or during pregnancy (Dharmananda 2003).**

Also, dried bitter orange fruit, and, less commonly, the peel are used in treating prolapse of the uterus and anus, diarrhea, and blood in the feces (Leung, Foster 1996). It has also been used as an expectorant and digestant (Tang, Eisenbrand, 1992).

Eclectic and Modern Medicinal Uses

Bitter orange was used by the Eclectic physicians of the late 19th and early 20th centuries. According to the entry for bitter orange in *King’s American Dispensatory*, a reference of significant regard by herbalists and naturopaths who explore the empirical use of herbs by the Eclectic medical movement, bitter orange peel was used as a digestive tonic and as a flavoring agent for other medicines.

Orange peel is aromatic and slightly tonic, but is seldom used except to cover the taste of disagreeable medicines or to lessen their tendency to nausea, and for these purposes it is frequently added to bitter tinctures, infusions, etc., as quassia, Peruvian bark, etc.; though care should be taken not to subject it to long boiling on account of its oil, which will thus be dissipated. For tonic use, the rind of the Seville orange is preferred; its dose in substance is from 30 to 60 grains 3 times a day. (Felter and Lloyd, 1898).

In modern European herbal medicine, bitter orange peel is for dyspepsia and related conditions. According to the package insert from the German Standard License it is used as a supportive measure in treating stomach complaints, *e.g.*, insufficient formation of gastric juice, and to stimulate the appetite (Bisset, Wichtl 1994). The German Commission E recognizes the medicinal value of bitter orange peel for loss of appetite and dyspeptic complaints; daily dosages are given in ranges of 4-6 grams for the dried peel, 2-3 grams for the tincture, and 1-2 grams for the extract (Blumenthal *et al.* 1998).

Chemistry

One of the chemicals of primary interest in bitter orange peel in today’s market is synephrine. Synephrine was initially created synthetically as a sympathomimetic drug (see below), and was later discovered and isolated from the leaves and fruits of various species of *Citrus*, particularly *C. aurantium* (Tang, Eisenbrand 1992). Synephrine has also been reportedly found in the *fruit* and *peel* of some varieties of tangerine (*e.g.*, *C. reticulata*, aka *chenpi* in TCM; unripe fruit peel = *qingpi*), and even possibly in sweet orange (*C. sinensis*). In general, the levels vary greatly, from 0.1% to 2.0%. Synephrine is created in the fruit’s growth in a chemical pathway involving tyramine and *N*-methyltyramine (Tang, Eisenbrand 1992).

Synephrine is an alkaloid (a pharmacologically active class of nitrogen-containing chemical compounds). Its chemical structure is similar to ephedrine, the primary active alkaloid in ephedra, aka *ma-huang*. There are only two chemical differences between ephedrine and synephrine: in synephrine one of the ring carbons is hydroxylated (a hydroxyl group {OH} replaces a hydrogen atom {H}), and a side chain methyl group (CH₃; Me) is replaced by hydrogen. Synephrine is found mainly in the medicinal products derived from citrus, although it has been reported in small amounts in the Chinese evodia fruit (*Evodia rutaecarpa*), *wu zhu yu* in Chinese. Synephrine is also found in a few other plants, including the rubber tree (Wheat and Stewart 1970) (see below).

Synephrine has been incorrectly characterized in some of the published literature. The type of synephrine found in bitter orange peel is p-synephrine (para-synephrine), not m-synephrine, which is what is said to be in bitter orange by various authors. M-synephrine (meta-synephrine) is also called phenylephrine (aka neosynephrine). A comprehensive review of the presence and distribution of synephrine and chemically similar compounds (tyrmaine, n-methyltyramine, hordenine, octopamine) in higher plants was published in 1970, showing that with a few exceptions of non-food plants, synephrine is found mainly in the genus *Citrus* (Wheaton, Stewart 1970).

Synephrine and related alkaloids appear to be present in slightly higher quantities in the unripe fruit than in the ripe fruit. The amount of synephrine in blue citrus (*qing pi*), an immature citrus fruit, is 0.26% and in citrus (*chen pi*), a mature citrus fruit, the level is 0.22%. In an evaluation of four different dried citrus fruits used in Japanese herbal medicine, the synephrine content did not show much variation. Some citrus materials that have been assayed in China have a higher synephrine content; in one study, synephrine levels in citrus fruits and peels ranged from as little 0.1% to a very high 2.0%, while most reports place the level at about 0.25%. One Japanese study found that the level of synephrine was found to decrease corresponding with an increase in the diameter of the dried immature fruits of the variety known in Japan as *kijitsu* (*C. unshiu*), which was found to have higher synephrine levels than *C. aurantium* or *C. hassaku* (Hosoda et al., 1990).

Because synephrine is found in the fruits of various species of *Citrus*, it is also inevitably found in the juices of numerous popular citrus varieties, making the presence of synephrine more widespread in the conventional food supply than many people probably recognize. The synephrine levels of various citrus juices is shown in Table 2.

Table 1: Synephrine Levels in Bitter Orange Materials		
Material	mg	% (mg/100 g)
Fresh fruit	270 mg	0.020
Dried fruit	380	0.352
Dried extract	3000	3.003 – 3.079
Products	250-2500	0.250 – 0.989
<i>Source: Pellati et al. 2002</i>		

Table 2 Synephrine Levels in Citrus Juices	
Fruit & Variety	Synephrine level***
Orange	
Hamlin	22
Navel	15
Pineapple	27
Valencia	19
Tangerine	
Dancy	125
Lemon	
Meyer	2
Cleopatra mandarin	280
***Values are stated in mg/liter of juice for single juice sample (in most cases). (from Wheaton, Stewart 1965)	

Numerous dietary supplements currently on the market contain varying levels of bitter orange peel extract, at various levels of standardization to synephrine. As can be expected, there are also various other herbal and other ingredients included in these formulations.

Regarding synephrine levels in these supplements, the synephrine levels also vary, both in the amount in each dosage form (capsule or tablet) and/or in the amount of synephrine a consumer would ingest on a daily basis, based on the products' directions for use.

The following dietary supplement products were chosen at random from a Google search of the Internet: Cytodyne Xenadrine EFX, one of the leading products in the market, contains a variety of nutritional ingredients, plus the Proprietary Thermodyne Complex, totaling 1,415 mg per

tablet. This complex contains tyrosine, standardized extracts of green tea, cocoa, yerba mate, ginger root, bitter orange (standardized to synephrine and other alkaloids and amines), plus other ingredients (www.cytodyne.com) accessed Feb. 2, 2002). There is no information on the website that allows a determination of the bitter orange peel extract levels nor the synephrine and other amine levels in each dose. Directions suggest two capsules before morning exercise, and two in the afternoon with 8 ounces of water, not to exceed four capsules per day (written in upper case type). There is also an extensive warning given, including the suggestion that persons under 150 pounds may want to use half the recommended levels for the first week.

MetaSlim contains 150mg bitter orange extract (concentrated to 6:1, containing 6% synephrine). The recommended dose is 1-2 tablets in the morning, providing a one-time daily dose of 24 mg synephrine. (www.zooscape.com, accessed Jan. 28, 2002)

Trim Fit with Advantra Z – Tonalin (produced by Quest of Canada): One daily dose (six capsules) contains Advantra-ZT (a proprietary bitter orange peel extract, standardized to 4% synephrine. The total weight of bitter orange peel in six capsules is 1,050 mg (= 42mg synephrine). The product also contains green tea extract, Tonalin (a source of conjugated linoleic acid, CLA), St. John's wort (*Hypericum perforatum*), and other ingredients. (www.zooscape.com, accessed Jan. 28, 2002)

There has been confusion in the popular literature about the purported presence of another alkaloid in bitter orange peel, octopamine. An issue of the *Cornell Department of Nutrition Newsletter* stated that octopamine, in invertebrates, is used as a pesticide and, in humans, is known as a “false neurotransmitter” because it alters the normal function of the brain and is believed to stimulate the production of growth hormone. It also acknowledges studies supporting the belief that octopamine could be considered as an endogenous selective beta-3 adrenoceptor agonist and could be useful in weight loss. It may also be useful in glucose transport. Presently, says the newsletter, it is being marketed as a weight-loss product having thermogenic properties and as an appetite suppressant. The Cornell publication warns consumers about the potential additive effect of the octopamine and synephrine (Anon, Cornell newsletter 1999). However, various analytical studies on bitter orange peel, particularly on the immature peel, like the Chinese *zhi shi* material, has produced no evidence that octopamine is present in any appreciable levels (Pellati 2002; Wheaton, Stewart 1970).

Look for Part 2

Limitations of space being what they are, we are going to break off this discussion at this point and pick it up in a forthcoming Part 2. At that time, we will consider synephrine's pharmacology, clinical trials on bitter orange peel extracts, safety data for bitter orange and synephrine, and regulatory issues, and we will present a list of references.

Mark Blumenthal is the founder and executive director of the American Botanical Council (ABC) in Austin, TX, a non-profit organization, and is editor of its journal *HerbalGram*. He also served as lead editor of two books in English on the German Commission E monographs, one of

the world's most comprehensive considerations of herbal medicine. His most recent booklength effort is *The ABC Clinical Guide to Herbs*, in which he and six co-author/editors present extensive information on 29 of the most popular herbs sold in the U.S. market today. A frequent lecturer and talk-show guest, Blumenthal has been in the natural food and herb industries for over three decades, functioning as a wholesaler, manufacturer, journalist, consultant and educator.

Author's Notes

** At press time, the FDA has not yet published its final rule regarding how and when the ban would go into effect.*

*** It should be noted that spleen deficiency does not refer to the organ known as the spleen in western anatomy. In TCM "the spleen and stomach represent the digestive system. The spleen plays an essential role involving the transportation and transformation of nutrients, control of blood flow and responsibility for anxiety. The spleen also is related to the muscles. When patients have chronic fatigue and digestive disorders, they are often diagnosed by [TCM] as spleen deficient. Generally, this means that the spleen's role is dysfunctional. Because of spleen deficiencies, nutrients cannot be distributed properly for the body's needs. The body lacks energy, so fatigue occurs. Spleen deficiency also causes digestive dysfunction. Typical symptoms are poor appetite, bloating of the abdomen or chronic diarrhea." (Ren 2001).*

Bitter Orange Peel and Synephrine: Part 2

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By Mark Blumenthal

This is the second part of a comprehensive article on bitter orange, the first part having been published in *WholeFoods* in March 2004. The article was originally planned and much of it was written in late 2003 and early 2004, when the FDA had just announced its intention to ban the then increasingly controversial herb ephedra (*Ephedra sinica*) from all dietary supplements, said ban going into effect on April 12, 2004. For several years prior to the ban, many dietary supplement manufacturers had started the trend toward "ephedra-free" supplements for weight loss and/or athletic performance, many of these supplements containing bitter orange extract.

When I originally wrote the initial drafts of this article for *WholeFoods*, in order to include many of the details I thought were important to understanding the various aspects of bitter orange and its current role in the dietary supplement industry, I wrote an article that became too long for the

magazine to publish in one issue. Hence the first half, dealing mainly with the botany, geographical distribution, chemistry, food use and other aspects of bitter orange was published last year. I intended to revise and complete the second half, dealing with pharmacology, clinical trials and safety—and publish it shortly afterward. However, other editorial, organizational and personal priorities became paramount for me, and the completion of part 2 was set aside. Now, after a full year, we are happy to present the second half.

Confusion on Adverse Events and Bitter Orange

During the intervening year, there has been some interesting controversy surrounding bitter orange. However, the controversy is somewhat different from that which surrounded and eventually created the demise of ephedra. Whereas ephedra went down after various reports of deaths of several highprofile athletes and after years of concern about reports of serious adverse events associated with its use, the pharmacovigilance field and the media have been relatively quiet about bitter orange, at least compared to ephedra. To my knowledge, there have been few confirmed, reliable adverse event reports implicating bitter orange and/or bitter orange-containing dietary supplements with any *serious* injury or death. Not that there haven't been some *stories about some such reports*. If this sounds like a contradiction, I'll explain. In April 2004 *The New York Times* published a story (Hurley, 2004) about bitter orange that stated that the reporter had received from FDA some data saying that there were 85 adverse reactions (adverse event reports, AERs) and seven deaths associated with bitter orange. This was big news to many people in the herb industry as well as people in the research and academic communities who were not familiar with such reports. The American Herbal Products Association's president, Michael McGuffin, published a deconstruction of these putative AERs, finding that many were either duplicates in the FDA's AER database or were associated with products containing *both* bitter orange *and* ephedra, and thus most of these reports cannot be used to help evaluate the relative safety or risks of bitter orange (McGuffin, 2004). In fact, in McGuffin's analysis, he finds only one serious AER that can be clearly attributable to a supplement containing bitter orange.

The American Association of Poison Control Centers' Toxic Exposure Surveillance System [TESS] report for 2003 contains about 40 incidents related to bitter orange as a single ingredient and as a multi-ingredient supplement. However, these 40 incidents cannot be interpreted as all related to adverse events, either minor or serious. Besides, the TESS system has been shown to be unreliable insofar as determining which reports are actually merely consumer inquiries or incident reports as compared to actual reports of minor or serious adverse reactions [Kingston and Blumenthal, 2003].

Consequently, some of the reports associated with bitter orange in the TESS database cannot be viewed *a priori* as "adverse."

In Canada one publication has suggested some adverse events associated with bitter orange preparations. Writing in a newsletter published by Health Canada on adverse event reports, Scott Jordan, Ph.D. and colleagues state that between January 1, 1998 and February 28, 2004 Health

Canada received 16 reports “in which products containing bitter orange or synephrine were suspected of being associated with cardiovascular ARs [adverse events], including tachycardia [rapid heart beat], cardiac arrest, ventricular fibrillation, transient collapse and blackout.” (Jordan *et al*, 2004). All cases were considered serious. However, a review of these cases indicates that in eight instances the products involved also contained both *Ephedra*/ephedrine and caffeine—a combination that has been widely discussed for its potential risks. Only one case involved a suspect product containing bitter orange but no caffeine or *Ephedra*/ephedrine. In seven cases the suspect product also contained caffeine. Two of the 16 patients died, both of whom had taken products containing *Ephedra*/ephedrine and caffeine in addition to bitter orange. The authors state that evaluation of these reports is challenging because of many factors such as the lack of information on the ingested dose of synephrine, the contributory effects of other (multiple) ingredients such as *Ephedra* and caffeine, and the ambiguity of the reported information.

A Serious Adverse Event Case

A recent report of a myocardial infarction (MI or heart attack) in a 55-year-old woman will no doubt become increasingly cited as a serious AER warranting the possible closer restriction of bitter orange in dietary supplements (DS) (Nykamp *et al*, 2004). The woman reportedly had a history of smoking tobacco, was reportedly inactive (did not exercise) and had a *heart murmur*—any or all of which could have contributed to her MI. For one year, she had been using a product called “Edita’s Skinny Pill” containing 300 mg bitter orange (company materials did not specify if this was powdered herb or an extract). The authors of the report conclude that, “the acute lateral-wall MI was possibly associated with bitter orange.” The authors conjecture that the patient’s use of the bitter orange DS may have precipitated an MI based on her underlying but previously undetected cardiovascular disease; they employed the Naranjo probability scale to confirm the possible association with bitter orange. In February, 2004, Edita Kaye, founder of The Fountain of Youth Group in Ponte Vedra, FL, agreed to stop marketing “Skinny” dietary supplements without “reliable scientific evidence” that they work, under a proposed settlement with the Federal Trade Commission, after the FTC accused her of false advertising and deceptive trade practices in a lawsuit filed in January. Kaye, a medical journalist, had been under investigation after unveiling “Skinny Pills for Kids” in 2002 (Early, 2004).

Reviews of Bitter Orange

A few months after the *New York Times* article appeared, a review paper (Fugh-Berman and Myers, 2004) was published in a scientific journal. After reviewing the clinical trials on bitter orange, the authors concluded that from an efficacy perspective, “the only published trial [referring to Colker *et al.*, 1999] of *C. aurantium*- containing weight-loss product [a combination 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.” (Fugh- Berman and Myers, 2004). With respect to safety, the authors state, “*C. aurantium* would be expected [emphasis added to denote that this is still somewhat speculative] to have sympathomimetic effects, but *C. aurantium* extracts have not been associated with adverse effects to date.”

The authors properly point out that no trials have been conducted on bitter orange alone; they are all based on combination products, in which caffeine-containing herbs are usually included. The authors warn consumers to avoid taking bitter orange products until bitter orange's safety has been adequately established by more research. However, the only adverse cardiovascular effects related to bitter orange and synephrine they could find were based on animal and human research in which bitter orange or synephrine were *injected not ingested*. Big difference! They also write, "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." (Fugh-Berman and Myers, 2004)

During 2004 there have been other scientific reviews of bitter orange. The most ambitious has been an 87-page report by the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences (NIEHS), an institute of the National Institutes of Health (NIH) (NTP, 2004). NTP contracted for the report because bitter orange was nominated by a "private individual" (unnamed) for a toxicological review due to its increased popularity in "ephedra-free" dietary supplements "and limited data to demonstrate its safety for this use." (NTP, 2004)

This report is probably the most comprehensive compilation of data on bitter orange conducted to date, based on 18 pages of references (the American Botanical Council's *Herbal Medicine: Expanded Commission E Monographs* [Blumenthal, 2000] is cited eight times). Interestingly, and consistent with this author's findings, the NTP report states that the only "authoritative" review of bitter orange is the brief therapeutic monograph published by the German Commission E, intended for use as a package insert for bitter orange preparations sold as nonprescription medications for loss of appetite and dyspeptic complaints in Germany (Blumenthal *et al.*, 1998).

The NTP report covers the following subject areas: Chemistry, Production Processes, Production and Import Volumes (not supplied, noted as "no data available"), Uses, Environmental Occurrence and Persistence, Human Exposure, Regulatory Status, Toxicological Data (includes many subheadings), and Structure-Activity Relationships.

The NTP report on bitter orange, synephrine, and octopamine is a comprehensive literature review intended as a background document to be presented to government officials who will eventually determine whether a material (an herbal ingredient or an isolated chemical in the food supply, for example) that has been nominated for such review should be evaluated for its safety. The NTP review provides information on what previous studies have been published and what endpoints should be studied in future reviews and new research. The report is not intended to be a policy document but merely to help establish priorities in future research. The NTP report has not been made available to the public, nor has it resulted in any publicly available recommendations to the FDA or other relevant government agencies, at least insofar as this writer has been able to determine. (In January 2005 this writer attempted to clarify the current status of this document but have received no response by the time this article was completed.)

(Personal communication to William Eastin, Toxicology Operations Branch at the NIEHS/NTP, January 22, 2005).

The Executive Summary of the NTP report contains the following language in a section called “Human Data”: “Many studies have been conducted regarding the effects of products whose ingredients include both ephedrine and bitter orange. Some report no adverse effects, while others report that the use of bitter orange with stimulants such as ephedra causes cardiotoxicity. When used in products for weight loss, which may be combined with ephedra, adverse effects included sensitivity to light, an increase in blood pressure, and heightened anxiousness. Similarly, studies of supplements containing synephrine plus caffeine are also controversial. The combination of synephrine and caffeine (in other herbs such as guarana and maté) has been reported to have the same potential in inducing cardiac arrhythmias, hypertension, heart attacks, and strokes as that of ephedra and caffeine.” (NTP, 2004).

The Abstract of the NTP report states: “Extracts used in many dietary supplements and herbal weight-loss formulas as an alternative to ephedra have concentrations of the sympathomimetic alkaloid synephrine that are often much higher than the synephrine concentrations reported for traditional extracts of the dried fruit or peel. Concentrations of octopamine in extracts are less than those reported for synephrine. Weight-loss formulas usually contain 100-200 mg bitter orange extract, which provides 10-40 mg synephrine per dose.” (NTP, 2004)

The Structure-Activity Relationships section “discusses the physiological effects, including toxicity, of certain structural analogs of synephrine and octopamine and briefly reviews studies that compare the cardiovascular effects of synephrine and/or octopamine with those of other biogenic amines. The structural analogs include the catecholamines; several bronchodilators including ephedrine and terbutyline; nasal decongestants including phenylephrine, phenylpropanolamine, and pseudoephedrine; and appetite suppressants such as amphetamines.” (NTP, 2004) Many of these data are derived from injected (intravenous [i.v] or intraperitoneal [i.p.]) administration to animals and humans of various isomers of synephrine and also analogs (other chemical compounds with a structure similar to synephrine). The relationship of the activities of these other compounds and various modes of administration may be of questionable relevance to orally consumed synephrine in bitter orange preparations, but they are included in this report as part of the totality of dataset.

It bears emphasis that the NTP report makes no conclusions regarding the proposed toxicity of bitter orange and/or synephrine with respect to any recommendations for any regulatory action.

Of considerable importance in the NTP report is the statement that it focuses on the para isomers of synephrine and octopamine found in bitter orange peel, i.e., p-synephrine and p-octopamine, “the most frequently noted biogenic amines found in the peel.” Unless otherwise stated, the report’s use of the terms “octopamine” and “synephrine” designates the para isomers; “in most cases, when authors [of studies cited in the text] did not specify the form, the para form was meant.” [NTP, 2004] This is crucial to the understanding of the data cited in the report, as the m

and other isomers of synephrine are known to have different pharmacological activity than the isomer.

Pharmacology

As noted in the Chemistry section of Part 1 of this article (see *WholeFoods*, March 2004), synephrine is *chemically similar* to ephedrine. This chemical similarity has led some observers to presume that the pharmacological activity of synephrine is identical to ephedrine—a conclusion that does not appear to be fully supported by the available literature.

Because of the chemical similarity with ephedrine, there has been confusion as to whether synephrine affects the central nervous system (CNS). According to the NTP report (2004), it does not affect the CNS (“Pharmacologically, synephrine is similar to ephedrine but does not have its central nervous system (CNS) effects.”). Both ephedrine and synephrine affect alpha-adrenergic receptors and, to a lesser extent, beta-adrenergic receptors. Other alkaloids, *e.g.*, octopamine, in bitter orange have similar actions. Both ephedrine and synephrine (only when injected, according to the available research) can raise blood pressure and have other effects on the cardiac function which, when under professional care and administration of proper dosages, may benefit selected patients.

But the action of synephrine is dependent on several important factors: aside from dosage, the *isomeric form* of the synephrine is critical, as is the *mode of administration*. Different types or isomers of synephrine can have varying pharmacological effects, and the various modes of administration (*e.g.*, intravenous [i.v.], the route often used in pharmacological testing on animals, versus oral) can produce markedly differing actions on cardiovascular parameters than oral administration, which, obviously, is the route used in human ingestion of dietary supplements.

Synephrine is considered a non-selective beta-3 agonist. It is a generally accepted theory of pharmacology that beta-3 agonists affect body weight and fat mass (Preuss *et al.*, 2002), activating lipolysis, the breaking down of fats (Carpene *et al.*, 1999). In a study on animals and humans, synephrine was found to be “partially active” in humans (Carpene *et al.*, 1999). Normally, according to one source with considerable experience in the area of the pharmacology of synephrine, *synephrine is not well-absorbed in the gastrointestinal tract* (Jones, 1999). As an isolated pure drug, synephrine is often administered via injection; thus, the pharmacological effects observed for synephrine when injected are not generally applicable to its effects when it is consumed as part of a bitter orange extract-containing dietary supplement. This issue of mode of administration and of the relatively poor oral absorption of synephrine is obviously significant, particularly for dietary supplements, which, by legal definition are consumed orally. Unfortunately, published reports have sometimes confused these factors, thereby producing conflicting results and possibly misleading both professional and public understanding of the relative safety of synephrine.

Synephrine has also been reported to be a sympathomimetic alpha1-adrenoceptor agonist, *i.e.*, like ephedra alkaloids, it can stimulate the sympathetic nervous system, producing what has been generally referred to as a “fight or flight” response. However, synephrine reportedly enters into and is less active on the CNS than ephedrine (Jones, 1999). Therefore, synephrine is believed to have fewer adverse effects on the beta 1 and 2 receptors than ephedrine (Jones, 1999; Kalman, 1999). According to literature discussing the potential benefits of bitter orange in weight-loss formulations, “The theory behind the use of *Citrus aurantium* is that it will augment thermogenesis [the production of body heat through increased metabolism and the resultant loss of calories and weight] and calorie consumption, but at the same time, produce less cardiovascular perturbation than ephedrine” (Arch and Ainsworth, 1983). However, this older paper has been questioned. More recent studies suggest that octopamine works fairly well in stimulating lipolysis in rat fat *in vitro*, but not very well in human fat *in vitro* (Carpene *et al.*, 1999).

Despite the promise of this hypothesis, there apparently are not any well-accepted drugs for inducing weight loss that use this proposed mechanism.

A potential concern about bitter orange is whether it will interact with a variety of prescription drugs. Bitter orange (like grapefruit and grapefruit juice) contains a compound that inhibits an enzyme CYP3A4, part of the cytochrome P450 digestive enzyme system in the small intestine; this enzyme can alter the metabolism of drugs, in this case by inhibiting the production of the metabolizing enzymes, thereby potentially boosting the drugs’ levels in the blood and thus their activity. Synephrine is a substrate for monoamine oxidase (MAO) A and B, according to research on rat brain mitochondria (Suzuki *et al.*, 1979). This can be considered a rationale for a warning on the potential interaction between synephrine and monoamine oxidase-inhibiting drugs (MAOIs) which can cause an increase in synephrine’s potential stimulant activity, as is the case with ephedra supplements and OTC drugs containing ephedra alkaloids (ephedrine and pseudoephedrine) and foods containing tyramine.

A form of synephrine (*m*-synephrine) is sold as a drug in Europe (neosynephrine; Sympatol). It is officially listed in the Nordic and the German pharmacopeias and is mainly used for treatment of asthma and hypotension. Clinical testing has demonstrated that when given by an i.v. infusion to healthy volunteers at a rate of 4 mg/minute, synephrine increased systolic and mean arterial blood pressure, increased cardiac index, and decreased peripheral vascular resistance, but did not affect diastolic pressure and heart rate (Hofstetter *et al.*, 1985). This suggests that synephrine can be considered a stimulant of cardiac performance, usually *when administered via injection*. However, these effects are based on the isolated synephrine and are not reported in the literature as actions for the crude bitter orange peel or immature fruit extracts, its decoction, or other traditional preparations of citrus materials used as orally administered medicinal preparations in traditional Chinese medicine (TCM). Some research shows that these effects are seen as properties of *zhi-shih* aqueous extract or isolated synephrine. These materials have been used in China to treat shock (Chang and But 1986) along with isolated ginsenoside saponins from Asian ginseng (*Panax ginseng*) (Dharmananda 2003), again, usually via injection.

In China, in cases of shock, i.v. synephrine and Nmethyltyramine are administered, depending on the severity of the shock, at doses of 20-60 mg each, diluted in normal saline or glucose solution (Chang & But 1987). Intravenously administered synephrine has a biological half-life (*i.e.*, the time it takes for one-half of a dose of a substance to metabolize in the body and lose its pharmacological activity) of about two hours (Hengstmann cited in Tang, Eisenbrand 1992). Again, one cannot assume a direct relationship between the activity of intravenously administered, isolated synephrine to the orally consumed bitter orange extracts found in dietary supplements.

Clinical Studies

Clinical trials on preparations containing bitter orange peel extracts have basically targeted weight loss (at least two studies up to 2002), increased thermogenesis (three trials), and its safety profile (one trial). A recent comprehensive review of the medical literature by Stephen Bent and colleagues at the University California at San Francisco revealed only seven randomized clinical trials on bitter orange (Bent *et al.*, 2004) This literature search identified a total of 157 titles of scientific and medical papers published on bitter orange (or in which bitter orange was mentioned). Six studies (three of which were published as abstracts only) were excluded from the review because the tested preparations contained the herb ephedra and/or ephedrine in addition to bitter orange (three studies) or weight loss was not reported as a primary outcome measure (three studies). One study (Colker *et al.*, 1999) satisfied all inclusion criteria for the review (see below). Bent and his colleagues concluded that, “This systematic review found no evidence that the herb, citrus aurantium, is effective for weight loss. Safety information is extremely limited, and, because citrus aurantium contains the sympathomimetic drug msynephrine [sic*] (phenylephrine), consumption of the herb *may lead* [emphasis added to denote speculation] to increases in blood pressure, pulse, and the risk of adverse cardiovascular events.” [*Note: bitter orange does *not* contain *m*-synephrine [*metal*-synephrine; it contains the *p*-synephrine [*para*-synephrine] isomer in its levo and devo rotary racemic forms.]

The Bent review excluded one randomized, controlled, crossover trial because the trial did not report a weight-loss outcome; it measured blood pressure and pulse changes in 12 normal subjects after they drank fresh citrus aurantium *juice* compared with a water placebo (patients were not blinded) (Penzak *et al.* 2001, see below).

The trial by Colker *et al.* (1999), noted above, tested a bitter orange, caffeine and St. John’s wort (SJW) combination. In a sixweek double-blind, randomized, placebocontrolled trial, 23 healthy overweight (body mass index of 25 kg/m²; this is considered overweight but not obese; the BMI parameter for obesity begins at 30 kg/m²+) adults (age or sex not given) were assigned to one of three groups: (A) an herbal mixture containing bitter orange (6% synephrine) 975 mg, St. John’s wort (*Hypericum perforatum*) extract standardized to 0.3% hypericin, 900 mg, and caffeine 528 mg; (B) a maltodextrin placebo; or (C) a control group without placebo. The subjects used an American Heart Association Step One diet and an exercise program three days per week under the supervision of a trainer. Outcomes were assessed at baseline, three and six weeks, and included change in weight, percent body fat, fat mass, and basal metabolic rate. Subjects in

Group A lost what the authors deem a significant amount of weight (1.4 kg) and body fat (2.9%) compared to the placebo group, but the control group lost about as much as the treatment group, thus rendering these results of questionable value. The Bent review assessed the quality score of this trial at 3 out of a possible 5 “because the randomization technique was not described and reasons for the withdrawal of three subjects were not stated.”

Several small, unpublished clinical trials have been conducted with bitter orange extract with other herbs and dietary supplement ingredients. Since they have not been published in accessible medical, pharmacy, or nutrition journals, it has not yet been possible for this writer to determine at the time of this writing (end of January 2005) to what extent these unpublished studies are accurately presented, or to what extent a peer review process that accompanies the publication process would alter some of the trials’ conclusions. Some of these unpublished trials are summarized below.

One small unpublished trial on 10 healthy adults (eight female, two male) conducted by Miami Research Associates (www.miamiresearch.com), using one serving of Xenadrine EFX (manufactured by Cytodyne LLC, Farmingdale, NY) a combination product containing green tea extract, bitter orange extract and numerous other ingredients, ingested after a meal, claimed to result in no appreciable increase in blood pressure and showed an increase in metabolic rate (Kalman *et al.*, 2002a). Another very small trial by the same research group tested the effects on blood pressure and resting metabolic rate of Xenadrine EFX with two ephedra-containing supplements in six normal, healthy adults (Kalman *et al.*, 2002b).

The authors report that bitter orange-containing product does not cause any significant change in heart rate, systolic or diastolic blood pressure 60 minutes after ingestion. They report, too, that the resting metabolic rate was significantly elevated after administration of Xenadrine EFX, but with such a small sample size, such results need a larger trial to show a significant effect. A third trial by the same research group, tested on 16 overweight adults over four weeks, employed Xenadrine EFX and exercise and mild reduction in caloric intake (Kalman *et al.*, 2003). Over 14 days, when compared to baseline values, those receiving the Xenadrine EFX product had a lower appetite rating at day seven, but this was non-significant by day 14. There were no significant negative effects on blood pressure, heart rate, serial EKGs, blood sugar, renal function, hepatic function or blood count in the two groups. Sleep quality was negatively impacted in the EFX group (versus placebo), but whether this was due to the action of the product or the combination of the product and exercise deserves further attention, say the authors. Subjects in the EFX group compared to placebo experienced a 60.4% reduction in fatigue levels ($p=0.0256$).

An unpublished study for Jamieson Laboratories in Canada by Penny Kendall-Reed, N.D., was designed to determine the effectiveness of a weight-loss product called Ultra Slim Down (Jamieson Laboratories, Toronto, Ontario, Canada), a product that was to be marketed as an agent that helps convert carbohydrates and fat into energy and thus reduces body weight more effectively (Kendall-Reed, 2000). Ultra Slim Down consists of two main products, what the author terms a “carbohydrate burner” and a “fat absorber” (chitosan). The ingredients in the herbal carbohydrate burner include CitraMax (containing 125 mg hydroxycitric acid [HCA])

derived from the fruit of the *Garcinia cambogia* tree, purportedly useful in helping the body convert dietary carbohydrates into energy rather than storing them as fat). Other ingredients included 125 mg of a thermogenic herb formulation known as Advantra Z (Nutraceutical, Wayne, NJ), derived from the immature fruits of bitter orange, and 50 mg of cola nut (*Cola nitida*, *C. acuminata*), a caffeine-containing herb to provide enhanced energy levels. After 10 weeks, the study report states that subjects in the group with the product only lost an average of 10.2 pounds (range: 10-12 pounds) and the group taking the product and employing exercise lost an average of 14.5 pounds (range 3.5- 23 pounds); the control group (no product, no exercise) lost 7.64 pounds (range 1-15 pounds).

The significance of these trials is unclear. It would be preferable if the herbal materials tested were subjected to a larger group of test subjects and the trials were published in peer-reviewed journals.

Finally, one U.S. trial on adults with normal blood pressure tested Seville orange juice (SOJ), not bitter orange peel (Penzak, 2001); note: Seville orange is another common name for bitter orange. SOJ, like grapefruit juice, has been used in medical trials to “knock out” or deactivate the intestinal and hepatic enzyme substrate cytochrome P450 (CYP) 3A4 in drug bioavailability studies. The purpose of this particular study was to determine the synephrine and octopamine levels in SOJ and SOJ’s cardiovascular effects in adults with normal blood pressure. The test subjects consumed eight ounces of SOJ and water in a crossover fashion followed by a repeat ingestion eight hours later. Various cardiovascular-related (hemodynamic) measurements were assessed hourly for five hours after consumption of the juice, *i.e.*, heart rate; systolic, diastolic, and mean arterial pressure. The investigators stated that the bitter orange juice had no significant effects on blood pressure or pulse, but, according to Bent *et al.*, “they did not provide confidence intervals to exclude clinically important changes in these hemodynamic measures.” (Bent *et al* 2004)

The SOJ was analyzed by high-performance liquid chromatography (HPLC). The average level of synephrine was 56.9 +/- 0.52 micrograms per milliliter (computed by Bent *et al* [2004] as approximately 13 to 14 mg of synephrine) and no octopamine was detected (consistent with other research, despite some erroneous reports of its presence in bitter orange; see Chemistry section in part 1, March 2004). Of particular interest is that the measurements of the hemodynamics showed no significant difference between the water and the SOJ groups, leading the authors to conclude that “SOJ ingestion by normotensive subjects is expected to be safe.” (However, according to Bent *et al.* [2004] the researchers “did not provide confidence intervals to exclude clinically important changes in these hemodynamic measures.”) Penzak *et al.* cautioned that people with severe hypertension, tachyarrhythmias (increased, irregular heart beat), and narrow-angle glaucoma and those taking MAOI drugs should avoid SOJ consumption as well as persons taking decongestant-containing cold preparations (*e.g.*, those with pseudoephedrine) should also refrain from taking SOJ. (Because of its synephrine content, some of the same cautions apply to people taking dietary supplements containing bitter orange peel extract. See below.)

Safety of bitter orange and synephrine

There is currently much concern being expressed in the media about the overall safety and potential risks associated with bitter orange-containing dietary supplements. Some warnings that are found in the professional literature (*e.g.*, Jellin 2002) are based mainly on the chemical similarity of synephrine to ephedrine, without many data from actual adverse event reports (AERs). The German Commission E monograph for bitter orange peel says that there are no contraindications but that photosensitization may occur in fair-skinned individuals (Blumenthal *et al.*, 1998). Curiously, writing over 100 years ago Felter and Lloyd state, “Large quantities of it [bitter orange peel] have caused violent colic, convulsions, and even death.” (Felter and Lloyd 1898) However, they do not give any indication regarding the level of the purported toxic dosage.

One leading, authoritative text on Chinese pharmacological research says that bitter orange “has a low toxicity and a wide safety range.” (Chang & But 1987). It notes that most observations of cardiovascular activity have occurred with intravenous administration of *zhi shi* decoction, synephrine, and N-methyltyramine in cases of treating infections, anaphylactic or cardiogenic shock resulting from other causes. These preparations were deemed “effective when given intravenously, but not orally.” (Chang & But 1987). This observation by a respected Chinese research team tends to support the question raised above about the oral availability of synephrine.

An unpublished acute oral toxicity study was performed on rats to determine the relative safety of a single dose of a leading bitter orange extract-containing supplement called Advantra Z, manufactured by Nutraceutical, Inc., headquartered in Wayne, NJ (Douds, 1997). A limit test was performed wherein one group of five male and five female rats received a single oral administration of the test material at a dose of 10,000 mg/kg body weight and the rats were observed until they were sacrificed after 14 days. No mortality occurred in any of the rats during the test. The most notable clinical abnormalities observed during the study included rough coat, decreased activity, congested breathing, dark material around the facial area, decreased defecation, salivation, soft stools and urine/fecal stain. These clinical abnormalities were observed during the first few days after dosing, but then disappeared, with the exception of residual slight hair loss which was still present in one animal for 14 days and in another after seven days. A slight body weight loss was noted for one female rat between days seven and 14 body weight interval. However, since the animals were young adults and still growing, body weight gain was noted for all other animals during the test period. No significant gross internal pathological findings were observed at autopsy on day 14. Under the conditions performed in this test, the acute oral LD50 (the amount of a substance required to kill 50% of the test population) of Advantra Z was estimated to be greater than 10,000 mg/kg in the rat. That is, this test concluded that it would require an extremely high dose of Advantra to kill 50% of the rats, thereby suggesting the relative safety of Advantra when given one time in a high dose.

A reliable book and database on herb safety (Brinker 2001, 2004) suggests the following contraindications for bitter orange based on empirical reasons: stomach or intestinal ulcers, due

to bitter orange's tonic effect on the gastrointestinal tract; in children, due to the presumption that excessive doses can produce "toxic effects"; and ultraviolet or solarium light, due to the potential photosensitizing effect. Additionally, the bitter orange juice and/or its preparations are contraindicated in cases of severe high blood pressure, rapid heart rate, and narrow-angle glaucoma due to its synephrine content (the author notes this as speculative), even though 8 oz. of the juice did not affect blood pressure or heart rate in normal subjects.

A U.S. Military "fact sheet" on bitter orange contains information taken mainly from *The Natural Medicines Comprehensive Database* (Jellin *et al.* 2002). The "fact" sheet makes the following statements: It acknowledges that bitter orange is used in foods and is safe, but it states, "However, bitter orange is not safe when used in high doses." It states bitter orange can cause hypertension and "cardiovascular toxicity" and that these effects "can be exacerbated" when used with other stimulants (*e.g.*, caffeine, coffee, cola nut, ephedra, guarana, and mate). Regarding potential drug interactions, the military sheet states that bitter orange can increase stomach acid and can thus interfere with antacid (calcium carbonate, *e.g.*, Tums, and aluminum/magnesium hydroxide (Maalox) as well as ulcer medications (*e.g.*, Prilosec, Zantac *et al.*). These interactions appear speculative, at least at this time. Other potential interactions noted by the fact sheet include the following drugs: anti-anxiety drugs (*e.g.*, alprazolam [Zanax]), blood pressure medications, cholesterol-lowering drugs (the statins), decongestants, antidepressants, allergy drugs, HIV drugs, anti-fungals, sedatives, anti-nausea drugs, steroids, weight-loss drugs, and erectile dysfunction drugs (sildenafil aka Viagra). These interactions warrant attention, as the inhibition by 40% of the isozyme CYP3A4 of the P-450 enzyme system by bitter orange would probably increase the activity of drugs that are substrates to CYP3A4 enzymes. Brinker's herb-drug interactions database also notes these potential interactions (Brinker 2004).

Regulatory Issues

Bitter orange flowers, peel, and peel oil are generally recognized as safe (GRAS) as *foods* according to the Food and Drug Administration (FDA). Viewing the websites of FDA's Investigations Operations Manual (revised March 3, 2003) produced by the FDA's Office of Regulatory Affairs shows that the flowers and peel of bitter orange are listed as safe food ingredients (FDA Inspection Manual, 2003). In the FDA's "EAFUS: A Food Additive Database" ("*Everything*" Added to Food in the United States" (EAFUS) both bitter orange peel extract and bitter orange peel oil are considered "ASP", *i.e.*, "Fully up-to-date toxicology information has been sought." bitter orange peel extract is noted as document number 2486 and bitter orange peel oil is number 2487, denoting the PAFA (Priority-based Assessment of Food Additives) database number of the *Food Additive Safety Profile* volume containing the printed source information concerning the substance. Bitter orange peel oil is listed with the Chemical Abstract Service (CAS) Registry Number (#068916-04-1) and bitter orange peel extract has a numerical code assigned by the FDA's Center for Food Safety and Nutrition (CFSAN) (#977081-87-0) since it does not have a CAS Registry Number. Both substances are specifically listed in Title 21 of the *Code of Federal Regulations* (FDA EAFUS, 2004). Most of the extracts found in dietary supplements are usually derived from the whole, immature fruit.

Much of the current interest in bitter orange has been a result of numerous articles in the media, many of which have focused on the fact that bitter orange has become the primary substitute ingredient for ephedra in ephedra-free products. While many articles have reported on the increased popularity of bitter orange as part of the post-ephedra ban news coverage, some articles and editorials seem to have jumped on bitter orange as the media's potential new "whipping boy," various writers making what is probably the erroneous conclusion that bitter orange is equal to ephedra in activity and potential toxicity. Such a rush to judgment does not appear to be warranted by the available evidence.

An example of the media's targeting of bitter orange and synephrine is epitomized in a commentary in *Business Week*: "With the potential threat of harm from ephedra-free products, leaving the law unchanged is too great a risk. But unless the FDA can argue that the synephrine in bitter orange is pharmacologically close enough to ephedrine to be covered by the coming ban, the agency will find it tough to restrict," writes the author, J. Carey (Carey 2004).

With mounting concern about potential safety issues being expressed by media, health authorities and government officials, the future of bitter orange and its principal alkaloid synephrine as dietary supplement ingredients is uncertain. synephrine's chemical similarity to ephedra, and the possibility that it may exhibit pharmacologically similar yet milder activity (even without any CNS activity), would appear to be negative strikes against it, so far as the media, medical professionals, congressional members, and even regulators are concerned. Like ephedra, whose alkaloids are FDA-approved drug ingredients, bitter orange's synephrine also has the potential disadvantage of being recognized as a drug. The potentially saving grace related to bitter orange is that it is a food and it is GRAS, albeit in serving sizes that are presumably significantly smaller than the synephrine levels in many supplements.

Another factor that might mitigate in bitter orange's favor is its probable lower level of activity of synephrine than ephedra alkaloids, probably due, at least in part, to synephrine's absorption differences when ingested (*i.e.*, compared to the i.v. route) and the possibility that it does not cross the blood-brain barrier.

There are relatively few reports of adverse events related to bitter orange or synephrine-containing dietary supplements. An independent scientific review of all the literature on bitter orange and synephrine is warranted, similar to what has been initiated by the NTP, especially before any regulatory actions are contemplated. How regulators are going to handle this issue remains to be seen, but at present, the future of bitter orange appears uncertain, particularly since the safety of synephrine appears to be going through a process of prejudgment based on the compound's *chemical* similarity to ephedrine.

For example, in the preamble to the final rules banning dietary supplements containing ephedra published by FDA on February 11, 2004 (released on February 6, 2004), FDA states numerous times that the agency's concerns about the safety of ephedra also extend to other sympathomimetic agents, which would include bitter orange. On pages 194-5 of the prepublication version of the final rule, FDA makes the following statement:

“Synephrine is a sympathomimetic agent, and these agents are a class of compounds that also includes ephedrine alkaloids. A number of other potential herbal sources of sympathomimetics probably exist. These ingredients may pose risks that are similar to those of ephedra. If consumers switched to substitute products containing these ingredients, similar health risks might be expected as those with products containing ephedrine alkaloids.” (FDA, 2004).

Thus, while FDA does not specifically mention bitter orange itself, it does appear to be concerned with synephrine, and thus, presumably by logical extension, bitter orange as an synephrine-containing ingredient. This is consistent with former FDA Commissioner Mark McClellan’s statement at the University of Mississippi College of Pharmacy on January 20, 2004, where he said that bitter orange is one of the supplement ingredients that is under review; (the two others are (1) herbs containing the nephrotoxic compound aristolochic acid [few of these herbs are found in the U.S. market; the herb industry has cooperated with FDA and other regulators to stop the importation of such herbs, usually from China], and (2) usnic acid found in species of *Usnea*). While the statement quoted above from the preamble of the ephedra regulations was written as part of FDA’s economic analysis on the impact of its ephedra ban, it can be interpreted as representative of the agency’s thinking about the relative safety of all sympathomimetic agents in dietary supplements. Some industry experts have expressed discomfort with the legal strategy FDA has developed to ban ephedra, yet three leading trade associations (the Council for Responsible Nutrition (CRN), the National Nutritional Foods Association (NNFA), and the Utah Natural Products Alliance (UNPA)) did not mount a legal challenge to the ephedra ban.

It is possible that the agency may attempt to use the same or similar strategy to attempt to remove other herbs from the market, *i.e.*, if the FDA thinks that they present an “unreasonable risk of injury or illness” when sold as dietary supplements. Depending on how the agency’s internally or externally commissioned investigations turn out, bitter orange may be one of the herbs. However, FDA may have a more difficult time with bitter orange, as the agency does not seem to possess—at this time at least—a significant number of serious or even minor adverse event reports (AERs) that it can release to the media and Congress to demonstrate that bitter orange in dietary supplements constitutes an “unreasonable risk of illness or injury.”

However, FDA might use the risk/benefit criterion it has employed in supporting its ephedra ban to try to build a case that the synephrine in bitter orange is too similar to ephedrine in ephedra to allow bitter orange’s continued sale as a dietary supplement ingredient, and may attempt to remove bitter orange even before potentially serious bitter orange-related AERs (*i.e.*, if they even occur) begin to be reported. Under such a risk/benefit analysis, it is predictable that FDA, or perhaps some other party—*i.e.*, if the FDA contracts out for an independent scientific review—might conclude that there is possibly more risk compared to a relatively low level of adequately recognized benefit for bitter orange. If this scenario happens, bitter orange-based weight-loss supplements may end up in a similar situation as ephedra. And bitter orange might be targeted for possible removal from the market, even without any significant evidence of risk.

Because bitter orange and its extracts have been used as an ingredient in dietary supplements for some years now, many manufacturers may assume that they qualify as “old dietary ingredients” under the terms of the Dietary Supplement Health and Education Act of 1994 (DSHEA) and are thus “grandfathered” as presumably safe for use.

Yet, there is another way for FDA to move forward on bitter orange, and that relates to this issue of new dietary ingredients (NDIs). It is possible that synephrine in bitter orange could be considered an NDI due to the relatively high levels of synephrine compared to synephrine levels in bitter orange acknowledged as GRAS by FDA. At a conference on dietary supplements sponsored by the Scripps Clinic in La Jolla, CA in January 2005, during a panel on regulation, Mark Ledoux, CEO of Natural Alternatives International, a manufacturer of dietary supplements in San Marcos, CA, stated that he believed that bitter orange extracts standardized to relatively high levels of synephrine *are* NDIs as they meet the “chemically altered” criterion for determination of NDI status. Susan Walker, M.D., director, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition at the FDA agreed, thereby providing a possible hint at what FDA may be thinking regarding its potential future actions on bitter orange. Ledoux also pointed out that 75-day pre-market notification for NDIs for herbal extracts in use post- 1994 are relatively rare since most herbal extracts sold today were also in use prior to the passage of DSHEA in 1994.

It should be remembered that FDA was able to remove the controversial steroid androstenedione from the dietary supplement market by simply calling it an NDI, thereby classifying supplements containing this ingredient as being misbranded or adulterated. Since most manufacturers of dietary supplements containing bitter orange and synephrine have probably not filed the required 75-day NDI notification as required by DSHEA, it would be most convenient for FDA to simply state that bitter orange in the form in which the synephrine content exceeded the levels naturally found in bitter orange peel and which are approved GRAS, would be deemed an NDI and thus, technically, unsafe until formal procedures could document the safety to FDA’s satisfaction.

At a time when American health officials have recognized that an epidemic of obesity has become one of America’s biggest health challenges, the question remains as to what extent public health officials will welcome, or at least be willing to tolerate, what appears to be a relatively safe food substance with the ability to aid dieters in their quest for an *adjunct* to modification of their diets and increased exercise—the two *primary* methods that people should always use first when attempting to lose weight.

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extensive information on 29 of the most popular herbs sold in the U.S. market today. A frequent lecturer and talk-show guest, Blumenthal has been in the natural food and herb industries for over three decades, functioning as a wholesaler, manufacturer, journalist, consultant and educator.

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